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Pairing Regression and Configurational Analysis in Health Services Research:Modeling Outcomes in an Observational Cohort Using a Split-Sample Design

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Pairing Regression and Configurational Analysis in Health Services Research: Modeling Outcomes in an Observational Cohort Using a Split-Sample Design

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ABSTRACT

Objectives To use configurational analysis and logistic regression within a single dataset to compare results from the two methods.

Design Secondary analysis of an observational cohort; a split-sample design involved randomly dividing patients into training and validation samples.

Participants and Setting Patients with transient ischemic attack (TIA) in US Department of Veterans Affairs hospitals.

Primary and Secondary Outcome Measures The patient outcome was the combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-TIA**.** The quality-of-care outcome was the “without-fail” rate (proportion of patients who received all processes for which they were eligible, among seven processes).

Results For the recurrent stroke or death outcome, configurational analysis yielded a three-pathway model identifying a set of (validation sample) patients where the prevalence was 15.0% (83/552), substantially higher than the overall prevalence of 11.0% (relative difference of 36%). The configurational model had a sensitivity (coverage) of 84.7% and specificity of 40.6%. The logistic regression model identified six factors associated with the combined endpoint (c-statistic, 0.632; sensitivity, 63.3%; specificity, 63.1%). None of these factors were elements of the configurational model. For the quality outcome, configurational analysis yielded a single-pathway model identifying a set of (validation sample) patients where the without-fail rate was 64.3% (231/359), nearly twice the overall prevalence (33.7%). The configurational model had a sensitivity (coverage) of 77.3% and specificity of 78.2%. The logistic regression model identified seven factors associated with the without-fail rate (c-statistic, 0.822; sensitivity, 80.3%; specificity, 84.2%). Two factors were also identified in the configurational analysis.

Conclusions Configurational analysis and logistic regression represent different methods that can yield complementary results when paired together. Configurational models optimize sensitivity with relatively few conditions. Logistic regression models discriminate cases from controls and provided inferential relationships between outcomes and independent variables.

Article Summary

Strengths and Limitations of this Study

- Logistic regression and configurational methods (CNA) were applied to the same data to examine similarities and differences in results.
- The split sample approach to development and validation of models is a key methodological strength.
- The results are based on data from the US Department of Veterans Affairs and may not generalize to other healthcare systems.

INTRODUCTION

Configurational Comparative Methods (CCMs) have been used in a wide variety of disciplines since at least the 1990s and have recently started to gain traction in the general medical research literature[1-4] as well as within implementation science.[5] CCMs draw upon mathematical approaches conceptually different from those used in regression modeling, which is commonly used in health services research. Specifically, CCMs draw upon Boolean algebra and set theory to identify specific combinations of conditions that lead to an outcome of interest as well as determine if multiple solution paths yield the same outcome (i.e., equifinality).[6-8]

Although CCMs and logistic regression provide complementary results and offer the potential for synergistic understanding of complex clinical situations, few studies in the medical literature[9] have used both approaches within a single dataset.[10-13] The objective of the current study was to use both CCMs and logistic regression to independently derive and validate two models (one for mortality or recurrent stroke and the other for quality of care) among patients with transient ischemic attack (TIA). Two outcomes were chosen because they provided different methodological aspects. The combined endpoint of death or recurrent stroke was relatively uncommon in this cohort of TIA patients and therefore presented the problem of predicting rare but important events. The quality of care metric was available for the majority of patients, however few robust predictors of quality at the patient level have been identified.[14]

METHODS

This analysis was part of the Protocol-guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) project to improve quality of TIA care in Veterans Health Administration (VA) facilities.[15-17] We identified patients with TIA who were cared for in any VA Emergency Department (ED) or inpatient setting based on primary discharge codes for TIA (International Classification of Disease [ICD]-10 G45.0, G45.1, G45.8, G45.9, I67.848) during the period October 2016 and September 2017. The unit of analysis was the TIA patient.

Patient and Public Involvement Statement

This analysis did not have patient or public involvement.

Data Sources

Electronic health record data were obtained from the VA Corporate Data Warehouse (CDW).[18 19] CDW data included: inpatient and outpatient data files (e.g., clinical encounters with associated diagnostic and procedure codes) in the five-years pre-event to identify past medical history,[20] healthcare utilization, and receipt of procedures (Current Procedural Terminology [CPT], Healthcare Common Procedures Coding System [HCPCS], and *ICD*-9 and *ICD*-10 procedure codes). CDW data were also used for vital signs, laboratory data, allergies, imaging, orders, medications and clinical consults. Mortality status was obtained from the VA Vital Status File.[21] Recurrent stroke events were identified using a combination of VA CDW data and fee-basis data (which describes healthcare services that were paid for by the VA but that were obtained by Veterans in non-VA facilities). The study was approved by the human subjects committee at the Indiana University School of Medicine Institutional Review Board and the Richard L. Roudebush VA medical center Research and Development Committee.

Primary and Secondary Outcome Measures

The combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-discharge from the index TIA event was the primary patient outcome. Recurrent ischemic stroke events included ED visits or hospitalizations and were identified on the basis of *ICD*-10 codes.

The quality of care outcome was the "without-fail" rate (also referred to as defect-free[22 23] care), which is an "all-or-none" measure of care quality.[24] It was calculated as the proportion of Veterans with TIA who received all of the processes of care for which they were eligible from among seven processes: brain imaging, carotid artery imaging, neurology consultation, hypertension control, anticoagulation for atrial fibrillation, antithrombotics, and high/moderate potency statins.[25 26] Processes of care were ascertained using electronic health record data using validated algorithms.[26 27] The without-fail rate was based on guideline[28 29] recommended processes of care and has been associated with improved outcomes.[30] Given the all-or-none nature of the without-fail rate, it can be a relatively difficult outcome to change and even small improvements in the absolute rate may reflect substantial changes in practice at the facility level.[24] For the without-fail rate, quality measures were recoded such that pass=1, not eligible=0, and fail=0.

Analytic Overview

We analyzed this same dataset with configurational analysis and logistic regression modeling. We randomly divided the overall dataset (n=3079) into a ~70% training sample (2192/3079) and ~30% validation sample (887/3079). The training sample was independently analyzed by a configurational analyst (EJM) and a biostatistician (AJP). For the combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-discharge from the index TIA event, we included both baseline patient characteristics (e.g., age) as well as processes of care (e.g., hypertension control) in the modeling. The without-fail model included only processes of care. Model performance was tested using the validation sample.

Configurational Analysis

Configurational analyses were conducted with Coincidence Analysis–a relatively new approach within the broader family of CCMs[31]–using the R package “cna.”[32]

Definitions

Variables were baseline characteristics of patients (e.g., history of hypertension) which could be expressed with a dichotomous scale or a continuous scale. A condition is when a factor takes on a specific value (e.g., history of hypertension was present). Consistency or positive predictive value is the number of cases covered by the solution with the outcome of interest versus all cases covered by the solution. Coverage or sensitivity is the number of cases covered by the solution with the outcome of interest versus all cases with the outcome of interest. Complexity is the number of discrete conditions in a configuration. Ambiguity describes a situation where more than one model generated by the configurational analysis fit the data equally well.

Analytic Steps

We began with a multi-step data reduction approach that has been described previously.[1 2 33-35] Briefly, we used the “minimally sufficient conditions” function in the R package “cna” to examine all 75 candidate factors (e.g., demographics, past medical history, characteristics of the index cerebrovascular event, vital signs, laboratory data, medications, and processes of care) in the analysis with the outcome of interest across all 2192 cases in the training sample and identify bundles of conditions with the strongest connections to the outcome condition. We performed this process separately for the two outcomes of interest: mortality or recurrent stroke within one year; and the without-fail rate. When analyzing these combinations of conditions, we considered all 1- and 2- and 3-condition bundles instantiated in the dataset (meaning patients with these specific combinations of configurations were present within the sample) that satisfied the consistency threshold.

We used a dual minimum threshold to identify patient characteristics to use in model iteration: a prevalence threshold of ≥0.145 (via the “consistency” function available in the R “cna” package) and a coverage score of ≥0.15. These cutoffs were selected to ensure individual configurations were clinically relevant. Specifically, given that the overall outcome rate of death or stroke at one-year post-TIA was (349/3079) 11.3%, a prevalence threshold of ≥0.145 identified configurations with a mortality or stroke rate at least three points higher (i.e., 14.5% vs. 11.3%) in absolute terms than the overall population, or ≥ 25% higher in relative terms. For the without-fail rate, the overall outcome rate was 34.4% (1058/3079) and the prevalence threshold was set at ≥ 50%, a rate that was at least 15 points higher in absolute terms (i.e., 50% vs. 34.4%), or ≥ 40% higher in relative terms. In this sense, the configurational analysis sought to identify distinct “phenotypes” of patients who had substantially different outcome rates (as a group) than the overall sample. The coverage threshold of ≥0.15 ensured that the configurations applied to at least 15% of individuals with the outcome and was used to avoid overfitting.

We next generated a “condition table” to list and organize the output. In a condition table, rows list configurations of conditions that meet a specified prevalence threshold, and column variables include outcome status, condition, consistency, coverage, and complexity. We generated condition tables by specifying a prevalence threshold of 1.0 (i.e., 100%). If we did not find any potential configurations that met our initial dual threshold (i.e., prevalence threshold of 1.0 and a coverage score of ≥ 0.15), we then iteratively lowered the specified prevalence threshold by 0.05 (e.g., from 1.0 to 0.95, etc.) and repeated the process of generating a new condition table. We continued this process until at a given prevalence threshold it was possible to identify at least two potential configurations (or “phenotypes”) of patient characteristics that met the specified prevalence threshold as well as the ≥15% coverage level. Using this approach, we inductively analyzed the training sample and identified a subset of five candidate difference-making factors to use in the subsequent modeling phase.

We next developed candidate models with these five factors by iteratively using the model-building function within the "cna" software package in R. We assessed models based on their overall consistency and coverage, as well as potential model ambiguity.[36] We selected a final model based on these same criteria.

Logistic Regression

Multivariable logistic regression was conducted using SAS Enterprise guide v7.11. Models were constructed using forward and backward selection procedures in the HPLOGISTIC procedure using the Schwarz Bayesian Criterion. Patient clinical characteristics as well as processes of care were included in the modeling. Final models for the backward and forward procedure identified the same set of variables for each outcome. To calculate sensitivity and specificity, we chose a cut-point of the estimated probabilities at which the distance between (1,0) and the receiver operating characteristics (ROC) curve was minimized in the ROC diagram for the training sample. In this way, each patient was dichotomized as yes versus no for risk of the outcome.

Model Comparisons

The sensitivity (coverage), specificity, positive predictive value, negative predictive value and the c-statistic were examined and compared between the methods for both outcomes. For the logistic regression, the first area under the ROC (c-statistic) was calculated with all the variables in the model and used the continuous predicted probability (Tables 1 and 3). As described above, for the comparison of the two methods (Tables 2 and 4), we used a cut-point on the probability that maximized the sensitivity and specificity. We created a new variable describing the predicted outcome (1 if p > cut-point; 0 otherwise). We then performed logistic regression using only that variable as the independent variable. This variable was also used to calculate sensitivity and specificity. Similarly, for the configurational analysis, we created a predicted outcome variable based on the configurational groupings and use that as the independent variable in the logistic regression to obtain a c-statistic.

Patient and Public Involvement

There was no patients or public involvement in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

The overall sample consisted of 3079 Veterans between the ages of 24 to 99 years (median age, 70 years; interquartile range 64-78) who presented at a VA medical facility with a TIA between October 2016 and September 2017. The baseline characteristics of the patients within the training and validation samples are provided in Supplemental Table 1 and Supplemental Table 2 and the process of care data are provided in Supplemental Table 3. All patients had complete data both for the outcomes and 75 potential explanatory factors, which included specific TIA processes of care as well as risk factors for recurrent stroke or death.

Patient Outcome: Death or Recurrent Stroke at One-Year

Configurational Results

Among the training sample patients, the prevalence of the combined endpoint of death or recurrent stroke at one-year post-TIA was 11.5% (251/2192). Configurational analysis yielded a three-pathway model comprised of five conditions, where the prevalence of death or stroke was 14.5% (193/1330). The configurational analysis identified the following three pathways: (1) having a history of TIA AND a history of hypertension AND not being prescribed a non-steroidal anti-inflammatory drug (NSAID); (2) having a HASBLED score[37] (a measure of bleeding risk) of ≥3; or (3) having a history of dementia (Table 1).

Table 1. Modeling Results for Outcome of Death or Recurrent Stroke at One-Year Post-TIA

Patient Characteristic or Process of Care	**Training Sample** *Sample Prevalence: 11.5%*		**Validation Sample** *Sample Prevalence: 11.0%*	
Logistic Regression				
	OR (95% CI)	**P-value**		
Age	1.03 (1.02, 1.05)	<0.001		
Charlson comorbidity index	1.2 (1.1, 1.2)	<0.001		
APACHE*	1.04 (1.02, 1.06)	<0.001	**	
Current smoker	1.8 (1.3, 2.4)	<0.001		
Palliative care/hospice	2.9 (1.7, 5.1)	<0.001		
History of stroke	1.8 (1.3, 2.6)	0.001		
c-statistic	0.747		0.691	
Configurational Analysis				
Pathways	**Pathway Prevalence††**	**Pathway Coverage**	**Pathway Prevalence**	**Pathway Coverage**
History of TIA *AND* History of Hypertension *AND* Not taking NSAID†	14.8%	55.8%	14.2%	57.1%
HAS-BLED§ score of ≥3	18.5%	54.2%	16.3%	50.0%
History of dementia	21.9%	15.9%	20.0%	17.3%
Overall Model Results	14.5%	76.9%	15.0%	84.7%

*APACHE refers to the Acute Physiology And Chronic Health Evaluation measure of physiologic disease severity.
†NSAID refers to non-steroidal anti-inflammatory medications.
§The HAS-BLED score describes the risk of major bleeding.
**We did not refit the model in the validation sample, but rather, we use estimates from the training model to estimate the probabilities in the validation model.
††Pathway prevalence refers to the outcome rate for that specific combination of conditions.

Among patients in the validation sample, the death or stroke rate one-year post-TIA was 11.0% (98/887) overall, and 15.0% (83/552) for patients within the three-pathway configurational model, 36% relatively higher than the overall rate. This performance in the validation sample was better than in the training sample, where the same configurational three-pathway model rate was 26% relatively higher than the overall rate (i.e., 14.5% compared with 11.5%). The configurational model had a coverage (sensitivity) of 84.7% in the validation sample, identifying 83 of 98 patients with the outcome of death or recurrent stroke at one-year; this outperformed the 76.9% coverage score (193/251) in the training sample (Table 1). The configurational model had a specificity of 41.4% in the training sample and 40.6% in the validation sample (Table 2).

Table 2. Test Characteristics of the Logistic Regression and Configuration Models for Death or Recurrent Stroke Rate at One-Year Post-TIA

Training Sample	**Recurrent Stroke or Death at One-Year (11.5%)**			**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**C-Statistic**
				n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	(95%CI)
Configurational Analysis Classification	No	Yes	Totals	193/251 76.9 (71.2, 82.0)	804/1941 41.4 (39.2, 43.7)	193/1330 14.5 (12.7, 16.5)	804/862 93.3 (91.4, 94.9)	0.592 (0.563, 0.620)
No	804	58	862					
Yes	1137	193	1330					
Totals	1941	251	2192					
Logistic Regression Classification	No	Yes	Totals	189/251 75.3 (69.5, 80.5)	1209/1941 62.3 (60.1, 64.4)	189/921 20.5 (18.0, 20.3)	1209/1271 95.1 (93.8, 96.2)	0.688 (0.659, 0.717)
No	1209	62	1271					
Yes	732	189	921					
Totals	1941	251	2192					
Validation Sample	**Recurrent Stroke or Death at One-Year (11.0%)**							
Configurational Analysis Classification	No	Yes	Totals	83/98 84.7 (76.0, 91.2)	320/789 40.6 (37.1, 44.1)	83/552 15.0 (12.2, 18.3)	320/335 95.5 (92.7, 97.5)	0.626 (0.587, 0.666)
No	320	15	335					
Yes	469	83	552					
Totals	789	98	887					
Logistic Regression Classification	No	Yes	Totals	62/98 63.3 (52.9, 72.8)	498/789 63.1 (59.6, 66.5)	62/353 17.6 (13.7, 21.9)	498/534 93.3 (90.8, 95.2)	0.632 (0.581, 0.683)
No	498	36	534					
Yes	291	62	353					
Totals	789	98	887					

Logistic Regression Results

The logistic regression model identified six factors that were associated with the combined endpoint of death or recurrent stroke at one-year post-TIA (Table 1): age, Charlson comorbidity index,[38] the modified APACHE score,[39] current smoking status, palliative care or hospice, and history of stroke. None of these six factors were elements of the configurational model. The c-statistic for the primary model on training sample was 0.747 and 0.691 for the validation sample (Table 1). The c-statistics for logistic models used to calculate sensitivity and specificity (Table 2) were 0.592 for the training sample and 0.688 for the validation sample. The sensitivity was 75.3% in the training sample and 63.3% in the validation sample (Table 2). The specificity was 62.3% in the development sample and 63.1% in the validation sample.

Quality of Care Outcome: the Without-Fail Rate

Configurational Results

Among the training sample patients, the prevalence of the without-fail rate was 34.6%. The configurational analysis (Table 4) yielded a single-pathway model with the conjunct of two processes—discharged on a high or moderate potency statin AND neurology consultation—where the without-fail rate was 67.3% (567/843). The final configurational model included 567 of the 759 patients with the outcome (i.e., 74.7% coverage; Table 3).

Table 3. Modeling Results for Outcome of Without-Fail Rate

Process of Care	Training Sample *Sample Prevalence: 34.6%*		Validation Sample *Sample Prevalence: 33.7%*	
Logistic Regression				
	OR (95% CI)	**P-value**		
Carotid Artery Imaging	5.0 (3.7, 6.7)	<0.001	**	
Hypertension Medication Intensification	0.4 (0.3, 0.6)	<0.001		
Hypertension Control	1.5 (1.2, 1.8)	0.001		
Discharged on any Statin	0.7 (0.5, 0.9)	0.002		
High or Moderate Potency Statin	5.9 (4.5, 7.7)	<0.001		
Antithrombotic by Day 2	0.2 (0.2, 0.3)	<0.001		
Neurology Consult	8.3 (6.1, 11.3)	<0.001		
C-statistic	0.842		0.841	
Configurational Analysis				
Pathway	**Pathway Prevalence**	**Pathway Coverage**	**Pathway Prevalence**	**Pathway Coverage**
Discharged with high or moderate potency statin AND Neurology consult	67.3%	74.7%	64.3%	77.3%
Overall Model Rates	67.3%	74.7%	64.3%	77.3%

**We did not refit the model in the validation sample, but rather, we use estimates from the training model to estimate the probabilities in the validation model.

Among the validation sample patients, the without-fail rate was 33.7%. When applied to the validation sample, the single-pathway configurational model yielded a without-fail rate of 64.3% (231/359), which was nearly twice the observed prevalence. This model covered 231 of the 299 cases with the outcome (i.e., 77.3% coverage; Table 3). The configurational model had a specificity of 80.7% in the training sample 78.2% in the validation sample (Table 4).

Logistic Regression Results

The logistic regression model identified seven factors that were associated with the without-fail rate: carotid artery imaging, hypertension medication intensification, hypertension control, discharged on statin, discharged on high or moderate potency statin, antithrombotics by hospital day two, and neurology consultation (see Table 3). Two of these factors were also identified in the configurational analysis: discharged on a high or moderate potency statin and neurology consultation. The c-statistics were higher for this model of quality than for the patient outcome model. In the primary model the c-statistic for the training sample was 0.842 and 0.841 in the validation sample (Table 3). In the model used to calculate sensitivity and specificity the c-statistic was 0.823 for the training sample, and 0.822 for the validation sample (Table 4). The sensitivity was 76.7% in the training sample and 80.3% in the validation sample. The specificity was 87.9% in the training sample and 84.2% in the validation sample.

Table 4. Test Characteristics of the Logistic Regression and Configuration Models for Without-Fail Rate at One-Year Post-TIA

Training Sample	**Without-Fail Rate (34.6%)**			**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**C-Statistic**
				n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	(95%CI)
Configurational Analysis Classification	No	Yes	Totals	567/759	1157/1433	567/843	1157/1349	0.777
No	1157	192	1349	74.7 (71.5, 77.8)	80.7 (78.6, 82.8)	67.3 (64.0, 70.4)	85.8 (83.8, 87.6)	(0.759, 0.796)
Yes	276	567	843					
Totals	1433	759	2192					
Logistic Regression Classification	No	Yes	Totals	582/759	1259/1433	582/756	1259/1436	0.823
No	1259	177	1436	76.7 (73.5, 79.6)	87.9 (86.1, 89.5)	77.0 (73,.8, 79.9)	87.7 (85.9, 89.3)	(0.805, 0.840)
Yes	174	582	756					
Totals	1433	759	2192					
Validation Sample	**Without-Fail Rate (33.7%)**							
Configurational Analysis Classification	No	Yes	Totals	231/299	460/588	231/359	460/528	0.777
No	460	68	528	77.3 (72.1, 81.9)	78.2 (74.7, 81.5)	64.3 (59.1, 69.3)	87.1 (84,0, 89.9)	(0.748, 0.801)
Yes	128	231	359					
Totals	588	299	887					
Logistic Regression Classification	No	Yes	Totals	240/299	495/588	240/333	495/554	0.822
No	495	59	554	80.3 (75.3, 84.6)	84.2 (81.0, 87.0)	72.1 (66.9, 76.8)	89.4 (86.5, 91.8)	(0.795, 0.849)
Yes	93	240	333					
Totals	588	299	887					

DISCUSSION

This study analyzed one of the largest sample sizes used to date in a published configurational analysis, is one of the first to use a split-sample design featuring training and validation samples, and is one of the first to directly compare configurational and logistic regression results using identical data. The models developed by applying logistic regression and configurational analysis within the training sample were confirmed when tested against the validation sample. This was true for both the "one-year death or recurrent stroke" outcome and the "without-fail" quality-of-care outcome. The results of this study demonstrate that configurational analyses and logistic regression, when applied to the same dataset, can provide complimentary findings and lead to different insights. Key differences in the findings from the two methods as they were applied in the current study included: the focus of optimization; the goal of making stochastic inferences versus empiric insights; and the possibility of conjunctivity.

Logistic regression models include variables to infer the absence and presence of the outcome and maximizes the likelihood for the observed data in a parametrically well-structured model. The configurational models, by contrast, identified "phenotypes" where particular groups of individuals sharing a specific bundle of characteristics had outcome rates substantially different from that of the overall sample. The logistic regression model is useful in making statistical inference for variables' effects on the binary outcome of interest, though it can be applied to predict the outcome if a cut-off probability threshold is provided. In contrast, the configurational models pinpointed specific combinations of factor values that linked directly to the positive outcome of interest.

An expected pattern in results is that configurational analysis has an advantage over logistic regression in prediction of a dichotomous outcome when prevalence is low. This pattern was evident in the model of recurrent stroke or death at one-year post-TIA, where in the validation sample, the sensitivity was higher in the configurational model (84.7% [95%CI: 76.0-91.2%]) than in the logistic regression model (63.3% [95%CI: 52.9-72.8%]). Both approaches had equivalent c-statistics (configurational model, 0.626 [95%CI: 0.587-0.666]; logistic model, 0.632 [0.581-0.683]). However, this advantage may diminish if the prevalence of the outcome is not rare; which was evident in the model using the quality outcome, where in the validation sample, the sensitivity was similar in both approaches (configurational model, 77.3% [95%CI: 72.1-81.9%]; logistic model, 80.3% [95%CI: 75.3-84.6%]), and the c-statistics were also similar (configurational model, 0.777 [95%CI; 0.748-0.801]; logistic model, 0.822 [95%CI: 0.795-0.849]).

The models of the one-year recurrent stroke or death rate differed dramatically with no overlap between the factors included in the logistic regression model and the conditions in the configurational model. This observation may be attributed to correlations between variables. For example, the finding that increasing age was negatively correlated with taking NSAIDS (r=-0.215, p<0.0001; Supplemental Table 2) may partially account for why age was a variable that was included in the logistic model whereas not taking NSAIDs was a configuration that was included in one of the pathways in the configurational model. In contrast, the models of the without-fail rate were overlapping. The configurational results were more parsimonious. Certainly, the logistic regression models could be further developed if parsimony was particularly of interest.

The configurational results for the quality outcome (Table 3) provide an example of Boolean conjunctivity, where a bundle of conditions that jointly appear together are sufficient for the outcome. Conjunctivity is an attractive characteristic of configurational methods and particularly relevant to studies in health care settings given the inherent complexity within clinical medicine and health services research. In other words, it is expected that for some complex phenomena that it is a combination of conditions—rather than a single factor alone—which can explain the outcome.

The use of configurational methods is increasing within health services research in general and in implementation science in particular.[40] The complimentary application of logistic regression and configurational methods may be particularly fruitful for implementation science for describing patterns and identifying predictors of care at a particular site, especially if the outcome is uncommon.

Several limitations of this study should be noted. First, the results are based on data from the US Department of Veterans Affairs, and therefore, may not be generalizable to other healthcare systems.

Second, the outcomes used in this study were chosen to provide variation in prevalence rates and associations between variables and outcomes; however future studies could consider datasets with different characteristics (e.g., smaller sample sizes).

Third, for all analyses, the process of care variables were originally coded as pass among those eligible, fail among those eligible, and ineligible. However, patients who were not eligible for processes of care were generally the most critically ill patients (e.g., hospice); being not eligible for a process was a strong predictor of mortality. By combining the fail among eligible and ineligible categories we were able to retain all patients in the analyses. We included the variables that described eligibility in the modeling and as expected hospice was associated with the combined endpoint of death or recurrent stroke.

Fourth, to calculate sensitivity and specificity, we chose a cut-point of the estimated probabilities at which the receiver operating characteristics (ROC) curve was minimized; different thresholds could have been used (e.g., to optimize sensitivity).

Fifth, previous work has demonstrated that conjuncts in configurational methods are not synonymous with interactions in regression.[41] We did not systematically explore interactions within the logistic regression modelling.

Finally, we presented an example of how logistic regression and configurational methods could be used on the same data to glean different information. The analytic approaches are fundamentally different; we do not intend to suggest that one method is better than another but to rather to highlight their complementary uses. Future studies should consider both circumstances where other methods (e.g., decision-tree analysis) can be used with configurational methods, and situations when alternative methods might be used in series rather than in parallel (e.g., for variable selection or for dichotomizing continuous variables).

CONCLUSIONS

Configurational analysis and logistic regression represent fundamentally different analytic methods. When joined together, however, they can yield complementary insights when analyzing identical data. Configurational models optimize sensitivity with relatively few conditions and allow for equifinality. Logistic regression models provide inferential relationships between binary outcomes and independent variables as well as clinically useful measures to interpret effects (i.e., odds ratio). Pairing these two diverse approaches offers a major new analytic option to health services researchers interested in leveraging multiple methodological perspectives to explore and model complex phenomena with greater nuance and understanding.

COMPETING INTERESTS The authors declare that they have no competing interests.

DATA SHARING STATEMENT The data that support the findings of this study must remain on US Department of Veterans Affairs servers. Please contact the corresponding author if you are interested in working with these data.

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AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript. EJM and AJP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DMB: obtained funding and was responsible for the design and conduct of the PREVENT study which is the data source used in the analyses; participated in data analysis conceptualization, interpretation of the results, and drafting and revising the manuscript.

LJM: obtained the PREVENT data which is the data source used in the analyses and participated in data analysis conceptualization

EJM, AJP: planned and executed the data analysis, participated in interpretation of the results, and drafting and revising the manuscript.

YZ, JD: participated in the interpretation of the results and the framing of the manuscript especially with regard to the mathematical and statistical foundations of the methods and the statistical applications of both methods.

JJS: participated in interpretation of results and manuscript editing.

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REFERENCES

1. Yakovchenko V, Miech EJ, Chinman MJ, et al. Strategy Configurations Directly Linked to Higher Hepatitis C Virus Treatment Starts: An Applied Use of Configurational Comparative Methods. *Med Care* 2020;58(5):e31-e38. doi: 10.1097/mlr.0000000000001319 [published Online First: 2020/03/19]
2. Hickman SE, Miech EJ, Stump TE, et al. Identifying the Implementation Conditions Associated With Positive Outcomes in a Successful Nursing Facility Demonstration Project. *The Gerontologist* 2020;60(8):1566-74. doi: 10.1093/geront/gnaa041 [published Online First: 2020/05/23]
3. Palinkas LA, Mendon SJ, Hamilton AB. Innovations in Mixed Methods Evaluations. *Annual review of public health* 2019;40:423-42. doi: 10.1146/annurev-publhealth-040218-044215 [published Online First: 2019/01/12]
4. Harris K, Kneale D, Lasserson TJ, et al. School-based self-management interventions for asthma in children and adolescents: a mixed methods systematic review. *The Cochrane database of systematic reviews* 2019;1(1):Cd011651. doi: 10.1002/14651858.CD011651.pub2 [published Online First: 2019/01/29]
5. Cragun D. Configurational comparative methods. The Handbook on Implementation Science. Cheltenham: Edward Elgar Publishing 2020.
6. Cragun D, Pal T, Vadaparampil S, et al. Qualitative Comparative Analysis A Hybrid Method for Identifying Factors Associated With Program Effectiveness. *Journal of Mixed Methods Research* 2015
7. Ragin C. The comparative method: moving beyond qualitative and quantitative strategies. Berkeley, CA: University of California Press 1987.
8. Thiem A. Conducting Configurational Comparative Research With Qualitative Comparative Analysis:A Hands-On Tutorial for Applied Evaluation Scholars and Practitioners. *American Journal of Evaluation* 2017;38(3):420-33. doi: 10.1177/1098214016673902
9. del Carmen Giménez-Espert M, Valero-Moreno S, Prado-Gascó V. Evaluation of emotional skills in nursing using regression and QCA models: A transversal study. . *Nurse education today* 2019;74:31-7.
10. Ragin C, Fiss P. Intersectional inequality: University of Chicago Press; 2016.
11. Ragin C, Shulman D, Weinberg A, et al. Complexity, generality, and qualitative comparative analysis. . *Field Methods* 2003;15:323-40.
12. Ebbinghaus B, Visser J. When institutions matter: Union growth and decline in Western Europe, 1950–1995. *European Sociological Review* 1999;15:135-58.
13. Grofman B, Schneider C. An introduction to crisp set QCA, with a comparison to binary logistic regression. *Political Research Quarterly* 2009;62:662-72.
14. Bravata D, Wells C, Lo A, et al. Processes of Care Associated with Acute Stroke Outcomes. *Archives of internal medicine* 2010;170(9):804-10.
15. Bravata DM, Myers LJ, Perkins AJ, et al. Assessment of the Protocol-Guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) Program for Improving Quality of Care for Transient Ischemic Attack: A Nonrandomized Cluster Trial. *JAMA network open* 2020;3(9):e2015920. doi: 10.1001/jamanetworkopen.2020.15920 [published Online First: 2020/09/09]
16. Bravata DM, Myers LJ, Homoya B, et al. The protocol-guided rapid evaluation of veterans experiencing new transient neurological symptoms (PREVENT) quality improvement program: rationale and methods. *BMC neurology* 2019;19(1):294. doi: 10.1186/s12883-019-1517-x [published Online First: 2019/11/22]

17. Li J, Zhang Y, Myers LJ, et al. Power calculation in stepped-wedge cluster randomized trial with reduced intervention sustainability effect. *J Biopharm Stat* 2019;29(4):663-74. doi: 10.1080/10543406.2019.1633658 [published Online First: 2019/07/19]
18. Development VHSR. VA Informatics and Computing Infrastructure (VINCI), 2008 [Available from: https://www.hsrd.research.va.gov/for_researchers/vinci/default.cfm accessed December 10 2020.
19. VA Informatics and Computing Infrastructure (VINCI). In: Affairs USDoV, ed., 2008.
20. Borzecki AM, Wong AT, Hickey EC, et al. Can we use automated data to assess quality of hypertension care? *The American journal of managed care* 2004;10(7 Pt 2):473-79.
21. Sohn MW, Arnold N, Maynard C, et al. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Population health metrics* 2006;4:2. doi: 10.1186/1478-7954-4-2 [published Online First: 2006/04/12]
22. Man S, Zhao X, Uchino K, et al. Comparison of Acute Ischemic Stroke Care and Outcomes Between Comprehensive Stroke Centers and Primary Stroke Centers in the United States. *Circulation Cardiovascular quality and outcomes* 2018;11(6):e004512. doi: 10.1161/circoutcomes.117.004512 [published Online First: 2018/05/26]
23. Fonarow GC, Reeves MJ, Smith EE, et al. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. *Circulation Cardiovascular quality and outcomes* 2010;3(3):291-302. doi: 10.1161/circoutcomes.109.921858 [published Online First: 2010/02/24]
24. Nolan T, Berwick DM. All-or-none measurement raises the bar on performance. *Jama* 2006;295(10):1168-70. doi: 10.1001/jama.295.10.1168 [published Online First: 2006/03/09]
25. Bravata D, Myers L, Homoya B, et al. The Protocol-Guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) Quality Improvement Program: Rationale and Methods. *BMC neurology* 2019;19(1):294. doi: 10.1186/s12883-019-1517-x.
26. Bravata DM, Myers LJ, Cheng E, et al. Development and Validation of Electronic Quality Measures to Assess Care for Patients With Transient Ischemic Attack and Minor Ischemic Stroke. *Circulation Cardiovascular quality and outcomes* 2017;10(9) doi: 10.1161/circoutcomes.116.003157 [published Online First: 2017/09/16]
27. Bravata D, Myers L, Arling G, et al. The Quality of Care for Veterans with Transient Ischemic Attack and Minor Stroke. *JAMA Neurology* 2018;75(4):419-27. doi: 10.1001/jamaneurol.2017.4648.
28. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2014;45(7):2160-236. doi: 10.1161/str.0000000000000024 [published Online First: 2014/05/03]
29. Smith EE, Saver JL, Alexander DN, et al. Clinical performance measures for adults hospitalized with acute ischemic stroke: performance measures for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2014;45(11):3472-98. doi: 10.1161/str.0000000000000045 [published Online First: 2014/09/27]
30. Bravata DM, Myers LJ, Reeves M, et al. Processes of Care Associated With Risk of Mortality and Recurrent Stroke Among Patients With Transient Ischemic Attack and Nonsevere Ischemic Stroke. *JAMA network open* 2019;2(7):e196716. doi: 10.1001/jamanetworkopen.2019.6716 [published Online First: 2019/07/04]
31. Whitaker R, Sperber N, Baumgartner M, et al. Coincidence analysis: a new method for causal inference in implementation science. . *Implementation Science* 2020;15:108.
32. CNA: Causal Modeling with Coincidence Analysis. R package version 2.1.1. [program], 2018.
33. Cohen D, Sweeney S, Miller W, et al. Improving smoking and blood pressure outcomes: the interplay between operational changes and local context. *Annals of Family Medicine* 2021;19:240-48.

34. Coury J, Miech EJ, Styer P, et al. What's the "secret sauce"? How implementation variation affects the success of colorectal cancer screening outreach. *Implement Sci Commun* 2021;2(1):5. doi: 10.1186/s43058-020-00104-7 [published Online First: 2021/01/13]
35. Petrik AF, Green B, Schneider J, et al. Factors Influencing Implementation of a Colorectal Cancer Screening Improvement Program in Community Health Centers: an Applied Use of Configurational Comparative Methods. *Journal of general internal medicine* 2020;35(Suppl 2):815-22. doi: 10.1007/s11606-020-06186-2 [published Online First: 2020/10/28]
36. Baumgartner M, Thiem A. Model ambiguities in configurational comparative research. *Sociological Methods & Research* 2017;46(4):954-87.
37. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138(5):1093-100. doi: 10.1378/chest.10-0134 [published Online First: 2010/03/20]
38. Charlson M, Pompei P, Ales K, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987;40:373-83.
39. Knaus W, Wagner D, Draper E, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100:1619-36.
40. Cohen D, Sweeney S, Miller W, et al. Improving Smoking and Blood Pressure Outcomes: The Interplay Between Operational Changes and Local Context. *Annals of Family Medicine* 2021;19 240-48. doi: https://doi.org/10.1370/afm.2668
41. Thiem A, Baumgartner M, Bol D. Still Lost in Translation! A correction of three misunderstandings between configurational comparativists and regressional analysts *Comparative Political Studies* 2016;49(6):742-74.

Supplemental Table 1. Baseline Characteristics of the Training and Validation Samples

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Overall	2192	251 (11.4)		759 (34.6)		887	98 (11.0)		299 (33.7)	
Current Smoker			0.004		0.003			0.558		0.435
No	1593 (72.7)	163 (10.2)		521 (32.7)		627 (70.7)	72 (11.5)		206 (32.8)	
Yes	599 (27.3)	88 (14.7)		238 (39.7)		260 (29.3)	26 (10.0)		93 (35.8)	
Palliative or Hospice Care			<0.001		<0.001			<0.00		<0.001
No	2124 (96.9)	221 (10.4)		694 (32.7)		863 (97.3)	87 (10.1)		278 (32.2)	
Yes	68 (3.1)	30 (44.1)		65 (95.6)		24 (2.7)	11 (45.8)		21 (87.5)	
Diabetes			<0.001		<0.001			0.004		<0.001
No	1255 (57.2)	116 (9.2)		393 (31.1)		528 (59.5)	45 (8.5)		144 (27.3)	
Yes	937 (42.8)	135 (14.4)		366 (39.1)		359 (40.5)	53 (14.8)		155 (43.2)	
Atrial Fibrillation			<0.001		0.146			0.088		0.851
No	1834 (83.7)	184 (10.0)		623 (34.0)		735 (82.9)	75 (10.2)		249 (33.9)	
Yes	358 (16.3)	67 (18.7)		136 (38.0)		152 (17.1)	23 (15.1)		50 (32.9)	
Myocardial Infarction			0.009		<0.001			0.301		0.174
No	2032 (92.7)	222 (10.9)		679 (33.4)		822 (92.8)	88 (10.7)		272 (33.1)	
Yes	160 (7.3)	29 (18.1)		80 (50.0)		65 (7.3)	10 (15.4)		27 (41.5)	
TIA*			0.156		<0.001			0.219		<0.001
No	738 (33.7)	74 (10.0)		151 (20.5)		314 (35.4)	29 (9.2)		69 (22.0)	
Yes	1454 (66.3)	177 (12.2)		608 (41.8)		573 (64.6)	69 (12.0)		230 (40.1)	
Stroke			<0.001		<0.001			0.010		0.013
No	1903 (86.8)	188 (9.9)		631 (33.2)		788 (88.8)	79 (10.0)		254 (32.2)	
Yes	289 (13.2)	63 (21.8)		128 (44.3)		99 (11.2)	19 (19.2)		45 (45.4)	
CHF*			<0.001		<0.001			0.038		0.005
No	1860 (84.8)	182 (9.8)		613 (33.0)		747 (84.2)	75 (10.0)		237 (31.7)	
Yes	332 (15.2)	69 (20.8)		146 (44.0)		140 (15.8)	23 (16.4)		62 (44.3)	
COPD*			<0.001		0.785			0.600		0.012
No	1723 (78.6)	175 (10.2)		594 (34.5)		699 (78.8)	75 (10.7)		221 (31.6)	
Yes	469 (21.4)	76 (16.2)		165 (35.2)		188 (21.2)	23 (12.2)		78 (41.5)	

Supplemental Table 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
PVD*			<0.001		<0.001			0.017		0.001
No	1867 (85.2)	187 (10.0)		611 (32.7)		749 (84.4)	74 (9.9)		235 (31.4)	
Yes	64 (19.8)	64 (19.7)		148 (45.5)		138 (15.6)	23 (17.4)		64 (46.4)	
Dementia			<0.001		0.685			0.010		0.071
No	2009 (91.6)	211 (10.5)		693 (34.5)		802 (90.4)	81 (10.1)		278 (34.7)	
Yes	183 (8.4)	40 (21.9)		66 (36.1)		85 (9.6)	17 (20.0)		21 (24.7)	
Chronic Kidney Disease			<0.001		<0.001			0.004		0.007
No	1794 (81.8)	180 (10.0)		586 (32.7)		732 (82.5)	70 (9.6)		232 (31.7)	
Yes	398 (18.2)	71 (17.8)		173 (43.5)		155 (17.5)	28 (18.1)		67 (43.2)	
Cancer			<0.001		0.094			0.178		1.00
No	1958 (89.3)	199 (10.2)		666 (34.0)		787 (88.7)	83 (10.6)		265 (33.7)	
Yes	234 (10.7)	52 (22.2)		93 (39.7)		100 (11.3)	15 (15.0)		34 (34.0)	
Hypertension			<0.001		<0.001			0.006		<0.001
No	528 (24.1)	33 (6.2)		125 (23.7)		215 (24.2)	13 (6.0)		46 (21.4)	
Yes	1664 (75.9)	218 (13.1)		634 (38.1)		672 (75.8)	85 (12.7)		253 (37.6)	
Renal Disease			<0.001		<0.001			0.006		0.008
No	1802 (82.2)	182 (10.1)		590 (32.7)		737 (83.1)	71 (9.6)		234 (31.8)	
Yes	390 (17.8)	69 (17.7)		169 (43.3)		150 (16.9)	27 (18.0)		65 (43.3)	
Hyperlipidemia			0.003		<0.001			0.739		<0.001
No	816 (37.2)	72 (8.8)		213 (26.1)		325 (36.6)	34 (10.5)		76 (23.4)	
Yes	1376 (62.8)	179 (13.0)		546 (39.7)		562 (63.4)	64 (11.4)		223 (39.7)	
Arrhythmia			0.001		0.421			0.114		0.035
No	1910 (87.1)	201 (10.5)		655 (34.3)		770 (86.8)	80 (10.4)		249 (32.3)	
Yes	282 (12.9)	50 (17.7)		104 (36.9)		117 (13.2)	18 (15.4)		50 (42.7)	
Sleep Apnea			0.608		0.058			0.669		0.014
No	1779 (81.2)	207 (11.6)		599 (33.7)		737 (83.1)	80 (10.8)		235 (31.9)	
Yes	413 (18.8)	44 (10.7)		160 (38.7)		150 (16.9)	18 (12.0)		64 (42.7)	
Alcohol Abuse			0.591		0.858			0.021		0.220
No	2045 (93.3)	232 (11.3)		707 (34.6)		823 (92.8)	85 (10.3)		282 (34.3)	
Yes	147 (6.7)	19 (12.9)		52 (35.4)		64 (7.2)	13 (20.3)		17 (26.6)	

Supplemental Table 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Depression			0.577		0.240			0.308		0.613
No	1690 (77.1)	190 (11.2)		574 (34.0)		683 (77.0)	80 (11.7)		227 (33.2)	
Yes	502 (22.9)	61 (12.2)		185 (36.8)		204 (23.0)	18 (8.8)		72 (35.3)	
Liver Disease			0.088		0.705			0.492		0.763
No	2062 (94.1)	230 (11.2)		712 (34.5)		836 (94.2)	91 (10.9)		283 (33.8)	
Yes	130 (5.9)	21 (16.2)		47 (36.2)		51 (5.8)	7 (13.7)		16 (31.4)	
Cirrhosis			0.002		0.417			0.060		0.094
No	2150 (98.1)	239 (11.1)		742 (34.5)		867 (97.8)	93 (10.7)		296 (34.1)	
Yes	42 (1.9)	12 (28.6)		17 (40.5)		20 (2.2)	5 (25.0)		3 (15.0)	
Migraines			0.571		0.315			0.511		0.287
No	2120 (96.7)	245 (11.6)		730 (34.4)		862 (97.2)	97 (11.2)		288 (33.4)	
Yes	72 (3.3)	6 (8.3)		29 (40.3)		25 (2.8)	1 (4.0)		11 (44.0)	
Bleeding			0.052		0.154			1.000		1.000
No	2179 (99.4)	247 (11.3)		752 (34.5)		883 (99.6)	98 (11.1)		298 (33.8)	
Yes	13 (0.6)	4 (30.8)		8 (53.8)		4 (0.4)	0 (0.0)		1 (25.0)	
Intracranial Hemorrhage			<0.001		0.221			0.185		0.118
No	2080 (94.9)	225 (10.8)		714 (34.3)		848 (95.6)	91 (10.7)		281 (33.1)	
Yes	112 (5.1)	26 (23.2)		45 (40.2)		39 (4.4)	7 (18.0)		18 (46.2)	
Dialysis			0.226		0.311			0.001		0.128
No	2165 (98.8)	246 (11.4)		747 (34.5)		879 (99.1)	93 (10.6)		294 (33.4)	
Yes	27 (1.2)	5 (18.5)		12 (44.4)		8 (0.9)	5 (62.5)		5 (62.5)	
Pacemaker			0.129		<0.001			0.481		0.160
No	1957 (89.3)	217 (11.1)		652 (33.3)		796 (89.7)	86 (10.8)		262 (32.9)	
Yes	235 (10.7)	34 (14.5)		107 (45.5)		91 (10.3)	12 (13.2)		37 (40.7)	
Valvular Disease			0.099		0.311			0.143		0.496
No	2053 (93.7)	229 (11.2)		705 (34.3)		823 (92.8)	87 (10.6)		275 (33.4)	
Yes	139 (6.3)	22 (15.8)		54 (38.8)		64 (7.2)	11 (17.2)		24 (37.5)	
Venous Thromboembolism			0.102		0.118			0.376		0.337
No	2113 (96.4)	237 (11.2)		725 (34.3)		856 (96.5)	93 (10.9)		286 (33.4)	
Yes	79 (3.6)	14 (17.7)		34 (43.0)		31 (3.5)	5 (16.1)		13 (41.9)	

Supplemental Table 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Carotid endarterectomy or stent			1.000		0.061			0.011		0.068
No	2172 (99.1)	249 (11.5)		748 (34.4)		878 (99.0)	94 (10.7)		293 (33.4)	
Yes	20 (0.9)	2 (10.0)		11 (55.0)		9 (1.0)	4 (44.4)		6 (66.7)	
CABG/PTCA*			0.687		0.414			0.506		0.411
No	2177 (99.3)	249 (11.4)		752 (34.5)		881 (99.3)	97 (11.0)		296 (33.6)	
Yes	15 (0.7)	2 (13.3)		7 (46.7)		6 (0.7)	1 (16.7)		3 (50.0)	
Pancreatitis			0.057		1.000			1.000		0.342
No	2173 (99.1)	246 (11.3)		753 (34.6)		882 (99.4)	98 (11.1)		296 (33.6)	
Yes	19 (0.9)	5 (26.3)		6 (31.6)		5 (0.6)	0 (0.0)		3 (60.0)	
Hemiplegia			0.293		<0.001			0.227		0.086
No	1876 (85.6)	209 (11.1)		611 (32.6)		759 (85.6)	80 (10.5)		247 (32.5)	
Yes	316 (14.4)	42 (13.3)		148 (46.8)		128 (14.4)	18 (14.1)		52 (40.6)	
Speech Deficit			0.424		0.200			0.298		0.293
No	2091 (95.4)	237 (11.3)		718 (34.3)		849 (95.7)	92 (10.8)		283 (33.3)	
Yes	101 (4.6)	14 (13.9)		31 (40.6)		38 (4.3)	6 (15.8)		16 (42.1)	
Syncope			0.711		0.345			0.033		0.240
No	1568 (71.5)	177 (11.3)		533 (34.0)		631 (71.1)	79 (12.5)		205 (32.5)	
Yes	624 (28.5)	74 (11.9)		226 (36.2)		256 (28.9)	19 (7.4)		94 (36.7)	
Amaurosis Fugax			0.876		0.044			1.000		0.102
No	2088 (95.3)	240 (11.5)		713 (34.2)		843 (95.0)	93 (11.0)		279 (33.1)	
Yes	104 (4.7)	11 (10.6)		46 (44.2)		44 (5.0)	5 (11.4)		20 (45.4)	
Concomitant MI*			0.231		0.056			0.346		0.056
No	2147 (98.0)	243 (11.3)		737 (34.3)		862 (97.2)	94 (10.9)		286 (33.2)	
Yes	45 (2.0)	8 (17.8)		22 (48.9)		25 (2.8)	4 (16.0)		13 (52.0)	
Concomitant CHF*			<0.001		0.228			0.309		0.007
No	2154 (98.3)	238 (11.0)		742 (34.4)		864 (97.4)	94 (10.9)		285 (33.0)	
Yes	38 (1.7)	13 (34.2)		17 (44.7)		23 (2.6)	4 (17.4)		14 (60.9)	
Aspirin			0.207		<0.001			0.801		<0.001
No	521 (23.8)	68 (13.0)		138 (26.5)		208 (23.4)	24 (11.5)		45 (21.6)	
Yes	1671 (76.2)	183 (11.0)		621 (37.2)		679 (76.6)	74 (10.9)		254 (37.4)	

Supplemental Table 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Warfarin			0.091		0.020			0.066		0.375
No	1941 (88.6)	214 (11.0)		655 (33.8)		784 (88.4)	81 (10.3)		260 (33.2)	
Yes	251 (11.4)	37 (14.7)		104 (41.4)		103 (11.6)	17 (16.5)		39 (37.9)	
Statin			0.793		<0.001			0.404		<0.001
No	393 (17.9)	43 (10.9)		51 (13.0)		161 (18.2)	21 (13.0)		17 (10.6)	
Yes	1799 (82.1)	208 (11.6)		708 (39.4)		726 (81.8)	77 (10.6)		282 (38.8)	
Antihypertensive			<0.001		0.006			0.037		0.006
No	351 (16.0)	20 (5.7)		99 (28.2)		137 (15.4)	8 (5.8)		32 (23.4)	
Yes	1841 (84.0)	231 (12.6)		660 (35.8)		750 (84.6)	90 (12.0)		267 (35.6)	
NSAID			0.009		0.395			0.040		0.446
No	1683 (76.8)	209 (12.4)		591 (35.1)		686 (77.3)	84 (12.2)		236 (34.4)	
Yes	509 (23.2)	42 (8.2)		168 (33.0)		201 (22.7)	14 (7.0)		63 (31.3)	
Clopidogrel			0.028		0.006			0.810		0.003
No	1541 (70.3)	161 (10.4)		505 (32.8)		644 (72.6)	70 (10.9)		198 (30.8)	
Yes	651 (29.7)	90 (13.8)		254 (39.0)		243 (27.4)	28 (11.5)		101 (41.6)	

*TIA refers to transient ischemic attack; CHF to congestive heart failure; COPD to chronic obstructive pulmonary disease; PVD to peripheral vascular disease; CABG/PTCA to coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; MI to myocardial infarction; and concomitant disease indicates conditions that were present at the time of the index transient ischemic attack.

Supplemental Table 2. Correlation Matrix

Variable*	History TIA	History Hypertension	NSAID	History Dementia	HASBLED	Age	CCI	APACHE	Current Smoker	Palliative/Hospice	History Stroke
History TIA	1.000	0.292	0.012	0.054	0.120	-0.017	0.115	0.081	0.062	0.044	0.072
P-value		<0.001	0.566	0.011	<0.001	0.419	<0.001	<0.001	0.004	0.040	0.001
History Hypertension		1.000	0.009	0.070	0.282	0.138	0.326	0.215	0.032	0.076	0.112
P-value			0.670	0.001	<0.001	<0.001	<0.001	<0.001	0.137	<0.001	<0.001
NSAID			1.000	-0.061	-0.045	-0.215	-0.076	-0.077	0.085	-0.036	-0.010
P-value				0.005	0.037	<0.001	<0.001	<0.001	<0.001	0.091	0.642
History Dementia				1.000	0.126	0.210	0.164	0.046	-0.030	0.174	0.102
P-value					<0.001	<0.001	<0.001	0.033	0.165	<0.001	<0.001
HASBLED					1.000	0.372	0.523	0.276	-0.008	0.147	0.361
P-value						<0.001	<0.001	<0.001	0.725	<0.001	<0.001
Age						1.000	0.166	0.201	-0.242	0.100	-0.031
P-value							<0.001	<0.001	<0.001	<0.001	0.145
Charlson Comorbidity Index							1.000	0.292	0.047	0.165	0.261
P-value								<0.001	0.027	<0.001	<0.001
APACHE								1.000	-0.104	0.092	0.028
P-value									<0.001	<0.001	0.184
Current Smoker									1.000	0.044	0.067
P-value										0.040	0.002
Palliative/Hospice										1.000	0.094
P-value											<0.001
History Stroke											1.000

*TIA refers to transient ischemic attack; NSAID refers to non-steroidal anti-inflammatory medications; the HASBLED score describes the risk of major bleeding; and the APACHE refers to the Acute Physiology And Chronic Health Evaluation measure of physiologic disease severity.

Supplemental Table 3. Processes of Care in the Training and Validation Samples

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Overall	2192	251 (11.4)		759 (34.6)		887	98 (11.0)		299 (33.7)	
Carotid Artery Imaging			<0.001		<0.001			<0.001		<0.001
Fail	563 (25.7)	64 (11.4)		0 (0.0)		204 (23.0)	23 (11.3)		0 (0.0)	
Pass	1553 (70.8)	155 (10.0)		687 (44.2)		655 (73.8)	63 (9.6)		275 (42.0)	
Ineligible	76 (3.5)	32 (42.1)		72 (94.7)		28 (3.2)	12 (42.9)		24 (85.7)	
Hypertension Medication Intensification			0.207		<0.001			0.755		0.005
Fail	363 (16.6)	32 (8.8)		98 (27.0)		152 (17.1)	19 (12.5)		47 (30.9)	
Pass	344 (15.7)	39 (11.3)		86 (25.0)		125 (14.1)	12 (9.6)		28 (22.4)	
Ineligible	1485 (65.7)	180 (12.1)		575 (38.7)		610 (68.8)	67 (11.0)		224 (36.7)	
Hypertension Control			<0.001		<0.001			<0.001		<0.001
Fail	365 (16.6)	31 (8.5)		0 (0.0)		173 (19.5)	11 (6.4)		0 (0.0)	
Pass	1193 (54.4)	99 (8.3)		470 (39.4)		472 (53.2)	42 (8.9)		201 (42.6)	
No Follow-Up BP	295 (13.5)	26 (8.8)		90 (30.5)		127 (14.3)	8 (6.3)		33 (26.0)	
Ineligible	339 (15.5)	95 (28.0)		199 (58.7)		115 (13.0)	37 (32.2)		65 (56.5)	
Discharge on Statin			<0.001		<0.001			<0.001		<0.001
Fail	547 (24.9)	53 (9.7)		83 (15.2)		220 (24.8)	22 (10.0)		26 (11.8)	
Pass	1308 (59.7)	126 (9.6)		525 (40.1)		532 (60.0)	45 (8.5)		216 (40.6)	
Ineligible	337 (15.4)	72 (21.4)		151 (44.8)		135 (15.2)	31 (23.0)		57 (42.2)	
High or Moderate Potency Statin			<0.001		<0.001			0.003		<0.001
Fail	697 (31.8)	61 (8.8)		0 (0.0)		304 (34.3)	30 (9.9)		0 (0.0)	
Pass	1133 (51.7)	120 (10.6)		567 (50.0)		463 (52.2)	43 (9.3)		231 (49.9)	
Ineligible	362 (16.5)	70 (19.3)		192 (53.0)		120 (13.5)	25 (20.8)		68 (56.7)	
Brain Imaging			0.186		<0.001			0.380		<0.001
Fail	86 (3.9)	9 (10.5)		0 (0.0)		40 (4.5)	6 (15.0)		0 (0.0)	
Pass	2062 (94.1)	233 (11.3)		737 (35.7)		830 (93.6)	89 (10.7)		291 (35.1)	
Ineligible	44 (2.0)	9 (20.4)		22 (50.0)		17 (1.9)	3 (17.7)		8 (47.1)	
Telemetry			<0.001		<0.001			0.095		<0.001
Fail	430 (19.6)	30 (7.0)		173 (40.2)		177 (20.0)	13 (7.3)		60 (33.9)	
Pass	773 (35.3)	76 (9.8)		330 (42.7)		337 (38.0)	35 (10.4)		145 (43.0)	
Ineligible	989 (45.1)	145 (14.7)		256 (25.9)		373 (42.0)	50 (13.4)		94 (25.2)	

Supplemental Table 3. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Holter			<0.001		<0.001			<0.001		0.033
Fail	1343 (61.3)	126 (9.4)		396 (29.5)		521 (58.7)	51 (9.8)		158 (30.3)	
Pass	377 (17.2)	26 (6.9)		164 (43.5)		175 (19.7)	10 (5.7)		70 (40.0)	
Ineligible	472 (21.5)	99 (21.0)		199 (42.2)		191 (21.5)	37 (19.4)		71 (37.2)	
Antithrombotic by Day 2			<0.001		<0.001			<0.001		<0.001
Fail	99 (4.5)	11 (11.1)		0 (0.0)		49 (5.5)	6 (12.2)		0 (0.0)	
Pass	1881 (85.8)	188 (10.0)		645 (34.3)		760 (85.7)	71 (9.3)		257 (33.8)	
Ineligible	212 (0.7)	52 (24.5)		114 (53.8)		78 (8.8)	21 (26.9)		42 (53.9)	
Anticoagulation for Atrial Fibrillation			0.047		<0.001			0.505		<0.001
Fail	75 (3.4)	15 (20.0)		0 (0.0)		28 (3.2)	4 (14.3)		0 (0.0)	
Pass	233 (10.6)	30 (12.9)		92 (39.5)		103 (11.6)	14 (13.6)		34 (33.0)	
Ineligible	1884 (86.0)	206 (10.9)		667 (35.4)		756 (85.2)	80 (10.6)		265 (35.1)	
INR for Patients on Warfarin			0.709		0.682			0.649		0.987
Fail	7 (0.3)	1 (14.3)		2 (28.6)		3 (0.3)	0 (0.0)		1 (33.3)	
Pass	108 (5.0)	11 (10.1)		42 (35.8)		52 (5.9)	7 (13.5)		17 (32.7)	
Ineligible	2076 (94.7)	239 (11.5)		715 (34.4)		832 (93.8)	91 (10.9)		281 (33.8)	
HbA1c Measured			0.095		<0.001			0.154		<0.001
Fail	171 (7.8)	18 (10.5)		37 (21.6)		61 (6.9)	9 (14.8)		12 (19.7)	
Pass	797 (36.4)	107 (13.4)		312 (39.2)		307 (34.6)	40 (13.0)		133 (43.3)	
Ineligible	1224 (55.8))	126 (10.3)		410 (33.5)		519 (58.5)	40 (9.4)		154 (29.7)	
Hypoglycemic Medication Intensification			0.981		0.352			0.437		0.036
Fail	103 (4.7)	12 (11.6)		40 (38.8)		60 (6.8)	8 (13.3)		29 (48.3)	
Pass	72 (3.3)	8 (11.1)		29 (40.3)		12 (1.3)	0 (0.0)		5 (41.7)	
Ineligible	2017 (92.0)	231 (11.5)		690 (34.2)		815 (91.9)	90 (11.0)		265 (32.5)	
DVT Prophylaxis			0.811		<0.001			0.672		0.001
Fail	150 (6.8)	15 (10.0)		41 (27.3)		66 (7.4)	9 (13.6)		22 (33.3)	
Pass	814 (37.1)	97 (11.9)		365 (44.8)		321 (36.2)	33 (10.3)		134 (41.7)	
Ineligible	1228 (56.0)	139 (11.3)		353 (28.8)		500 (56.4)	56 (11.2)		143 (28.6)	

Supplemental Table 3. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Rehabilitation Consult			<0.001		<0.001			<0.001		<0.001
Fail	1088 (49.6)	93 (8.6)		273 (25.1)		422 (47.6)	31 (7.4)		105 (24.9)	
Pass	1017 (46.4)	123 (12.1)		409 (40.2)		435 (49.0)	55 (12.6)		169 (38.9)	
Ineligible	87 (4.0)	35 (40.2)		77 (88.5)		30 (3.4)	12 (40.0)		25 (83.3)	
Speech Language Therapy Consult			0.011		<0.001			0.528		<0.001
Fail	1013 (46.2)	99 (9.8)		403 (39.8)		427 (48.1)	42 (9.8)		153 (35.8)	
Pass	487 (22.2)	52 (10.7)		207 (42.5)		205 (23.1)	25 (12.2)		97 (47.3)	
Ineligible	692 (31.6)	100 (14.4)		149 (21.5)		255 (28.8)	31 (12.2)		49 (19.2)	
SATS Referral for Alcohol Use			0.933		0.767			0.201		0.267
Fail	141 (6.4)	17 (12.1)		51 (36.2)		59 (6.7)	9 (15.3)		16 (27.1)	
Pass	15 (0.7)	1 (6.7)		4 (26.7)		4 (0.4)	1 (25.0)		0 (0.0)	
Ineligible	2036 (92.9)	233 (11.4)		704 (34.6)		824 (92.9)	88 (10.7)		283 (34.3)	
Neurology Consult			<0.001		<0.001			<0.001		<0.001
Fail	642 (29.3)	72 (11.2)		0 (0.0)		245 (27.6)	25 (10.2)		0 (0.0)	
Pass	1482 (67.6)	149 (10.1)		694 (46.8)		618 (69.7)	62 (10.0)		278 (45.0)	
Ineligible	68 /(3.1)	30 (44.1)		65 (95.6)		24 (2.7)	11 (45.8)		21 (87.5)	

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-12
Bias	9	Describe any efforts to address potential sources of bias	7-12
Study size	10	Explain how the study size was arrived at	7-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12, Suppl File
Outcome data	15*	Report numbers of outcome events or summary measures over time	12, Suppl File

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-20
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-20
Discussion			
Key results	18	Summarise key results with reference to study objectives	21-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23-24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-24
Generalisability	21	Discuss the generalisability (external validity) of the study results	23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Pairing Regression and Configurational Analysis in Health Services Research:Modeling Outcomes in an Observational Cohort Using a Split-Sample Design

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Pairing Regression and Configurational Analysis in Health Services Research: Modeling Outcomes in an Observational Cohort Using a Split-Sample Design

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KEY WORDS configurational analysis, logistic regression, observational cohort, applied methodology

ABSTRACT

Background Configurational methods are increasingly being used in health services research.

Objectives To use configurational analysis and logistic regression within a single dataset to compare results from the two methods.

Design Secondary analysis of an observational cohort; a split-sample design involved randomly dividing patients into training and validation samples.

Participants and Setting Patients with transient ischemic attack (TIA) in US Department of Veterans Affairs hospitals.

Measures The patient outcome was the combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-TIA**.** The quality-of-care outcome was the without-fail rate (proportion of patients who received all processes for which they were eligible, among seven processes).

Results For the recurrent stroke or death outcome, configurational analysis yielded a three-pathway model identifying a set of (validation sample) patients where the prevalence was 15.0% (83/552), substantially higher than the overall prevalence of 11.0% (relative difference, 36%). The configurational model had a sensitivity (coverage) of 84.7% and specificity of 40.6%. The logistic regression model identified six factors associated with the combined endpoint (c-statistic, 0.632; sensitivity, 63.3%; specificity, 63.1%). None of these factors were elements of the configurational model.

For the quality outcome, configurational analysis yielded a single-pathway model identifying a set of (validation sample) patients where the without-fail rate was 64.3% (231/359), nearly twice the overall prevalence (33.7%). The configurational model had a sensitivity (coverage) of 77.3% and specificity of 78.2%. The logistic regression model identified seven factors associated with the without-fail rate (c-statistic, 0.822; sensitivity, 80.3%; specificity, 84.2%). Two of these factors were also identified in the configurational analysis.

Conclusions Configurational analysis and logistic regression represent different methods that can enhance our understanding of a dataset when paired together. Configurational models optimize sensitivity with relatively few conditions. Logistic regression models discriminate cases from controls and provided inferential relationships between outcomes and independent variables.

Strengths and Limitations of this Study

- Logistic regression and configurational methods (CNA) were applied to the same data to examine similarities and differences in results.
- The split-sample approach to development and validation of models is a key methodological strength.
- The results are based on data from the Department of Veterans Affairs and may not generalize to other healthcare systems.

INTRODUCTION

Configurational Comparative Methods (CCMs) have been used in a wide variety of disciplines since at least the 1990s and have recently started to gain traction in the general medical research literature[1-4] as well as within implementation science.[5 6] CCMs draw upon mathematical approaches that are fundamentally different from those used in regression modeling, which is commonly used in health services research. Specifically, CCMs draw upon Boolean algebra and set theory to identify specific combinations of conditions that lead to an outcome of interest as well as determine if multiple solution paths yield the same outcome (i.e., equifinality).[7-9]

Although CCMs and logistic regression offer the potential for synergistic understanding of complex clinical situations, few studies in the medical literature[10] have used both approaches within a single dataset.[11-14] The objective of the current study was to use both CCMs and logistic regression to independently derive and validate two models (one for mortality or recurrent stroke and the other for quality of care) among patients with transient ischemic attack (TIA). Two outcomes were chosen because they provided different methodological challenges. The combined endpoint of death or recurrent stroke is relatively uncommon among TIA patients[15 16] and therefore presented the problem of predicting rare but important events; which may, for example, limit logistic regression modeling due to constraints on the number of outcome events per independent variable.[17 18] The quality of care metric was available for the majority of patients, however few robust predictors of quality at the patient level have been previously identified.[19] In contrast, if a small set of key variables were strongly associated with an outcome, it would be expected that both regression and configurational methods would produce similar findings, limiting the potential insights available from comparing results across methods. Furthermore, if a variable is only weakly associated with an outcome, then the inconsistent relationship between configurations and an outcome could hinder the identification of a solution pathway from configurational methods. Across methods we sought to examine similarities and differences in factor selection (i.e., variables or configurations that were included in the final models) as well as compare sensitivity, specificity, c-statistics, and positive and negative predictive values.

METHODS

This analysis was part of the Protocol-guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) project to improve quality of TIA care in Veterans Health Administration (VA) facilities.[15 20 21] We identified patients with TIA who were cared for in any VA Emergency Department (ED) or inpatient setting based on primary discharge codes for TIA (International Classification of Disease [ICD]-10 G45.0, G45.1, G45.8, G45.9, I67.848) during the period October 2016 and September 2017. The unit of analysis was the TIA patient.

Patient and Public Involvement Statement

This analysis did not include patient or public involvement.

Data Sources

Electronic health record data were obtained from the VA Corporate Data Warehouse (CDW).[22 23] CDW data included: inpatient and outpatient data files (e.g., clinical encounters with associated diagnostic and procedure codes) in the five-years pre-event to identify past medical history,[24] healthcare utilization, and receipt of procedures (Current Procedural Terminology [CPT], Healthcare Common Procedures Coding System [HCPCS], and *ICD*-9 and *ICD*-10 procedure codes). CDW data were also used for vital signs, laboratory data, allergies, imaging, orders, medications and clinical consults. Mortality status was obtained from the VA Vital Status File.[25] Recurrent stroke events were identified using a combination of VA CDW data and fee-basis data (which describes healthcare services that were paid for by the VA but that were obtained by Veterans in non-VA facilities). The study was approved by the human subjects committee at the Indiana University School of Medicine Institutional Review Board and the Richard L. Roudebush VA medical center Research and Development Committee.

Outcomes

The combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-discharge from the index TIA event was the primary patient outcome. Recurrent ischemic stroke events included ED visits or hospitalizations and were identified on the basis of *ICD*-10 codes (I63, I66, I67.89, I97.81, and I97.82).

The quality of care outcome was the "without-fail" rate (also referred to as defect-free[26 27] care), which is an "all-or-none" measure of care quality.[28] It was calculated as the proportion of Veterans with TIA who received all of the processes of care for which they were eligible from among seven processes: brain imaging, carotid artery imaging, neurology consultation, hypertension control, anticoagulation for atrial fibrillation, antithrombotics, and high/moderate potency statins.[29 30] Processes of care were ascertained using electronic health record data using validated algorithms.[30 31] The without-fail rate was based on guideline[32 33] recommended processes of care and has been associated with improved outcomes.[34] Given the all-or-none nature of the without-fail rate, it can be a relatively difficult to change and even small improvements in the absolute rate may reflect substantial changes in practice.[28] For the regression analyses modeling the without-fail rate, quality measures were recoded such that pass=1, not eligible=0, and fail=0 to avoid reducing sample size by eliminating ineligible patients.

Analytic Overview

We analyzed this same dataset with configurational analysis and logistic regression modeling. We randomly divided the overall dataset (n=3079) into a ~70% training sample (2192/3079) and ~30% validation sample (887/3079).[35] The training sample was independently analyzed by a configurational analyst (EJM) and a biostatistician (AJP); this split-sample approach was used to enhance within-method validity. For the combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-discharge from the index TIA event, we included both baseline patient characteristics (e.g., age) as well as processes of care (e.g., hypertension control) in the modeling. The without-fail model included only processes of care. Model performance was tested using the validation sample.

Configurational Analysis

Configurational analyses were conducted with Coincidence Analysis–a relatively new approach within the broader family of CCMs[6]–using the R package "CNA."[36]

Definitions

Variables were baseline characteristics of patients (e.g., history of hypertension) which could be expressed with a dichotomous scale or a continuous scale. A configuration is the specific form of conditions (e.g., the history of hypertension was present). Consistency or positive predictive value is the number of cases covered by the solution with the outcome of interest versus all cases covered by the solution. Coverage or sensitivity is the number of cases covered by the solution with the outcome of interest versus all cases with the outcome of interest. Complexity is the number of discrete conditions in a configuration. Ambiguity describes a situation where more than one model generated by the configurational analysis fit the data equally well.

Analytic Steps

We began with a multi-step data reduction approach that has been described previously.[1 2 37-39] Briefly, we used the "minimally sufficient conditions" to examine all candidate factors (e.g., demographics, past medical history, characteristics of the index cerebrovascular event, vital signs, laboratory data, medications, and processes of care) in the analysis with the outcome of interest across all 2192 cases in the training sample and identify bundles of conditions with the strongest connections to the outcome condition. Factors in the analysis that were not already categorical or ordinal were binned; for example, age was categorized into 5-year increments (e.g., 55-59, 60-64, 65-69 years, etc.) We performed this process separately for the two outcomes of interest: mortality or recurrent stroke within one year; and the without-fail rate. When analyzing these combinations of conditions, we considered all 1- and 2- and 3-condition bundles instantiated in the dataset (meaning patients with these specific combinations of configurations were present within the sample) that satisfied the consistency threshold.

We used a dual minimum threshold to identify patient characteristics to use in model iteration: a prevalence threshold of ≥0.145 (via the "consistency" function available in the R "cna" package) and a coverage score of ≥0.15. These cutoffs were selected to ensure individual configurations were clinically relevant. Specifically, given that the overall outcome rate of death or stroke at one-year post-TIA was (349/3079) 11.3%, a prevalence threshold of ≥0.145 identified configurations with a mortality or stroke rate at least three points higher (i.e., 14.5% vs. 11.3%) in absolute terms than the overall population, or ≥ 25% higher in relative terms. For the without-fail rate, the overall outcome rate was 34.4% (1058/3079) and the prevalence threshold was set at ≥ 50%, a rate that was at least 15 points higher in absolute terms (i.e., 50% vs. 34.4%), or ≥ 40% higher in relative terms. In this sense, the configurational analysis sought to identify distinct "phenotypes" of patients who had substantially different outcome rates (as a group) than the overall sample. The coverage threshold of ≥0.15 ensured that the configurations applied to at least 15% of individuals with the outcome and was used to avoid overfitting.

We next generated a "condition table" to list and organize the output. In a condition table, rows list configurations of conditions that meet a specified prevalence threshold, and column variables include outcome status, condition, consistency, coverage, and complexity. We generated condition tables by specifying a prevalence threshold of 1.0 (i.e., 100%). If we did not find any potential configurations that met our initial dual threshold (i.e., prevalence threshold of 1.0 and a coverage score of ≥ 0.15), we then iteratively lowered the specified prevalence threshold by 0.05 (e.g., from 1.0 to 0.95, etc.) and repeated the process of generating a new condition table. We continued this process until at a given prevalence threshold it was possible to identify at least two potential configurations (or "phenotypes") of patient characteristics that met the specified prevalence threshold as well as the ≥15% coverage level. Using this approach, we inductively analyzed the training sample and identified a subset of five candidate difference-making factors to use in the subsequent modeling phase.

We next developed candidate models with these five factors by iteratively using the model-building function within the "cna" software package in R. We assessed models based on their overall consistency and coverage, as well as potential model ambiguity.[40] We selected a final model based on these same criteria.

Logistic Regression

Multivariable logistic regression was conducted using SAS Enterprise guide v7.11. Models were constructed using forward and backward selection procedures in the HPLOGISTIC procedure using the Schwarz Bayesian Criterion. Patient clinical characteristics as well as processes of care were included in the modeling. Final models for the backward and forward procedure identified the same set of variables for each outcome. To calculate sensitivity and specificity, we chose a cut-point of the estimated probabilities at which the distance between (1,0) and the receiver operating characteristics (ROC) curve was minimized in the ROC diagram for the training sample. We used a predicted probability of 0.096 as the cut-point for the clinical outcome, and 0.490 for the quality of care model. In this way, each patient was dichotomized as yes versus no for risk of the outcome.

Model Comparisons

The sensitivity (coverage), specificity, positive predictive value, negative predictive value and the c-statistic were examined and compared between the methods for both outcomes. For the logistic regression, the first area under the ROC (c-statistic) was calculated with all the variables in the model and used the continuous predicted probability. As described above, for the comparison of the two methods, we used a cut-point on the probability that maximized the sensitivity and specificity. We created a new variable describing the predicted outcome (1 if p > cut-point; 0 otherwise). We then performed logistic regression using only that variable as the independent variable. This variable was also used to calculate sensitivity and specificity. Similarly, for the configurational analysis, we created a predicted outcome variable based on the configurational groupings and use that as the independent variable in the logistic regression to obtain a c-statistic.

RESULTS

The overall sample consisted of 3079 Veterans between the ages of 24 to 99 years (median age, 70 years; interquartile range 64-78) who presented at a VA medical facility with a TIA between October 2016 and September 2017. The baseline characteristics of the patients within the training and validation samples are provided in Table 1 and the process of care data are provided in Supplemental Table B. All patients had complete data both for the outcomes and potential explanatory factors, which included specific TIA processes of care as well as risk factors for recurrent stroke or death.

Patient Outcome: Death or Recurrent Stroke at One-Year

Configurational Results

Among the training sample patients, the prevalence of the combined endpoint of death or recurrent stroke at one-year post-TIA was 11.5% (251/2192). Configurational analysis yielded a three-pathway model comprised of five conditions, where the prevalence of death or stroke was 14.5% (193/1330). The configurational analysis identified the following three pathways: (1) having a history of TIA AND a history of hypertension AND not being prescribed a non-steroidal anti-inflammatory drug (NSAID); (2) having a HASBLED score[41] (a measure of bleeding risk) of ≥3; or (3) having a history of dementia (Table 2).

Among patients in the validation sample, the death or stroke rate one-year post-TIA was 11.0% (98/887) overall, and 15.0% (83/552) for patients within the three-pathway configurational model, 36% relatively higher than the overall rate. This performance in the validation sample was better than in the training sample, where the same configurational three-pathway model rate was 26% relatively higher than the overall rate (i.e., 14.5% compared with 11.5%). The configurational model had a coverage (sensitivity) of 84.7% in the validation sample, identifying 83 of 98 patients with the outcome of death or recurrent stroke at one-year; this outperformed the 76.9% coverage score (193/251) in the training sample (Table 3). The configurational model had a specificity of 41.4% in the training sample and 40.6% in the validation sample (Table 3).

Logistic Regression Results

The logistic regression model identified six factors that were associated with the combined endpoint of death or recurrent stroke at one-year post-TIA (Table 2): age, Charlson comorbidity index,[42] the modified APACHE score,[43] current smoking status, palliative care or hospice, and history of stroke. None of these six factors were elements of the configurational model. The c-statistic for the primary model on training sample was 0.747 and 0.691 for the validation sample (Table 2). The c-statistics for logistic models used to calculate sensitivity and specificity (Table 3) were 0.592 for the training sample and 0.688 for the validation sample. The sensitivity was 75.3% in the training sample and 63.3% in the validation sample (Table 3). The specificity was 62.3% in the development sample and 63.1% in the validation sample.

Quality of Care Outcome: the Without-Fail Rate

Configurational Results

Among the training sample patients, the prevalence of the without-fail rate was 34.6%. The configurational analysis (Table 4) yielded a single-pathway model with the conjunct of two processes—discharged on a high or moderate potency statin AND neurology consultation—where the without-fail rate was 67.3% (567/843). The final configurational model included 567 of the 759 patients with the outcome (i.e., 74.7% coverage; Table 4).

Among the validation sample patients, the without-fail rate was 33.7%. When applied to the validation sample, the single-pathway configurational model yielded a without-fail rate of 64.3% (231/359), which was nearly twice the observed prevalence. This model covered 231 of the 299 cases with the outcome (i.e., 77.3% coverage; Table 4). The configurational model had a specificity of 80.7% in the training sample 78.2% in the validation sample (Table 5).

Logistic Regression Results

The logistic regression model identified seven factors that were associated with the without-fail rate: carotid artery imaging, hypertension medication intensification, hypertension control, discharged on statin, discharged on high or moderate potency statin, antithrombotics by hospital day two, and neurology consultation (see Table 4). Two of these factors were also identified in the configurational analysis: discharged on a high or moderate potency statin and neurology consultation. The c-statistics were higher for this model of quality than for the patient outcome model. In the primary model the c-statistic for the training sample was 0.842 and 0.841 in the validation sample (Table 4). In the model used to calculate sensitivity and specificity the c-statistic was 0.823 for the training sample, and 0.822 for the validation sample (Table 5). The sensitivity was 76.7% in the training sample and 80.3% in the validation sample. The specificity was 87.9% in the training sample and 84.2% in the validation sample.

DISCUSSION

This study analyzed one of the largest sample sizes used to date in a published configurational analysis, is one of the first to use a split-sample design featuring training and validation samples, and is also one of the first to directly compare configurational and logistic regression results using identical data. The models developed by applying logistic regression and configurational analysis within the training sample were confirmed when tested against the validation sample. This was true for both the one-year death or recurrent stroke outcome and the without-fail quality-of-care outcome. The results of this study demonstrate that configurational analyses and logistic regression, when applied to the same dataset, can expand our understanding of the data. Key differences in the findings from the two methods as they were applied in the current study included: the focus of optimization; the goal of making stochastic inferences versus empiric insights; and the possibility of conjunctivity.

Logistic regression models include variables to infer the absence and presence of the outcome and maximizes the likelihood for the observed data in a parametrically well-structured model. The configurational models, by contrast, identified “phenotypes” where particular groups of individuals sharing a specific bundle of characteristics had outcome rates substantially different from that of the overall sample. The logistic regression model is useful in making statistical inference for variables’ effects on the binary outcome of interest, though it can be applied to predict the outcome if a cut-off probability threshold is provided. In contrast, the configurational models pinpointed specific combinations of factor values that linked directly to the positive outcome of interest.

An expected pattern in results is that configurational analysis has an advantage over logistic regression in prediction of a dichotomous outcome when prevalence is low. This pattern was evident in the model of recurrent stroke or death at one-year post-TIA (with a prevalence of 11.5% in the development set), where in the validation sample, the sensitivity was higher in the configurational model (84.7% [95%CI: 76.0-91.2%]) than in the logistic regression model (63.3% [95%CI: 52.9-72.8%]). Both approaches had equivalent c-statistics (configurational model, 0.626 [95%CI: 0.587-0.666]; logistic model, 0.632 [0.581-0.683]). However, this advantage may diminish if the prevalence of the outcome is not rare; which was evident in the model using the quality outcome (with a prevalence of in the development set 34.6%), where in the validation sample, the sensitivity was similar in both approaches (configurational model, 77.3% [95%CI: 72.1-81.9%]; logistic model, 80.3% [95%CI: 75.3-84.6%]), and the c-statistics were also similar (configurational model, 0.777 [95%CI; 0.748-0.801]; logistic model, 0.822 [95%CI: 0.795-0.849]).

The models of the one-year recurrent stroke or death rate differed dramatically with no overlap between the factors included in the logistic regression model and the conditions in the configurational model. This observation may be attributed to correlations between variables. For example, the finding that increasing age was negatively correlated with taking NSAIDS (r=-0.215, p<0.0001; Supplemental Table A) may partially account for why age was a variable that was included in the logistic model whereas not taking NSAIDs was a configuration that was included in one of the pathways in the configurational model. In contrast, the models of the without-fail rate were overlapping. The configurational results were more parsimonious. Certainly, the logistic regression models could be further developed if parsimony was particularly of interest.

The configurational results for the quality outcome (Table 2) provide an example of Boolean conjunctivity, where a bundle of conditions that jointly appear together are sufficient for the outcome. Conjunctivity is an attractive characteristic of configurational methods and particularly relevant to studies in health care settings given the inherent complexity within clinical medicine and health services research. In other words, it is expected that for some complex phenomena that it is a combination of conditions—rather than a single factor alone—which can explain the outcome.

As described above, configurational methods differ from regression methods in terms of the underlying mathematical foundations, the focus on configurations of conditions (i.e., factor values) versus variables, and the results output.[44] The use of configurational methods is increasing within health services research in general and in implementation science in particular.[45] The pairing of logistic regression and configurational methods may be particularly fruitful for implementation science for describing difference-making patterns and identifying factors associated with an outcome at a particular site, especially if the outcome is uncommon or when there are few sites. Configurational methods are also increasingly used in mixed methods analyses; given the focus on cases, the persistent link to cases present throughout configurational analysis allows investigators to examine qualitative data from key illustrative cases.[46]

Because regression methods have been widely used in health services research, investigators have experience in applying them and best practices have emerged to address common methodological difficulties. Future research, conducted either on real-world data or in simulations,[47] should compare findings from configurational methods with regression analyses to advance our understanding of how configurational methods will perform in the following situations which are common in healthcare data: (1) the strength of the association between a variable and an outcome depends on the presence of another variable (e.g., if implementation success is related to champion characteristics only in the presence of leadership support for a program); (2) a rare characteristics is robustly associated with an outcome (e.g., patients presenting with coma are at markedly increased risk of mortality, however, coma is an uncommon clinical presentation); (3) variables that are at least modestly associated with an outcome are correlated; (4) missing data especially for factors that are at least modestly associated with an outcome; (5) limited diversity especially for configurations that are related to an outcome (e.g., few older persons included in a dataset where the outcome is mortality); and (6) nested data (e.g., patients within sites). Although regression analyses identify the same variables as being associated with an outcome whether modeling the presence or absence of an outcome, configurational methods sometimes produce different results depending on whether a positive or negative outcome is being modelled.[46] Future research should evaluate situations when this key difference between methods is most pronounced and hence most likely to provide novel insights.

Several limitations of this study should be noted. First, the results are based on data from the Department of Veterans Affairs, and therefore may not generalize to other healthcare systems.

Second, the outcomes used in this study were chosen to provide variation in prevalence rates and associations between variables and outcomes; however future studies could consider datasets with different characteristics (e.g., varying sample sizes).

Third, the process of care variables were originally coded as pass among those eligible, fail among those eligible, and ineligible. However, patients who were not eligible for processes of care were generally the most critically ill patients (e.g., hospice); being not eligible for a process was a strong predictor of mortality. By combining the fail among eligible and ineligible categories in the regression analyses we were able to retain all patients and as expected hospice was associated with the combined endpoint of death or recurrent stroke.

Fourth, to calculate sensitivity and specificity, we chose a cut-point of the estimated probabilities at which the receiver operating characteristics (ROC) curve was minimized; different thresholds could have been used (e.g., to optimize sensitivity). For example, one option would have been to use the observed probabilities as a cut-point. Another approach would have been to use 0.5 which would be unlikely to perform well with rare outcomes. An alternative would have been to target a specific sensitivity (i.e., 80%) in which case we would have used higher cut-points for both outcomes; this approach would have been at the expense of sensitivity. In contrast, we could have targeted a given specificity (i.e., 80%); in which case we would have used a lower predicted probability cut-point and sensitivity would have been reduced.

Fifth, previous work has demonstrated that conjuncts in configurational methods are not synonymous with interactions in regression.[44] We did not systematically explore interactions within the logistic regression modelling.

Finally, we presented an example of how logistic regression and configurational methods could be used on the same data to glean different information. The analytic approaches are fundamentally different; we do not intend to suggest that one method is better than another. Future studies should consider both circumstances where other methods (e.g., decision-tree analysis) can be used with configurational methods, and situations when alternative methods might be used in series rather than in parallel (e.g., for variable selection or for dichotomizing continuous variables).

CONCLUSIONS

Configurational analysis and logistic regression represent fundamentally different analytic methods. Configurational models optimize sensitivity with relatively few conditions and allow for equifinality. Logistic regression models provide inferential relationships between binary outcomes and independent variables as well as clinically useful measures to interpret effects (i.e., odds ratio). Pairing these two diverse approaches offers a major new analytic option to health services researchers interested in leveraging multiple methodological perspectives to explore and model complex phenomena with greater nuance and understanding.

AUTHORS' CONTRIBUTIONS

All authors read and approved the final manuscript. EJM and AJP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DMB: obtained funding and was responsible for the design and conduct of the PREVENT study which is the data source used in the analyses; participated in data analysis conceptualization, interpretation of the results, and drafting and revising the manuscript.

LJM: obtained the PREVENT data which is the data source used in the analyses and participated in data analysis conceptualization

EJM, AJP: planned and executed the data analysis, participated in interpretation of the results, and drafting and revising the manuscript.

YZ, JD: participated in the interpretation of the results and the framing of the manuscript especially with regard to the mathematical and statistical foundations of the methods and the statistical applications of both methods.

JJS: participated in interpretation of results and manuscript editing.

Table 1. Baseline Characteristics of the Training and Validation Samples

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Overall	2192	251 (11.4)		759 (34.6)		887	98 (11.0)		299 (33.7)	
Current Smoker			0.004		0.003			0.558		0.435
No	1593 (72.7)	163 (10.2)		521 (32.7)		627 (70.7)	72 (11.5)		206 (32.8)	
Yes	599 (27.3)	88 (14.7)		238 (39.7)		260 (29.3)	26 (10.0)		93 (35.8)	
Palliative or Hospice Care			<0.001		<0.001			<0.001		<0.001
No	2124 (96.9)	221 (10.4)		694 (32.7)		863 (97.3)	87 (10.1)		278 (32.2)	
Yes	68 (3.1)	30 (44.1)		65 (95.6)		24 (2.7)	11 (45.8)		21 (87.5)	
Diabetes			<0.001		<0.001			0.004		<0.001
No	1255 (57.2)	116 (9.2)		393 (31.1)		528 (59.5)	45 (8.5)		144 (27.3)	
Yes	937 (42.8)	135 (14.4)		366 (39.1)		359 (40.5)	53 (14.8)		155 (43.2)	
Atrial Fibrillation			<0.001		0.146			0.038		0.851
No	1834 (83.7)	184 (10.0)		623 (34.0)		735 (82.9)	75 (10.2)		249 (33.9)	
Yes	358 (16.3)	67 (18.7)		136 (38.0)		152 (17.1)	23 (15.1)		50 (32.9)	
Myocardial Infarction			0.009		<0.001			0.301		0.174
No	2032 (92.7)	222 (10.9)		679 (33.4)		822 (92.8)	88 (10.7)		272 (33.1)	
Yes	160 (7.3)	29 (18.1)		80 (50.0)		65 (7.3)	10 (15.4)		27 (41.5)	
TIA*			0.156		<0.001			0.219		<0.001
No	738 (33.7)	74 (10.0)		151 (20.5)		314 (35.4)	29 (9.2)		69 (22.0)	
Yes	1454 (66.3)	177 (12.2)		608 (41.8)		573 (64.6)	69 (12.0)		230 (40.1)	
Stroke			<0.001		<0.001			0.010		0.013
No	1903 (86.8)	188 (9.9)		631 (33.2)		788 (88.8)	79 (10.0)		254 (32.2)	
Yes	289 (13.2)	63 (21.8)		128 (44.3)		99 (11.2)	19 (19.2)		45 (45.4)	
CHF*			<0.001		<0.001			0.038		0.005
No	1860 (84.8)	182 (9.8)		613 (33.0)		747 (84.2)	75 (10.0)		237 (31.7)	
Yes	332 (15.2)	69 (20.8)		146 (44.0)		140 (15.8)	23 (16.4)		62 (44.3)	
COPD*			<0.001		0.785			0.600		0.012
No	1723 (78.6)	175 (10.2)		594 (34.5)		699 (78.8)	75 (10.7)		221 (31.6)	
Yes	469 (21.4)	76 (16.2)		165 (35.2)		188 (21.2)	23 (12.2)		78 (41.5)	

Table 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
PVD*			<0.001		<0.001			0.017		0.001
No	1867 (85.2)	187 (10.0)		611 (32.7)		749 (84.4)	74 (9.9)		235 (31.4)	
Yes	64 (19.8)	64 (19.7)		148 (45.5)		138 (15.6)	23 (17.4)		64 (46.4)	
Dementia			<0.001		0.685			0.010		0.071
No	2009 (91.6)	211 (10.5)		693 (34.5)		802 (90.4)	81 (10.1)		278 (34.7)	
Yes	183 (8.4)	40 (21.9)		66 (36.1)		85 (9.6)	17 (20.0)		21 (24.7)	
Chronic Kidney Disease			<0.001		<0.001			0.004		0.007
No	1794 (81.8)	180 (10.0)		586 (32.7)		732 (82.5)	70 (9.6)		232 (31.7)	
Yes	398 (18.2)	71 (17.8)		173 (43.5)		155 (17.5)	28 (18.1)		67 (43.2)	
Cancer			<0.001		0.094			0.178		1.00
No	1958 (89.3)	199 (10.2)		666 (34.0)		787 (88.7)	83 (10.6)		265 (33.7)	
Yes	234 (10.7)	52 (22.2)		93 (39.7)		100 (11.3)	15 (15.0)		34 (34.0)	
Hypertension			<0.001		<0.001			0.006		<0.001
No	528 (24.1)	33 (6.2)		125 (23.7)		215 (24.2)	13 (6.0)		46 (21.4)	
Yes	1664 (75.9)	218 (13.1)		634 (38.1)		672 (75.8)	85 (12.7)		253 (37.6)	
Renal Disease			<0.001		<0.001			0.006		0.008
No	1802 (82.2)	182 (10.1)		590 (32.7)		737 (83.1)	71 (9.6)		234 (31.8)	
Yes	390 (17.8)	69 (17.7)		169 (43.3)		150 (16.9)	27 (18.0)		65 (43.3)	
Hyperlipidemia			0.003		<0.001			0.739		<0.001
No	816 (37.2)	72 (8.8)		213 (26.1)		325 (36.6)	34 (10.5)		76 (23.4)	
Yes	1376 (62.8)	179 (13.0)		546 (39.7)		562 (63.4)	64 (11.4)		223 (39.7)	
Arrhythmia			0.001		0.421			0.114		0.035
No	1910 (87.1)	201 (10.5)		655 (34.3)		770 (86.8)	80 (10.4)		249 (32.3)	
Yes	282 (12.9)	50 (17.7)		104 (36.9)		117 (13.2)	18 (15.4)		50 (42.7)	
Sleep Apnea			0.608		0.058			0.669		0.014
No	1779 (81.2)	207 (11.6)		599 (33.7)		737 (83.1)	80 (10.8)		235 (31.9)	
Yes	413 (18.8)	44 (10.7)		160 (38.7)		150 (16.9)	18 (12.0)		64 (42.7)	
Alcohol Abuse			0.591		0.858			0.021		0.220
No	2045 (93.3)	232 (11.3)		707 (34.6)		823 (92.8)	85 (10.3)		282 (34.3)	
Yes	147 (6.7)	19 (12.9)		52 (35.4)		64 (7.2)	13 (20.3)		17 (26.6)	

Table 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Depression			0.577		0.240			0.308		0.613
No	1690 (77.1)	190 (11.2)		574 (34.0)		683 (77.0)	80 (11.7)		227 (33.2)	
Yes	502 (22.9)	61 (12.2)		185 (36.8)		204 (23.0)	18 (8.8)		72 (35.3)	
Liver Disease			0.088		0.705			0.492		0.763
No	2062 (94.1)	230 (11.2)		712 (34.5)		836 (94.2)	91 (10.9)		283 (33.8)	
Yes	130 (5.9)	21 (16.2)		47 (36.2)		51 (5.8)	7 (13.7)		16 (31.4)	
Cirrhosis			0.002		0.417			0.060		0.094
No	2150 (98.1)	239 (11.1)		742 (34.5)		867 (97.8)	93 (10.7)		296 (34.1)	
Yes	42 (1.9)	12 (28.6)		17 (40.5)		20 (2.2)	5 (25.0)		3 (15.0)	
Migraines			0.571		0.315			0.511		0.287
No	2120 (96.7)	245 (11.6)		730 (34.4)		862 (97.2)	97 (11.2)		288 (33.4)	
Yes	72 (3.3)	6 (8.3)		29 (40.3)		25 (2.8)	1 (4.0)		11 (44.0)	
Bleeding			0.052		0.154			1.000		1.000
No	2179 (99.4)	247 (11.3)		752 (34.5)		883 (99.6)	98 (11.1)		298 (33.8)	
Yes	13 (0.6)	4 (30.8)		8 (53.8)		4 (0.4)	0 (0.0)		1 (25.0)	
Intracranial Hemorrhage			<0.001		0.221			0.185		0.118
No	2080 (94.9)	225 (10.8)		714 (34.3)		848 (95.6)	91 (10.7)		281 (33.1)	
Yes	112 (5.1)	26 (23.2)		45 (40.2)		39 (4.4)	7 (18.0)		18 (46.2)	
Dialysis			0.226		0.311			0.001		0.128
No	2165 (98.8)	246 (11.4)		747 (34.5)		879 (99.1)	93 (10.6)		294 (33.4)	
Yes	27 (1.2)	5 (18.5)		12 (44.4)		8 (0.9)	5 (62.5)		5 (62.5)	
Pacemaker			0.129		<0.001			0.481		0.160
No	1957 (89.3)	217 (11.1)		652 (33.3)		796 (89.7)	86 (10.8)		262 (32.9)	
Yes	235 (10.7)	34 (14.5)		107 (45.5)		91 (10.3)	12 (13.2)		37 (40.7)	
Valvular Disease			0.099		0.311			0.143		0.496
No	2053 (93.7)	229 (11.2)		705 (34.3)		823 (92.8)	87 (10.6)		275 (33.4)	
Yes	139 (6.3)	22 (15.8)		54 (38.8)		64 (7.2)	11 (17.2)		24 (37.5)	
Venous Thromboembolism			0.102		0.118			0.376		0.337
No	2113 (96.4)	237 (11.2)		725 (34.3)		856 (96.5)	93 (10.9)		286 (33.4)	
Yes	79 (3.6)	14 (17.7)		34 (43.0)		31 (3.5)	5 (16.1)		13 (41.9)	

Table 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Carotid endarterectomy or stent			1.000		0.061			0.011		0.068
No	2172 (99.1)	249 (11.5)		748 (34.4)		878 (99.0)	94 (10.7)		293 (33.4)	
Yes	20 (0.9)	2 (10.0)		11 (55.0)		9 (1.0)	4 (44.4)		6 (66.7)	
CABG/PTCA*			0.687		0.414			0.506		0.411
No	2177 (99.3)	249 (11.4)		752 (34.5)		881 (99.3)	97 (11.0)		296 (33.6)	
Yes	15 (0.7)	2 (13.3)		7 (46.7)		6 (0.7)	1 (16.7)		3 (50.0)	
Pancreatitis			0.057		1.000			1.000		0.342
No	2173 (99.1)	246 (11.3)		753 (34.6)		882 (99.4)	98 (11.1)		296 (33.6)	
Yes	19 (0.9)	5 (26.3)		6 (31.6)		5 (0.6)	0 (0.0)		3 (60.0)	
Hemiplegia			0.293		<0.001			0.227		0.086
No	1876 (85.6)	209 (11.1)		611 (32.6)		759 (85.6)	80 (10.5)		247 (32.5)	
Yes	316 (14.4)	42 (13.3)		148 (46.8)		128 (14.4)	18 (14.1)		52 (40.6)	
Speech Deficit			0.424		0.200			0.298		0.293
No	2091 (95.4)	237 (11.3)		718 (34.3)		849 (95.7)	92 (10.8)		283 (33.3)	
Yes	101 (4.6)	14 (13.9)		31 (40.6)		38 (4.3)	6 (15.8)		16 (42.1)	
Syncope			0.711		0.345			0.033		0.240
No	1568 (71.5)	177 (11.3)		533 (34.0)		631 (71.1)	79 (12.5)		205 (32.5)	
Yes	624 (28.5)	74 (11.9)		226 (36.2)		256 (28.9)	19 (7.4)		94 (36.7)	
Amaurosis Fugax			0.876		0.044			1.000		0.102
No	2088 (95.3)	240 (11.5)		713 (34.2)		843 (95.0)	93 (11.0)		279 (33.1)	
Yes	104 (4.7)	11 (10.6)		46 (44.2)		44 (5.0)	5 (11.4)		20 (45.4)	
Concomitant MI*			0.231		0.056			0.346		0.056
No	2147 (98.0)	243 (11.3)		737 (34.3)		862 (97.2)	94 (10.9)		286 (33.2)	
Yes	45 (2.0)	8 (17.8)		22 (48.9)		25 (2.8)	4 (16.0)		13 (52.0)	
Concomitant CHF*			<0.001		0.228			0.309		0.007
No	2154 (98.3)	238 (11.0)		742 (34.4)		864 (97.4)	94 (10.9)		285 (33.0)	
Yes	38 (1.7)	13 (34.2)		17 (44.7)		23 (2.6)	4 (17.4)		14 (60.9)	
Aspirin			0.207		<0.001			0.801		<0.001
No	521 (23.8)	68 (13.0)		138 (26.5)		208 (23.4)	24 (11.5)		45 (21.6)	
Yes	1671 (76.2)	183 (11.0)		621 (37.2)		679 (76.6)	74 (10.9)		254 (37.4)	

Table 1. (continued)

Characteristic	Training Sample N (%)	Training Sample Death or Stroke N (%)	Training Sample P-value	Training Sample Without-Fail	Training Sample P-value	Validation Sample N (%)	Validation Sample Death or Stroke N (%)	Validation Sample P-value	Validation Sample Without-Fail	Validation Sample P-value
Warfarin			0.091		0.020			0.066		0.375
No	1941 (88.6)	214 (11.0)		655 (33.8)		784 (88.4)	81 (10.3)		260 (33.2)	
Yes	251 (11.4)	37 (14.7)		104 (41.4)		103 (11.6)	17 (16.5)		39 (37.9)	
Statin			0.793		<0.001			0.404		<0.001
No	393 (17.9)	43 (10.9)		51 (13.0)		161 (18.2)	21 (13.0)		17 (10.6)	
Yes	1799 (82.1)	208 (11.6)		708 (39.4)		726 (81.8)	77 (10.6)		282 (38.8)	
Antihypertensive			<0.001		0.006			0.037		0.006
No	351 (16.0)	20 (5.7)		99 (28.2)		137 (15.4)	8 (5.8)		32 (23.4)	
Yes	1841 (84.0)	231 (12.6)		660 (35.8)		750 (84.6)	90 (12.0)		267 (35.6)	
NSAID			0.009		0.395			0.040		0.446
No	1683 (76.8)	209 (12.4)		591 (35.1)		686 (77.3)	84 (12.2)		236 (34.4)	
Yes	509 (23.2)	42 (8.2)		168 (33.0)		201 (22.7)	14 (7.0)		63 (31.3)	
Clopidogrel			0.028		0.006			0.810		0.003
No	1541 (70.3)	161 (10.4)		505 (32.8)		644 (72.6)	70 (10.9)		198 (30.8)	
Yes	651 (29.7)	90 (13.8)		254 (39.0)		243 (27.4)	28 (11.5)		101 (41.6)	

*TIA refers to transient ischemic attack; CHF to congestive heart failure; COPD to chronic obstructive pulmonary disease; PVD to peripheral vascular disease; CABG/PTCA to coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; MI to myocardial infarction; and concomitant disease indicates conditions that were present at the time of the index transient ischemic attack.

Table 2. Modeling Results for Death or Recurrent Stroke at One-Year Post-TIA

Patient Characteristic or Process of Care	**Training Sample** *Sample Prevalence: 11.5%*		**Validation Sample** *Sample Prevalence: 11.0%*	
Configurational Analysis				
Pathways	**Pathway Prevalence††**	**Pathway Coverage**	**Pathway Prevalence**	**Pathway Coverage**
History of TIA *AND* History of Hypertension *AND* Not taking NSAID†	14.8%	55.8%	14.2%	57.1%
HAS-BLED§ score of ≥3	18.5%	54.2%	16.3%	50.0%
History of dementia	21.9%	15.9%	20.0%	17.3%
Overall Model Results	14.5%	76.9%	15.0%	84.7%
Logistic Regression				
	OR (95% CI)	**P-value**	**	
Age	1.03 (1.02, 1.05)	<0.001		
Charlson comorbidity index	1.2 (1.1, 1.2)	<0.001		
APACHE*	1.04 (1.02, 1.06)	<0.001		
Current smoker	1.8 (1.3, 2.4)	<0.001		
Palliative care/hospice	2.9 (1.7, 5.1)	<0.001		
History of stroke	1.8 (1.3, 2.6)	0.001		
c-statistic	0.747		0.691	

*APACHE refers to the Acute Physiology And Chronic Health Evaluation measure of physiologic disease severity.

†NSAID refers to non-steroidal anti-inflammatory medications.

§The HAS-BLED score describes the risk of major bleeding.

**We did not refit the model in the validation sample, but rather, we use estimates from the training model to estimate the probabilities in the validation model.

††Pathway prevalence refers to the outcome rate for the specific combination of configurations.

Table 3. Test Characteristics of the Logistic Regression and Configuration Models for Death or Recurrent Stroke Rate at One-Year Post- TIA

Training Sample	**Recurrent Stroke or Death at One-Year (11.5%)**			**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**C-Statistic**
				n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	(95%CI)
Configurational Analysis Classification	No	Yes	Totals	193/251 76.9 (71.2, 82.0)	804/1941 41.4 (39.2, 43.7)	193/1330 14.5 (12.7, 16.5)	804/862 93.3 (91.4, 94.9)	0.592 (0.563, 0.620)
No	804	58	862					
Yes	1137	193	1330					
Totals	1941	251	2192					
Logistic Regression Classification	No	Yes	Totals	189/251 75.3 (69.5, 80.5)	1209/1941 62.3 (60.1, 64.4)	189/921 20.5 (18.0, 20.3)	1209/1271 95.1 (93.8, 96.2)	0.688 (0.659, 0.717)
No	1209	62	1271					
Yes	732	189	921					
Totals	1941	251	2192					
Validation Sample	**Recurrent Stroke or Death at One-Year (11.0%)**							
Configurational Analysis Classification	No	Yes	Totals	83/98 84.7 (76.0, 91.2)	320/789 40.6 (37.1, 44.1)	83/552 15.0 (12.2, 18.3)	320/335 95.5 (92.7, 97.5)	0.626 (0.587, 0.666)
No	320	15	335					
Yes	469	83	552					
Totals	789	98	887					
Logistic Regression Classification	No	Yes	Totals	62/98 63.3 (52.9, 72.8)	498/789 63.1 (59.6, 66.5)	62/353 17.6 (13.7, 21.9)	498/534 93.3 (90.8, 95.2)	0.632 (0.581, 0.683)
No	498	36	534					
Yes	291	62	353					
Totals	789	98	887					

Table 4. Modeling Results for Without-Fail Rate

Process of Care	Training Sample *Sample Prevalence: 34.6%*		Validation Sample *Sample Prevalence: 33.7%*	
Configurational Analysis				
Pathway	**Pathway Prevalence**	**Pathway Coverage**	**Pathway Prevalence**	**Pathway Coverage**
High or moderate potency statin *AND* Neurology consult	67.3%	74.7%	64.3%	77.3%
Overall Model Rates	67.3%	74.7%	64.3%	77.3%
Logistic Regression				
	OR (95% CI)	**P-value**	**	
Carotid Artery Imaging	5.0 (3.7, 6.7)	<0.001		
Hypertension Medication Intensification	0.4 (0.3, 0.6)	<0.001		
Hypertension Control	1.5 (1.2, 1.8)	0.001		
Discharged on any Statin	0.7 (0.5, 0.9)	0.002		
High or Moderate Potency Statin	5.9 (4.5, 7.7)	<0.001		
Antithrombotic by Day 2	0.2 (0.2, 0.3)	<0.001		
Neurology Consult	8.3 (6.1, 11.3)	<0.001		
c-statistic	0.842		0.841	

**We did not refit the model in the validation sample, but rather, we use estimates from the training model to estimate the probabilities in the validation model.

Table 5. Test Characteristics of the Logistic Regression and Configuration Models for Without-Fail Rate at One-Year Post-TIA

Training Sample	**Without-Fail Rate (34.6%)**			**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**C-Statistic**
				n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	(95%CI)
Configurational Analysis Classification	No	Yes	Totals	567/759 74.7 (71.5, 77.8)	1157/1433 80.7 (78.6, 82.8)	567/843 67.3 (64.0, 70.4)	1157/1349 85.8 (83.8, 87.6)	0.777 (0.759, 0.796)
No	1157	192	1349					
Yes	276	567	843					
Totals	1433	759	2192					
Logistic Regression Classification	No	Yes	Totals	582/759 76.7 (73.5, 79.6)	1259/1433 87.9 (86.1, 89.5)	582/756 77.0 (73,.8, 79.9)	1259/1436 87.7 (85.9, 89.3)	0.823 (0.805, 0.840)
No	1259	177	1436					
Yes	174	582	756					
Totals	1433	759	2192					
Validation Sample	**Without-Fail Rate (33.7%)**							
Configurational Analysis Classification	No	Yes	Totals	231/299 77.3 (72.1, 81.9)	460/588 78.2 (74.7, 81.5)	231/359 64.3 (59.1, 69.3)	460/528 87.1 (84,0, 89.9)	0.777 (0.748, 0.801)
No	460	68	528					
Yes	128	231	359					
Totals	588	299	887					
Logistic Regression Classification	No	Yes	Totals	240/299 80.3 (75.3, 84.6)	495/588 84.2 (81.0, 87.0)	240/333 72.1 (66.9, 76.8)	495/554 89.4 (86.5, 91.8)	0.822 (0.795, 0.849)
No	495	59	554					
Yes	93	240	333					
Totals	588	299	887					

REFERENCES

1. Yakovchenko V, Miech EJ, Chinman MJ, et al. Strategy Configurations Directly Linked to Higher Hepatitis C Virus Treatment Starts: An Applied Use of Configurational Comparative Methods. *Med Care* 2020;58(5):e31-e38. doi: 10.1097/mlr.0000000000001319 [published Online First: 2020/03/19]
2. Hickman SE, Miech EJ, Stump TE, et al. Identifying the Implementation Conditions Associated With Positive Outcomes in a Successful Nursing Facility Demonstration Project. *The Gerontologist* 2020;60(8):1566-74. doi: 10.1093/geront/gnaa041 [published Online First: 2020/05/23]
3. Palinkas LA, Mendon SJ, Hamilton AB. Innovations in Mixed Methods Evaluations. *Annual review of public health* 2019;40:423-42. doi: 10.1146/annurev-publhealth-040218-044215 [published Online First: 2019/01/12]
4. Harris K, Kneale D, Lasserson TJ, et al. School-based self-management interventions for asthma in children and adolescents: a mixed methods systematic review. *The Cochrane database of systematic reviews* 2019;1(1):Cd011651. doi: 10.1002/14651858.CD011651.pub2 [published Online First: 2019/01/29]
5. Cragun D. Configurational comparative methods. The Handbook on Implementation Science. Cheltenham: Edward Elgar Publishing 2020.
6. Whitaker R, Sperber N, Baumgartner M, et al. Coincidence analysis: a new method for causal inference in implementation science. . *Implementation Science* 2020;15:108.
7. Cragun D, Pal T, Vadaparampil S, et al. Qualitative Comparative Analysis A Hybrid Method for Identifying Factors Associated With Program Effectiveness. *Journal of Mixed Methods Research* 2015
8. Ragin C. The comparative method: moving beyond qualitative and quantitative strategies. Berkeley, CA: University of California Press 1987.
9. Thiem A. Conducting Configurational Comparative Research With Qualitative Comparative Analysis:A Hands-On Tutorial for Applied Evaluation Scholars and Practitioners. *American Journal of Evaluation* 2017;38(3):420-33. doi: 10.1177/1098214016673902
10. del Carmen Giménez-Espert M, Valero-Moreno S, Prado-Gascó V. Evaluation of emotional skills in nursing using regression and QCA models: A transversal study. . *Nurse education today* 2019;74:31-7.
11. Ragin C, Fiss P. Intersectional inequality: University of Chicago Press; 2016.
12. Ragin C, Shulman D, Weinberg A, et al. Complexity, generality, and qualitative comparative analysis. . *Field Methods* 2003;15:323-40.
13. Ebbinghaus B, Visser J. When institutions matter: Union growth and decline in Western Europe, 1950–1995. *European Sociological Review* 1999;15:135-58.
14. Grofman B, Schneider C. An introduction to crisp set QCA, with a comparison to binary logistic regression. *Political Research Quarterly* 2009;62:662-72.
15. Bravata DM, Myers LJ, Perkins AJ, et al. Assessment of the Protocol-Guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) Program for Improving Quality of Care for Transient Ischemic Attack: A Nonrandomized Cluster Trial. *JAMA network open* 2020;3(9):e2015920. doi: 10.1001/jamanetworkopen.2020.15920 [published Online First: 2020/09/09]
16. Shah KH, Metz HA, Edlow JA. Clinical prediction rules to stratify short-term risk of stroke among patients diagnosed in the emergency department with a transient ischemic attack. *Annals of emergency medicine* 2009;53(5):662-73. doi: 10.1016/j.annemergmed.2008.08.004 [published Online First: 2008/10/14]

17. Concato J, Peduzzi P, Holford T, et al. Importance of events per independent variable in proportional hazards analysis I: Background, goals, and general strategy. *J Clin Epideminol* 1995(48):1495-501.
18. Peduzzi P, Concato J, Feinstein A, et al. Importance of events per independent variable in proportional hazards regression analysis II: Accuracy and precision of regression estimates. *J Clin Epideminol* 1995(48):1503-10.
19. Bravata D, Wells C, Lo A, et al. Processes of Care Associated with Acute Stroke Outcomes. *Archives of internal medicine* 2010;170(9):804-10.
20. Bravata DM, Myers LJ, Homoya B, et al. The protocol-guided rapid evaluation of veterans experiencing new transient neurological symptoms (PREVENT) quality improvement program: rationale and methods. *BMC neurology* 2019;19(1):294. doi: 10.1186/s12883-019-1517-x [published Online First: 2019/11/22]
21. Li J, Zhang Y, Myers LJ, et al. Power calculation in stepped-wedge cluster randomized trial with reduced intervention sustainability effect. *J Biopharm Stat* 2019;29(4):663-74. doi: 10.1080/10543406.2019.1633658 [published Online First: 2019/07/19]
22. Development VHSR. VA Informatics and Computing Infrastructure (VINCI), 2008 [Available from: https://www.hsrd.research.va.gov/for_researchers/vinci/default.cfm accessed December 10 2020.
23. VA Informatics and Computing Infrastructure (VINCI). In: Affairs USDoV, ed., 2008.
24. Borzecki AM, Wong AT, Hickey EC, et al. Can we use automated data to assess quality of hypertension care? *The American journal of managed care* 2004;10(7 Pt 2):473-79.
25. Sohn MW, Arnold N, Maynard C, et al. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Population health metrics* 2006;4:2. doi: 10.1186/1478-7954-4-2 [published Online First: 2006/04/12]
26. Man S, Zhao X, Uchino K, et al. Comparison of Acute Ischemic Stroke Care and Outcomes Between Comprehensive Stroke Centers and Primary Stroke Centers in the United States. *Circulation Cardiovascular quality and outcomes* 2018;11(6):e004512. doi: 10.1161/circoutcomes.117.004512 [published Online First: 2018/05/26]
27. Fonarow GC, Reeves MJ, Smith EE, et al. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. *Circulation Cardiovascular quality and outcomes* 2010;3(3):291-302. doi: 10.1161/circoutcomes.109.921858 [published Online First: 2010/02/24]
28. Nolan T, Berwick DM. All-or-none measurement raises the bar on performance. *Jama* 2006;295(10):1168-70. doi: 10.1001/jama.295.10.1168 [published Online First: 2006/03/09]
29. Bravata D, Myers L, Homoya B, et al. The Protocol-Guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) Quality Improvement Program: Rationale and Methods. *BMC neurology* 2019;19(1):294. doi: 10.1186/s12883-019-1517-x.
30. Bravata DM, Myers LJ, Cheng E, et al. Development and Validation of Electronic Quality Measures to Assess Care for Patients With Transient Ischemic Attack and Minor Ischemic Stroke. *Circulation Cardiovascular quality and outcomes* 2017;10(9) doi: 10.1161/circoutcomes.116.003157 [published Online First: 2017/09/16]
31. Bravata D, Myers L, Arling G, et al. The Quality of Care for Veterans with Transient Ischemic Attack and Minor Stroke. *JAMA Neurology* 2018;75(4):419-27. doi: 10.1001/jamaneurol.2017.4648.
32. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2014;45(7):2160-236. doi: 10.1161/str.0000000000000024 [published Online First: 2014/05/03]
33. Smith EE, Saver JL, Alexander DN, et al. Clinical performance measures for adults hospitalized with acute ischemic stroke: performance measures for healthcare professionals from the American

Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2014;45(11):3472-98. doi: 10.1161/str.0000000000000045 [published Online First: 2014/09/27]
34. Bravata DM, Myers LJ, Reeves M, et al. Processes of Care Associated With Risk of Mortality and Recurrent Stroke Among Patients With Transient Ischemic Attack and Nonsevere Ischemic Stroke. *JAMA network open* 2019;2(7):e196716. doi: 10.1001/jamanetworkopen.2019.6716 [published Online First: 2019/07/04]
35. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;54(8):774-81. doi: 10.1016/s0895-4356(01)00341-9 [published Online First: 2001/07/27]
36. CNA: Causal Modeling with Coincidence Analysis. R package version 2.1.1. [program], 2018.
37. Cohen D, Sweeney S, Miller W, et al. Improving smoking and blood pressure outcomes: the interplay between operational changes and local context. *Annals of Family Medicine* 2021;19:240-48.
38. Coury J, Miech EJ, Styer P, et al. What's the "secret sauce"? How implementation variation affects the success of colorectal cancer screening outreach. *Implement Sci Commun* 2021;2(1):5. doi: 10.1186/s43058-020-00104-7 [published Online First: 2021/01/13]
39. Petrik AF, Green B, Schneider J, et al. Factors Influencing Implementation of a Colorectal Cancer Screening Improvement Program in Community Health Centers: an Applied Use of Configurational Comparative Methods. *Journal of general internal medicine* 2020;35(Suppl 2):815-22. doi: 10.1007/s11606-020-06186-2 [published Online First: 2020/10/28]
40. Baumgartner M, Thiem A. Model ambiguities in configurational comparative research. *Sociological Methods & Research* 2017;46(4):954-87.
41. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138(5):1093-100. doi: 10.1378/chest.10-0134 [published Online First: 2010/03/20]
42. Charlson M, Pompei P, Ales K, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987;40:373-83.
43. Knaus W, Wagner D, Draper E, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100:1619-36.
44. Thiem A, Baumgartner M, Bol D. Still Lost in Translation! A correction of three misunderstandings between configurational comparativists and regressional analysts *Comparative Political Studies* 2016;49(6):742-74.
45. Cohen D, Sweeney S, Miller W, et al. Improving Smoking and Blood Pressure Outcomes: The Interplay Between Operational Changes and Local Context. *Annals of Family Medicine* 2021;19 240-48. doi: https://doi.org/10.1370/afm.2668
46. Rattray NA, Miech EJ, True G, et al. Modeling Contingency in Veteran Community Reintegration: A Mixed Methods Approach. *Journal of Mixed Methods Research*;0(0):15586898211059616. doi: 10.1177/15586898211059616
47. Baumgartner M. Qualitative Comparative Analysis and robust sufficiency. *Qual Quant* 2021:1-25. doi: 10.1007/s11135-021-01157-z [published Online First: 2021/06/29]

Supplemental File 1: Processes of Care in the Training and Validation Samples

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Overall	2192	251 (11.4)		759 (34.6)		887	98 (11.0)		299 (33.7)	
Carotid Artery Imaging			<0.001		<0.001			<0.001		<0.001
Fail	563 (25.7)	64 (11.4)		0 (0.0)		204 (23.0)	23 (11.3)		0 (0.0)	
Pass	1553 (70.8)	155 (10.0)		687 (44.2)		655 (73.8)	63 (9.6)		275 (42.0)	
Ineligible	76 (3.5)	32 (42.1)		72 (94.7)		28 (3.2)	12 (42.9)		24 (85.7)	
Hypertension Medication Intensification			0.207		<0.001			0.755		0.005
Fail	363 (16.6)	32 (8.8)		98 (27.0)		152 (17.1)	19 (12.5)		47 (30.9)	
Pass	344 (15.7)	39 (11.3)		86 (25.0)		125 (14.1)	12 (9.6)		28 (22.4)	
Ineligible	1485 (65.7)	180 (12.1)		575 (38.7)		610 (68.8)	67 (11.0)		224 (36.7)	
Hypertension Control			<0.001		<0.001			<0.001		<0.001
Fail	365 (16.6)	31 (8.5)		0 (0.0)		173 (19.5)	11 (6.4)		0 (0.0)	
Pass	1193 (54.4)	99 (8.3)		470 (39.4)		472 (53.2)	42 (8.9)		201 (42.6)	
No Follow-Up BP	295 (13.5)	26 (8.8)		90 (30.5)		127 (14.3)	8 (6.3)		33 (26.0)	
Ineligible	339 (15.5)	95 (28.0)		199 (58.7)		115 (13.0)	37 (32.2)		65 (56.5)	
Discharge on Statin			<0.001		<0.001			<0.001		<0.001
Fail	547 (24.9)	53 (9.7)		83 (15.2)		220 (24.8)	22 (10.0)		26 (11.8)	
Pass	1308 (59.7)	126 (9.6)		525 (40.1)		532 (60.0)	45 (8.5)		216 (40.6)	
Ineligible	337 (15.4)	72 (21.4)		151 (44.8)		135 (15.2)	31 (23.0)		57 (42.2)	
High or Moderate Potency Statin			<0.001		<0.001			0.003		<0.001
Fail	697 (31.8)	61 (8.8)		0 (0.0)		304 (34.3)	30 (9.9)		0 (0.0)	
Pass	1133 (51.7)	120 (10.6)		567 (50.0)		463 (52.2)	43 (9.3)		231 (49.9)	
Ineligible	362 (16.5)	70 (19.3)		192 (53.0)		120 (13.5)	25 (20.8)		68 (56.7)	
Brain Imaging			0.186		<0.001			0.380		<0.001
Fail	86 (3.9)	9 (10.5)		0 (0.0)		40 (4.5)	6 (15.0)		0 (0.0)	
Pass	2062 (94.1)	233 (11.3)		737 (35.7)		830 (93.6)	89 (10.7)		291 (35.1)	
Ineligible	44 (2.0)	9 (20.4)		22 (50.0)		17 (1.9)	3 (17.7)		8 (47.1)	
Telemetry			<0.001		<0.001			0.095		<0.001
Fail	430 (19.6)	30 (7.0)		173 (40.2)		177 (20.0)	13 (7.3)		60 (33.9)	
Pass	773 (35.3)	76 (9.8)		330 (42.7)		337 (38.0)	35 (10.4)		145 (43.0)	
Ineligible	989 (45.1)	145 (14.7)		256 (25.9)		373 (42.0)	50 (13.4)		94 (25.2)	

Supplementary File 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Holter			<0.001		<0.001			<0.001		0.033
Fail	1343 (61.3)	126 (9.4)		396 (29.5)		521 (58.7)	51 (9.8)		158 (30.3)	
Pass	377 (17.2)	26 (6.9)		164 (43.5)		175 (19.7)	10 (5.7)		70 (40.0)	
Ineligible	472 (21.5)	99 (21.0)		199 (42.2)		191 (21.5)	37 (19.4)		71 (37.2)	
Antithrombotic by Day 2			<0.001		<0.001			<0.001		<0.001
Fail	99 (4.5)	11 (11.1)		0 (0.0)		49 (5.5)	6 (12.2)		0 (0.0)	
Pass	1881 (85.8)	188 (10.0)		645 (34.3)		760 (85.7)	71 (9.3)		257 (33.8)	
Ineligible	212 (0.7)	52 (24.5)		114 (53.8)		78 (8.8)	21 (26.9)		42 (53.9)	
Anticoagulation for Atrial Fibrillation			0.047		<0.001			0.505		<0.001
Fail	75 (3.4)	15 (20.0)		0 (0.0)		28 (3.2)	4 (14.3)		0 (0.0)	
Pass	233 (10.6)	30 (12.9)		92 (39.5)		103 (11.6)	14 (13.6)		34 (33.0)	
Ineligible	1884 (86.0)	206 (10.9)		667 (35.4)		756 (85.2)	80 (10.6)		265 (35.1)	
INR for Patients on Warfarin			0.709		0.682			0.649		0.987
Fail	7 (0.3)	1 (14.3)		2 (28.6)		3 (0.3)	0 (0.0)		1 (33.3)	
Pass	108 (5.0)	11 (10.1)		42 (35.8)		52 (5.9)	7 (13.5)		17 (32.7)	
Ineligible	2076 (94.7)	239 (11.5)		715 (34.4)		832 (93.8)	91 (10.9)		281 (33.8)	
HbA1c Measured			0.095		<0.001			0.154		<0.001
Fail	171 (7.8)	18 (10.5)		37 (21.6)		61 (6.9)	9 (14.8)		12 (19.7)	
Pass	797 (36.4)	107 (13.4)		312 (39.2)		307 (34.6)	40 (13.0)		133 (43.3)	
Ineligible	1224 (55.8))	126 (10.3)		410 (33.5)		519 (58.5)	40 (9.4)		154 (29.7)	
Hypoglycemic Medication Intensification			0.981		0.352			0.437		0.036
Fail	103 (4.7)	12 (11.6)		40 (38.8)		60 (6.8)	8 (13.3)		29 (48.3)	
Pass	72 (3.3)	8 (11.1)		29 (40.3)		12 (1.3)	0 (0.0)		5 (41.7)	
Ineligible	2017 (92.0)	231 (11.5)		690 (34.2)		815 (91.9)	90 (11.0)		265 (32.5)	
DVT Prophylaxis			0.811		<0.001			0.672		0.001
Fail	150 (6.8)	15 (10.0)		41 (27.3)		66 (7.4)	9 (13.6)		22 (33.3)	
Pass	814 (37.1)	97 (11.9)		365 (44.8)		321 (36.2)	33 (10.3)		134 (41.7)	
Ineligible	1228 (56.0)	139 (11.3)		353 (28.8)		500 (56.4)	56 (11.2)		143 (28.6)	

Supplementary File 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Rehabilitation Consult			<0.001		<0.001			<0.001		<0.001
Fail	1088 (49.6)	93 (8.6)		273 (25.1)		422 (47.6)	31 (7.4)		105 (24.9)	
Pass	1017 (46.4)	123 (12.1)		409 (40.2)		435 (49.0)	55 (12.6)		169 (38.9)	
Ineligible	87 (4.0)	35 (40.2)		77 (88.5)		30 (3.4)	12 (40.0)		25 (83.3)	
Speech Language Therapy Consult			0.011		<0.001			0.528		<0.001
Fail	1013 (46.2)	99 (9.8)		403 (39.8)		427 (48.1)	42 (9.8)		153 (35.8)	
Pass	487 (22.2)	52 (10.7)		207 (42.5)		205 (23.1)	25 (12.2)		97 (47.3)	
Ineligible	692 (31.6)	100 (14.4)		149 (21.5)		255 (28.8)	31 (12.2)		49 (19.2)	
SATS Referral for Alcohol Use			0.933		0.767			0.201		0.267
Fail	141 (6.4)	17 (12.1)		51 (36.2)		59 (6.7)	9 (15.3)		16 (27.1)	
Pass	15 (0.7)	1 (6.7)		4 (26.7)		4 (0.4)	1 (25.0)		0 (0.0)	
Ineligible	2036 (92.9)	233 (11.4)		704 (34.6)		824 (92.9)	88 (10.7)		283 (34.3)	
Neurology Consult			<0.001		<0.001			<0.001		<0.001
Fail	642 (29.3)	72 (11.2)		0 (0.0)		245 (27.6)	25 (10.2)		0 (0.0)	
Pass	1482 (67.6)	149 (10.1)		694 (46.8)		618 (69.7)	62 (10.0)		278 (45.0)	
Ineligible	68 (3.1)	30 (44.1)		65 (95.6)		24 (2.7)	11 (45.8)		21 (87.5)	

Supplemental File 2: Correlation Matrix

Variable*	History TIA	History Hypertension	NSAID	History Dementia	HASBLED	Age	CCI	APACHE	Current Smoker	Palliative/Hospice	History Stroke
History TIA	1.000	0.292	0.012	0.054	0.120	-0.017	0.115	0.081	0.062	0.044	0.072
P-value		<0.001	0.566	0.011	<0.001	0.419	<0.001	<0.001	0.004	0.040	0.001
History Hypertension		1.000	0.009	0.070	0.282	0.138	0.326	0.215	0.032	0.076	0.112
P-value			0.670	0.001	<0.001	<0.001	<0.001	<0.001	0.137	<0.001	<0.001
NSAID			1.000	-0.061	-0.045	-0.215	-0.076	-0.077	0.085	-0.036	-0.010
P-value				0.005	0.037	<0.001	<0.001	<0.001	<0.001	0.091	0.642
History Dementia				1.000	0.126	0.210	0.164	0.046	-0.030	0.174	0.102
P-value					<0.001	<0.001	<0.001	0.033	0.165	<0.001	<0.001
HASBLED					1.000	0.372	0.523	0.276	-0.008	0.147	0.361
P-value						<0.001	<0.001	<0.001	0.725	<0.001	<0.001
Age						1.000	0.166	0.201	-0.242	0.100	-0.031
P-value							<0.001	<0.001	<0.001	<0.001	0.145
Charlson Comorbidity Index							1.000	0.292	0.047	0.165	0.261
P-value								<0.001	0.027	<0.001	<0.001
APACHE								1.000	-0.104	0.092	0.028
P-value									<0.001	<0.001	0.184
Current Smoker									1.000	0.044	0.067
P-value										0.040	0.002
Palliative/Hospice										1.000	0.094
P-value											<0.001
History Stroke											1.000

*TIA refers to transient ischemic attack; NSAID refers to non-steroidal anti-inflammatory medications; the HASBLED score describes the risk of major bleeding; and the APACHE refers to the Acute Physiology And Chronic Health Evaluation measure of physiologic disease severity.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-12
Bias	9	Describe any efforts to address potential sources of bias	7-12
Study size	10	Explain how the study size was arrived at	7-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12, Suppl File
Outcome data	15*	Report numbers of outcome events or summary measures over time	12, Suppl File

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-20
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-20
Discussion			
Key results	18	Summarise key results with reference to study objectives	21-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23-24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-24
Generalisability	21	Discuss the generalisability (external validity) of the study results	23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Pairing Regression and Configurational Analysis in Health Services Research:Modeling Outcomes in an Observational Cohort Using a Split-Sample Design

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Pairing Regression and Configurational Analysis in Health Services Research: Modeling Outcomes in an Observational Cohort Using a Split-Sample Design

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KEY WORDS configurational analysis, logistic regression, observational cohort, applied methodology

ABSTRACT

Background Configurational methods are increasingly being used in health services research.

Objectives To use configurational analysis and logistic regression within a single dataset to compare results from the two methods.

Design Secondary analysis of an observational cohort; a split-sample design involved randomly dividing patients into training and validation samples.

Participants and Setting Patients with transient ischemic attack (TIA) in US Department of Veterans Affairs hospitals.

Measures The patient outcome was the combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-TIA**.** The quality-of-care outcome was the without-fail rate (proportion of patients who received all processes for which they were eligible, among seven processes).

Results For the recurrent stroke or death outcome, configurational analysis yielded a three-pathway model identifying a set of (validation sample) patients where the prevalence was 15.0% (83/552), substantially higher than the overall prevalence of 11.0% (relative difference, 36%). The configurational model had a sensitivity (coverage) of 84.7% and specificity of 40.6%. The logistic regression model identified six factors associated with the combined endpoint (c-statistic, 0.632; sensitivity, 63.3%; specificity, 63.1%). None of these factors were elements of the configurational model.

For the quality outcome, configurational analysis yielded a single-pathway model identifying a set of (validation sample) patients where the without-fail rate was 64.3% (231/359), nearly twice the overall prevalence (33.7%). The configurational model had a sensitivity (coverage) of 77.3% and specificity of 78.2%. The logistic regression model identified seven factors associated with the without-fail rate (c-statistic, 0.822; sensitivity, 80.3%; specificity, 84.2%). Two of these factors were also identified in the configurational analysis.

Conclusions Configurational analysis and logistic regression represent different methods that can enhance our understanding of a dataset when paired together. Configurational models optimize sensitivity with relatively few conditions. Logistic regression models discriminate cases from controls and provided inferential relationships between outcomes and independent variables.

Strengths and Limitations of this Study

- Logistic regression and configurational methods (CNA) were applied to the same data to examine similarities and differences in results.
- The split-sample approach to development and validation of models is a key methodological strength.
- The results are based on data from the Department of Veterans Affairs and may not generalize to other healthcare systems.

INTRODUCTION

Configurational Comparative Methods (CCMs) have been used in a wide variety of disciplines since at least the 1990s and have recently started to gain traction in the general medical research literature[1-4] as well as within implementation science.[5 6] CCMs draw upon mathematical approaches that are fundamentally different from those used in regression modeling, which is commonly used in health services research. Specifically, CCMs draw upon Boolean algebra and set theory to identify specific combinations of conditions that lead to an outcome of interest as well as determine if multiple solution paths yield the same outcome (i.e., equifinality).[7-9]

Although CCMs and logistic regression offer the potential for synergistic understanding of complex clinical situations, few studies in the medical literature[10] have used both approaches within a single dataset.[11-14] The objective of the current study was to use both CCMs and logistic regression to independently derive and validate two models (one for mortality or recurrent stroke and the other for quality of care) among patients with transient ischemic attack (TIA). Two outcomes were chosen because they provided different methodological challenges. The combined endpoint of death or recurrent stroke is relatively uncommon among TIA patients[15 16] and therefore presented the problem of predicting rare but important events; which may, for example, limit logistic regression modeling due to constraints on the number of outcome events per independent variable.[17 18] The quality of care metric was available for the majority of patients, however few robust predictors of quality at the patient level have been previously identified.[19] In contrast, if a small set of key variables were strongly associated with an outcome, it would be expected that both regression and configurational methods would produce similar findings, limiting the potential insights available from comparing results across methods. Furthermore, if a variable is only weakly associated with an outcome, then the inconsistent relationship between configurations and an outcome could hinder the identification of a solution pathway from configurational methods. Across methods we sought to examine similarities and differences in factor selection (i.e., variables or configurations that were included in the final models) as well as compare sensitivity, specificity, c-statistics, and positive and negative predictive values.

METHODS

This analysis was part of the Protocol-guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) project to improve quality of TIA care in Veterans Health Administration (VA) facilities.[15 20 21] We identified patients with TIA who were cared for in any VA Emergency Department (ED) or inpatient setting based on primary discharge codes for TIA (International Classification of Disease [ICD]-10 G45.0, G45.1, G45.8, G45.9, I67.848) during the period October 2016 and September 2017. The unit of analysis was the TIA patient.

Patient and Public Involvement Statement

This analysis did not include patient or public involvement.

Data Sources

Electronic health record data were obtained from the VA Corporate Data Warehouse (CDW).[22 23] CDW data included: inpatient and outpatient data files (e.g., clinical encounters with associated diagnostic and procedure codes) in the five-years pre-event to identify past medical history,[24] healthcare utilization, and receipt of procedures (Current Procedural Terminology [CPT], Healthcare Common Procedures Coding System [HCPCS], and *ICD*-9 and *ICD*-10 procedure codes). CDW data were also used for vital signs, laboratory data, allergies, imaging, orders, medications and clinical consults. Mortality status was obtained from the VA Vital Status File.[25] Recurrent stroke events were identified using a combination of VA CDW data and fee-basis data (which describes healthcare services that were paid for by the VA but that were obtained by Veterans in non-VA facilities). The study was approved by the human subjects committee at the Indiana University School of Medicine Institutional Review Board and the Richard L. Roudebush VA medical center Research and Development Committee.

Outcomes

The combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-discharge from the index TIA event was the primary patient outcome. Recurrent ischemic stroke events included ED visits or hospitalizations and were identified on the basis of *ICD*-10 codes (I63, I66, I67.89, I97.81, and I97.82).

The quality of care outcome was the "without-fail" rate (also referred to as defect-free[26 27] care), which is an "all-or-none" measure of care quality.[28] It was calculated as the proportion of Veterans with TIA who received all of the processes of care for which they were eligible from among seven processes: brain imaging, carotid artery imaging, neurology consultation, hypertension control, anticoagulation for atrial fibrillation, antithrombotics, and high/moderate potency statins.[29 30] Processes of care were ascertained using electronic health record data using validated algorithms.[30 31] The without-fail rate was based on guideline[32 33] recommended processes of care and has been associated with improved outcomes.[34] Given the all-or-none nature of the without-fail rate, it can be a relatively difficult to change and even small improvements in the absolute rate may reflect substantial changes in practice.[28] For the regression analyses modeling the without-fail rate, quality measures were recoded such that pass=1, not eligible=0, and fail=0 to avoid reducing sample size by eliminating ineligible patients.

Analytic Overview

We analyzed this same dataset with configurational analysis and logistic regression modeling. We randomly divided the overall dataset (n=3079) into a ~70% training sample (2192/3079) and ~30% validation sample (887/3079).[35] The training sample was independently analyzed by a configurational analyst (EJM) and a biostatistician (AJP); this split-sample approach was used to enhance within-method validity. For the combined endpoint of all-cause mortality or recurrent ischemic stroke within one-year post-discharge from the index TIA event, we included both baseline patient characteristics (e.g., age) as well as processes of care (e.g., hypertension control) in the modeling. The without-fail model included only processes of care. Model performance was tested using the validation sample.

Configurational Analysis

Configurational analyses were conducted with Coincidence Analysis–a relatively new approach within the broader family of CCMs[6]–using the R package "CNA."[36]

Definitions

Variables were baseline characteristics of patients (e.g., history of hypertension) which could be expressed with a dichotomous scale or a continuous scale. A configuration is the specific form of conditions (e.g., the history of hypertension was present). Consistency or positive predictive value is the number of cases covered by the solution with the outcome of interest versus all cases covered by the solution. Coverage or sensitivity is the number of cases covered by the solution with the outcome of interest versus all cases with the outcome of interest. Complexity is the number of discrete conditions in a configuration. Ambiguity describes a situation where more than one model generated by the configurational analysis fit the data equally well.

Analytic Steps

We began with a multi-step data reduction approach that has been described previously.[1 2 37-39] Briefly, we used the "minimally sufficient conditions" to examine all 48 candidate factors (e.g., patient characteristics, past medical history, characteristics of the index cerebrovascular event, vital signs, laboratory data, medications, and processes of care) in the analysis with the outcome of interest across all 2192 cases in the training sample and identify bundles of conditions with the strongest connections to the outcome condition. Factors in the analysis that were not already categorical or ordinal were binned; for example, age was categorized into 5-year increments (e.g., 55-59, 60-64, 65-69 years, etc.) We performed this process separately for the two outcomes of interest: mortality or recurrent stroke within one year; and the without-fail rate. When analyzing these combinations of conditions, we considered all 1- and 2- and 3-condition bundles instantiated in the dataset (meaning patients with these specific combinations of configurations were present within the sample) that satisfied the consistency threshold.

We used a dual minimum threshold to identify patient characteristics to use in model iteration: a prevalence threshold of ≥0.145 (via the "consistency" function available in the R "cna" package using multi-value cna) and a coverage score of ≥0.15. These cutoffs were selected to ensure individual configurations were clinically relevant. Specifically, given that the overall outcome rate of death or stroke at one-year post-TIA was (349/3079) 11.3%, a prevalence threshold of ≥0.145 identified configurations with a mortality or stroke rate at least three points higher (i.e., 14.5% vs. 11.3%) in absolute terms than the overall population, or ≥ 25% higher in relative terms. For the without-fail rate, the overall outcome rate was 34.4% (1058/3079) and the prevalence threshold was set at ≥ 50%, a rate that was at least 15 points higher in absolute terms (i.e., 50% vs. 34.4%), or ≥ 40% higher in relative terms. In this sense, the configurational analysis sought to identify distinct “phenotypes” of patients who had substantially different outcome rates (as a group) than the overall sample. The coverage threshold of ≥0.15 ensured that the configurations applied to at least 15% of individuals with the outcome and was used to avoid overfitting.

We next generated a “condition table” to list and organize the output. In a condition table, rows list configurations of conditions that meet a specified prevalence threshold, and column variables include outcome status, condition, consistency, coverage, and complexity. We generated condition tables by specifying a prevalence threshold of 1.0 (i.e., 100%). If we did not find any potential configurations that met our initial dual threshold (i.e., prevalence threshold of 1.0 and a coverage score of ≥ 0.15), we then iteratively lowered the specified prevalence threshold by 0.05 (e.g., from 1.0 to 0.95, etc.) and repeated the process of generating a new condition table. We continued this process until at a given prevalence threshold it was possible to identify at least two potential configurations (or “phenotypes”) of patient characteristics that met the specified prevalence threshold as well as the ≥15% coverage level. Using this approach, we inductively analyzed the training sample and identified a subset of five candidate difference-making factors to use in the subsequent modeling phase.

We next developed candidate models with these five factors by iteratively applying the model-building function within the “cna” software package in R using multi-value cna. We assessed models based on their overall consistency and coverage, as well as potential model ambiguity.[40] We selected a final model based on these same criteria.

Logistic Regression

Multivariable logistic regression was conducted using SAS Enterprise guide v7.11. Models were constructed using forward and backward selection procedures in the HPLOGISTIC procedure using the Schwarz Bayesian Criterion. Patient clinical characteristics as well as processes of care were included in the modeling. Final models for the backward and forward procedure identified the same set of variables for each outcome. To calculate sensitivity and specificity, we chose a cut-point of the estimated probabilities at which the distance between (1,0) and the receiver operating characteristics (ROC) curve was minimized in the ROC diagram for the training sample. We used a predicted probability of 0.096 as the cut-point for the clinical outcome, and 0.490 for the quality of care model. In this way, each patient was dichotomized as yes versus no for risk of the outcome.

Model Comparisons

The sensitivity (coverage), specificity, positive predictive value, negative predictive value and the c-statistic were examined and compared between the methods for both outcomes. For the logistic regression, the first area under the ROC (c-statistic) was calculated with all the variables in the model and used the continuous predicted probability. As described above, for the comparison of the two methods, we used a cut-point on the probability that maximized the sensitivity and specificity. We created a new variable describing the predicted outcome (1 if p > cut-point; 0 otherwise). We then performed logistic regression using only that variable as the independent variable. This variable was also used to calculate sensitivity and specificity. Similarly, for the configurational analysis, we created a predicted outcome variable based on the configurational groupings and use that as the independent variable in the logistic regression to obtain a c-statistic.

RESULTS

The overall sample consisted of 3079 Veterans between the ages of 24 to 99 years (median age, 70 years; interquartile range 64-78) who presented at a VA medical facility with a

TIA between October 2016 and September 2017. The baseline characteristics of the patients within the training and validation samples are provided in Supplemental file 1 and the process of care data are provided in Supplemental file 2. All patients had complete data both for the outcomes and potential explanatory factors, which included specific TIA processes of care as well as risk factors for recurrent stroke or death.

Patient Outcome: Death or Recurrent Stroke at One-Year

Configurational Results

Among the training sample patients, the prevalence of the combined endpoint of death or recurrent stroke at one-year post-TIA was 11.5% (251/2192). Configurational analysis yielded a three-pathway model comprised of five conditions, where the prevalence of death or stroke was 14.5% (193/1330). The configurational analysis identified the following three pathways: (1) having a history of TIA AND a history of hypertension AND not being prescribed a non-steroidal anti-inflammatory drug (NSAID); (2) having a HASBLED score[41] (a measure of bleeding risk) of ≥3; or (3) having a history of dementia (Table 1).

Among patients in the validation sample, the death or stroke rate one-year post-TIA was 11.0% (98/887) overall, and 15.0% (83/552) for patients within the three-pathway configurational model, 36% relatively higher than the overall rate. This performance in the validation sample was better than in the training sample, where the same configurational three-pathway model rate was 26% relatively higher than the overall rate (i.e., 14.5% compared with 11.5%). The configurational model had a coverage (sensitivity) of 84.7% in the validation sample, identifying 83 of 98 patients with the outcome of death or recurrent stroke at one-year; this outperformed the 76.9% coverage score (193/251) in the training sample (Table 1). The configurational model had a specificity of 41.4% in the training sample and 40.6% in the validation sample (Table 2).

Logistic Regression Results

The logistic regression model identified six factors that were associated with the combined endpoint of death or recurrent stroke at one-year post-TIA (Table 1): age, Charlson comorbidity index,[42] the modified APACHE score,[43] current smoking status, palliative care or hospice, and history of stroke. None of these six factors were elements of the configurational model. The c-statistic for the primary model on training sample was 0.747 and 0.691 for the validation sample (Table 1). The c-statistics for logistic models used to calculate sensitivity and specificity (Table 2) were 0.592 for the training sample and 0.688 for the validation sample. The sensitivity was 75.3% in the training sample and 63.3% in the validation sample (Table 2). The specificity was 62.3% in the development sample and 63.1% in the validation sample.

Quality of Care Outcome: the Without-Fail Rate

Configurational Results

Among the training sample patients, the prevalence of the without-fail rate was 34.6%. The configurational analysis (Table 3) yielded a single-pathway model with the conjunct of two processes—discharged on a high or moderate potency statin AND neurology consultation—where the without-fail rate was 67.3% (567/843). The final configurational model included 567 of the 759 patients with the outcome (i.e., 74.7% coverage; Table 3).

Among the validation sample patients, the without-fail rate was 33.7%. When applied to the validation sample, the single-pathway configurational model yielded a without-fail rate of 64.3% (231/359), which was nearly twice the observed prevalence. This model covered 231 of the 299 cases with the outcome (i.e., 77.3% coverage; Table 3). The configurational model had a specificity of 80.7% in the training sample 78.2% in the validation sample (Table 4).

Logistic Regression Results

The logistic regression model identified seven factors that were associated with the without-fail rate: carotid artery imaging, hypertension medication intensification, hypertension control, discharged on statin, discharged on high or moderate potency statin, antithrombotics by hospital day two, and neurology consultation (see Table 3). Two of these factors were also identified in the configurational analysis: discharged on a high or moderate potency statin and neurology consultation. The c-statistics were higher for this model of quality than for the patient outcome model. In the primary model the c-statistic for the training sample was 0.842 and 0.841 in the validation sample (Table 3). In the model used to calculate sensitivity and specificity the c-statistic was 0.823 for the training sample, and 0.822 for the validation sample (Table 4). The sensitivity was 76.7% in the training sample and 80.3% in the validation sample. The specificity was 87.9% in the training sample and 84.2% in the validation sample.

DISCUSSION

This study analyzed one of the largest sample sizes used to date in a published configurational analysis, is one of the first to use a split-sample design featuring training and validation samples, and is also one of the first to directly compare configurational and logistic regression results using identical data. The models developed by applying logistic regression and configurational analysis within the training sample were confirmed when tested against the validation sample. This was true for both the one-year death or recurrent stroke outcome and the without-fail quality-of-care outcome. The results of this study demonstrate that configurational analyses and logistic regression, when applied to the same dataset, can expand our understanding of the data. Key differences in the findings from the two methods as they were applied in the current study included: the focus of optimization; the goal of making stochastic inferences versus empiric insights; and the possibility of conjunctivity.

Logistic regression models include variables to infer the absence and presence of the outcome and maximizes the likelihood for the observed data in a parametrically well-structured model. The configurational models, by contrast, identified “phenotypes” where particular groups of individuals sharing a specific bundle of characteristics had outcome rates substantially different from that of the overall sample. The logistic regression model is useful in making statistical inference for variables’ effects on the binary outcome of interest, though it can be applied to predict the outcome if a cut-off probability threshold is provided. In contrast, the configurational models pinpointed specific combinations of factor values that linked directly to the positive outcome of interest.

An expected pattern in results is that configurational analysis has an advantage over logistic regression in prediction of a dichotomous outcome when prevalence is low. This pattern was evident in the model of recurrent stroke or death at one-year post-TIA (with a prevalence of 11.5% in the development set), where in the validation sample, the sensitivity was higher in the configurational model (84.7% [95%CI: 76.0-91.2%]) than in the logistic regression model (63.3% [95%CI: 52.9-72.8%]). Both approaches had equivalent c-statistics (configurational model, 0.626 [95%CI: 0.587-0.666]; logistic model, 0.632 [0.581-0.683]). However, this advantage may diminish if the prevalence of the outcome is not rare; which was evident in the model using the quality outcome (with a prevalence of in the development set 34.6%), where in the validation sample, the sensitivity was similar in both approaches (configurational model, 77.3% [95%CI: 72.1-81.9%]; logistic model, 80.3% [95%CI: 75.3-84.6%]), and the c-statistics were also similar (configurational model, 0.777 [95%CI; 0.748-0.801]; logistic model, 0.822 [95%CI: 0.795-0.849]).

The models of the one-year recurrent stroke or death rate differed dramatically with no overlap between the factors included in the logistic regression model and the conditions in the configurational model. This observation may be attributed to correlations between variables. For example, the finding that increasing age was negatively correlated with taking NSAIDS (r=-0.215, p<0.0001; Supplemental file 3) may partially account for why age was a variable that was included in the logistic model whereas not taking NSAIDs was a configuration that was included in one of the pathways in the configurational model. In contrast, the models of the without-fail rate were overlapping. The configurational results were more parsimonious. Certainly, the logistic regression models could be further developed if parsimony was particularly of interest.

The configurational results for the quality outcome (Table 3) provide an example of Boolean conjunctivity, where a bundle of conditions that jointly appear together are sufficient for the outcome. Conjunctivity is an attractive characteristic of configurational methods and particularly relevant to studies in health care settings given the inherent complexity within clinical medicine and health services research. In other words, it is expected that for some complex phenomena that it is a combination of conditions—rather than a single factor alone—which can explain the outcome.

As described above, configurational methods differ from regression methods in terms of the underlying mathematical foundations, the focus on configurations of conditions (i.e., factor values) versus variables, and the results output.[44] The use of configurational methods is increasing within health services research in general and in implementation science in particular.[45] The pairing of logistic regression and configurational methods may be particularly fruitful for implementation science for describing difference-making patterns and identifying factors associated with an outcome at a particular site, especially if the outcome is uncommon or when there are few sites. Configurational methods are also increasingly used in mixed methods analyses; given the focus on cases, the persistent link to cases present throughout configurational analysis allows investigators to examine qualitative data from key illustrative cases.[46]

Because regression methods have been widely used in health services research, investigators have experience in applying them and best practices have emerged to address common methodological difficulties. Future research, conducted either on real-world data or in simulations,[47] should compare findings from configurational methods with regression analyses to advance our understanding of how configurational methods will perform in the following situations which are common in healthcare data: (1) the strength of the association between a variable and an outcome depends on the presence of another variable (e.g., if implementation success is related to champion characteristics only in the presence of leadership support for a program); (2) a rare characteristics is robustly associated with an outcome (e.g., patients presenting with coma are at markedly increased risk of mortality, however, coma is an uncommon clinical presentation); (3) variables that are at least modestly associated with an outcome are correlated; (4) missing data especially for factors that are at least modestly associated with an outcome; (5) limited diversity especially for configurations that are related to an outcome (e.g., few older persons included in a dataset where the outcome is mortality); and (6) nested data (e.g., patients within sites). Although regression analyses identify the same variables as being associated with an outcome whether modeling the presence or absence of an outcome, configurational methods sometimes produce different results depending on whether a positive or negative outcome is being modelled.[46] Future research should evaluate situations when this key difference between methods is most pronounced and hence most likely to provide novel insights.

Several limitations of this study should be noted. First, the results are based on data from the Department of Veterans Affairs, and therefore may not generalize to other healthcare systems.

Second, the outcomes used in this study were chosen to provide variation in prevalence rates and associations between variables and outcomes; however future studies could consider datasets with different characteristics (e.g., varying sample sizes).

Third, the process of care variables were originally coded as pass among those eligible, fail among those eligible, and ineligible. However, patients who were not eligible for processes of care were generally the most critically ill patients (e.g., hospice); being not eligible for a process was a strong predictor of mortality. By combining the fail among eligible and ineligible categories in the regression analyses we were able to retain all patients and as expected hospice was associated with the combined endpoint of death or recurrent stroke.

Fourth, to calculate sensitivity and specificity, we chose a cut-point of the estimated probabilities at which the receiver operating characteristics (ROC) curve was minimized; different thresholds could have been used (e.g., to optimize sensitivity). For example, one option would have been to use the observed probabilities as a cut-point. Another approach would have been to use 0.5 which would be unlikely to perform well with rare outcomes. An alternative would have been to target a specific sensitivity (i.e., 80%) in which case we would have used higher cut-points for both outcomes; this approach would have been at the expense of sensitivity. In contrast, we could have targeted a given specificity (i.e., 80%); in which case we would have used a lower predicted probability cut-point and sensitivity would have been reduced.

Fifth, previous work has demonstrated that conjuncts in configurational methods are not synonymous with interactions in regression.[44] We did not systematically explore interactions within the logistic regression modelling.

Finally, we presented an example of how logistic regression and configurational methods could be used on the same data to glean different information. The analytic approaches are fundamentally different; we do not intend to suggest that one method is better than another. Future studies should consider both circumstances where other methods (e.g., decision-tree analysis) can be used with configurational methods, and situations when alternative methods might be used in series rather than in parallel (e.g., for variable selection or for dichotomizing continuous variables).

CONCLUSIONS

Configurational analysis and logistic regression represent fundamentally different analytic methods. Configurational models optimize sensitivity with relatively few conditions and allow for equifinality. Logistic regression models provide inferential relationships between binary outcomes and independent variables as well as clinically useful measures to interpret effects (i.e., odds ratio). Pairing these two diverse approaches offers a major new analytic option to health services researchers interested in leveraging multiple methodological perspectives to explore and model complex phenomena with greater nuance and understanding.

AUTHORS' CONTRIBUTIONS

All authors read and approved the final manuscript. EJM and AJP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DMB: obtained funding and was responsible for the design and conduct of the PREVENT study which is the data source used in the analyses; participated in data analysis conceptualization, interpretation of the results, and drafting and revising the manuscript.

LJM: obtained the PREVENT data which is the data source used in the analyses and participated in data analysis conceptualization

EJM, AJP: planned and executed the data analysis, participated in interpretation of the results, and drafting and revising the manuscript.

YZ, JD: participated in the interpretation of the results and the framing of the manuscript especially with regard to the mathematical and statistical foundations of the methods and the statistical applications of both methods.

JJS: participated in interpretation of results and manuscript editing.

Table 1. Modeling Results for Death or Recurrent Stroke at One-Year Post-TIA

Patient Characteristic or Process of Care	**Training Sample** *Sample Prevalence: 11.5%*		**Validation Sample** *Sample Prevalence: 11.0%*	
Configurational Analysis				
Pathways	**Pathway Prevalence[††]**	**Pathway Coverage**	**Pathway Prevalence**	**Pathway Coverage**
History of TIA *AND* History of Hypertension *AND* Not taking NSAID[†]	14.8%	55.8%	14.2%	57.1%
HAS-BLED[§] score of ≥3	18.5%	54.2%	16.3%	50.0%
History of dementia	21.9%	15.9%	20.0%	17.3%
Overall Model Results	14.5%	76.9%	15.0%	84.7%
Logistic Regression				
	OR (95% CI)	**P-value**	**	
Age	1.03 (1.02, 1.05)	<0.001		
Charlson comorbidity index	1.2 (1.1, 1.2)	<0.001		
APACHE*	1.04 (1.02, 1.06)	<0.001		
Current smoker	1.8 (1.3, 2.4)	<0.001		
Palliative care/hospice	2.9 (1.7, 5.1)	<0.001		
History of stroke	1.8 (1.3, 2.6)	0.001		
c-statistic	0.747		0.691	

*APACHE refers to the Acute Physiology And Chronic Health Evaluation measure of physiologic disease severity.

[†]NSAID refers to non-steroidal anti-inflammatory medications.

[§]The HAS-BLED score describes the risk of major bleeding.

**We did not refit the model in the validation sample, but rather, we use estimates from the training model to estimate the probabilities in the validation model.

[††]Pathway prevalence refers to the outcome rate for the specific combination of configurations.

Table 2. Test Characteristics of the Logistic Regression and Configuration Models for Death or Recurrent Stroke Rate at One-Year Post- TIA

Training Sample	**Recurrent Stroke or Death at One-Year (11.5%)**			**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**C-Statistic**
				n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	(95%CI)
Configurational Analysis Classification	No	Yes	Totals	193/251 76.9 (71.2, 82.0)	804/1941 41.4 (39.2, 43.7)	193/1330 14.5 (12.7, 16.5)	804/862 93.3 (91.4, 94.9)	0.592 (0.563, 0.620)
No	804	58	862					
Yes	1137	193	1330					
Totals	1941	251	2192					
Logistic Regression Classification	No	Yes	Totals	189/251 75.3 (69.5, 80.5)	1209/1941 62.3 (60.1, 64.4)	189/921 20.5 (18.0, 20.3)	1209/1271 95.1 (93.8, 96.2)	0.688 (0.659, 0.717)
No	1209	62	1271					
Yes	732	189	921					
Totals	1941	251	2192					
Validation Sample	**Recurrent Stroke or Death at One-Year (11.0%)**							
Configurational Analysis Classification	No	Yes	Totals	83/98 84.7 (76.0, 91.2)	320/789 40.6 (37.1, 44.1)	83/552 15.0 (12.2, 18.3)	320/335 95.5 (92.7, 97.5)	0.626 (0.587, 0.666)
No	320	15	335					
Yes	469	83	552					
Totals	789	98	887					
Logistic Regression Classification	No	Yes	Totals	62/98 63.3 (52.9, 72.8)	498/789 63.1 (59.6, 66.5)	62/353 17.6 (13.7, 21.9)	498/534 93.3 (90.8, 95.2)	0.632 (0.581, 0.683)
No	498	36	534					
Yes	291	62	353					
Totals	789	98	887					

Table 3. Modeling Results for Without-Fail Rate

Process of Care	**Training Sample** *Sample Prevalence: 34.6%*		**Validation Sample** *Sample Prevalence: 33.7%*	
Configurational Analysis				
Pathway	**Pathway Prevalence**	**Pathway Coverage**	**Pathway Prevalence**	**Pathway Coverage**
High or moderate potency statin *AND* Neurology consult	67.3%	74.7%	64.3%	77.3%
Overall Model Rates	67.3%	74.7%	64.3%	77.3%
Logistic Regression				
	OR (95% CI)	**P-value**		
Carotid Artery Imaging	5.0 (3.7, 6.7)	<0.001		
Hypertension Medication Intensification	0.4 (0.3, 0.6)	<0.001		
Hypertension Control	1.5 (1.2, 1.8)	0.001	**	
Discharged on any Statin	0.7 (0.5, 0.9)	0.002		
High or Moderate Potency Statin	5.9 (4.5, 7.7)	<0.001		
Antithrombotic by Day 2	0.2 (0.2, 0.3)	<0.001		
Neurology Consult	8.3 (6.1, 11.3)	<0.001		
c-statistic	0.842		0.841	

**We did not refit the model in the validation sample, but rather, we use estimates from the training model to estimate the probabilities in the validation model.

Table 4. Test Characteristics of the Logistic Regression and Configuration Models for Without-Fail Rate at One-Year Post-TIA

Training Sample	**Without-Fail Rate (34.6%)**			**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**C-Statistic**
				n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	n/N % (95%CI)	(95%CI)
Configurational Analysis Classification	No	Yes	Totals	567/759 74.7 (71.5, 77.8)	1157/1433 80.7 (78.6, 82.8)	567/843 67.3 (64.0, 70.4)	1157/1349 85.8 (83.8, 87.6)	0.777 (0.759, 0.796)
No	1157	192	1349					
Yes	276	567	843					
Totals	1433	759	2192					
Logistic Regression Classification	No	Yes	Totals	582/759 76.7 (73.5, 79.6)	1259/1433 87.9 (86.1, 89.5)	582/756 77.0 (73,.8, 79.9)	1259/1436 87.7 (85.9, 89.3)	0.823 (0.805, 0.840)
No	1259	177	1436					
Yes	174	582	756					
Totals	1433	759	2192					
Validation Sample	**Without-Fail Rate (33.7%)**							
Configurational Analysis Classification	No	Yes	Totals	231/299 77.3 (72.1, 81.9)	460/588 78.2 (74.7, 81.5)	231/359 64.3 (59.1, 69.3)	460/528 87.1 (84,0, 89.9)	0.777 (0.748, 0.801)
No	460	68	528					
Yes	128	231	359					
Totals	588	299	887					
Logistic Regression Classification	No	Yes	Totals	240/299 80.3 (75.3, 84.6)	495/588 84.2 (81.0, 87.0)	240/333 72.1 (66.9, 76.8)	495/554 89.4 (86.5, 91.8)	0.822 (0.795, 0.849)
No	495	59	554					
Yes	93	240	333					
Totals	588	299	887					

REFERENCES

1. Yakovchenko V, Miech EJ, Chinman MJ, et al. Strategy Configurations Directly Linked to Higher Hepatitis C Virus Treatment Starts: An Applied Use of Configurational Comparative Methods. *Med Care* 2020;58(5):e31-e38. doi: 10.1097/mlr.0000000000001319 [published Online First: 2020/03/19]
2. Hickman SE, Miech EJ, Stump TE, et al. Identifying the Implementation Conditions Associated With Positive Outcomes in a Successful Nursing Facility Demonstration Project. *The Gerontologist* 2020;60(8):1566-74. doi: 10.1093/geront/gnaa041 [published Online First: 2020/05/23]
3. Palinkas LA, Mendon SJ, Hamilton AB. Innovations in Mixed Methods Evaluations. *Annual review of public health* 2019;40:423-42. doi: 10.1146/annurev-publhealth-040218-044215 [published Online First: 2019/01/12]
4. Harris K, Kneale D, Lasserson TJ, et al. School-based self-management interventions for asthma in children and adolescents: a mixed methods systematic review. *The Cochrane database of systematic reviews* 2019;1(1):Cd011651. doi: 10.1002/14651858.CD011651.pub2 [published Online First: 2019/01/29]
5. Cragun D. Configurational comparative methods. The Handbook on Implementation Science. Cheltenham: Edward Elgar Publishing 2020.
6. Whitaker R, Sperber N, Baumgartner M, et al. Coincidence analysis: a new method for causal inference in implementation science. . *Implementation Science* 2020;15:108.
7. Cragun D, Pal T, Vadaparampil S, et al. Qualitative Comparative Analysis A Hybrid Method for Identifying Factors Associated With Program Effectiveness. *Journal of Mixed Methods Research* 2015
8. Ragin C. The comparative method: moving beyond qualitative and quantitative strategies. Berkeley, CA: University of California Press 1987.
9. Thiem A. Conducting Configurational Comparative Research With Qualitative Comparative Analysis:A Hands-On Tutorial for Applied Evaluation Scholars and Practitioners. *American Journal of Evaluation* 2017;38(3):420-33. doi: 10.1177/1098214016673902
10. del Carmen Giménez-Espert M, Valero-Moreno S, Prado-Gascó V. Evaluation of emotional skills in nursing using regression and QCA models: A transversal study. . *Nurse education today* 2019;74:31-7.
11. Ragin C, Fiss P. Intersectional inequality: University of Chicago Press; 2016.
12. Ragin C, Shulman D, Weinberg A, et al. Complexity, generality, and qualitative comparative analysis. . *Field Methods* 2003;15:323-40.
13. Ebbinghaus B, Visser J. When institutions matter: Union growth and decline in Western Europe, 1950–1995. *European Sociological Review* 1999;15:135-58.
14. Grofman B, Schneider C. An introduction to crisp set QCA, with a comparison to binary logistic regression. *Political Research Quarterly* 2009;62:662-72.
15. Bravata DM, Myers LJ, Perkins AJ, et al. Assessment of the Protocol-Guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) Program for Improving Quality of Care for Transient Ischemic Attack: A Nonrandomized Cluster Trial. *JAMA network open* 2020;3(9):e2015920. doi: 10.1001/jamanetworkopen.2020.15920 [published Online First: 2020/09/09]
16. Shah KH, Metz HA, Edlow JA. Clinical prediction rules to stratify short-term risk of stroke among patients diagnosed in the emergency department with a transient ischemic attack. *Annals of emergency medicine* 2009;53(5):662-73. doi: 10.1016/j.annemergmed.2008.08.004 [published Online First: 2008/10/14]

17. Concato J, Peduzzi P, Holford T, et al. Importance of events per independent variable in proportional hazards analysis I: Background, goals, and general strategy. *J Clin Epideminol* 1995(48):1495-501.
18. Peduzzi P, Concato J, Feinstein A, et al. Importance of events per independent variable in proportional hazards regression analysis II: Accuracy and precision of regression estimates. *J Clin Epideminol* 1995(48):1503-10.
19. Bravata D, Wells C, Lo A, et al. Processes of Care Associated with Acute Stroke Outcomes. *Archives of internal medicine* 2010;170(9):804-10.
20. Bravata DM, Myers LJ, Homoya B, et al. The protocol-guided rapid evaluation of veterans experiencing new transient neurological symptoms (PREVENT) quality improvement program: rationale and methods. *BMC neurology* 2019;19(1):294. doi: 10.1186/s12883-019-1517-x [published Online First: 2019/11/22]
21. Li J, Zhang Y, Myers LJ, et al. Power calculation in stepped-wedge cluster randomized trial with reduced intervention sustainability effect. *J Biopharm Stat* 2019;29(4):663-74. doi: 10.1080/10543406.2019.1633658 [published Online First: 2019/07/19]
22. Development VHSR. VA Informatics and Computing Infrastructure (VINCI), 2008 [Available from: https://www.hsrd.research.va.gov/for_researchers/vinci/default.cfm accessed December 10 2020.
23. VA Informatics and Computing Infrastructure (VINCI). In: Affairs USDoV, ed., 2008.
24. Borzecki AM, Wong AT, Hickey EC, et al. Can we use automated data to assess quality of hypertension care? *The American journal of managed care* 2004;10(7 Pt 2):473-79.
25. Sohn MW, Arnold N, Maynard C, et al. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Population health metrics* 2006;4:2. doi: 10.1186/1478-7954-4-2 [published Online First: 2006/04/12]
26. Man S, Zhao X, Uchino K, et al. Comparison of Acute Ischemic Stroke Care and Outcomes Between Comprehensive Stroke Centers and Primary Stroke Centers in the United States. *Circulation Cardiovascular quality and outcomes* 2018;11(6):e004512. doi: 10.1161/circoutcomes.117.004512 [published Online First: 2018/05/26]
27. Fonarow GC, Reeves MJ, Smith EE, et al. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. *Circulation Cardiovascular quality and outcomes* 2010;3(3):291-302. doi: 10.1161/circoutcomes.109.921858 [published Online First: 2010/02/24]
28. Nolan T, Berwick DM. All-or-none measurement raises the bar on performance. *Jama* 2006;295(10):1168-70. doi: 10.1001/jama.295.10.1168 [published Online First: 2006/03/09]
29. Bravata D, Myers L, Homoya B, et al. The Protocol-Guided Rapid Evaluation of Veterans Experiencing New Transient Neurological Symptoms (PREVENT) Quality Improvement Program: Rationale and Methods. *BMC neurology* 2019;19(1):294. doi: 10.1186/s12883-019-1517-x.
30. Bravata DM, Myers LJ, Cheng E, et al. Development and Validation of Electronic Quality Measures to Assess Care for Patients With Transient Ischemic Attack and Minor Ischemic Stroke. *Circulation Cardiovascular quality and outcomes* 2017;10(9) doi: 10.1161/circoutcomes.116.003157 [published Online First: 2017/09/16]
31. Bravata D, Myers L, Arling G, et al. The Quality of Care for Veterans with Transient Ischemic Attack and Minor Stroke. *JAMA Neurology* 2018;75(4):419-27. doi: 10.1001/jamaneurol.2017.4648.
32. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2014;45(7):2160-236. doi: 10.1161/str.0000000000000024 [published Online First: 2014/05/03]
33. Smith EE, Saver JL, Alexander DN, et al. Clinical performance measures for adults hospitalized with acute ischemic stroke: performance measures for healthcare professionals from the American

Heart Association/American Stroke Association. *Stroke; a journal of cerebral circulation* 2014;45(11):3472-98. doi: 10.1161/str.0000000000000045 [published Online First: 2014/09/27]

34. Bravata DM, Myers LJ, Reeves M, et al. Processes of Care Associated With Risk of Mortality and Recurrent Stroke Among Patients With Transient Ischemic Attack and Nonsevere Ischemic Stroke. *JAMA network open* 2019;2(7):e196716. doi: 10.1001/jamanetworkopen.2019.6716 [published Online First: 2019/07/04]
35. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;54(8):774-81. doi: 10.1016/s0895-4356(01)00341-9 [published Online First: 2001/07/27]
36. CNA: Causal Modeling with Coincidence Analysis. R package version 2.1.1. [program], 2018.
37. Cohen D, Sweeney S, Miller W, et al. Improving smoking and blood pressure outcomes: the interplay between operational changes and local context. *Annals of Family Medicine* 2021;19:240-48.
38. Coury J, Miech EJ, Styer P, et al. What's the "secret sauce"? How implementation variation affects the success of colorectal cancer screening outreach. *Implement Sci Commun* 2021;2(1):5. doi: 10.1186/s43058-020-00104-7 [published Online First: 2021/01/13]
39. Petrik AF, Green B, Schneider J, et al. Factors Influencing Implementation of a Colorectal Cancer Screening Improvement Program in Community Health Centers: an Applied Use of Configurational Comparative Methods. *Journal of general internal medicine* 2020;35(Suppl 2):815-22. doi: 10.1007/s11606-020-06186-2 [published Online First: 2020/10/28]
40. Baumgartner M, Thiem A. Model ambiguities in configurational comparative research. *Sociological Methods & Research* 2017;46(4):954-87.
41. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138(5):1093-100. doi: 10.1378/chest.10-0134 [published Online First: 2010/03/20]
42. Charlson M, Pompei P, Ales K, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases* 1987;40:373-83.
43. Knaus W, Wagner D, Draper E, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991;100:1619-36.
44. Thiem A, Baumgartner M, Bol D. Still Lost in Translation! A correction of three misunderstandings between configurational comparativists and regressional analysts *Comparative Political Studies* 2016;49(6):742-74.
45. Cohen D, Sweeney S, Miller W, et al. Improving Smoking and Blood Pressure Outcomes: The Interplay Between Operational Changes and Local Context. *Annals of Family Medicine* 2021;19 240-48. doi: https://doi.org/10.1370/afm.2668
46. Rattray NA, Miech EJ, True G, et al. Modeling Contingency in Veteran Community Reintegration: A Mixed Methods Approach. *Journal of Mixed Methods Research*;0(0):15586898211059616. doi: 10.1177/15586898211059616
47. Baumgartner M. Qualitative Comparative Analysis and robust sufficiency. *Qual Quant* 2021:1-25. doi: 10.1007/s11135-021-01157-z [published Online First: 2021/06/29]

Supplemental File 1. Baseline Characteristics of the Training and Validation Samples

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Overall	2192	251 (11.4)		759 (34.6)		887	98 (11.0)		299 (33.7)	
Current Smoker			0.004		0.003			0.558		0.435
No	1593 (72.7)	163 (10.2)		521 (32.7)		627 (70.7)	72 (11.5)		206 (32.8)	
Yes	599 (27.3)	88 (14.7)		238 (39.7)		260 (29.3)	26 (10.0)		93 (35.8)	
Palliative or Hospice Care			<0.001		<0.001			<0.001		<0.001
No	2124 (96.9)	221 (10.4)		694 (32.7)		863 (97.3)	87 (10.1)		278 (32.2)	
Yes	68 (3.1)	30 (44.1)		65 (95.6)		24 (2.7)	11 (45.8)		21 (87.5)	
Diabetes			<0.001		<0.001			0.004		<0.001
No	1255 (57.2)	116 (9.2)		393 (31.1)		528 (59.5)	45 (8.5)		144 (27.3)	
Yes	937 (42.8)	135 (14.4)		366 (39.1)		359 (40.5)	53 (14.8)		155 (43.2)	
Atrial Fibrillation			<0.001		0.146			0.088		0.851
No	1834 (83.7)	184 (10.0)		623 (34.0)		735 (82.9)	75 (10.2)		249 (33.9)	
Yes	358 (16.3)	67 (18.7)		136 (38.0)		152 (17.1)	23 (15.1)		50 (32.9)	
Myocardial Infarction			0.009		<0.001			0.301		0.174
No	2032 (92.7)	222 (10.9)		679 (33.4)		822 (92.8)	88 (10.7)		272 (33.1)	
Yes	160 (7.3)	29 (18.1)		80 (50.0)		65 (7.3)	10 (15.4)		27 (41.5)	
TIA*			0.156		<0.001			0.219		<0.001
No	738 (33.7)	74 (10.0)		151 (20.5)		314 (35.4)	29 (9.2)		69 (22.0)	
Yes	1454 (66.3)	177 (12.2)		608 (41.8)		573 (64.6)	69 (12.0)		230 (40.1)	
Stroke			<0.001		<0.001			0.010		0.013
No	1903 (86.8)	188 (9.9)		631 (33.2)		788 (88.8)	79 (10.0)		254 (32.2)	
Yes	289 (13.2)	63 (21.8)		128 (44.3)		99 (11.2)	19 (19.2)		45 (45.4)	
CHF*			<0.001		<0.001			0.038		0.005
No	1860 (84.8)	182 (9.8)		613 (33.0)		747 (84.2)	75 (10.0)		237 (31.7)	
Yes	332 (15.2)	69 (20.8)		146 (44.0)		140 (15.8)	23 (16.4)		62 (44.3)	
COPD*			<0.001		0.785			0.600		0.012
No	1723 (78.6)	175 (10.2)		594 (34.5)		699 (78.8)	75 (10.7)		221 (31.6)	
Yes	469 (21.4)	76 (16.2)		165 (35.2)		188 (21.2)	23 (12.2)		78 (41.5)	

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Supplemental File 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
PVD*			<0.001		<0.001			0.017		0.001
No	1867 (85.2)	187 (10.0)		611 (32.7)		749 (84.4)	74 (9.9)		235 (31.4)	
Yes	64 (19.8)	64 (19.7)		148 (45.5)		138 (15.6)	23 (17.4)		64 (46.4)	
Dementia			<0.001		0.685			0.010		0.071
No	2009 (91.6)	211 (10.5)		693 (34.5)		802 (90.4)	81 (10.1)		278 (34.7)	
Yes	183 (8.4)	40 (21.9)		66 (36.1)		85 (9.6)	17 (20.0)		21 (24.7)	
Chronic Kidney Disease			<0.001		<0.001			0.004		0.007
No	1794 (81.8)	180 (10.0)		586 (32.7)		732 (82.5)	70 (9.6)		232 (31.7)	
Yes	398 (18.2)	71 (17.8)		173 (43.5)		155 (17.5)	28 (18.1)		67 (43.2)	
Cancer			<0.001		0.094			0.178		1.00
No	1958 (89.3)	199 (10.2)		666 (34.0)		787 (88.7)	83 (10.6)		265 (33.7)	
Yes	234 (10.7)	52 (22.2)		93 (39.7)		100 (11.3)	15 (15.0)		34 (34.0)	
Hypertension			<0.001		<0.001			0.006		<0.001
No	528 (24.1)	33 (6.2)		125 (23.7)		215 (24.2)	13 (6.0)		46 (21.4)	
Yes	1664 (75.9)	218 (13.1)		634 (38.1)		672 (75.8)	85 (12.7)		253 (37.6)	
Renal Disease			<0.001		<0.001			0.006		0.008
No	1802 (82.2)	182 (10.1)		590 (32.7)		737 (83.1)	71 (9.6)		234 (31.8)	
Yes	390 (17.8)	69 (17.7)		169 (43.3)		150 (16.9)	27 (18.0)		65 (43.3)	
Hyperlipidemia			0.003		<0.001			0.739		<0.001
No	816 (37.2)	72 (8.8)		213 (26.1)		325 (36.6)	34 (10.5)		76 (23.4)	
Yes	1376 (62.8)	179 (13.0)		546 (39.7)		562 (63.4)	64 (11.4)		223 (39.7)	
Arrhythmia			0.001		0.421			0.114		0.035
No	1910 (87.1)	201 (10.5)		655 (34.3)		770 (86.8)	80 (10.4)		249 (32.3)	
Yes	282 (12.9)	50 (17.7)		104 (36.9)		117 (13.2)	18 (15.4)		50 (42.7)	
Sleep Apnea			0.608		0.058			0.669		0.014
No	1779 (81.2)	207 (11.6)		599 (33.7)		737 (83.1)	80 (10.8)		235 (31.9)	
Yes	413 (18.8)	44 (10.7)		160 (38.7)		150 (16.9)	18 (12.0)		64 (42.7)	
Alcohol Abuse			0.591		0.858			0.021		0.220
No	2045 (93.3)	232 (11.3)		707 (34.6)		823 (92.8)	85 (10.3)		282 (34.3)	
Yes	147 (6.7)	19 (12.9)		52 (35.4)		64 (7.2)	13 (20.3)		17 (26.6)	

Supplemental File 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Depression			0.577		0.240			0.308		0.613
No	1690 (77.1)	190 (11.2)		574 (34.0)		683 (77.0)	80 (11.7)		227 (33.2)	
Yes	502 (22.9)	61 (12.2)		185 (36.8)		204 (23.0)	18 (8.8)		72 (35.3)	
Liver Disease			0.088		0.705			0.492		0.763
No	2062 (94.1)	230 (11.2)		712 (34.5)		836 (94.2)	91 (10.9)		283 (33.8)	
Yes	130 (5.9)	21 (16.2)		47 (36.2)		51 (5.8)	7 (13.7)		16 (31.4)	
Cirrhosis			0.002		0.417			0.060		0.094
No	2150 (98.1)	239 (11.1)		742 (34.5)		867 (97.8)	93 (10.7)		296 (34.1)	
Yes	42 (1.9)	12 (28.6)		17 (40.5)		20 (2.2)	5 (25.0)		3 (15.0)	
Migraines			0.571		0.315			0.511		0.287
No	2120 (96.7)	245 (11.6)		730 (34.4)		862 (97.2)	97 (11.2)		288 (33.4)	
Yes	72 (3.3)	6 (8.3)		29 (40.3)		25 (2.8)	1 (4.0)		11 (44.0)	
Bleeding			0.052		0.154			1.000		1.000
No	2179 (99.4)	247 (11.3)		752 (34.5)		883 (99.6)	98 (11.1)		298 (33.8)	
Yes	13 (0.6)	4 (30.8)		8 (53.8)		4 (0.4)	0 (0.0)		1 (25.0)	
Intracranial Hemorrhage			<0.001		0.221			0.185		0.118
No	2080 (94.9)	225 (10.8)		714 (34.3)		848 (95.6)	91 (10.7)		281 (33.1)	
Yes	112 (5.1)	26 (23.2)		45 (40.2)		39 (4.4)	7 (18.0)		18 (46.2)	
Dialysis			0.226		0.311			0.001		0.128
No	2165 (98.8)	246 (11.4)		747 (34.5)		879 (99.1)	93 (10.6)		294 (33.4)	
Yes	27 (1.2)	5 (18.5)		12 (44.4)		8 (0.9)	5 (62.5)		5 (62.5)	
Pacemaker			0.129		<0.001			0.481		0.160
No	1957 (89.3)	217 (11.1)		652 (33.3)		796 (89.7)	86 (10.8)		262 (32.9)	
Yes	235 (10.7)	34 (14.5)		107 (45.5)		91 (10.3)	12 (13.2)		37 (40.7)	
Valvular Disease			0.099		0.311			0.143		0.496
No	2053 (93.7)	229 (11.2)		705 (34.3)		823 (92.8)	87 (10.6)		275 (33.4)	
Yes	139 (6.3)	22 (15.8)		54 (38.8)		64 (7.2)	11 (17.2)		24 (37.5)	
Venous Thromboembolism			0.102		0.118			0.376		0.337
No	2113 (96.4)	237 (11.2)		725 (34.3)		856 (96.5)	93 (10.9)		286 (33.4)	
Yes	79 (3.6)	14 (17.7)		34 (43.0)		31 (3.5)	5 (16.1)		13 (41.9)	

Supplemental File 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Carotid endarterectomy or stent			1.000		0.061			0.011		0.068
No	2172 (99.1)	249 (11.5)		748 (34.4)		878 (99.0)	94 (10.7)		293 (33.4)	
Yes	20 (0.9)	2 (10.0)		11 (55.0)		9 (1.0)	4 (44.4)		6 (66.7)	
CABG/PTCA*			0.687		0.414			0.506		0.411
No	2177 (99.3)	249 (11.4)		752 (34.5)		881 (99.3)	97 (11.0)		296 (33.6)	
Yes	15 (0.7)	2 (13.3)		7 (46.7)		6 (0.7)	1 (16.7)		3 (50.0)	
Pancreatitis			0.057		1.000			1.000		0.342
No	2173 (99.1)	246 (11.3)		753 (34.6)		882 (99.4)	98 (11.1)		296 (33.6)	
Yes	19 (0.9)	5 (26.3)		6 (31.6)		5 (0.6)	0 (0.0)		3 (60.0)	
Hemiplegia			0.293		<0.001			0.227		0.086
No	1876 (85.6)	209 (11.1)		611 (32.6)		759 (85.6)	80 (10.5)		247 (32.5)	
Yes	316 (14.4)	42 (13.3)		148 (46.8)		128 (14.4)	18 (14.1)		52 (40.6)	
Speech Deficit			0.424		0.200			0.298		0.293
No	2091 (95.4)	237 (11.3)		718 (34.3)		849 (95.7)	92 (10.8)		283 (33.3)	
Yes	101 (4.6)	14 (13.9)		31 (40.6)		38 (4.3)	6 (15.8)		16 (42.1)	
Syncope			0.711		0.345			0.033		0.240
No	1568 (71.5)	177 (11.3)		533 (34.0)		631 (71.1)	79 (12.5)		205 (32.5)	
Yes	624 (28.5)	74 (11.9)		226 (36.2)		256 (28.9)	19 (7.4)		94 (36.7)	
Amaurosis Fugax			0.876		0.044			1.000		0.102
No	2088 (95.3)	240 (11.5)		713 (34.2)		843 (95.0)	93 (11.0)		279 (33.1)	
Yes	104 (4.7)	11 (10.6)		46 (44.2)		44 (5.0)	5 (11.4)		20 (45.4)	
Concomitant MI*			0.231		0.056			0.346		0.056
No	2147 (98.0)	243 (11.3)		737 (34.3)		862 (97.2)	94 (10.9)		286 (33.2)	
Yes	45 (2.0)	8 (17.8)		22 (48.9)		25 (2.8)	4 (16.0)		13 (52.0)	
Concomitant CHF*			<0.001		0.228			0.309		0.007
No	2154 (98.3)	238 (11.0)		742 (34.4)		864 (97.4)	94 (10.9)		285 (33.0)	
Yes	38 (1.7)	13 (34.2)		17 (44.7)		23 (2.6)	4 (17.4)		14 (60.9)	
Aspirin			0.207		<0.001			0.801		<0.001
No	521 (23.8)	68 (13.0)		138 (26.5)		208 (23.4)	24 (11.5)		45 (21.6)	
Yes	1671 (76.2)	183 (11.0)		621 (37.2)		679 (76.6)	74 (10.9)		254 (37.4)	

Supplemental File 1. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Warfarin			0.091		0.020			0.066		0.375
No	1941 (88.6)	214 (11.0)		655 (33.8)		784 (88.4)	81 (10.3)		260 (33.2)	
Yes	251 (11.4)	37 (14.7)		104 (41.4)		103 (11.6)	17 (16.5)		39 (37.9)	
Statin			0.793		<0.001			0.404		<0.001
No	393 (17.9)	43 (10.9)		51 (13.0)		161 (18.2)	21 (13.0)		17 (10.6)	
Yes	1799 (82.1)	208 (11.6)		708 (39.4)		726 (81.8)	77 (10.6)		282 (38.8)	
Antihypertensive			<0.001		0.006			0.037		0.006
No	351 (16.0)	20 (5.7)		99 (28.2)		137 (15.4)	8 (5.8)		32 (23.4)	
Yes	1841 (84.0)	231 (12.6)		660 (35.8)		750 (84.6)	90 (12.0)		267 (35.6)	
NSAID			0.009		0.395			0.040		0.446
No	1683 (76.8)	209 (12.4)		591 (35.1)		686 (77.3)	84 (12.2)		236 (34.4)	
Yes	509 (23.2)	42 (8.2)		168 (33.0)		201 (22.7)	14 (7.0)		63 (31.3)	
Clopidogrel			0.028		0.006			0.810		0.003
No	1541 (70.3)	161 (10.4)		505 (32.8)		644 (72.6)	70 (10.9)		198 (30.8)	
Yes	651 (29.7)	90 (13.8)		254 (39.0)		243 (27.4)	28 (11.5)		101 (41.6)	

*TIA refers to transient ischemic attack; CHF to congestive heart failure; COPD to chronic obstructive pulmonary disease; PVD to peripheral vascular disease; CABG/PTCA to coronary artery bypass grafting or percutaneous transluminal coronary angioplasty; MI to myocardial infarction; and concomitant disease indicates conditions that were present at the time of the index transient ischemic attack.

Supplemental File 2: Processes of Care in the Training and Validation Samples

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Overall	2192	251 (11.4)		759 (34.6)		887	98 (11.0)		299 (33.7)	
Carotid Artery Imaging			<0.001		<0.001			<0.001		<0.001
Fail	563 (25.7)	64 (11.4)		0 (0.0)		204 (23.0)	23 (11.3)		0 (0.0)	
Pass	1553 (70.8)	155 (10.0)		687 (44.2)		655 (73.8)	63 (9.6)		275 (42.0)	
Ineligible	76 (3.5)	32 (42.1)		72 (94.7)		28 (3.2)	12 (42.9)		24 (85.7)	
Hypertension Medication Intensification			0.207		<0.001			0.755		0.005
Fail	363 (16.6)	32 (8.8)		98 (27.0)		152 (17.1)	19 (12.5)		47 (30.9)	
Pass	344 (15.7)	39 (11.3)		86 (25.0)		125 (14.1)	12 (9.6)		28 (22.4)	
Ineligible	1485 (65.7)	180 (12.1)		575 (38.7)		610 (68.8)	67 (11.0)		224 (36.7)	
Hypertension Control			<0.001		<0.001			<0.001		<0.001
Fail	365 (16.6)	31 (8.5)		0 (0.0)		173 (19.5)	11 (6.4)		0 (0.0)	
Pass	1193 (54.4)	99 (8.3)		470 (39.4)		472 (53.2)	42 (8.9)		201 (42.6)	
No Follow-Up BP	295 (13.5)	26 (8.8)		90 (30.5)		127 (14.3)	8 (6.3)		33 (26.0)	
Ineligible	339 (15.5)	95 (28.0)		199 (58.7)		115 (13.0)	37 (32.2)		65 (56.5)	
Discharge on Statin			<0.001		<0.001			<0.001		<0.001
Fail	547 (24.9)	53 (9.7)		83 (15.2)		220 (24.8)	22 (10.0)		26 (11.8)	
Pass	1308 (59.7)	126 (9.6)		525 (40.1)		532 (60.0)	45 (8.5)		216 (40.6)	
Ineligible	337 (15.4)	72 (21.4)		151 (44.8)		135 (15.2)	31 (23.0)		57 (42.2)	
High or Moderate Potency Statin			<0.001		<0.001			0.003		<0.001
Fail	697 (31.8)	61 (8.8)		0 (0.0)		304 (34.3)	30 (9.9)		0 (0.0)	
Pass	1133 (51.7)	120 (10.6)		567 (50.0)		463 (52.2)	43 (9.3)		231 (49.9)	
Ineligible	362 (16.5)	70 (19.3)		192 (53.0)		120 (13.5)	25 (20.8)		68 (56.7)	
Brain Imaging			0.186		<0.001			0.380		<0.001
Fail	86 (3.9)	9 (10.5)		0 (0.0)		40 (4.5)	6 (15.0)		0 (0.0)	
Pass	2062 (94.1)	233 (11.3)		737 (35.7)		830 (93.6)	89 (10.7)		291 (35.1)	
Ineligible	44 (2.0)	9 (20.4)		22 (50.0)		17 (1.9)	3 (17.7)		8 (47.1)	
Telemetry			<0.001		<0.001			0.095		<0.001
Fail	430 (19.6)	30 (7.0)		173 (40.2)		177 (20.0)	13 (7.3)		60 (33.9)	
Pass	773 (35.3)	76 (9.8)		330 (42.7)		337 (38.0)	35 (10.4)		145 (43.0)	
Ineligible	989 (45.1)	145 (14.7)		256 (25.9)		373 (42.0)	50 (13.4)		94 (25.2)	

Supplementary File 2. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Holter			<0.001		<0.001			<0.001		0.033
Fail	1343 (61.3)	126 (9.4)		396 (29.5)		521 (58.7)	51 (9.8)		158 (30.3)	
Pass	377 (17.2)	26 (6.9)		164 (43.5)		175 (19.7)	10 (5.7)		70 (40.0)	
Ineligible	472 (21.5)	99 (21.0)		199 (42.2)		191 (21.5)	37 (19.4)		71 (37.2)	
Antithrombotic by Day 2			<0.001		<0.001			<0.001		<0.001
Fail	99 (4.5)	11 (11.1)		0 (0.0)		49 (5.5)	6 (12.2)		0 (0.0)	
Pass	1881 (85.8)	188 (10.0)		645 (34.3)		760 (85.7)	71 (9.3)		257 (33.8)	
Ineligible	212 (0.7)	52 (24.5)		114 (53.8)		78 (8.8)	21 (26.9)		42 (53.9)	
Anticoagulation for Atrial Fibrillation			0.047		<0.001			0.505		<0.001
Fail	75 (3.4)	15 (20.0)		0 (0.0)		28 (3.2)	4 (14.3)		0 (0.0)	
Pass	233 (10.6)	30 (12.9)		92 (39.5)		103 (11.6)	14 (13.6)		34 (33.0)	
Ineligible	1884 (86.0)	206 (10.9)		667 (35.4)		756 (85.2)	80 (10.6)		265 (35.1)	
INR for Patients on Warfarin			0.709		0.682			0.649		0.987
Fail	7 (0.3)	1 (14.3)		2 (28.6)		3 (0.3)	0 (0.0)		1 (33.3)	
Pass	108 (5.0)	11 (10.1)		42 (35.8)		52 (5.9)	7 (13.5)		17 (32.7)	
Ineligible	2076 (94.7)	239 (11.5)		715 (34.4)		832 (93.8)	91 (10.9)		281 (33.8)	
HbA1c Measured			0.095		<0.001			0.154		<0.001
Fail	171 (7.8)	18 (10.5)		37 (21.6)		61 (6.9)	9 (14.8)		12 (19.7)	
Pass	797 (36.4)	107 (13.4)		312 (39.2)		307 (34.6)	40 (13.0)		133 (43.3)	
Ineligible	1224 (55.8))	126 (10.3)		410 (33.5)		519 (58.5)	40 (9.4)		154 (29.7)	
Hypoglycemic Medication Intensification			0.981		0.352			0.437		0.036
Fail	103 (4.7)	12 (11.6)		40 (38.8)		60 (6.8)	8 (13.3)		29 (48.3)	
Pass	72 (3.3)	8 (11.1)		29 (40.3)		12 (1.3)	0 (0.0)		5 (41.7)	
Ineligible	2017 (92.0)	231 (11.5)		690 (34.2)		815 (91.9)	90 (11.0)		265 (32.5)	
DVT Prophylaxis			0.811		<0.001			0.672		0.001
Fail	150 (6.8)	15 (10.0)		41 (27.3)		66 (7.4)	9 (13.6)		22 (33.3)	
Pass	814 (37.1)	97 (11.9)		365 (44.8)		321 (36.2)	33 (10.3)		134 (41.7)	
Ineligible	1228 (56.0)	139 (11.3)		353 (28.8)		500 (56.4)	56 (11.2)		143 (28.6)	

Supplementary File 2. (continued)

Characteristic	Training Sample					Validation Sample				
	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value	N (%)	Death or Stroke N (%)	P-value	Without-Fail	P-value
Rehabilitation Consult			<0.001		<0.001			<0.001		<0.001
Fail	1088 (49.6)	93 (8.6)		273 (25.1)		422 (47.6)	31 (7.4)		105 (24.9)	
Pass	1017 (46.4)	123 (12.1)		409 (40.2)		435 (49.0)	55 (12.6)		169 (38.9)	
Ineligible	87 (4.0)	35 (40.2)		77 (88.5)		30 (3.4)	12 (40.0)		25 (83.3)	
Speech Language Therapy Consult			0.011		<0.001			0.528		<0.001
Fail	1013 (46.2)	99 (9.8)		403 (39.8)		427 (48.1)	42 (9.8)		153 (35.8)	
Pass	487 (22.2)	52 (10.7)		207 (42.5)		205 (23.1)	25 (12.2)		97 (47.3)	
Ineligible	692 (31.6)	100 (14.4)		149 (21.5)		255 (28.8)	31 (12.2)		49 (19.2)	
SATS Referral for Alcohol Use			0.933		0.767			0.201		0.267
Fail	141 (6.4)	17 (12.1)		51 (36.2)		59 (6.7)	9 (15.3)		16 (27.1)	
Pass	15 (0.7)	1 (6.7)		4 (26.7)		4 (0.4)	1 (25.0)		0 (0.0)	
Ineligible	2036 (92.9)	233 (11.4)		704 (34.6)		824 (92.9)	88 (10.7)		283 (34.3)	
Neurology Consult			<0.001		<0.001			<0.001		<0.001
Fail	642 (29.3)	72 (11.2)		0 (0.0)		245 (27.6)	25 (10.2)		0 (0.0)	
Pass	1482 (67.6)	149 (10.1)		694 (46.8)		618 (69.7)	62 (10.0)		278 (45.0)	
Ineligible	68 (3.1)	30 (44.1)		65 (95.6)		24 (2.7)	11 (45.8)		21 (87.5)	

Supplemental File 3: Correlation Matrix

Variable*	History TIA	History Hypertension	NSAID	History Dementia	HASBLED	Age	CCI	APACHE	Current Smoker	Palliative/Hospice	History Stroke
History TIA	1.000	0.292	0.012	0.054	0.120	-0.017	0.115	0.081	0.062	0.044	0.072
P-value		<0.001	0.566	0.011	<0.001	0.419	<0.001	<0.001	0.004	0.040	0.001
History Hypertension		1.000	0.009	0.070	0.282	0.138	0.326	0.215	0.032	0.076	0.112
P-value			0.670	0.001	<0.001	<0.001	<0.001	<0.001	0.137	<0.001	<0.001
NSAID			1.000	-0.061	-0.045	-0.215	-0.076	-0.077	0.085	-0.036	-0.010
P-value				0.005	0.037	<0.001	<0.001	<0.001	<0.001	0.091	0.642
History Dementia				1.000	0.126	0.210	0.164	0.046	-0.030	0.174	0.102
P-value					<0.001	<0.001	<0.001	0.033	0.165	<0.001	<0.001
HASBLED					1.000	0.372	0.523	0.276	-0.008	0.147	0.361
P-value						<0.001	<0.001	<0.001	0.725	<0.001	<0.001
Age						1.000	0.166	0.201	-0.242	0.100	-0.031
P-value							<0.001	<0.001	<0.001	<0.001	0.145
Charlson Comorbidity Index							1.000	0.292	0.047	0.165	0.261
P-value								<0.001	0.027	<0.001	<0.001
APACHE								1.000	-0.104	0.092	0.028
P-value									<0.001	<0.001	0.184
Current Smoker									1.000	0.044	0.067
P-value										0.040	0.002
Palliative/Hospice										1.000	0.094
P-value											<0.001
History Stroke											1.000

*TIA refers to transient ischemic attack; NSAID refers to non-steroidal anti-inflammatory medications; the HASBLED score describes the risk of major bleeding; and the APACHE refers to the Acute Physiology And Chronic Health Evaluation measure of physiologic disease severity.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-12
Bias	9	Describe any efforts to address potential sources of bias	7-12
Study size	10	Explain how the study size was arrived at	7-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12, Suppl File
Outcome data	15*	Report numbers of outcome events or summary measures over time	12, Suppl File

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-20
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-20
Discussion			
Key results	18	Summarise key results with reference to study objectives	21-24
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23-24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-24
Generalisability	21	Discuss the generalisability (external validity) of the study results	23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.