Comparison of existing bleeding risk prediction models to large scale patient-level prediction models

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Janssen Research & Development

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Prediction Problem

Amongst new users of Warfarin or direct oral anticoagulants (DOACs) with prior non-valvular atrial fibrillation, who will develop the outcome of a major bleeding event within a year of the start of treatment?

ATRIA **CHADS$_2$**

TARGET-BLEED **OAC-RISK**

ORBIT **CHA$_2$DS$_2$-VASc**

Methods

Databases Used:

- IBM® MarketScan® Commercial Database (CCAE)
- IBM® MarketScan® Medicare Supplemental Database (MDCR)
- IBM® MarketScan® Multi-state Medicaid Database (MDCD)
- Optum© De-Identified Clinformatics® Data Mart Database – Date of Death (DOD)

Validating the risk scores

The five risk scores were applied to the target populations across the four databases.

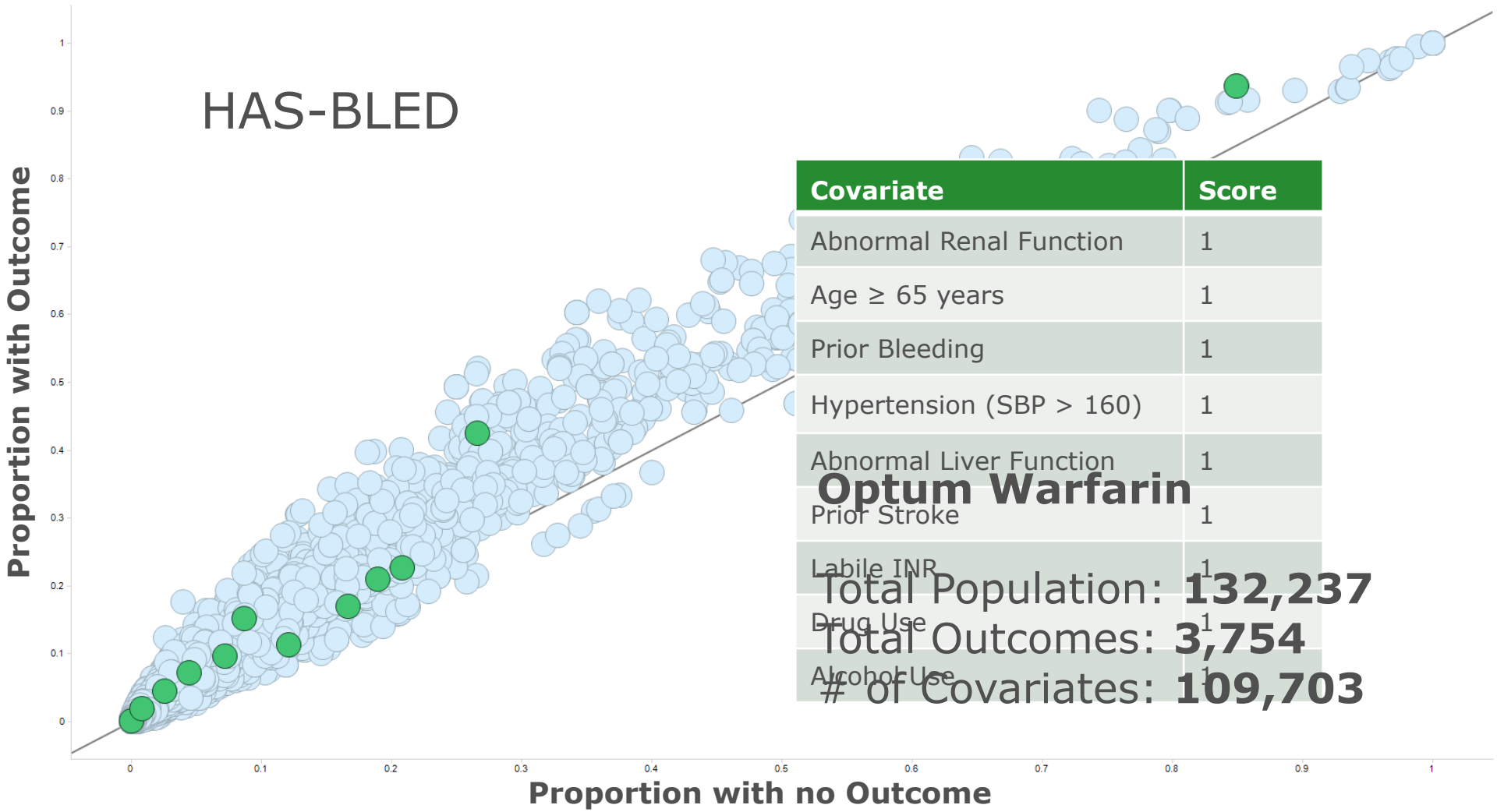
Learning the PLP model

Model: A regularized LASSO logistic regression model was trained separately on the four US claims databases.

Training: 75% of the data from each of the four databases were used to train the models, with 10-fold cross validation implemented to identify the optimal hyper-parameters.

Comparison: Performance of the existing models and learned models were evaluated and compared using the AUC discriminative measure.

Evaluating Candidate Predictors of Bleeding



Covariate	Score
Abnormal Renal Function	1
Age ≥ 65 years	1
Prior Bleeding	1
Hypertension (SBP > 160)	1
Abnormal Liver Function	1
Prior Stroke	1
Labile INR	1
Drug Use	1
Alcohol Use	1

Optum Warfarin

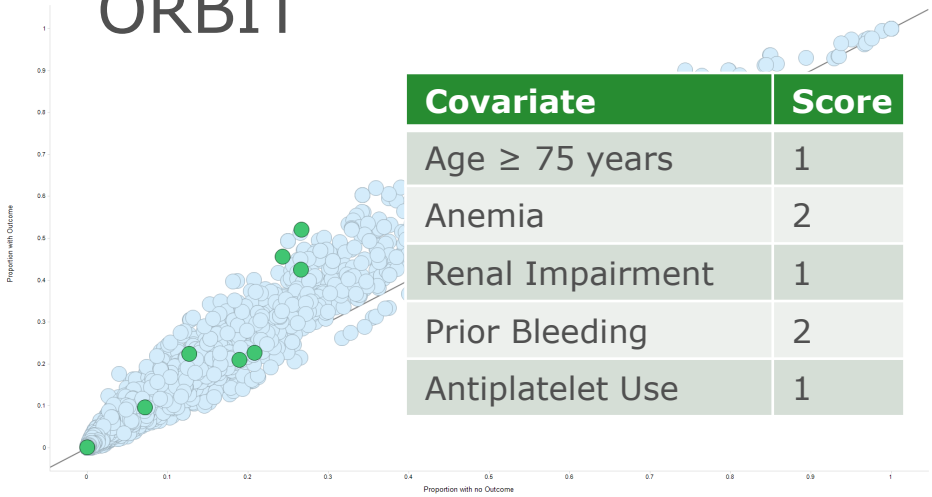
Total Population: **132,237**

Total Outcomes: **3,754**

# of Covariates: **109,703**

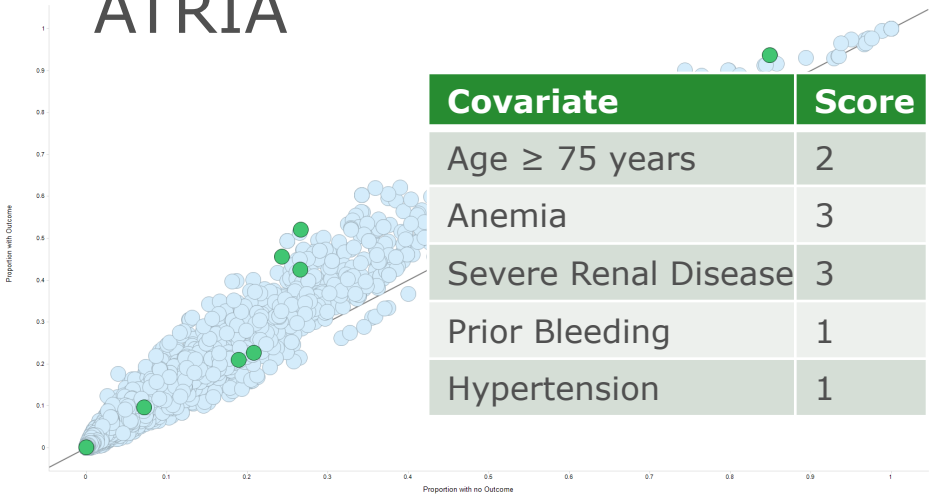
Examining predictors in existing models

ORBIT



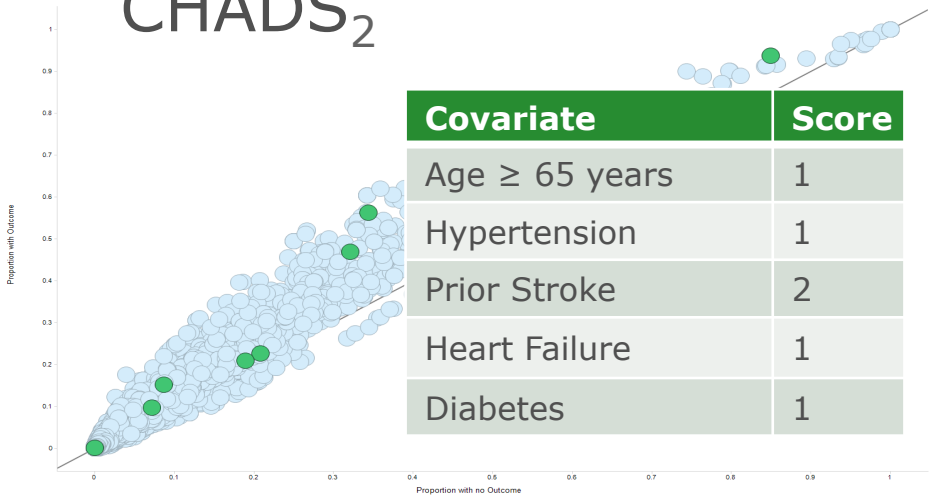
Covariate	Score
Age ≥ 75 years	1
Anemia	2
Renal Impairment	1
Prior Bleeding	2
Antiplatelet Use	1

ATRIA



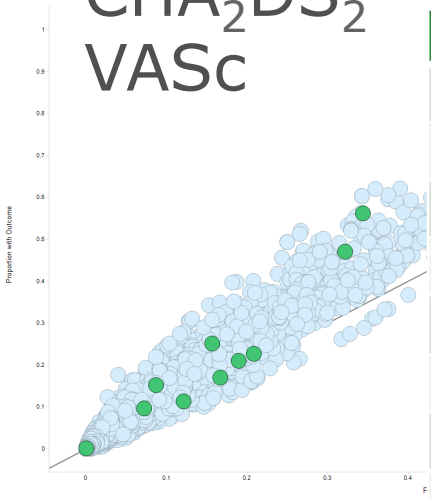
Covariate	Score
Age ≥ 75 years	2
Anemia	3
Severe Renal Disease	3
Prior Bleeding	1
Hypertension	1

$CHADS_2$



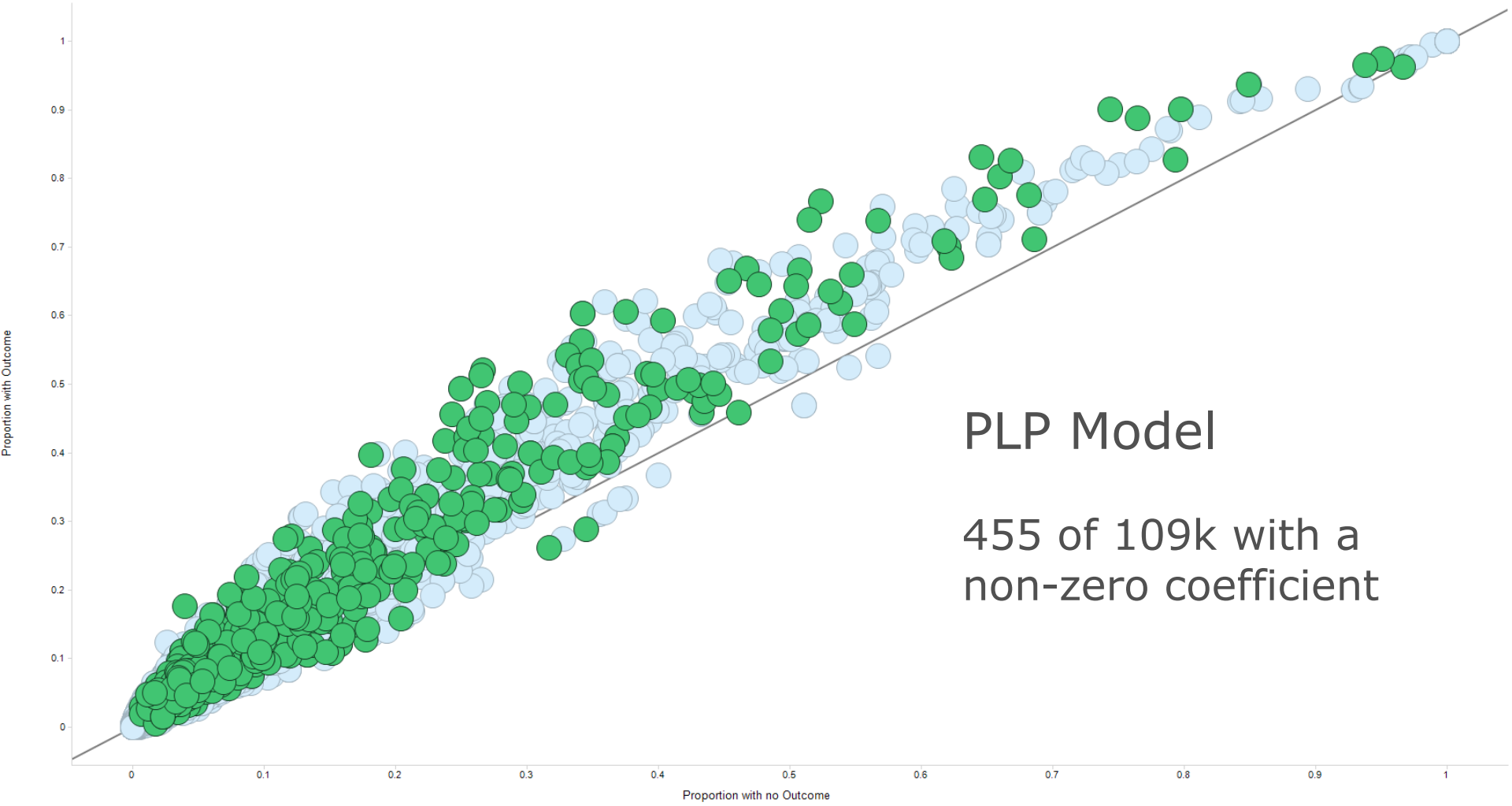
Covariate	Score
Age ≥ 65 years	1
Hypertension	1
Prior Stroke	2
Heart Failure	1
Diabetes	1

CHA_2DS_2-VASc



Covariate	Score
Age ≥ 65 years	1
Age ≥ 75 years	1
Hypertension	1
Prior Stroke	2
Heart Failure	1
Diabetes	1
Vascular Disease	1
Female Gender	1

What Covariates did LASSO Choose?



PLP Model

455 of 109k with a non-zero coefficient

PLP Model vs Risk Scores

PLP Model

Sensitivity: 50%

At-risk threshold: 4%

Specificity: 83%

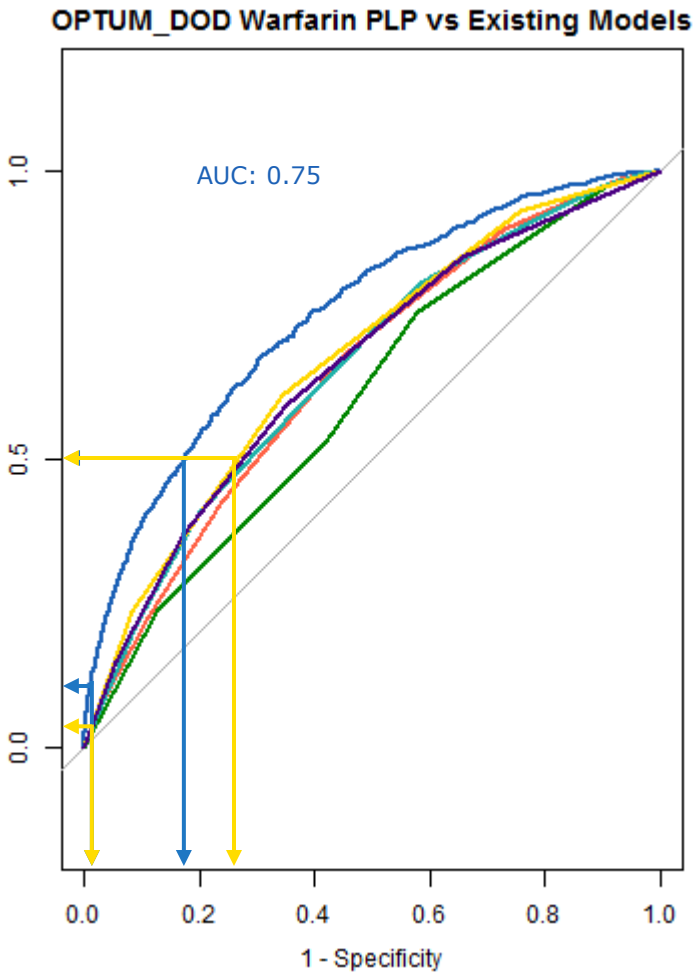
+PV: 8%

Specificity: 99%

At-risk threshold: 18%

Sensitivity: 8%

+PV: 22%



PLP Model: 0.75

HAS-BLED

At-risk threshold: 2.2%

Specificity: 65%

+PV: 4.5%

At-risk threshold: 6.4%

Sensitivity: 0.63%

+PV: 6.6%

.68

Sc: 0.66

5

PLP Model Performance

The Optum Warfarin model for predicting major bleed achieved an internal validation AUC of 0.75 (0.73-0.76)

Figure 1: ROC plot for the Optum Warfarin model

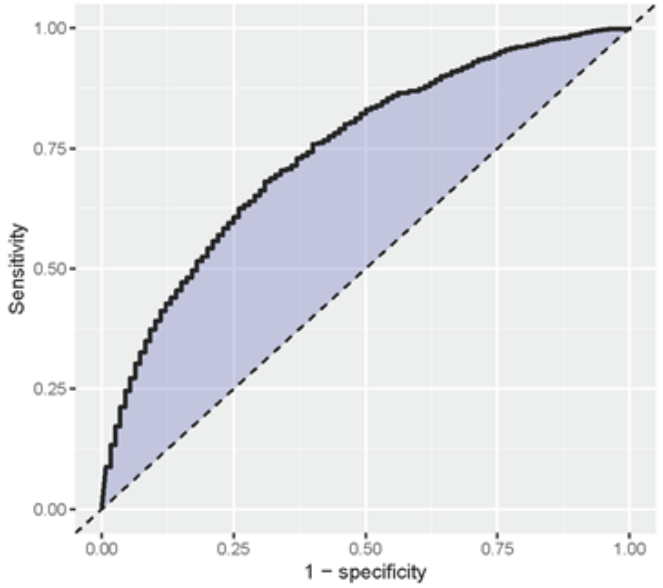


Figure 2: Calibration plot for the Optum Warfarin model

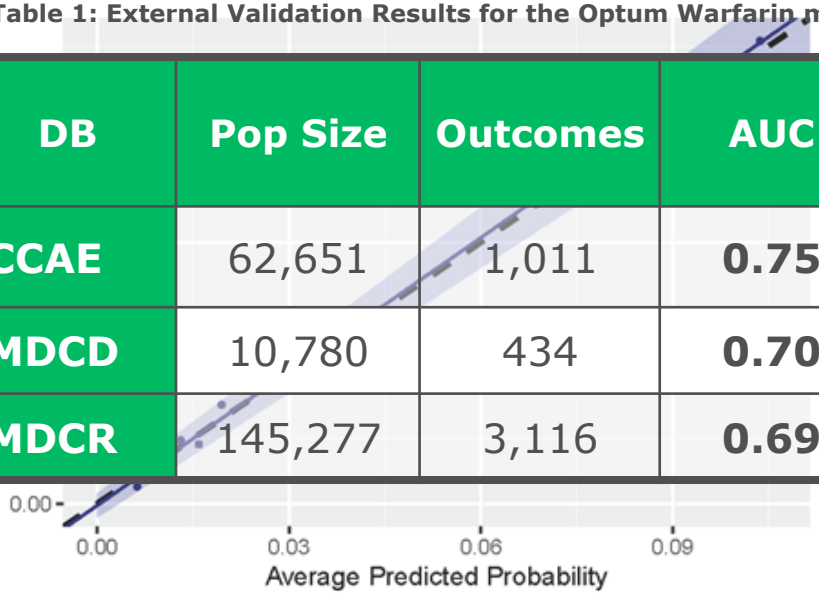


Table 1: External Validation Results for the Optum Warfarin model

DB	Pop Size	Outcomes	AUC
CCAE	62,651	1,011	**0.75**
MDCD	10,780	434	**0.70**
MDCR	145,277	3,116	**0.69**

Conclusion

PLP models developed using the PLP framework to predict major bleeding **consistently outperform** risk scores currently used in clinical practice.

The **patient-level prediction framework offers an efficient way to train, test, and validate large-scale prediction models** across a network of observational databases.