Supplemental Material

Development and Validation of a score to detect paroxysmal atrial fibrillation after stroke

AS5F–patient selection for prolonged Holter-ECG

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Supplemental Tables

Supplemental Table 1: Detailed consideration of the TRIPOD Guideline[1] within the manuscript

TRIPOD Checklist: Prediction Model Development and Validation			
Section/Topic	Item	Checklist Item	Page
Title and Abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted	See Title page
Abstract	2	Provide a summary of objectives, study design, settings, participants, sample size, predictors, outcome, statistical analysis, results and conclusions	3
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models	4
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both	4
Methods			
Source of data	4a	Describe the study design or source of data (e.g. randomized trial, cohort, or registry data), separately for the development and validation data sets, if	5

		applicable	
	4b	Specify the key study dates, including start of accrual, end of accrual, and if applicable end of follow-up	5, references to original studies
Participants	5a	Specify the key elements of the study settings (primary care, secondary care, general population) including number and location of centres.	5, references to original studies
	5b	Describe eligibility criteria for participants	5, references to original studies
	5c	Give details of treatments received, if relevant	n.a.
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed	6
	6b	Report any actions to blind assessments of the outcome to be predicted	Data-, and ECG-analysis was performed blinded as described in the methods of the three included studies[2-4]
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured	6-7, references to original studies
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors	Data-, and ECG-analysis was performed blinded as described in the methods of the three included studies[2-4]
Sample Size	8	Explain how the study size was arrived at	5
Missing data	9	Describe how missing data were handles (e.g. complete-cases analysis, single imputation,	6

		multiple imputation) with details of any imputation method	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses	Stat. analyses section
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation	Stat. analyses section
	10c	For validation, describe how the predictions were calculated	Stat. analyses section
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	Stat. analyses section
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done	No model updating necessary
Risk groups	11	Provide details on how risk groups were created, if done	Stat. analyses section
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome and predictors.	Outcomes, study population section
Results			
Participants	13a	Describe the flow of participants of the study including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful	6-8, references to original studies
	13b	Describe the characteristics of the participants (demographics, clinical features, available predictors), including the number of participants with missing data	9-10, references to original studies

		for predictors and outcome	
	13c	For validation, show a comparison with the development data of distribution of important variables (demographics, predictors and outcome)	Table 1
Model development	14a	Specify the number of participants and outcome events in each analysis	Study population section
	14b	If done, report the unadjusted association between each candidate predictor and outcome	Table 2
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e. all regression coefficients, and model intercept or baseline survival at a given time point).	Supplement, Figure 1
	15b	Explain how to use the prediction model	10-11, Figure 1c
Model performance	16	Report performance measures (with CIs) for the prediction model	Results section
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance)	No model updating necessary
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data)	17-18
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	14-15

	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies and other relevant evidence	16-17
Implications	20	Discuss the potential clinical use of the model and implications for future research	16
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator and data sets.	The study protocol is published within the original studies of the three included trials. Data-sets are available on request. Web calculator: http://www.unimedizin-mainz.de/neurologie/header/as5f.html
Funding	22	Give the source of funding and the role of the funders of the present study.	2

Supplemental Table 2: Point estimator and Confidence intervals for the Performance measures of the AS5F-Score

Performance measures	Point estimator	95%-Confidence interval
Apparent Performance: ROC-AUC	0.779	[0.717, 0.840]
Apparent Performance: Intercept calibration line	0.001	[-0.014, 0.017]
Apparent Performance: Slope calibration line	0.971	[0.725, 1.217]
Internal Validation: ROC-AUC	0.760	[0.700, 0.819]
Internal validation: Intercept calibration line	0.006	[-0.007, 0.017]
Internal validation: Slope calibration line	0.861	[0.491, 1.439]
External Validation (72h outcome): ROC-AUC	0.752	[0.666, 0.837]
External Validation (72h outcome): Intercept calibration line	0.008	[-0.034, 0.051]
External Validation (72h outcome):	1.058	[0.523, 1.593]

Slope calibration line		
External Validation (full study outcome): ROC-AUC	0.765	[0.692, 0.838]
External Validation (full study outcome): Intercept calibration line	0.011	[-0.033, 0.055]
External Validation (full study outcome): Slope calibration line	1.813	[1.257, 2.368]

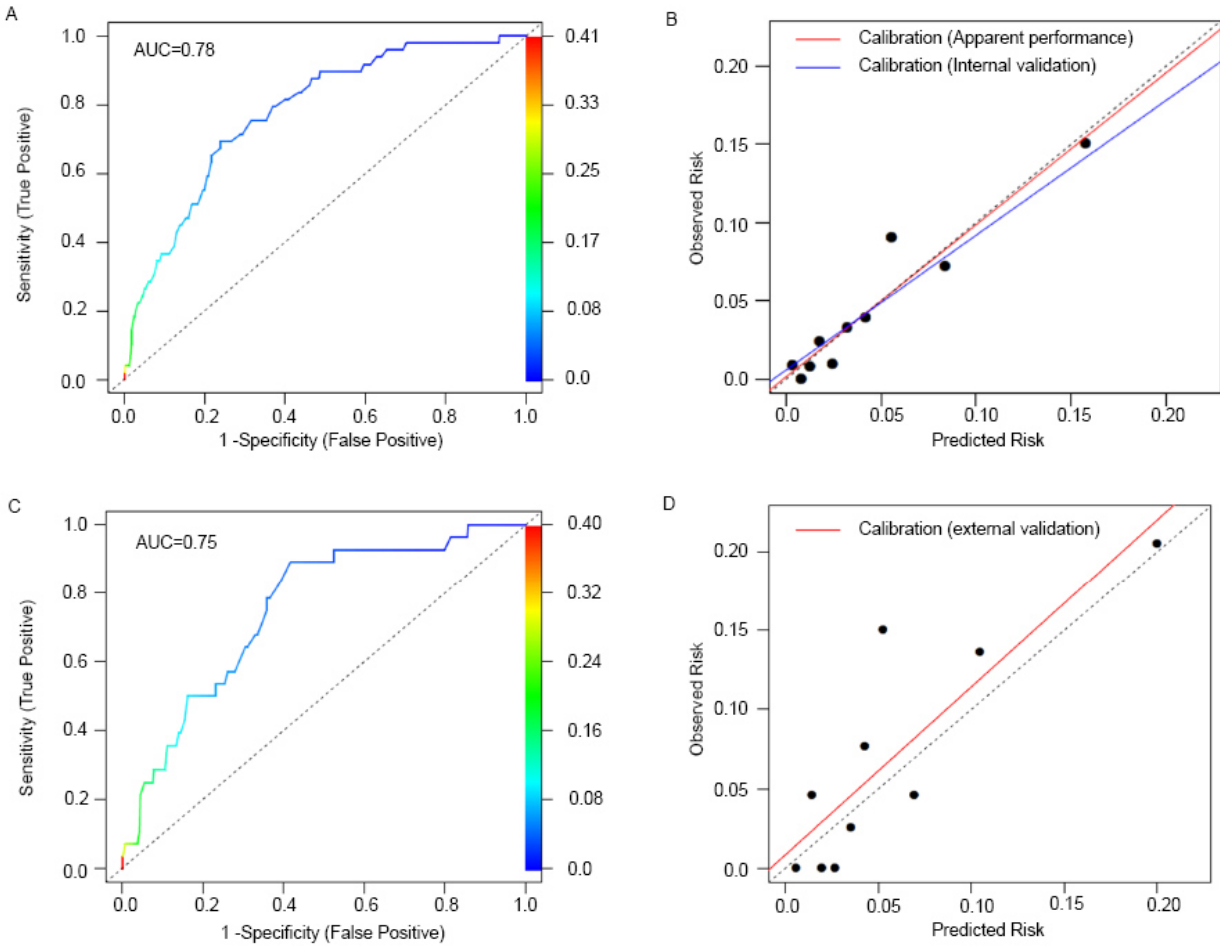
Supplemental Table 3: Quality-measures of the low/high-risk classification system, based on the AS5F-Score and the cutoff value which maximised the Youden-Index on the IDEAS-cohort.

Cohort	Performance measures	Point estimator	95%-confidence interval
IDEAS (training-/development data)	Sensitivity	0.69	(0.55, 0.82)
	Specificity	0.76	(0.73, 0.79)
	NPV	0.98	(0.97, 0.99)
	PPV	0.12	(0.08, 0.16)
FIND-AF-Studies, 72h-outcome (validation data)	Sensitivity	0.68	(0.48, 0.84)
	Specificity	0.66	(0.62, 0.71)
	NPV	0.97	(0.94, 0.98)
	PPV	0.13	(0.08, 0.19)

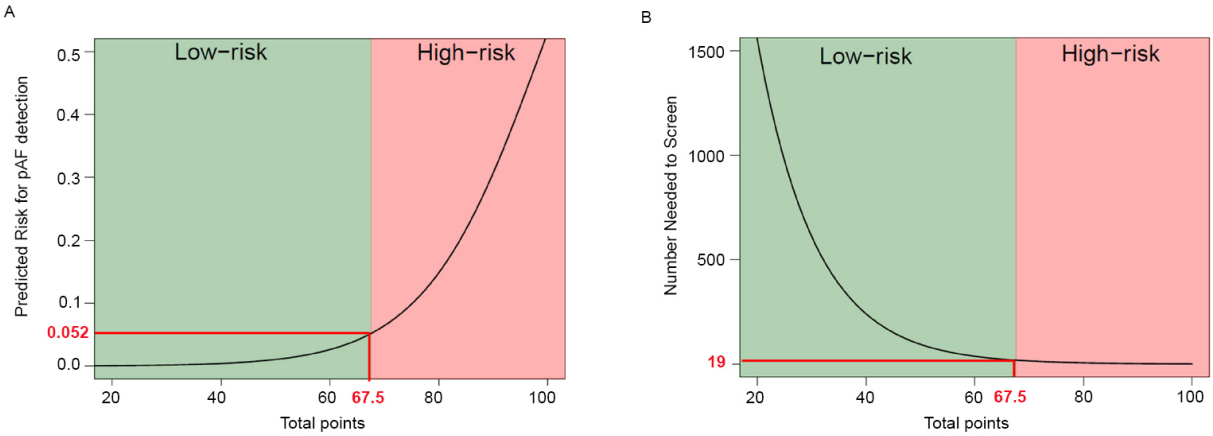
Supplemental Figures

$$P(\text{AF within 72h}) = \frac{\exp\left(-9.21 + 0.07 \cdot (\text{age in years}) + 0.87 \cdot 1(\text{stroke \& NIH-SS} \leq 5) + 1.98 \cdot 1(\text{stroke \& NIH-SS} > 5)\right)}{1 + \exp\left(-9.21 + 0.07 \cdot (\text{age in years}) + 0.87 \cdot 1(\text{stroke \& NIH-SS} \leq 5) + 1.98 \cdot 1(\text{stroke \& NIH-SS} > 5)\right)}$$

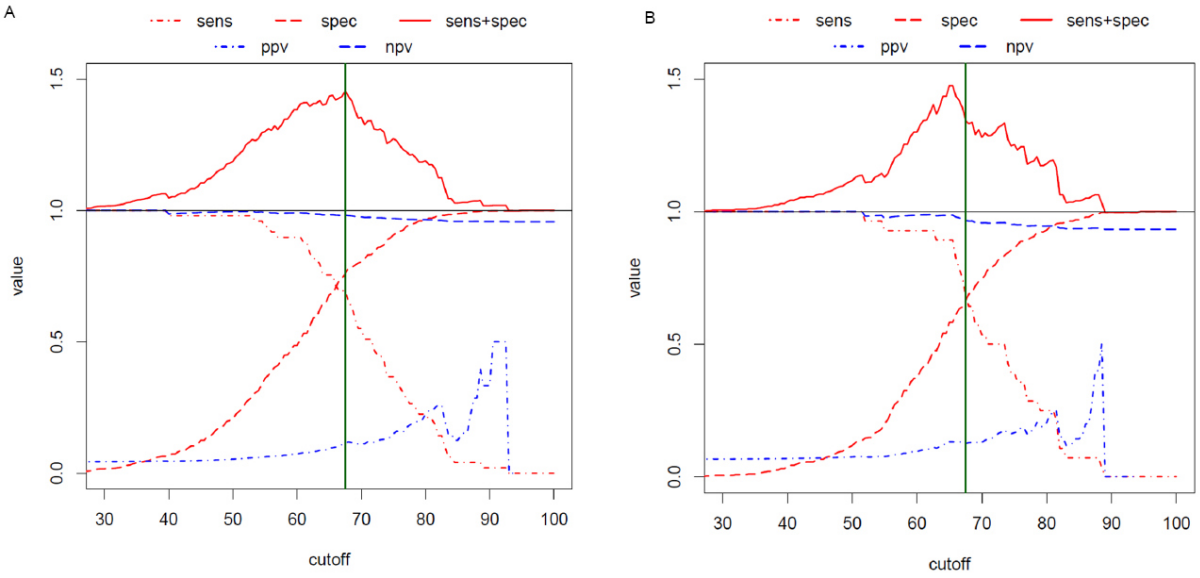
Supplemental Figure 1: Final model for calculation of individual risk prediction. AF = atrial fibrillation, NIH-SS = National Institutes of Health Stroke Scale



Supplemental Figure 2: Score development and validation. A) AS5F apparent performance on the IDEAS cohort (ROC-AUC 0.78). B) The score's apparent performance (red line: calibration line intercept <0.01 and slope 0.97) only slightly differed from the adjusted measures obtained in the internal validation step (blue line: ROC-AUC 0.78, calibration line intercept <0.01 and slope 0.86), which reflects the internal validity of AS5F. C, D) The score underwent an external validation on the Find-AF[3] and Find-AF$_{randomised}$[4] cohorts and kept its discriminative performance (ROC-AUC 0.75, see panel C) and its predictive accuracy (calibration line intercept <0.01 and slope 1.06, see panel D), using the 72h-outcome of both studies.



Supplemental Figure 3: A) Classification in low- and high-risk patients with an AS5F cut-off score of 67.5 total points, reflecting a predicted risk of 5.2% for detection of pAF within a 72h Holter-ECG monitoring. B) The Number Needed to Screen for an AS5F score of 67.5 is 19.



Supplemental Figure 4: Performance measures of the low-/high-risk classification system, based on the AS5F-Score for all cutoff-values (y-axis) and the cutoff value (x-axis) which maximized the Youden-Index (green line) on the IDEAS-development-cohort (A) and the Find-AF studies-validation cohort (B). sens: sensitivity, spec: specificity, sens+spec: sensitivity + specificity, ppv: positive predictive value, npv: negative predictive value.

Supplemental References

1. Moons KG, Altman DG, Reitsma JB,et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of internal medicine*. 2015;162:W1-73.
2. Grond M, Jauss M, Hamann G, et al. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. *Stroke.* 2013;44:3357-64.
3. Stahrenberg R, Weber-Krüger M, Seegers J, et al. Enhanced detection of paroxysmal atrial fibrillation by early and prolonged continuous holter monitoring in patients with cerebral ischemia presenting in sinus rhythm. *Stroke.* 2010;41:2884-8.
4. Wachter R, Gröschel K, Gelbrich G, et al. Find AFI and Coordinators. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. *The Lancet Neurology*. 2017;16:282-290.