Supplementary Material

Refined Atrial Fibrillation Screening and Cost-effectiveness in the German Population

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Supplementary Methods

Study participants

Response rate

The response rate was 62%.

Covariates

For the current analyses, 121 clinical and biomarker variables from the GHS were available. We also defined smoking status (never smokers and former smokers versus current smokers). The diagnosis of diabetes mellitus was based on a physician diagnosis of diabetes and/or a study fasting blood glucose concentration of ≥126mg/dL (minimum 8-hour fast) or a blood glucose level of ≥200mg/dL. Dyslipidemia was defined as a physician´s diagnosis and/or an LDL/HDL ratio of >3.5 measured in the study. Hypertension comprised anti-hypertensive drug treatment and/or a mean systolic blood pressure of ≥140mmHg and/or a mean diastolic blood pressure of ≥90mmHg measured on site. All individuals underwent a multi-modal echocardiography with an iE33 echocardiography system with a S5-1 sector array transducer (Royal Philips Electronics, Amsterdam, The Netherlands). Examinations were performed using a standardized protocol by trained and certified medical technical assistants at a single centre. C-reactive protein, N-terminal pro B-type natriuretic peptide (Nt-proBNP) were measured by routine methods.[1] Cardiac symptoms, a history of myocardial infarction and stroke were self-reported. Heart failure was defined clinically (New York Heart Association classification, heart failure medication) and by echocardiographic left ventricular ejection fraction <55%. A left ventricular mass index of >95g/m^2 in woman and >115g/m^2 in men was defined as left ventricular hypertrophy assessed by echocardiography.

Statistical methods

The prevalence data was weighted for sex 1:1, place of residence 1:1 (urban and rural areas) and equal parts for the four age decades of the population in Mainz and Mainz-Bingen area (December 31, 2008).[2] Mean values and standard deviations were presented for symmetric continuous

variables, median and 25th/75th percentiles for skewed continuous variables, and proportions and 95% confidence intervals for categorical variables.

For the estimation of heart failure risk and risk of stroke or death, respective risk algorithms from the literature were applied.[3, 4] Heart failure risk scores were truncated at the upper risk estimate of ≥45% to avoid inaccuracies due to extreme observations.

Imputation

We imputed missing values in predictor data using proximity as outlined in.[5-7] The proximities give an intrinsic measure of similarities between the individuals/data. For continuous predictors, the imputed value is the weighted average of the non-missing observations, where the weights are the proximities. For categorical predictors, the imputed value is the category with the largest average proximity.

Cost-effectiveness analyses

The prevalence of unknown AF was taken from GHS. The proportion of persistent OAC users in AF,[8] incidence rates for stroke, all-cause mortality and major bleeding were retrieved from published data.[9] Costs for the screening included an invitation letter to the German population aged 65-74 and a subsequent general practitioner (GP) visit with a 12 lead ECG in 62% of individuals based on the response rate as seen in GHS. Furthermore, the cost-effectiveness analysis accounted for lifetime costs for a first stroke, costs for major bleeding events and annual treatment costs for vitamin K antagonists (VKAs) and non-vitamin K oral anticoagulants (NOACs). Costs included GP visits, blood work (INR tests and creatinine measurement) and drug prescriptions.[10] Details on input data (including their sources) and assumptions of the analyses are provided below. The target variables of the cost-effectiveness analyses were costs per quality-adjusted life-year (QALY) gained and costs per stroke prevented.

Sensitivity analyses were performed for the prevalence of undetected AF, the proportion of OAC uptake, and the proportion of NOAC prescription in anticoagulant users.

In addition, refined screening scenarios (other than age cut-off (65 years) alone) were assessed by using an age cut-off plus clinical AF risk score based threshold of 5% and 10%, and age cut-off plus a point of care testing of Nt-proBNP to pre-select individuals at higher risk of AF before performing a 12-lead ECG. We used Nt-proBNP measurements in all participants without known AF and examined different cut-offs. Additional assumptions were the costs for a point-of-care test for Nt-proBNP of 10 EUR and a 100 percent participation rate in the 12-lead ECG after positive Nt-proBNP testing.

Input data for cost-effectiveness model

AF prevalence

1. Prevalence of known AF stratified by age and gender.[11]
2. Prevalence of unknown AF stratified by age based on new AF in GHS. Different scenarios investigated in sensitivity analysis.

Outcomes after AF

Incidence of stroke, major bleeds and mortality following AF (treated vs. untreated AF) stratified by time since AF, age and gender.[12] Estimates for treated AF are based on VKA only, i.e. not considering NOACs.

Proportion of OAC treated AF

1. Prevalence of OAC treatment in patients with known AF stratified by NOAC/VKA.[13] Different scenarios investigated in sensitivity analysis.
2. VKA to NOAC ratio assumed to be 1:1 in the base analysis. Different scenarios investigated in sensitivity analysis.

Population data

Population of Mainz and Mainz-Bingen area stratified by residence, age and sex from 12/2008.[14]

Economic transformations

1. Prices converted to 04/2018 numbers based on (SEA-VPI-Nr. 06 - "Gesundheitspflege").[15]
2. Discount rate: 5%.

Screening approach

- Step 1: Invitation letter to be sent to all Germans aged 65-74
- Step 2: 12 lead ECG to be performed at GP assuming a participation rate of 62% based on the response rate as seen in Gutenberg Health Study and a sensitivity and specificity of the Gutenberg Health Study in clinic ECG (100% and 98%, respectively)

QALYs

1. QALYs lost after ischaemic stroke.[16]

2. QALYs lost due to major bleeding.[17]
3. QALYs lost due to VKA treatment.[17] Same QALY loss for VKA and NOAC used.

Costs

Input data:

1. Lifetime costs for a first ischaemic stroke[18][1]
2. Costs for a major bleeding requiring hospitalisation[2]
3. Costs for OAC treatment
    a. VKA
        i. Phenprocoumon [19]
        ii. INR tests[20]
        iii. Quartalspauschale [20]
        iv. Kidney function control[20]
    b. NOACs[21]
        i. Apixaban, Edoxaban, Rivaroxaban, Dabigatran[21]
        ii. Quartalspauschale [20]
        iii. Kidney function control [20]
4. Costs for screening
    a. Invitation letter[22]
    b. GP visit including 12 lead ECG [20]

Note:

1. Inpatient costs in the first year after stroke in Kolominsky-Rabas replaced with costs for initial stroke hospitalisation in Hamburg 2016
2. Average cost of hospital treatment for bleeding
3. The following assumptions were made:
    a. Dose 4mg/day, INR test every 2 weeks (Ziffer 32026 "Thromboplastinzeit"), 4x Quartalspauschale (55-74), 1x Kidney function control including optional blood work
    b. NOAC medication costs based on mean costs for the 4 NOAC products, 1x Quartalspauschale (55-74), 1x Kidney function control including optional blood work
4. The following assumptions were made:
    a. -
    b. Quartalspauschale (55-74)

[1] Cost of hospital treatment for Stroke on average in 2016 University Clinic Hamburg = 5.483,82 € per admission (Inpatient Costs) The average cost of hospital treatment for Stroke was provided by the UKE central controlling division for 2016 based on the DRG-System for the ICD Code I63.-

[2] Cost of hospital treatment for Bleeding/Hemorrhage on average in 2016 University Clinic Hamburg = 12.012,01 € per admission
The average cost was provided by the UKE central controlling division for 2016 based on the DRG-System for the ICD Code ICD Code I61; K92.0 – K92.2; K28.0-K28.2; K25.0-K25.2 (all combined in average)

Supplementary Table 1. Cardiac medication in the total sample by AF status, weighted for age and sex of the population in Mainz and in Mainz-Bingen Area (n=14,937).

	No AF n=14,557	**Known AF n=355**	**New AF n=25**
Antithrombotic Therapy			
Heparin, (%)	0.1	1.2	0
Oral anticoagulants, (%)	0.7	35.3	0
Antiplatelet agents, (%)	7.4	29.1	26.9
Antiarrhythmics			
Class I, (%)	0.0	5.0	0
Class III, (%)	0.1	8.4	0
Class IV, (%)	0.6	5.7	3.7
Digitalis, (%)	0.2	13.7	0
Beta blockers, (%)	13.4	59.2	40.3
Other medication			
ACE-inhibitors, AT II antagonists, direct renin-inhibitors, (%)	19.9	54.3	45.9
Statins (%)	9.6	33.0	25.8
Insulin, (%)	1.7	4.8	13.5
Oral antidiabetics, (%)	3.8	8.7	10.2
Thyroid hormone therapy, (%)	11.6	16.1	6.9

Provided are the number and percent of individuals.

Supplementary Table 2. Median 5-year predicted risk of atrial fibrillation applying a recent risk prediction algorithm[23] in individuals by AF status distributed by age decades .

	Age decades in years	Risk Score
No atrial fibrillation	35-44	0.2 (0.1/0.3)
	45-54	0.6 (0.4/0.9)
	55-64	1.7 (1.1/2.6)
	65-74	5.2 (3.5/8.1)
Known atrial fibrillation	35-44	0.4 (0.2/0.8)
	45-54	0.9 (0.6/2.1)
	55-64	3.0 (1.9/5.1)
	65-74	8.6 (5.4/13.4)
New atrial fibrillation	35-44	0.2
	45-54	1.5 (0.9/3.3)
	55-64	2.7 (1.8/4.0)
	65-74	10.0 (7.0/13.8)

Provided are the median and 25^{th}/75^{th} percentiles. Data are weighted for residence, age and sex of the population in Mainz and in Mainz-Bingen area.

Supplementary Table 3. Number needed to screen for different Nt-proBNP cut-offs.

%ile	Nt-proBNP, ng/L	Number needed to screen	Sensitivity	Specificity	Sum	Weighted Sum
70	97.5	15.74	0.73	0.71	1.44	1.59
71	100.3	15.22	0.73	0.72	1.45	1.59
72	103.5	14.84	0.72	0.73	1.45	1.59
73	106.4	14.48	0.71	0.74	1.45	1.59
74	109.7	14.02	0.7	0.75	1.46	1.6
75	113.1	13.55	0.7	0.76	1.46	1.6
76	116.6	13.08	0.69	0.77	1.46	1.6
77	120.3	12.6	0.68	0.78	1.47	1.6
78	124.5	12.17	0.67	0.79	1.47	1.6
79	129	11.84	0.66	0.8	1.47	1.6
80	133.3	11.38	0.65	0.81	1.47	1.6
81	139.12	10.92	0.64	0.82	1.47	1.6
82	144.3	10.44	0.64	0.83	1.47	1.6
83	149.9	10.05	0.62	0.84	1.47	1.59
84	156.7	9.54	0.61	0.85	1.47	1.59
85	163.1	9.1	0.6	0.86	1.47	1.59
86	170.8	8.73	0.58	0.87	1.46	1.57
87	178.6	8.38	0.56	0.88	1.45	1.56
88	188.1	7.79	0.56	0.89	1.45	1.56
89	199.7	7.18	0.55	0.9	1.45	1.56
90	211.0	6.73	0.53	0.91	1.44	1.55
91	227.7	6.15	0.52	0.92	1.44	1.55
92	243.7	5.56	0.51	0.93	1.44	1.54
93	263.3	5.13	0.48	0.94	1.42	1.52
94	287.1	4.55	0.46	0.95	1.41	1.5
95	326.5	3.93	0.44	0.96	1.4	1.49

Provided are the percentile and respective Nt-proBNP concentrations.

Supplementary Table 4. Number of strokes avoided and costs per QALY gained by AF test based on Nt-proBNP

Quantile	Threshold[1] [ng/L]	Sensitivity	Specificity	New AF	Stokes avoided	Costs per stroke avoided [€]	Costs per QALY gained [€]
ECG only[2]	NA	1.00	0.98	25733	1122	117,498	30,361
Nt-proBNP[3]							
0.15	19.85	0.94	0.15	24189	1054	157,755	40,763
0.16	20.97	0.94	0.16	24189	1054	156,991	40,566
0.17	22.03	0.94	0.17	24189	1054	156,227	40,368
0.18	23.08	0.94	0.18	24189	1054	155,463	40,171
0.19	23.97	0.93	0.19	23932	1043	156,061	40,325
0.20	25.06	0.93	0.20	23932	1043	155,289	40,126
0.21	25.87	0.92	0.21	23675	1032	155,890	40,281
0.22	26.98	0.92	0.22	23675	1032	155,110	40,080
0.23	28.00	0.92	0.23	23675	1032	154,329	39,878
0.24	29.07	0.91	0.24	23417	1021	154,927	40,033
0.25	30.11	0.91	0.26	23417	1021	153,349	39,625
0.26	31.24	0.91	0.27	23417	1021	152,560	39,421
0.27	32.19	0.91	0.28	23417	1021	151,771	39,217
0.28	33.15	0.91	0.29	23417	1021	150,982	39,013
0.29	34.21	0.91	0.30	23417	1021	150,193	38,809
0.30	35.44	0.90	0.31	23160	1009	150,751	38,954
0.31	36.56	0.90	0.32	23160	1009	149,953	38,747
0.32	37.51	0.90	0.33	23160	1009	149,155	38,541
0.33	38.60	0.90	0.34	23160	1009	148,358	38,335
0.34	39.66	0.89	0.35	22903	998	148,902	38,476
0.35	40.81	0.88	0.36	22645	987	149,459	38,620
0.36	41.85	0.88	0.37	22645	987	148,643	38,409

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Quantile	Threshold[1] [ng/L]	Sensitivity	Specificity	New AF	Stokes avoided	Costs per stroke avoided [€]	Costs per QALY gained [€]
0.37	42.98	0.88	0.38	22645	987	147,827	38,198
0.38	44.09	0.88	0.39	22645	987	147,011	37,987
0.39	45.28	0.88	0.40	22645	987	146,195	37,776
0.40	46.59	0.88	0.41	22645	987	145,379	37,565
0.41	47.61	0.87	0.42	22388	976	145,901	37,700
0.42	48.97	0.86	0.43	22131	965	146,436	37,838
0.43	50.31	0.85	0.44	21873	953	146,983	37,980
0.44	51.49	0.85	0.45	21873	953	146,139	37,762
0.45	52.84	0.85	0.46	21873	953	145,294	37,543
0.46	54.07	0.84	0.47	21616	942	145,834	37,683
0.47	55.61	0.83	0.48	21359	931	146,387	37,826
0.48	57.12	0.83	0.49	21359	931	145,522	37,602
0.49	58.43	0.83	0.50	21359	931	144,657	37,379
0.50	59.92	0.82	0.51	21101	920	145,203	37,520
0.51	61.28	0.82	0.52	21101	920	144,327	37,294
0.52	62.50	0.82	0.53	21101	920	143,451	37,067
0.53	63.81	0.81	0.54	20844	909	143,989	37,206
0.54	65.37	0.81	0.55	20844	909	143,102	36,977
0.55	67.24	0.81	0.56	20844	909	142,216	36,748
0.56	68.96	0.80	0.57	20587	897	142,745	36,885
0.57	70.70	0.79	0.58	20329	886	143,287	37,025
0.58	72.44	0.79	0.59	20329	886	142,378	36,790
0.59	74.48	0.79	0.60	20329	886	141,469	36,555
0.60	76.29	0.78	0.61	20072	875	142,002	36,693
0.61	78.15	0.78	0.62	20072	875	141,081	36455
0.62	79.96	0.78	0.63	20072	875	140,160	36,217

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Quantile	Threshold[1] [ng/L]	Sensitivity	Specificity	New AF	Stokes avoided	Costs per stroke avoided [€]	Costs per QALY gained [€]
0.63	82.18	0.78	0.64	20072	875	139,240	35,979
0.64	84.24	0.77	0.65	19815	864	139,751	36,111
0.65	86.05	0.77	0.66	19815	864	138,818	35,870
0.66	88.21	0.76	0.67	19557	852	139,330	36,002
0.67	90.50	0.75	0.68	19300	841	139,856	36,138
0.68	92.54	0.75	0.69	19300	841	138,898	35,891
0.69	94.95	0.74	0.70	19043	830	139,425	36,027
0.70	97.46	0.73	0.71	18785	819	139,966	36,167
0.71	100.30	0.73	0.72	18785	819	138,983	35,913
0.72	103.50	0.72	0.73	18528	808	139,525	36,053
0.73	106.50	0.71	0.74	18271	796	140,084	36,197
0.74	109.80	0.70	0.75	18013	785	140,657	36,345
0.75	113.10	0.70	0.76	18013	785	139,632	36,080
0.76	116.60	0.69	0.77	17756	774	140,207	36,229
0.77	120.40	0.68	0.78	17499	763	140,800	36,382
0.78	124.60	0.67	0.79	17241	751	141,410	36,540
0.79	129.10	0.66	0.80	16984	740	142,039	36,702
0.80	133.40	0.65	0.81	16727	729	142,687	36,870
0.81	139.20	0.64	0.82	16469	718	143,356	37,043
0.82	144.40	0.64	0.83	16469	718	142,234	36,753
0.83	150.00	0.62	0.84	15955	695	144,758	37,405
0.84	156.67	0.61	0.85	15697	684	145,493	37,595
0.85	163.10	0.60	0.86	15440	673	146,253	37,791
0.86	170.80	0.58	0.87	14925	651	149,089	38,524
0.87	178.60	0.56	0.88	14411	628	152,128	39,309
0.88	188.10	0.56	0.89	14411	628	150,846	38,978

Quantile	Threshold[1] [ng/L]	Sensitivity	Specificity	New AF	Stokes avoided	Costs per stroke avoided [€]	Costs per QALY gained [€]
0.89	199.66	0.55	0.90	14153	617	151,772	39,217
0.90	211.00	0.53	0.91	13639	594	155,084	40,073
0.91	227.66	0.52	0.92	13381	583	156,145	40,347
0.92	243.70	0.51	0.93	13124	572	157,248	40,632
0.93	263.30	0.48	0.94	12352	538	163,824	42,331
0.94	287.05	0.46	0.95	11837	516	168,164	43,453
0.95	326.54	0.44	0.96	11323	494	172,899	44,676

A graphical representation of the results is provided in **Supplementary Figures 4** and **5**.

Abbreviations: AF, atrial fibrillation; NA, not applicable; Nt-proBNP, N-terminal pro B-type natriuretic peptide; QALY, quality-adjusted life year.

[1]: Positive AF test result if Nt-proBNP is above the given threshold.

[2]: Screening based on ECG only, i.e. without previous Nt-proBNP test.

[3]: Screening based on Nt-proBNP test and subsequent ECG in individuals with positive Nt-proBNP test.

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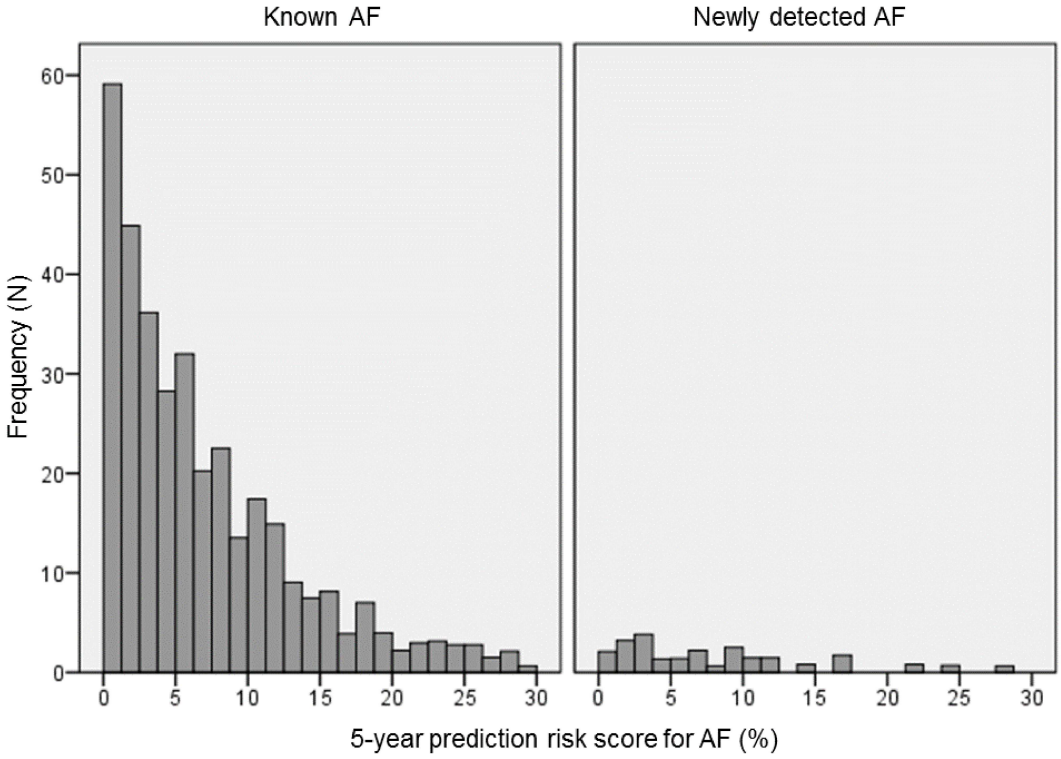
Supplementary Figure 1. Distribution of predicted 5-year risk of AF [23] among individuals with known and new AF. Data are weighted for residence, age and sex of the population in Mainz and in Mainz-Bingen area.



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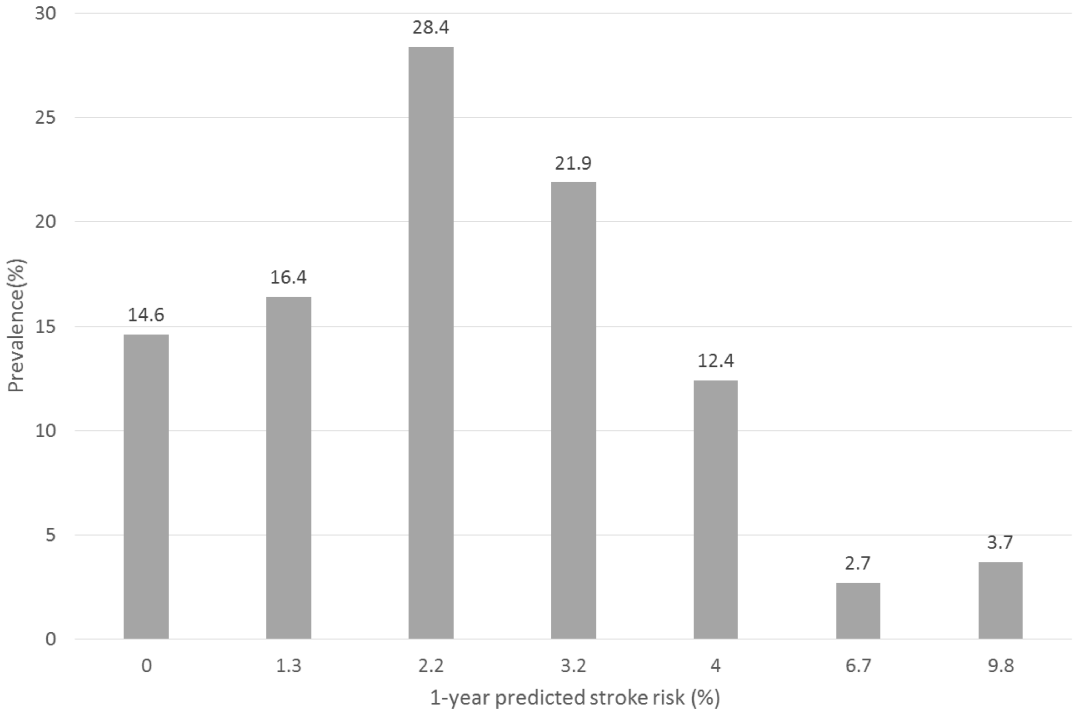
Supplementary Figure 2. Annual stroke risk for individuals with new AF (n=25), adjusted for intake of warfarin.[24]



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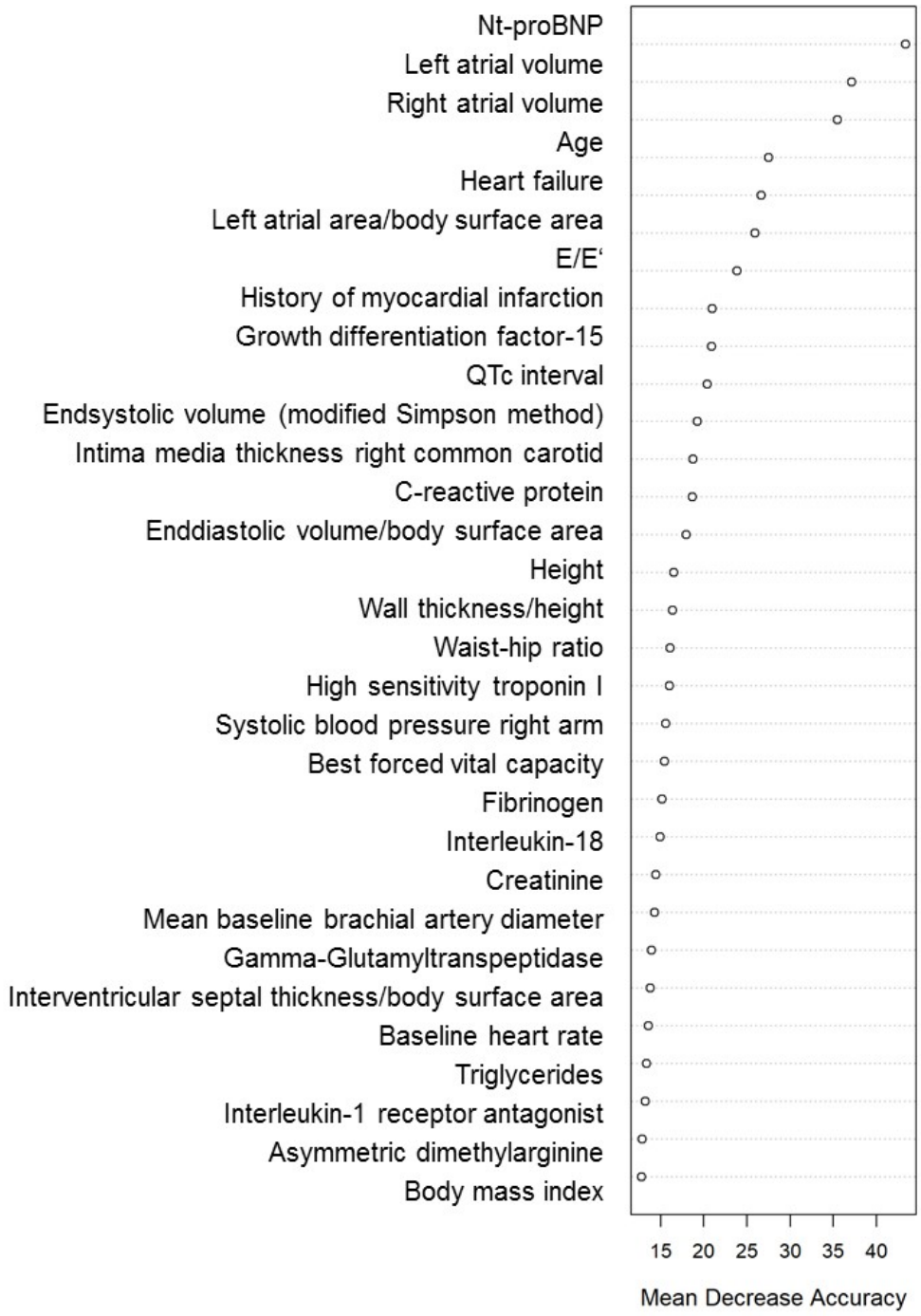
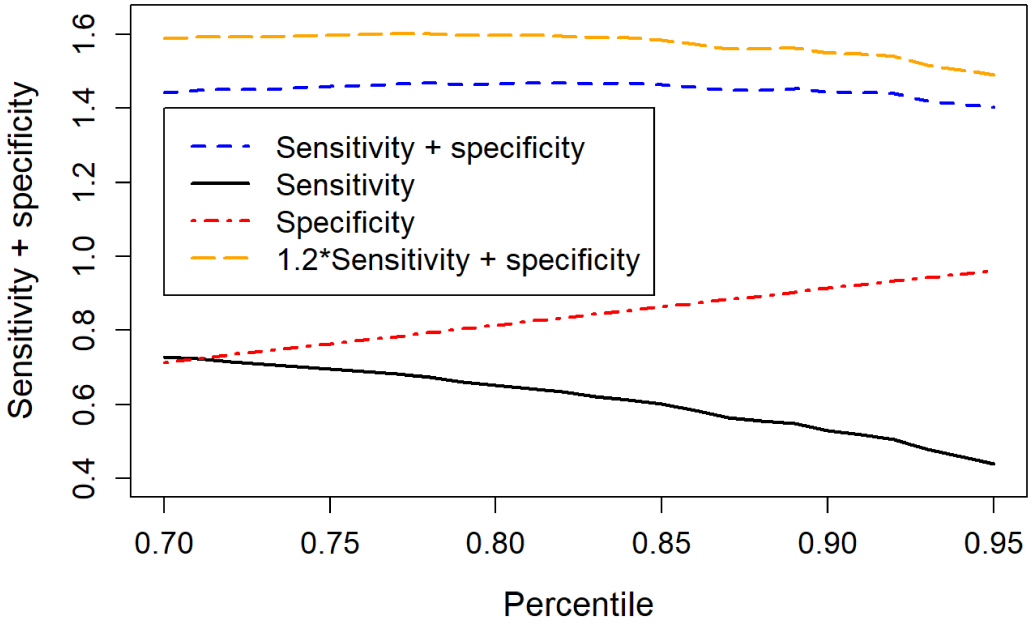
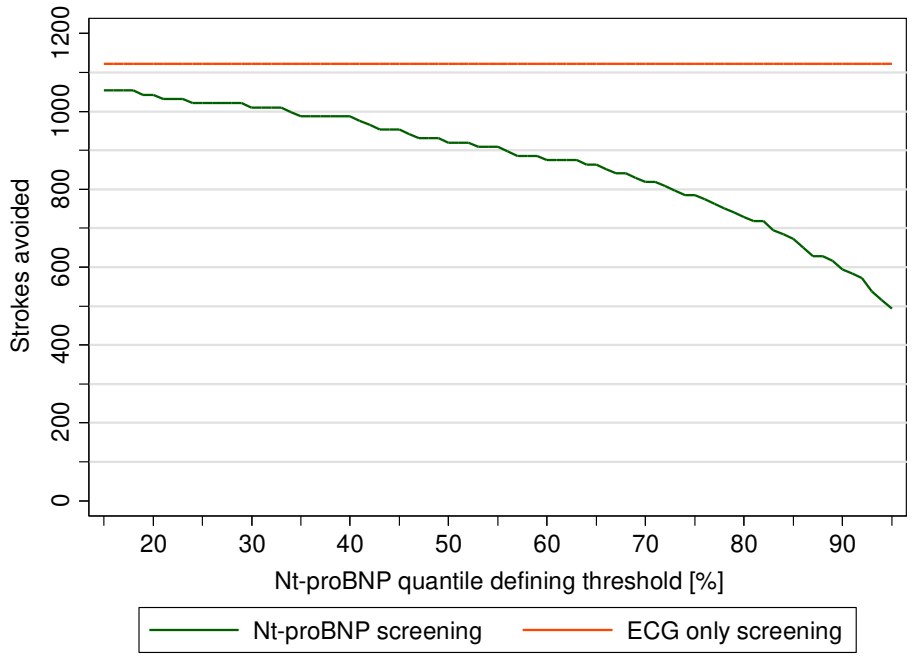
Supplementary Figure 3. Random forest selection of variables by importance (N=15005).



Supplementary Figure 4. Sensitivity and specificity for Nt-proBNP across the upper percentiles of Nt-proBNP concentrations. Nt-proBNP stands for N-terminal pro B-type natriuretic peptide.

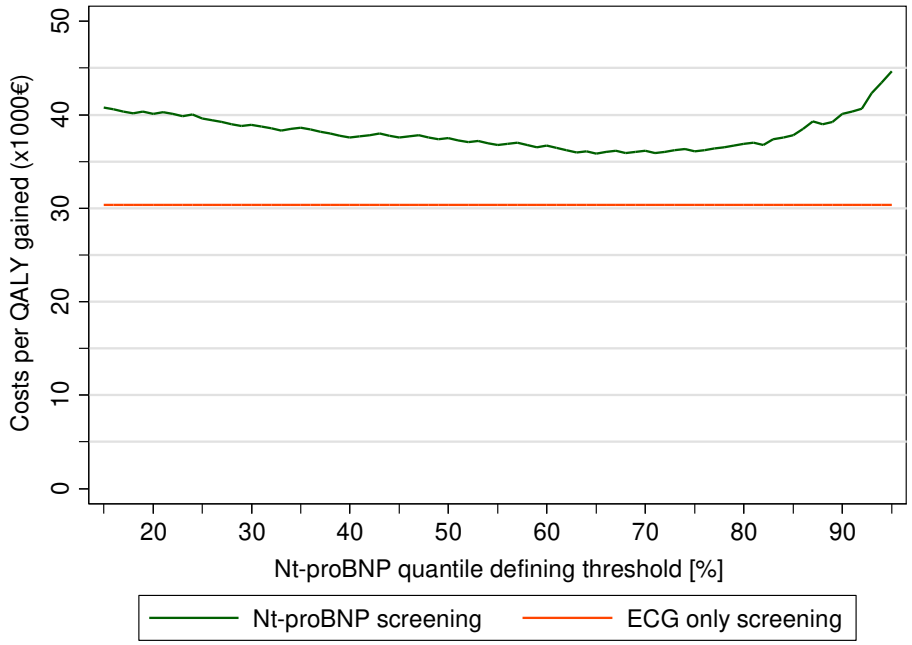


Supplementary Figure 5. Number of strokes avoided by Nt-proBNP quantile.
Nt-proBNP stands for N-terminal pro B-type natriuretic peptide.



Supplementary Figure 6. Costs per QALY gained by Nt-proBNP quantile.

Nt-proBNP stands for N-terminal pro B-type natriuretic peptide; QALY for quality-adjusted life year.



Supplementary Table 5. Distribution of individuals with known AF (n=355) and new AF (n=25) by AF risk scoring weighted for residence, age and sex of the population in Mainz and in Mainz-Bingen Area (n=14,937).

Atrial fibrillation status	**Risk Score <5%**	**Risk Score 5-10%**	**Risk Score >10%**
Known atrial fibrillation, N (%)	168 (7.7)	88 (0.6)	7 (0.0)
New atrial fibrillation, N (%)	10 (3.2)	7 (0.6)	8 (0.1)

Distribution of individuals with known AF (n=344) and new AF (n=25) by Nt-proBNP threshold (120 ng/L) weighted for residence, age and sex of the population in Mainz and in Mainz-Bingen Area (n=14,103).

Atrial fibrillation status	**Nt-proBNP <120%**	**Nt-proBNP >120%**
Known atrial fibrillation, N (%)	120 (0.9)	224 (1.6)
New atrial fibrillation, N (%)	4(0.0)	21 (0.1)

Mean values and standard deviations for continuous variables, median and 25th/75th percentiles for skewed continuous variables, or percent and a 95% confidence interval for categorical variables.

Nt-proBNP stands for N-terminal pro B-type natriuretic peptide. AF stands for atrial fibrillation

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