

SUPPLEMENTARY MATERIAL

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A biomarker-based risk score to predict risk of death in patients with atrial fibrillation: The ABC (Age, Biomarkers, Clinical history) risk score

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Supplementary Table I

C-indices for all-cause mortality according to the different ABC-risk scores; ABC-death, ABC-stroke, and ABC-bleeding

	Full cohort
<i>Derivation cohort</i>	
ABC-death	0.74 [0.73, 0.76]
ABC-stroke	0.68 [0.67, 0.70]
ABC-bleeding	0.70 [0.68, 0.72]
CHA ₂ DS ₂ -VASc	0.59 [0.57, 0.61]
<i>Validation cohort</i>	
ABC-death	0.74 [0.72, 0.76]
ABC-stroke	0.67 [0.65, 0.69]
ABC-bleeding	0.70 [0.68, 0.73]
CHA ₂ DS ₂ -VASc	0.58 [0.56, 0.61]

Supplementary Table II

C-indices for all-cause mortality according to the different ABC-risk scores; ABC-death, ABC-stroke, and ABC-bleeding

<i>Derivation cohort</i>	
ABC-death score	0.74 [0.73, 0.76]
ABC-stroke score	0.68 [0.67, 0.70]
ABC-bleeding score	0.70 [0.68, 0.72]
<i>Validation cohort</i>	
ABC-death score	0.74 [0.72, 0.76]
ABC-stroke score	0.67 [0.65, 0.69]
ABC-bleeding score	0.70 [0.68, 0.73]

Supplementary Table III

Event rates and hazard ratios between ABC-death risk classes for the derivation and the validation cohorts

Risk class	N	Events	Incidence rate*	Hazard ratio
Derivation cohort				
Low (0 - 2 %)	6488	183	1.39 [1.20, 1.61]	1.00 (ref)
Intermediate (2 - 5 %)	5556	368	3.44 [3.10, 3.81]	2.49 [2.09, 2.97]
High (5 - 10 %)	1872	286	8.37 [7.43, 9.40]	6.07 [5.45, 7.31]
Very high (> 10 %)	695	210	18.49 [16.07, 21.16]	13.54 [11.10, 16.51]
Validation cohort				
Low (0 - 2 %)	3642	84	1.14 [0.91, 1.42]	1.00 (ref)
Intermediate (2 - 5 %)	3262	225	3.51 [3.06, 4.00]	3.07 [2.39, 3.95]
High (5 - 10 %)	1161	166	7.55 [6.45, 8.79]	6.63 [5.10, 8.62]
Very high (> 10 %)	483	119	14.25 [11.81, 17.05]	12.60 [9.53, 16.66]

* per 100 person-years

Supplementary Table IV

C-indices for the contemporary ABC-death score without GDF-15 in the full cohorts and in subgroups

A. All-cause mortality

	Full cohort	No prior stroke/TIA	No prior heart failure	TTR <65%	NOAC*
<i>Derivation cohort; Events/N</i>	1047/14611	816/11858	575/10080	354/4165	506/7319
ABC-death (cTnT)	0.74 [0.72, 0.75]	0.74 [0.72, 0.76]	0.72 [0.70, 0.74]	0.75 [0.72, 0.77]	0.74 [0.71, 0.76]
ABC-death (cTnI)	0.74 [0.73, 0.76]	0.75 [0.73, 0.76]	0.73 [0.71, 0.75]	0.74 [0.71, 0.77]	0.74 [0.72, 0.77]
<i>Validation cohort; Events/N</i>	594/8548	474/6893	324/6095	101/1119	391/5697
ABC-death (cTnT)	0.73 [0.71, 0.75]	0.73 [0.71, 0.76]	0.70 [0.68, 0.73]	0.74 [0.69, 0.79]	0.74 [0.72, 0.77]
ABC-death (cTnI)	0.71 [0.69, 0.73]	0.71 [0.69, 0.73]	0.68 [0.65, 0.70]	0.70 [0.64, 0.75]	0.72 [0.70, 0.75]

B. Cardiovascular mortality

	Full cohort	No prior stroke/TIA	No prior heart failure	TTR <65%	NOAC*
<i>Derivation cohort; Events/N</i>	532/14611	406/11858	268/10080	196/4165	506/7319
ABC-death (cTnT)	0.76 [0.74, 0.78]	0.76 [0.73, 0.78]	0.74 [0.71, 0.77]	0.78 [0.74, 0.81]	0.74 [0.71, 0.77]
ABC-death (cTnI)	0.74 [0.72, 0.75]	0.76 [0.74, 0.78]	0.75 [0.72, 0.78]	0.77 [0.74, 0.81]	0.75 [0.72, 0.78]
<i>Validation cohort; Events/N</i>	385/8548	306/6893	182/6095	76/1119	391/5697
ABC-death (cTnT)	0.76 [0.74, 0.79]	0.76 [0.73, 0.79]	0.71 [0.67, 0.75]	0.77 [0.72, 0.82]	0.76 [0.73, 0.79]
ABC-death (cTnI)	0.74 [0.72, 0.77]	0.74 [0.71, 0.77]	0.68 [0.64, 0.72]	0.73 [0.67, 0.79]	0.75 [0.67, 0.78]

TTR - Time in therapeutic range (INR 2.0-3.0)

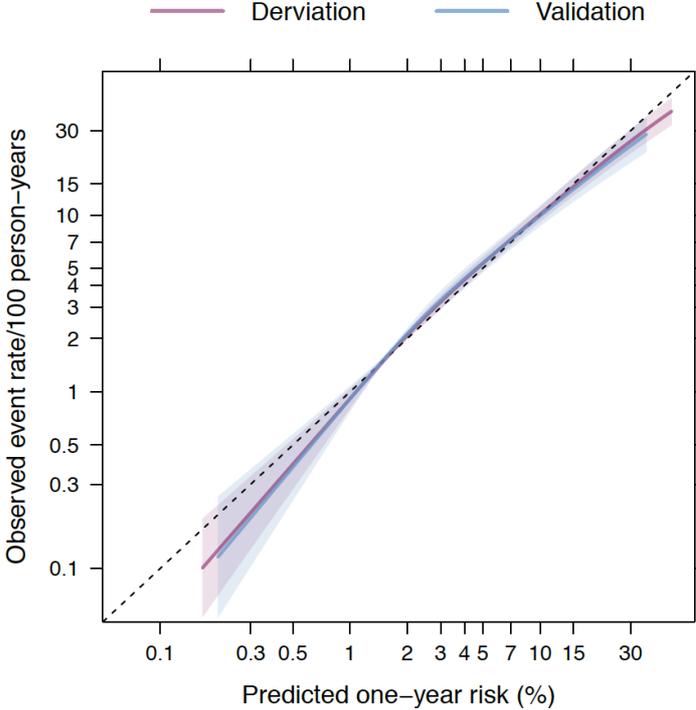
Contemporary ABC-death - Age, Biomarkers (cardiac troponin and NT-proBNP), Clinical history of heart failure)

NOAC - non-vitamin K antagonist oral anticoagulation

*Apixaban in the derivation cohort and dabigatran in the validation cohort

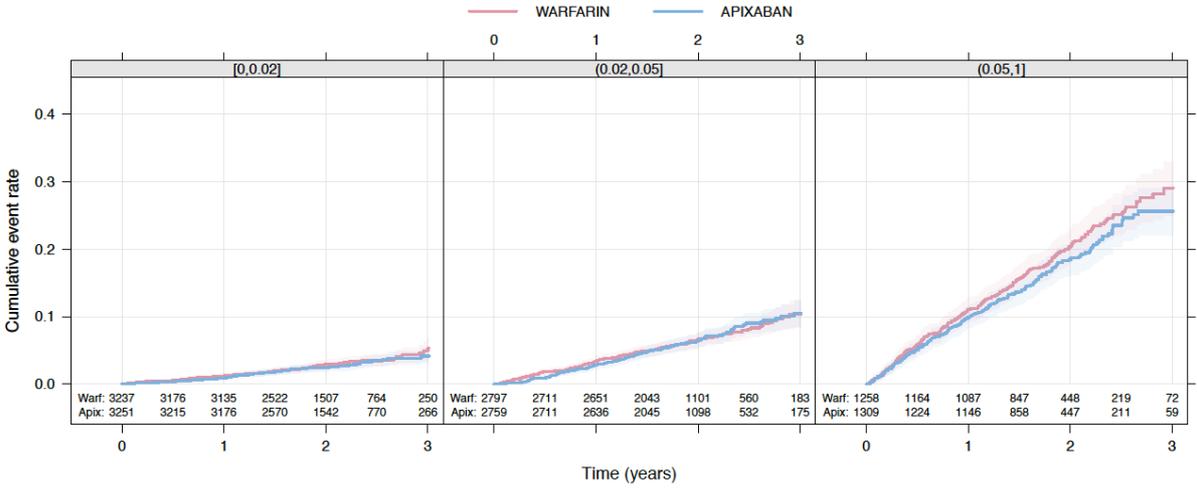
Supplementary Figure I

Calibration of the ABC-death model for all-cause mortality



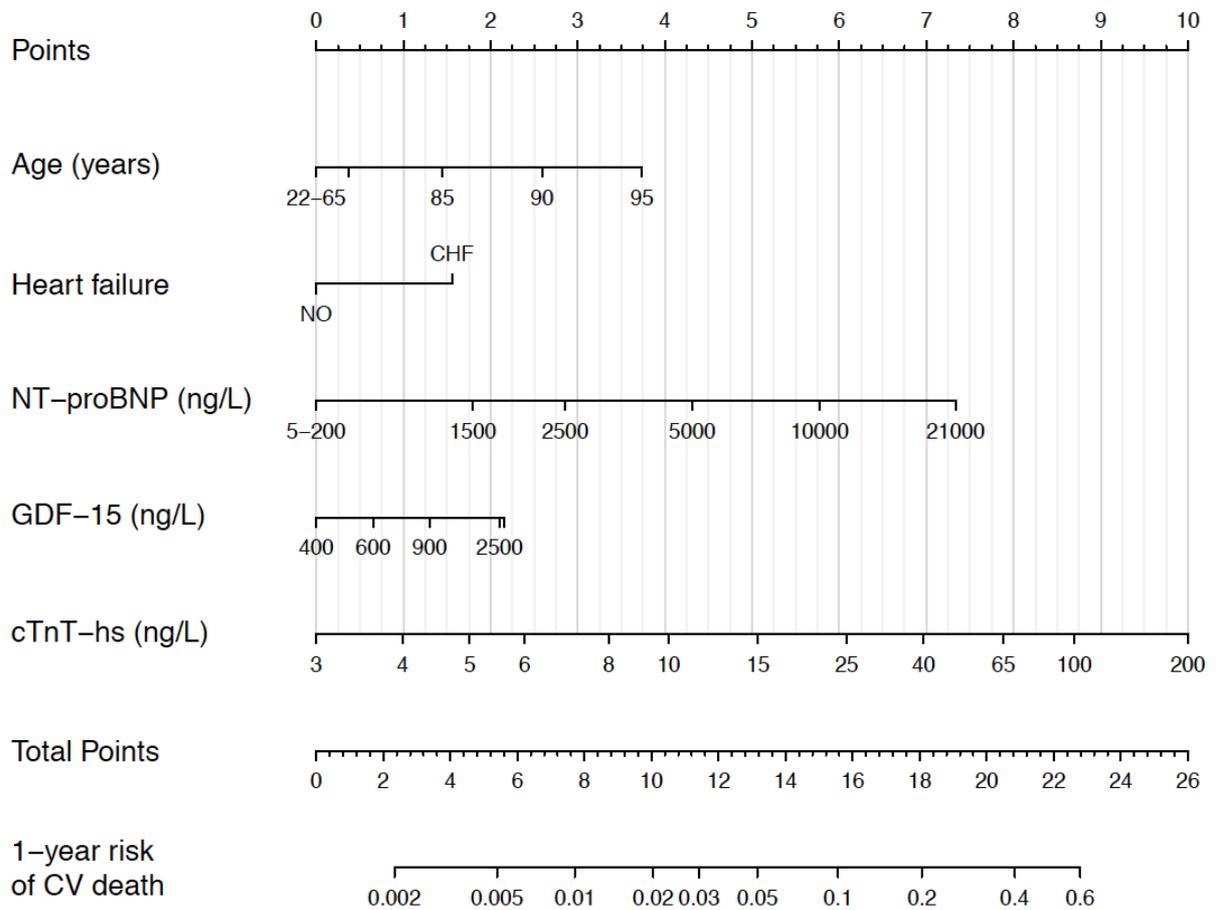
Supplementary Figure II

Kaplan–Meier estimated cumulative event rate by randomized treatment (colour) by predicted ABC-death risk classes (panel): 0-1%, 1–2%, and $\geq 2\%$ for all-cause mortality



Supplementary Figure III

Nomogram for the ABC-death for cardiovascular mortality



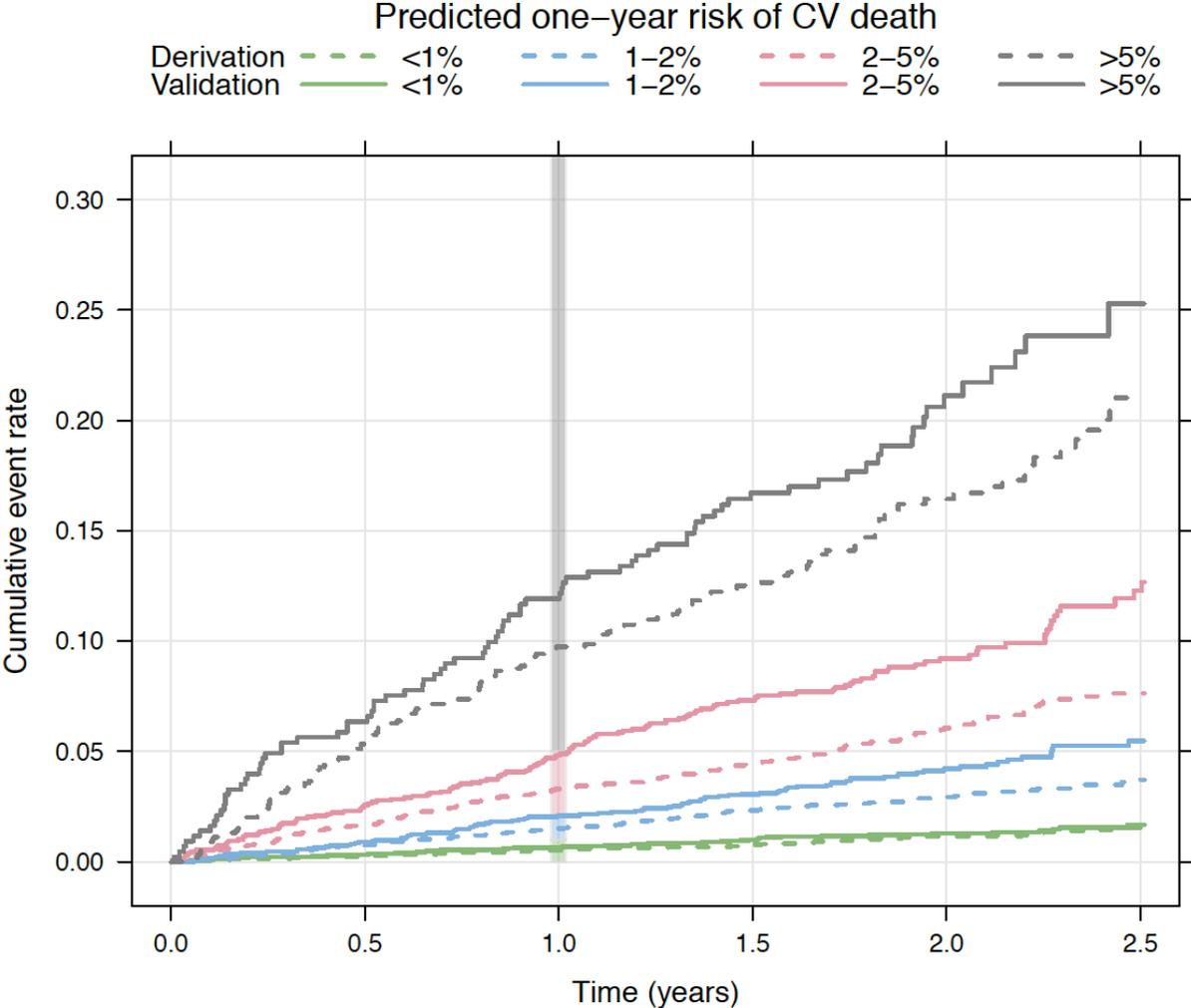
For each predictor, read the points assigned on the 0-10 scale at the top and then sum these points. Find the number on the “Total Points” scale and then read the corresponding predictions of 1-year risk of death below it.

Continuous variables are represented from the 1st to the 99th percentiles.

The prediction model is preferably used as a web-based calculator or app.

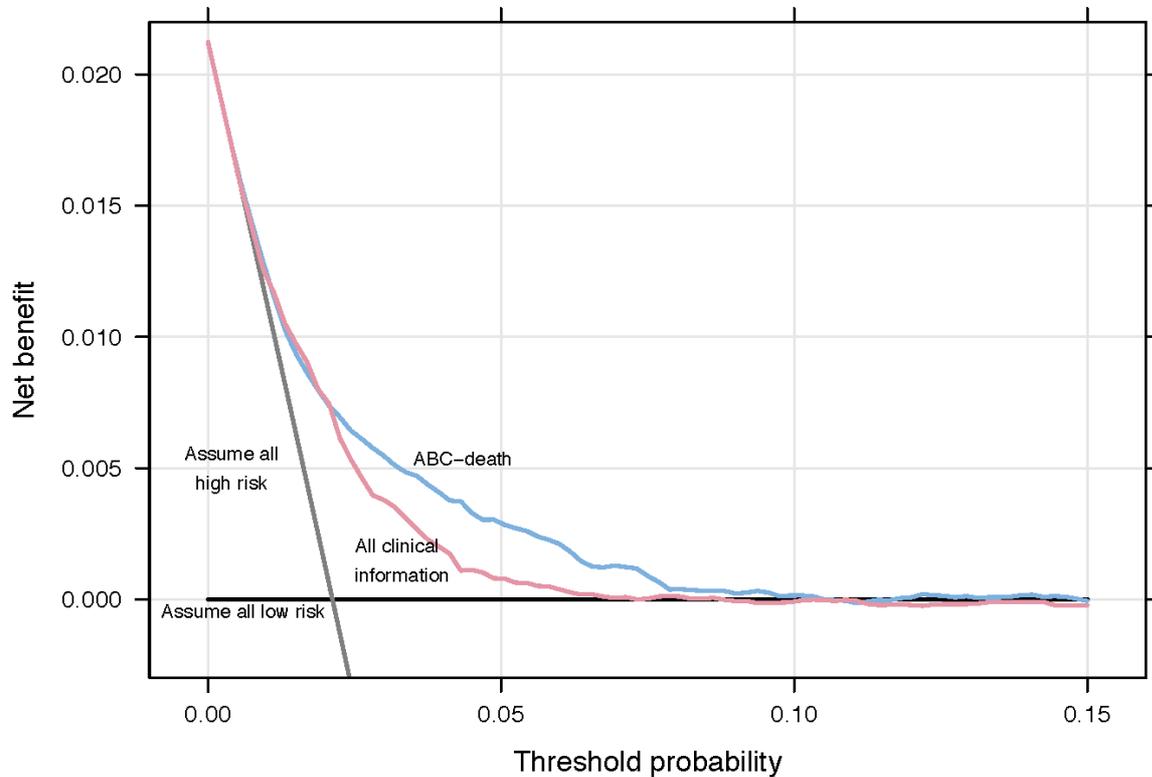
Supplementary Figure IV

Cumulative risk of cardiovascular death by predicted 1-year ABC-death risk group for the derivation (dashed lines, n=14,611) and the validation (solid lines, n=8,548) data



Supplementary Figure VI

Decision curve analysis for cardiovascular mortality



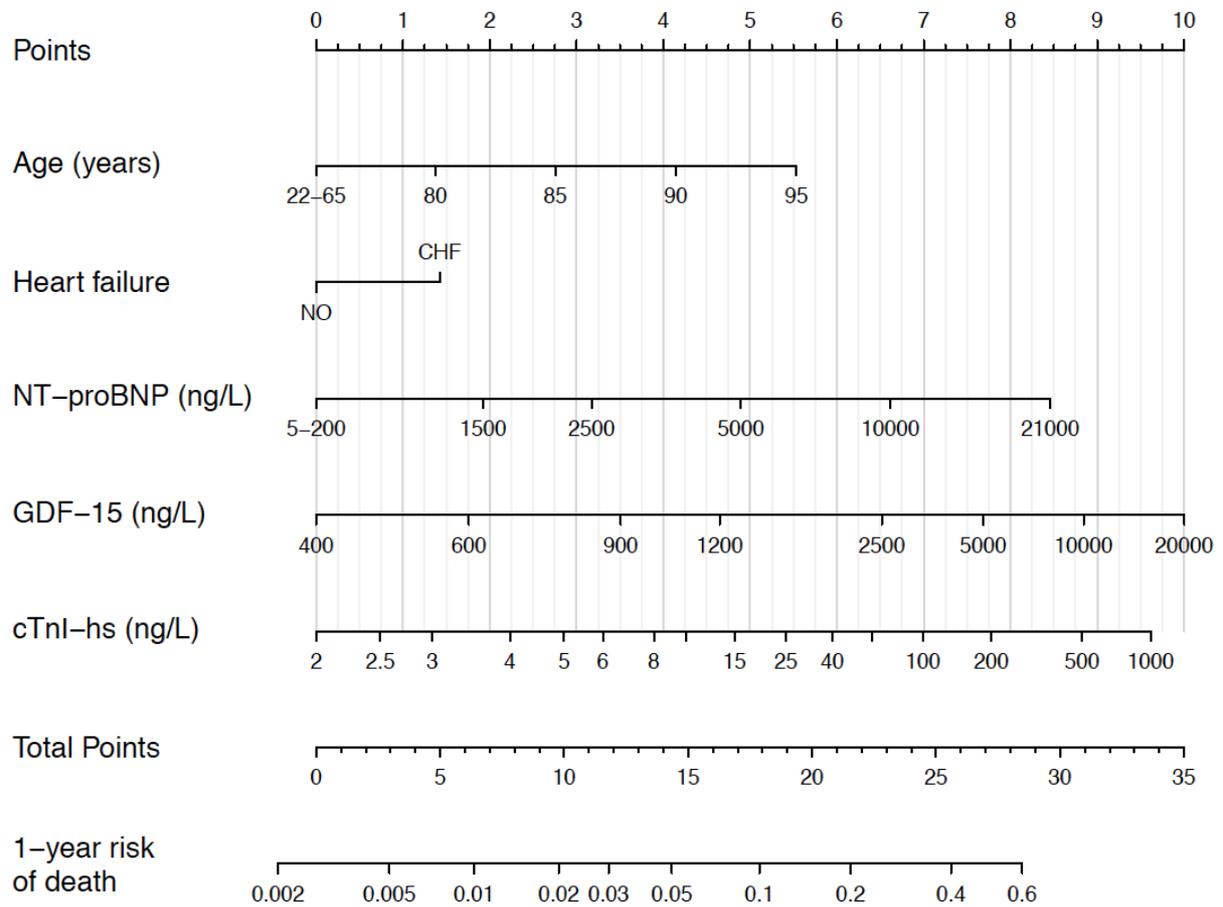
Net benefit of using a model to predict one-year event of cardiovascular death as compared with strategies of "assume high risk to all" or "assume low risk to all" for different thresholds. A multivariable model based on all clinical information was used for comparison. The analysis is based on 24,348 patients from the ARISTOTLE and RE-LY trials.

ABC-death - Age, Biomarkers (cardiac troponin, NT-proBNP, and GDF-15), Clinical history of heart failure)

All clinical information - a model solely consisting of clinical variables (age, gender, smoking, alcohol, prior stroke/TIA, diabetes, hypertension, heart failure, prior myocardial infarction, peripheral arterial disease, vascular disease, AF-type, and prior bleeding)

Supplementary Figure VI

Nomogram for the ABC-death score using cTnI-hs (instead of cTnT-hs)



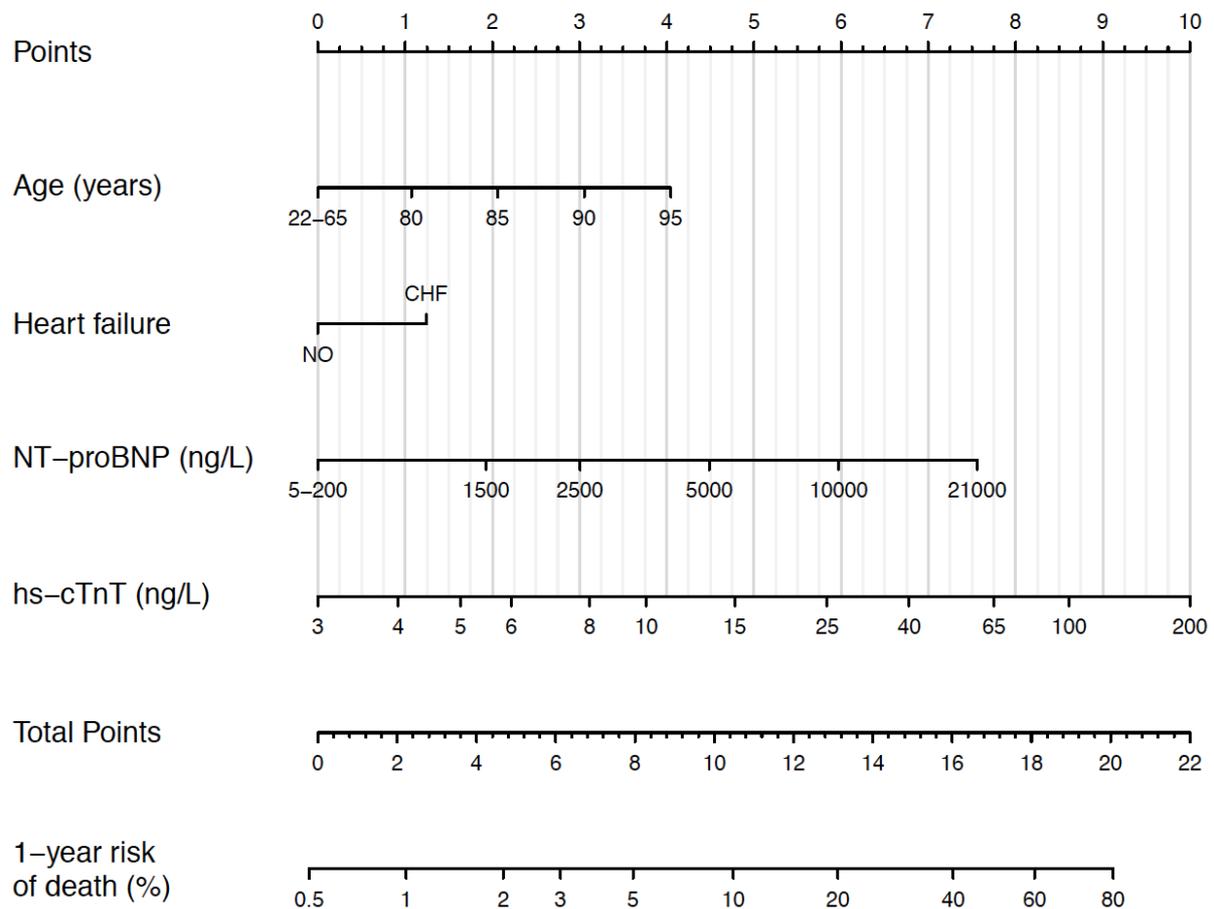
For each predictor, read the points assigned on the 0-10 scale at the top and then sum these points. Find the number on the “Total Points” scale and then read the corresponding predictions of 1-year risk of death below it.

Continuous variables are represented from the 1st to the 99th percentiles.

The prediction model is preferably used as a web-based calculator or app.

Supplementary Figure VII

Nomogram for the ABC-death score without GDF-15 for all-cause mortality



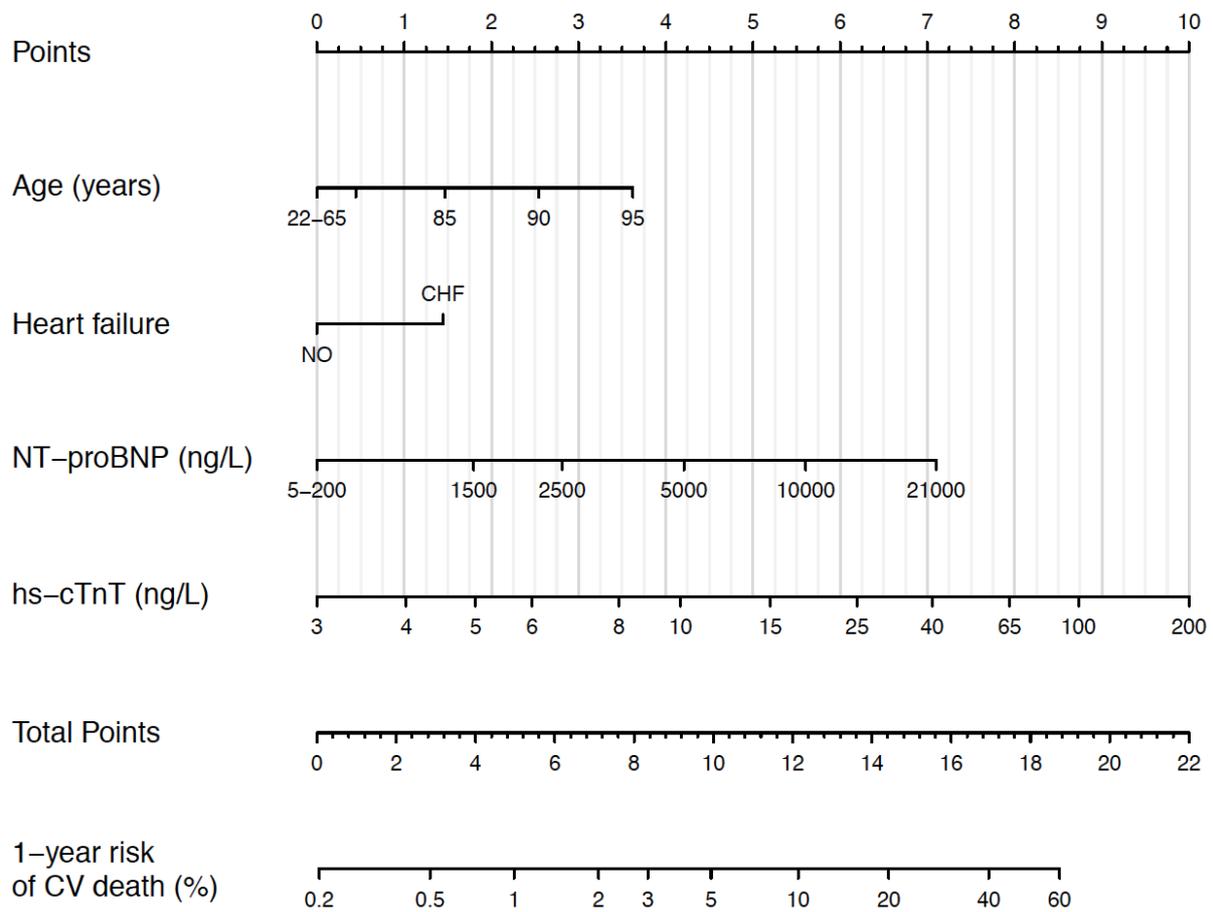
For each predictor, read the points assigned on the 0-10 scale at the top and then sum these points. Find the number on the “Total Points” scale and then read the corresponding predictions of 1-year risk of death below it.

Continuous variables are represented from the 1st to the 99th percentiles.

The prediction model is preferably used as a web-based calculator or app.

Supplementary Figure VIII

Nomogram for the ABC-death score without GDF-15 for cardiovascular mortality



For each predictor, read the points assigned on the 0-10 scale at the top and then sum these points. Find the number on the “Total Points” scale and then read the corresponding predictions of 1-year risk of death below it.

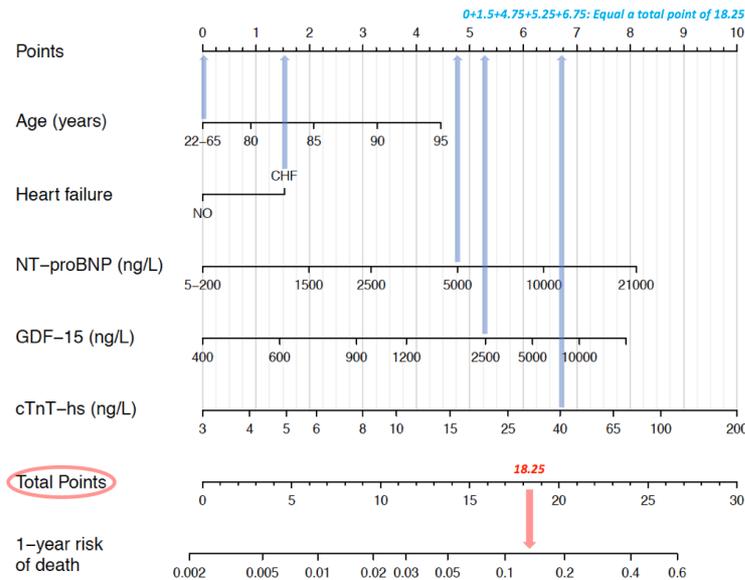
Continuous variables are represented from the 1st to the 99th percentiles.

The prediction model is preferably used as a web-based calculator or app.

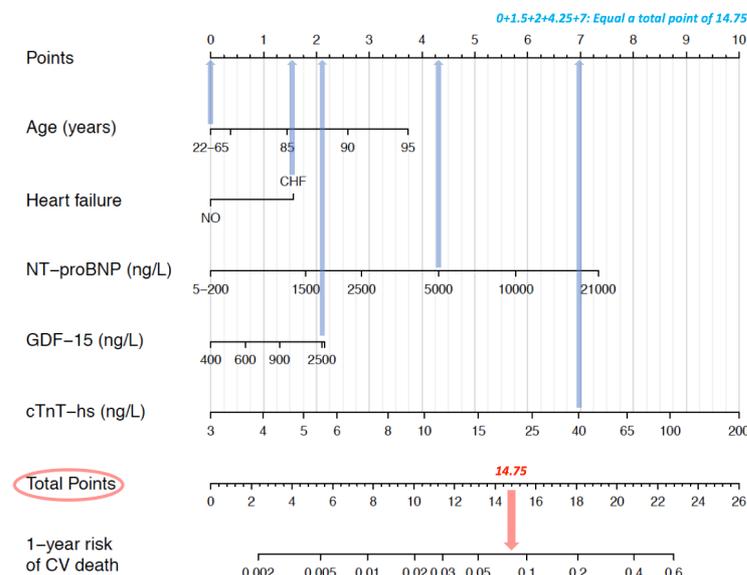
Supplementary Figure IX

Exemplified application of the nomogram

Example: A 64-year old man with atrial fibrillation, hypertension, chronic heart failure, NT-proBNP level of 5000 ng/L, GDF-15 2500 ng/L, and troponin T (high sensitivity) of 40 ng/L. By using the ABC-death score nomogram receives 0p for age, 1.5p for heart failure, 4.75p for NT-proBNP, 5.25p for GDF-15, and 6.75p for troponin levels. A total of 18.25p would equal a predicted 1-year risk of all-cause mortality of approximately 14%.



For the same patient, by using the ABC-death score nomogram for cardiovascular mortality, receives 0p for age, 1.5p for heart failure, 4.25p for NT-proBNP, 2p for GDF-15, and 7p for troponin levels. A total of 14.75p would equal a predicted 1-year risk of cardiovascular mortality of approximately 8%.



Summary of the derivation and validation cohorts

Derivation cohort

ARISTOTLE was a double blind, randomised clinical trial that enrolled 18,201 patients with AF at increased risk for stroke at 1034 clinical sites in 39 countries between December 2006 and April 2010. Patients included had paroxysmal, persistent or permanent AF, or atrial flutter, and one or more of the following risk factors; age ≥ 75 years, prior stroke, transient ischemic attack (TIA), or systemic embolus, heart failure, diabetes mellitus, or hypertension requiring pharmacologic treatment. Among the exclusion criteria were; clinically significant mitral stenosis, mechanical heart valve, recent stroke, previous intracranial haemorrhage, creatinine clearance less than 25 mL/min, or active alcohol or drug abuse. Participants were randomised to warfarin (n=9,081) or apixaban (n=9,120). The median length of follow-up was 1.7 years for the 14,537 participants with biomarker samples available at randomisation after exclusion of 45 (0.3%) patients with missing data.

External validation cohort

RE-LY was a prospective, multicentre, randomized trial comparing two blinded doses of dabigatran with open label warfarin that enrolled 18,113 patients with AF at 951 clinical sites in 44 countries between December 2005 and Mars 2009. Inclusion criteria were documented atrial fibrillation and at least one of the following risk factors for stroke: previous stroke or TIA; congestive heart failure or reduced left ventricular ejection fraction (<40%); at least 75 years of age; or at least 65 years of age with diabetes mellitus, hypertension, or coronary artery disease. Exclusion criteria included severe heart valve disorder, recent stroke, creatinine clearance less than 30 mL/min, or active liver disease. The median length of follow-up was 1.9 years for the 8,548 participants with biomarker samples available at randomisation.

Statistical methods (detailed)

In the first step a model including all candidate predictors (listed in Figure 1 in the main article) was fitted in 14,611 patients from the ARISTOTLE trial. The full model was then approximated, blinded for the outcome to avoid overfitting, by a smaller model including the most predictive variables. The approximation was done in the following way. First an ordinary least squares model was fitted with the estimated linear predictor from the full model as outcome and including the same predictors as in the full model. This model had, by definition, an R-squared of 1.0. A fast backward elimination algorithm was then applied to the model removing the least important variables until a good enough approximation was achieved with as few variables kept as possible. An alternative model was created in the same manner but replacing cTnT-hs with cTnI-hs. Similarly, a model was developed for cardiovascular mortality. In a subset of patients with additional biomarkers available, an extended biomarker model was developed which also incorporated D-dimer and IL-6 among the candidate variables. The final models were presented as nomograms. Risk categories were created according to 0-2%, 2-5%, 5-10%, and >10% risk for death within one year and 0-1%, 1-2%, 2-5%, and >5% for cardiovascular death within one year. The reason for choosing different class limits is that the incidence rate for cardiovascular death is lower than for total death.

Internal and external model validation

The model was internally validated using 150 bootstrap samples. External validation was conducted in 8,548 patients from the RE-LY trial. In the validation the predicted risk for each subject in the validation cohort was estimated by applying the model using the model coefficients derived in the derivation cohort. Thus, the model was not refitted in the validation data. In order to thoroughly compare the prognostication of death, the new

biomarker-based risk model was evaluated against a multivariable model solely based on clinical variables and the widely used CHA₂DS₂-VASc score, although originally created for stroke prediction.

Discrimination was assessed by Harrell's c-index²⁶ and by comparing Kaplan-Meier curves and hazard ratios between the predefined risk categories. Calibration was assessed by comparing observed one-year event rates with predictions from the final model. Clinical usefulness and net benefit were estimated with decision curve analysis.²⁷ The decision curve analysis estimate the net benefit of using the model for assigning subjects to either low or high risk for each possible threshold in comparison to not using the model and thus assuming either that everyone is at low risk or that everyone is at high risk. The net benefit at a given threshold gives the increased true positive rate without an increase of the false positive rate as compared to the two naïve approaches of assuming all low or all high risk. At a given threshold, the model with the highest net benefit is the superior model. The final model was also evaluated in different subgroups; without a history of stroke, without heart failure diagnosis, low time in therapeutic range (TTR), and in the groups randomised to apixaban and dabigatran therapy, respectively.

The analyses followed the framework for derivation and validation of prediction models proposed by Harrell, Steyerberg and Vergouwe, and Royston and Altman.^{26, 28, 29} The reporting followed the recently published TRIPOD statement.³⁰ All analyses were performed using R version 3.2.

ABC-death score equations

Models for all-cause mortality

Note that, in all models, before entering the variables in the equations, Age and NT-proBNP should be truncated as

$$\text{Age} = \max(\text{Age}, 65)$$

$$\text{NT-proBNP} = \max(\text{NT-proBNP}, 200)$$

and the biomarkers should be naturally log-transformed as

$$\text{hs-cTnT} = \ln(\text{hs-cTnT})$$

$$\text{hs-cTnI} = \ln(\text{hs-cTnI})$$

$$\text{NT-proBNP} = \ln(\text{NT-proBNP})$$

$$\text{GDF15} = \ln(\text{GDF15})$$

with hs-cTnT:

$$\text{Prob}(\text{death within one year}) = 1 - 0.9763^{\exp\{X_b\}}$$

where

$$\begin{aligned} X_b = & -7.218 + 0.3416 \text{ Heart failure} \\ & - 0.01305 \text{ Age} + 0.0001723 \max(\text{Age} - 66, 0)^3 \\ & - 0.0003446 \max(\text{Age} - 74, 0)^3 + 0.0001723 \max(\text{Age} - 82, 0)^3 \\ & + 0.04248 \text{ NT-proBNP} + 0.04728 \max(\text{NT-proBNP} - 5.303, 0)^3 \\ & - 0.1139 \max(\text{NT-proBNP} - 6.708, 0)^3 + 0.0666 \max(\text{NT-proBNP} - 7.705, 0)^3 \\ & + 0.7963 \text{ GDF15} - 0.1923 \max(\text{GDF15} - 6.608, 0)^3 \\ & + 0.3410 \max(\text{GDF15} - 7.231, 0)^3 - 0.1487 \max(\text{GDF15} - 8.037, 0)^3 \\ & + 0.6875 (\text{hs-cTnT} - 0.07336 \max(\text{hs-cTnT} - 1.705, 0)^3 \\ & + 0.1344 \max(\text{hs-cTnT} - 2.389, 0)^3 - 0.06104 \max(\text{hs-cTnT} - 3.211, 0)^3 \end{aligned}$$

with hs-cTnI:

$$\text{Prob}(\text{death within one year}) = 1 - 0.9770^{\exp\{X_b\}}$$

where

$$\begin{aligned} X_b = & -7.525 + 0.2902 \text{ Heart failure} \\ & - 0.006738 \text{ Age} + 0.0001651 \max(\text{Age} - 66, 0)^3 \\ & - 0.0003303 \max(\text{Age} - 74, 0)^3 + 0.0001651 \max(\text{Age} - 82, 0)^3 \\ & + 0.009926 \text{ NT-proBNP} + 0.04911 \max(\text{NT-proBNP} - 5.303, 0)^3 \\ & - 0.1183 \max(\text{NT-proBNP} - 6.708, 0)^3 + 0.06919 \max(\text{NT-proBNP} - 7.705, 0)^3 \\ & + 0.8850 \text{ GDF15} - 0.2036 \max(\text{GDF15} - 6.608, 0)^3 \\ & + 0.3611 \max(\text{GDF15} - 7.231, 0)^3 - 0.1575 \max(\text{GDF15} - 8.037, 0)^3 \\ & + 0.6761 \text{ hs-cTnI} - 0.07783 \max(\text{hs-cTnI} - 0.8329, 0)^3 \\ & + 0.1262 \max(\text{hs-cTnI} - 1.686, 0)^3 - 0.04841 \max(\text{hs-cTnI} - 3.059, 0)^3 \end{aligned}$$

Models for cardiovascular death

Note that, in all models, before entering the variables in the equations, Age and NT-proBNP should be truncated as

$$\text{Age} = \max(\text{Age}, 70)$$

$$\text{NT-proBNP} = \max(\text{NT-proBNP}, 200)$$

and the biomarkers should be naturally log-transformed as

$$\text{hs-cTnT} = \ln(\text{hs-cTnT})$$

$$\text{hs-cTnI} = \ln(\text{hs-cTnI})$$

$$\text{NT-proBNP} = \ln(\text{NT-proBNP})$$

$$\text{GDF15} = \ln(\text{GDF15})$$

with hs-cTnT:

$$\text{Prob}(\text{death within one year}) = 1 - 0.9876^{\exp\{X_b\}}$$

where

$$\begin{aligned} X_b = & -5.952 + 0.4635 \text{ Heart failure} \\ & - 0.01244 \text{ Age} + 0.0003442 \max(\text{Age} - 71, 0)^3 \\ & - 0.0006393 \max(\text{Age} - 77, 0)^3 + 0.0002951 \max(\text{Age} - 84, 0)^3 \\ & + 0.05166 \text{ NT-proBNP} + 0.05677 \max(\text{NT-proBNP} - 5.303, 0)^3 \\ & - 0.1367 \max(\text{NT-proBNP} - 6.708, 0)^3 + 0.07998 \max(\text{NT-proBNP} - 7.705, 0)^3 \\ & + 0.4796 \text{ GDF15} - 0.1769 \max(\text{GDF15} - 6.608, 0)^3 \\ & + 0.3137 \max(\text{GDF15} - 7.231, 0)^3 - 0.1368 \max(\text{GDF15} - 8.037, 0)^3 \\ & + 1.026 \text{ hs-cTnT} - 0.1508 \max(\text{hs-cTnT} - 1.705, 0)^3 \\ & + 0.2763 \max(\text{hs-cTnT} - 2.389, 0)^3 - 0.1255 \max(\text{hs-cTnT} - 3.211, 0)^3 \end{aligned}$$

with hs-cTnI:

$$\text{Prob}(\text{death within one year}) = 1 - 0.9881^{\exp\{X_b\}}$$

where

$$\begin{aligned} X_b = & -6.723 + 0.3977 \text{ Heart failure} \\ & - 0.001642 \text{ Age} + 0.0003115 \max(\text{Age} - 71, 0)^3 \\ & - 0.0005785 \max(\text{Age} - 77, 0)^3 + 0.000267 \max(\text{Age} - 84, 0)^3 \\ & + 0.01869 \text{ NT-proBNP} + 0.05777 \max(\text{NT-proBNP} - 5.303, 0)^3 \\ & - 0.1391 \max(\text{NT-proBNP} - 6.708, 0)^3 + 0.08138 \max(\text{NT-proBNP} - 7.705, 0)^3 \\ & + 0.6364 \text{ GDF15} - 0.2133 \max(\text{GDF15} - 6.608, 0)^3 \\ & + 0.3782 \max(\text{GDF15} - 7.231, 0)^3 - 0.1649 \max(\text{GDF15} - 8.037, 0)^3 \\ & + 0.9549 \text{ hs-cTnI} - 0.1157 \max(\text{hs-cTnI} - 0.8329, 0)^3 \\ & + 0.1877 \max(\text{hs-cTnI} - 1.686, 0)^3 - 0.07197 \max(\text{hs-cTnI} - 3.059, 0)^3 \end{aligned}$$