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Prediction of early death after atrial fibrillation diagnosis using a machine learning approach: A French nationwide cohort study

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Abstract:

Aims: Atrial fibrillation is associated with important mortality but the usual clinical risk factor based scores only modestly predict mortality. This study aimed to develop machine learning models for the prediction of death occurrence within the year following atrial fibrillation diagnosis and compare predictive ability against usual clinical risk scores.

Methods and Results: We used a nationwide cohort of 2,435,541 newly diagnosed atrial fibrillation patients seen in French hospitals from 2011 to 2019. Three machine learning models were trained to predict mortality within the first year using a training set (70% of the cohort). The best model was selected to be evaluate and compared with previously published scores on the validation set (30% of the cohort). Discrimination of the best model was evaluated using the C index. Within the first year following atrial fibrillation diagnosis, 342,005 patients (14.4%) died after a period of 83 (SD 98) days (median 37 [10-129]). The best machine learning model selected was a deep neural network with a C index of 0.785 (95% CI, 0.781-0.789) on the validation set. Compared to clinical risk scores, the selected model was superior to the CHA_2DS_2-VASc and HAS-BLED risk scores and superior to dedicated scores such as Charlson Comorbidity Index and Hospital Frailty Risk Score to predict death within the year following atrial fibrillation diagnosis (C indexes: 0.597; 0.562; 0.643; 0.626 respectively. P<0.0001).

Conclusion: Machine learning algorithms predict early death after atrial fibrillation diagnosis and may help clinicians to better risk stratify atrial fibrillation patients at high risk of mortality.

Translational Perspective:

Atrial fibrillation is responsible for a substantial proportion of short-term mortality making futile, complex and expensive, cardiovascular procedures/devices or therapies that will not change overall prognosis due to competing risk between cardiovascular and non-cardiovascular death. Machine learning algorithms predict early mortality in atrial fibrillation patients with a better ability than previously developed traditional clinical risk scores. A Machine learning approach may help clinicians to better stratify atrial fibrillation patients at high risk of mortality and may assist physicians in decision-making when managing atrial fibrillation patients in a holistic and integrated care manner.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an estimated prevalence in adults between 2% and 4%, and is associated with a high burden of morbidity and mortality [1,2]. During the last decades, improvements in the care of patients with AF have been confirmed, including the development of stroke and bleeding risk calculators and the validation of the benefits of oral anticoagulation on stroke and survival [3-6].

However, mortality is the most frequent major clinical event after the diagnosis of AF with a cumulative incidence of 19.5%, 28.2% and 48.8% at 1, 2 and 5 years respectively and an overall 1-year all-cause mortality which has not improved from 2007 to 2015 despite a significant reduction in the rate of cardiovascular (CV) death [7-9]. This trend has been observed globally, with age-standardized AF mortality rates remaining stable between 1990 and 2017 but increasing in poorer countries [10]. Although stroke is the most feared complication of AF, stroke accounted for only 7.0% of deaths in AF, with sudden cardiac death (22.25%), progressive heart failure (15.1%), and non-CV death (35.8%) accounting for the majority of deaths in the RE-LY trial [11]. Indeed, a high residual risk of stroke and CV complications remains despite the use of oral anticoagulation [12,13].

Recognizing AF patients particularly at risk of non-CV death is therefore crucial for the management of concomitant non-CV conditions and hence reducing mortality. Even though the existence of an association between contemporary clinical risk scores such as CHA_2DS_2-VASc score or HAS-BLED score and increased risk of all-cause death has been previously reported, these scores are not dedicated for the prediction of death and importantly, the predictive ability is modest [14]. More integrative tools such as the Charlson Comorbidity Index (CCI, as a measure of multimorbidity) or Hospital Frailty Risk Score (HFRS, as a measure of frailty) have been specifically developed to predict mortality but without wide validation in AF populations [15,16].

Machine learning (ML) is emerging as a new method for improving the prediction of adverse outcomes in the field of CV disease, including AF [17]. Highly effective in large data sets with a multiplicity of variables, it has already been effective for prognostic prediction and decision making in several diseases [18-20].

This study firstly aimed to train and evaluate machine learning models for the prediction of death occurrence within the year following AF diagnosis and second, to compare predictive ability again the usual clinical risk scores.

2. Method

2.1. Study population

This longitudinal cohort study was based on the French hospitalization database, the PMSI (Programme de Médicalisation des Systèmes d'Information), covering hospital care across the entire population. In France, each hospital discharge from one of the 1,546 French healthcare facilities, whether public or private hospital, must be registered in the National Hospital Discharge Database. A standardized discharge summary is collected for every hospital stay and categorized into a single medical or surgical diagnosis-related group based on the International Classification of

Diseases, Tenth Revision (ICD-10). A unique patient identification number make it possible to link multiple hospital stays across time corresponding to a single patient without revealing his or her identity. The reliability of PMSI data has already been assessed and used previously to study patients with stroke and AF [21-23].

Data for all patients admitted with AF in France from January 2011 to December 2019 were collected from the PMSI. The study included adults (aged ≥18 years) with a diagnosis of atrial fibrillation (ICD-10 code I48 and its subsections) coded as the primary diagnosis (ie, the health problem that justified admission to hospital), the related diagnosis (ie, potential chronic disease or health state during hospital stay), or the significantly associated diagnosis (ie, comorbidity or associated complication) who were hospitalized between January 1, 2011, and December 31, 2019. Baseline characteristics corresponded to all the diagnoses collected at discharge of the first hospital stay were a diagnosis of AF was reported, as well as past clinical history in the year before the admission to establish history before atrial fibrillation.

The medical information contained in the database is anonymous and protected by professional confidentiality. Consequently, ethics review was not required and patient consent was not sought. The study was conducted retrospectively, patients were not involved in its conduct, and there was no impact on their care. This type of study was approved by the institutional review board of the Pole Coeur Thorax Vaisseaux from the Trousseau University Hospital (Tours, France) on December 1, 2015, and registered as a clinical audit. Procedures for data collection and management were approved by the Conseil National de l'Informatique et des Libertés (CNIL), the independent national ethics committee protecting human rights in France, which ensures that all information is kept confidential and anonymous (authorization no. 1749007).

2.2. Follow-Up and Outcomes

Each patient was followed until death or 31st December 2019. All-cause mortality was defined as any death occurring during follow-up and cause of death (CV or non-CV) was identified based on the main diagnosis during hospitalisation resulting in death based on ICD-10 codes (CV death: I00–I99 – Diseases of the heart and circulatory system; non-CV death: any other ICD-10 codes). The main outcome was the occurrence of all cause death within the year following the diagnosis of atrial fibrillation.

2.3. Feature selection and model development

From the imputed dataset, continuous variables were centralized to the mean and scaled to the standard deviation, whereas categorical variables were coded into binary numbers (0 and 1). Then, the whole dataset was randomly split into derivation (training set) and validation cohort (test set) (7:3). To increase the prediction accuracy and make the model practical, only most critical variables (features) in the derivation cohort were subsequently used for model building after feature selection by a random forest classifier (RFC).

Best selected features then served as an input to train three well-accepted ML models, including logistic regression with L2 regularization (LR), RFC and deep neural network (DNN) [17]. ML models were implemented in Python using open-source packages: Scikit-learn version 1.1.1.

A random train-test split methodology and cross-validation were then applied, as previously published, and is described as follows [24]: ML models were trained and optimized on the derivation cohort (training set) using a random search algorithm with 5-fold cross-validation: the training set was split into 5-fold validation sets. For each validation set, the corresponding training set was

given by the remaining 4 folds. Each candidate model was fitted and hyper-parameters tuned in each training set. The performance measure was then performed on the validation sets. Predictive ability of each ML models was assessed using C index and compared to each other. All models were trained, optimized and evaluated using the same 5-fold cross-validation and were therefore applied on the same whole training set. The model with the best performance was finally selected for analysis on the held-out validation cohort (test set) for final evaluation to evaluate the models' generalization performance and compared to clinical scores.

2.4. Model evaluation and comparison

Area under the ROC curve (AUC) of the best ML model selected was calculated on the validation cohort and C index was compared to predictive ability of clinical scores previously described such as the CHA_2DS_2-VASc score (**Supplemental table 1**), the HAS-BLED score (**Supplemental table 2**), the Charlson Comorbidity Index (CCI) (**Supplemental table 3**), and the Hospital Frailty Risk Score (HFRS) (**Supplemental table 4**) for each patient [3,4,15,16]. Although CHA_2DS_2-VASc and HAS-BLED scores are used to evaluate the thromboembolic and bleeding risk in AF patients, they are also predictors of death in AF patients [14]. The CCI is dedicated tool to evaluate the burden of multimorbidity and is associated with an increased risk of all-cause death. CCI uses a system of relative weights to evaluate the impact of a list of chronic conditions on mortality risk, based on the evaluation of 17 chronic conditions. The HFRS was developed to evaluate frailty in hospitalised patients. The score was built according to the ICD-10 codes related to 109 clinical conditions. HFRS was established as an accurate tool to evaluate frailty in comparison to established frailty scales and validated in nationwide French population [25].

As previously described in the literature, the category of highest thromboembolic risk patients was defined as a CHA_2DS_2-VASc score$\geq$2, the category of highest bleeding risk patients as a HAS-

BLED≥3, the category of patients with the most multimorbidity as a CCI≥4 and the category of the frailest patients as a HFRS≥15.

2.5. Statistical analysis

Qualitative variables were described using counts and percentages, and continuous quantitative variables were described as mean±SD or median [interquartile range]. Comparisons were made using parametric or nonparametric tests, as appropriate: The Wilcoxon signed rank and Kruskal Wallis tests were used for comparing values between 2 independent groups, and the Chi^2 test was used to compare categorical data. Receiver operating characteristic curves were constructed, and Harrell C indexes (i.e., AUC) were calculated as a measure of model performance and compared using the DeLong test [26]. Net reclassification improvement was calculated according to the methods described by Pencina et al. to assess the reclassification performance of the scores [27]. Clinical usefulness and net benefit of the best ML model in comparison to the best clinical score were estimated using decision curve analysis [28]. Multivariate logistic regression was used, and results were expressed as odds ratio (OR) and 95% confidence intervals (95%CI). Analyses were performed using Python version 3.09 and STATA version 16.0 (Stata Corp, College Station, TX). All statistical significance levels were two-sided, and the significant differences were expressed as $p < 0.05$.

3. Results

Among 2,435,541 patients diagnosed with AF from 2011 to 2019 and included for analysis, 617,737 (25.4%) deaths were recorded during a mean follow-up of 2.0 ± 2.3 years (median 1.1 [0.07-3.39]) in whom were 187,186 (7.7%) CV death and 430,551 (17.7%) non-CV death (**Figure 1)**. Among patient dead from CV cause, 80,913 (43.2%) died from heart failure and 43,429 (23.2%) died from stroke or systemic embolism. Overall, incidence rates (95% CI) for the study outcomes

were accordingly 12.69 %/year (12.66-12.72) for all-cause death, 3.84 %/year (3.83-3.86) for CV death and 8.84 %/year (8.82-3.87) for non-CV death.

Early deaths, within the year following the first episode of AF, occurred in 342,005 patients after a mean time of 83 ± 98 days and represented 55.4% of all deaths and 14.04% of the whole population. These patients were older than patients still alive at one year with a mean age of 81.29±10.28 years vs. 76.53±12.23 years respectively (P<0.0001) and had more comorbidities as highlighted by clinical scores (mean CHA_2DS_2-VASc score 3.96±1.53 vs. 3.38±1.62, HAS-BLED score 2.61±1.12 vs. 2.34±1.19, CCI 4.56±2.67 vs. 3.28±2.78 and HFRS 11.69±8.57 vs. 8.88±9.19, P<0.0001 for each) (**Table 1**). Patients still alive at one year had significantly more dyslipidemia (21.9% vs. 19.2%, P<0.0001), obesity (14.6% vs. 12.3%, P<0.0001), sleep apnea syndrome (5.3% vs.4.4%, P<0.0001) and gastroesophageal reflux (2.3% vs. 2.0%, P<0.0001).

Among deaths recorded at one year, 107,715 were CV death (31.5%) and 234,290 non-CV death (68.5%). CV deaths occurred earlier than non-CV deaths (mean time 73 ± 95 days for CV death and 88 ± 99 days for non-CV death). Patients who died from non-CV death were younger than patients who died from CV death (mean age 80.66±10.44 vs. 82.66±9.78 years, P<0.0001) (**Table 2**), and had less prevalent cardiovascular comorbidities and more prevalent extra cardiac comorbidities than patients who died from CV death. Hence the CHA_2DS_2-VASc and HAS-BLED scores were lower in patient who died from non-CV death than CV death (3.74±1.51 vs. 4.45±1.46, P<0.0001 and 2.57±1.14 vs. 2.71±1.07, P<0.0001 respectively). Conversely, CCI and HFRS were higher in patients who died from non-CV death than CV death (4.75±2.75 vs. 4.14±2.45, P<0.0001 and 12.32±8.72 vs. 10.34±8.05, P<0.0001 respectively).

Among 110 variables available, only the 18 most important were selected, as adding any other variable did not improve prediction (**Supplemental figure 1)**. Most critical features selected for analysis were age, presence of cancer metastasis, resuscitated cardiac arrest, cancer, congestive heart failure, decubitus ulcers, renal failure, pneumonia, lung disease, difficulty in walking, malnutrition, anemia, impaired mobility, liver disease, acute renal failure, renal disease, blood transfusion and urinary tract infection (**Supplemental figure 2, Supplemental table 5)**.

After hyperparameter tuning using the derivation cohort (training set), ML algorithms had good predictive performances based on C indexes: LR 0.780 (95% CI, 0.778- 0.781), RF 0.785 (95% CI, 0.782 - 0.788), DNN 0.786 (95% CI, 0.783- 0.789). The DNN model showed the best predictive performances and was therefore selected as the best model for further evaluation (P=0.0001 vs LR, P=0.19 vs RF). The chosen hyperparameters are displayed in **Supplemental table 6**.

Once evaluated on the held-out validation cohort (test set), DNN had a good C index: 0.785 (95% CI, 0.781 - 0.789). The model was well calibrated to the validation cohorts (**Supplemental Figure 3**). The optimal cut-point was defined as the point closest to the point (0,1) on the ROC curve and was 0.16. Thus, we stratified AF patients into a low-risk group (<0.16) and high-risk group (≥0.16). At this decision threshold, sensitivity was 73.1%, specificity 69.1%, negative predicted value 94% and positive predicted value 28.1%. The incidence of all cause death at one year rises in a stepwise fashion from 13.8 per 1000 patients for the first quintile to 352.4 per 1000 for the fifth quintile (**Figure 2**).

When compared to the previously described clinical scores, DNN showed significantly higher predictive ability: CHA_2DS_2-VASc score: 0.596 (95% CI, 0.592- 0.602), HAS-BLED score: 0.562 (95% CI, 0.557 - 0.567), CCI: 0.643 (95% CI, 0.638 - 0.648) and HFRS: 0.626 (95% CI, 0.622 - 0.631) (P<0.0001) (**Figure 3, Panel A**).

The DNN had a positive net reclassification improvement and integrated discriminatory improvement compared with the CHA_2DS_2-VASc score (79% (P<0.0001) and 13% (P<0.0001), respectively), HAS-BLED score (82% (P<0.0001) and 14% (P<0.0001), respectively), CCI ((79% (P<0.0001) and 12% (P<0.0001), respectively) and modified HFRS (80% (P<0.0001) and 13% (P<0.0001]) respectively). Using decision curve analysis, our DNN showed better clinical usefulness compared with the traditional scores (**Figure 3, Panel B**).

Predictive abilities of our DNN model were broadly similar when applied to early non-CV death prediction (C index 0.786 (95%CI, 0.782 - 0.791), while slightly lower when applied to early CV death prediction (C index 0.724 (95%CI, 0.716 - 0.731) (**Figure 4**). In both cases, DNN model was significantly superior to all clinical scores described above (P<0.0001) even after stratification on age (**Supplemental table 7**).

Univariable and multivariable logistic regression analyses for association between clinical risk scores and outcomes occurrence are reported in **Table 3**. After adjustment on baseline clinical characteristics, the DNN was independently associated with increased risk of all cause death (odd ratio (OR) 1.56 (95% CI, 1.54-1.58) for each decile, OR 4.00 (95% CI, 3.78-4.22) DNN≥0.16 vs. <0.16, P<0.0001), non-CV death (OR 1.57 (95% CI, 1.55-1.59) for each decile, OR 4.50 (95% CI, 4.21-4.80) DNN≥0.16 vs. <0.16, P<0.0001) and CV death (OR 1.34 (95% CI, 1.31-1.37) for each decile, OR 2.26 (95% CI, 2.05-2.47) DNN≥0.16 vs. <0.16, P<0.0001). DNN was also independently associated with increased risk of all cause death when using Cox regression analysis and increased risk of non-CV and CV death when using Fine-Gray competing analysis (**Supplemental table 8**).

4. Discussion

In a large nationwide French hospital data base of 2,435,541 AF patients, ML scoring was an effective method for the prediction of 1-year all-cause mortality as well as non-CV and CV death. When compared to contemporary clinical risk scores, this approach had a significantly better predictive ability to target patients with a higher risk of mortality. These findings suggest that ML could have a crucial clinical role in assessing prognostic risk in patients with AF and improve holistic management of AF patients to reduce mortality.

4.1. Mortality rates across studies

With an overall one-year mortality rate of 14.1% (342,005 patients), including 68.5% (234,290 patients) of non-CV deaths, rates reported in our cohort are higher than results previously reported by Singh et al (8% at one year) with a similar ratio between CV and non-CV death [9]. However, these cohort included data from hospital-based care but also physician services and patients were therefore younger and had less comorbidities explaining a lower mortality. Our results are more consistent with Piccini et al who reported a one-year mortality rate of 19.5% with slightly older and comorbid patients than in our cohort [8].

4.2. Morbidity, frailty and mortality

It has been reported that comorbid long-term health conditions (LTC) and especially multimorbidity, defined as the presence of one more LTC in addition to an index condition, are frequent in AF patients when compared to non-AF patients and is associated with mortality in AF patients [29-33]. This additional risk is added to AF itself which is already an independent risk factor for all-cause mortality [30]. In the same way, the high mean CHA_2DS_2-VASc score in our cohort reflects CV comorbidities and high CCI reflects non-CV comorbidities. These scores were even

higher in AF patients who died at one year when compared to patients still alive. Both scores were independently associated to one-year mortality underlying the burden of multimorbidity.

Frailty is another concept developed recently. While multimorbidity and frailty represent two different ways of looking at the complexity of older persons and share some aspects, frailty differs from multimorbidity by integrating the concept of functional loss [34,35]. Moreover, multimorbidity is monodimensional and grounds its roots in the somewhat inadequate framework of "disease", whereas frailty implies a more exhaustive and comprehensive assessment of the individual, facilitating the implementation of multidimensional and tailored interventions. Indeed, AF patients are frequently frail with an estimated prevalence of 40% reported across the literature, and frailty is also strongly associated to mortality [36]. In our cohort, patients had an intermediate risk profile, with a mean±SD HFRS of 9.3±9.2 which increased to 11.69±8.57 for patients who died at one year and HFRS was independently associated with death at one years.

4.3. Variable selection

Age plays a pivotal role in our algorithm and was the most important variable selected by Random Forest. More surprisingly, only one CV comorbidity (congestive heart failure) was included in our model. All other selected variables were non-CV underlying the burden of non-CV multimorbidity and frailty on survival. To some extent, this is consistent with previous observations. For example, Singh et al reported that heart failure contributed to 3.8% of all deaths and was the second CV cause of death after ischemic heart disease, being responsible for 16% of all deaths [9]. Cancer and respiratory failure were the most common non-CV cause of death accounting for 30% and 10% respectively. Interestingly, ischemic heart disease was not retained by our model, and stroke deaths were infrequent (2.7%). Of note, the GARFIELD-AF and ROCKET-AF studies have previously shown that heart failure and sudden cardiac death are the major reasons for death of AF patients taking oral anticoagulant medication [37,38].

Other selected variables related to non-CV conditions such as cancer, renal disease and lung disease are strongly associated with mortality in AF patients [30,33]. Once again, these conditions are found out with the common thromboembolic risk scores.

Another strength of random forest feature selection is the identification of variable un- or poorly described such as difficulty in walking, blood transfusion or urinary tract infection. Difficulty in walking or impaired mobility are not intuitively risk factors of death, but when considered as surrogates of falls, this is consistent with the REGARDS study which have shown association between the risk of falls and mortality particularly in AF population [39].

4.4. Risk stratification of mortality

AF guidelines have mainly focused on identifying patients with different risks of stroke and major bleeding [40-42]. Prior prognostic models for stroke and bleeding in AF showed only modest predictive performance when evaluated to predict the outcome of death [14]. On the other hand, scores such as CCI and HFRS assessing mortality through multimorbidity and frailty have been developed from hospitalized patients but not especially on AF patient cohorts [15,16]. Additionally, HFRS was not fitted on patients under 75 years. Hence, assessing mortality remain a challenge, especially in patients with AF.

Few recent studies aimed to propose new dedicated scores developed with ML methods to predict the occurrence of all-cause death in AF patients [43-46]. Reported predictive ability ranged from 0.77 to 0.85 (c-index) which is comparable to our model. However, the GARFIELD-AF and BASIC-AF risk scores need to integrate biological and echocardiography variables unlike our only clinical factor based ML model [43,44]. Additionally, Lasso-Cox model and ABC risk score use variables not routinely available such as GDF-15, monoamine oxidase, cholinesterase, blood urea nitrogen in the clinical setting that might decrease their practicality in everyday clinical practice [45,46]. Moreover,

clinical variables used as input for these models were only cardiovascular items except cancer for Lasso-Cox model and dementia for GARFIELD-AF, and biomarker are non-specific, likely reflecting a sick patient or a sick heart [47].

Yet we know that non-CV deaths represent the majority of mortality and that multimorbidity and frailty are strong predictors of mortality in AF patients, reflecting the clinical complexity of such patients [48]. Thus, including non-CV conditions multimorbidity and frailty to our model could explain the good performance of our model, similar to the others, even without biological or echography parameters. Unsurprisingly, the management of concurrent comorbidities (not limited to cardiovascular ones) is a pillar of the integrated and holistic management of AF patients, and how such a management approach can improve prognosis in clinically complex patients, characterized – among others – by frailty and multimorbidity [49,50]. Of note, our model was built using exhaustive real-life data at the country level, unlike other models derived from a single-center cohort or randomized control trial that might induce selection bias [44-46]. This would confer a good reproducibility of our results when applied for external validation but need to be confirmed in other populations (e.g. North America, Asia).

Potential Clinical practical implications and perspectives

Healthcare systems increasingly adopt electronic health records (EHR) for the management of patients. As AF is frequently associated with multimorbidity or frailty which are strong predictors of mortality, this obviates the current need for separate stroke and bleeding risk scores to aid mortality calculations for each individual. Indeed, the predictable aspect of survival outcomes in AF patients appear virtually all non-AF rhythm related and many are non-cardiac. More integrative and dedicated tools might allow the clinician to evaluate all these risks separately when deciding on whether to recommend management strategies. Indeed, our DNN model has the potential to be

incorporated into online calculators, mobile applications, or routine electronic record systems and to automatically predict mortality (total, non-CV and CV) and would allow users to base treatment decisions on more precise measures of risk. Alerts can be implemented in case of a 'high risk' score to flag up those patients at high risk of early death.

Populations and medical practices change very rapidly and models are quickly outdated. This model has also the possibility to be implemented in nationwide administrative datasets and trained in real time to provide up to date versions of the model in order to fit perfectly the data over time. Moreover, using ICD-10 codes internationally enable comparisons and validation to be carried out in different populations across the world. Future attempts to modify the prognosis of AF patients in clinical trials may ultimately need to select out lower risk subsets using modeling approaches (eg. using machine learning), where the effects of unmodifiable relationships are much smaller and there is a better causal pathway between AF and AF-related adverse outcomes.

5. Limitations

Despite a large amount of data, ideal to feed and train ML algorithms, the nature of PMSI data base derived from ICD-10 codes and therefore composed almost exclusively by categorical features minimize algorithms performances because of a lack of granularity. Moreover, diagnoses during outpatient visits were not included in our analysis and were possibly. Echocardiographic, biological and imaging parameters were also lacking.

6. Conclusion

Machine learning algorithms predict mortality in AF patients with a better ability than previously developed traditional clinical risk scores. A ML approach may help clinicians to better stratify AF patients at high risk of total, non-CV and CV mortality and may assist physicians in decision-making when managing AF patients in a holistic and integrated care manner.

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Conflict of interest:

Bisson has been a consultant or speaker for Astra-Zeneca, Bayer, BMS/Pfizer, Medtronic, Vitorpharma and Alnylam. Angoulvant has been a consultant or speaker for Amgen, Astra-Zeneca, Bayer, BMS/Pfizer, MSD, Novartis, Novo Nordisk, Sanofi, Servier. Lip has been a consultant or speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthem. No fees are received personally**.** He is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. LF reports consulting fees for AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Novo Nordisk and Novartis and lecture fees for AstraZeneca, Bayer, BMS/Pfizer, Boehringer Ingelheim and Zoll. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Data availability statement:

Access to the PMSI (the French hospitalization database) is controlled by the CNIL, the independent national ethics committee protecting human rights in France. Due to the sensitive nature of the database, data sharing is not authorized according to the French legislation.

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Figures

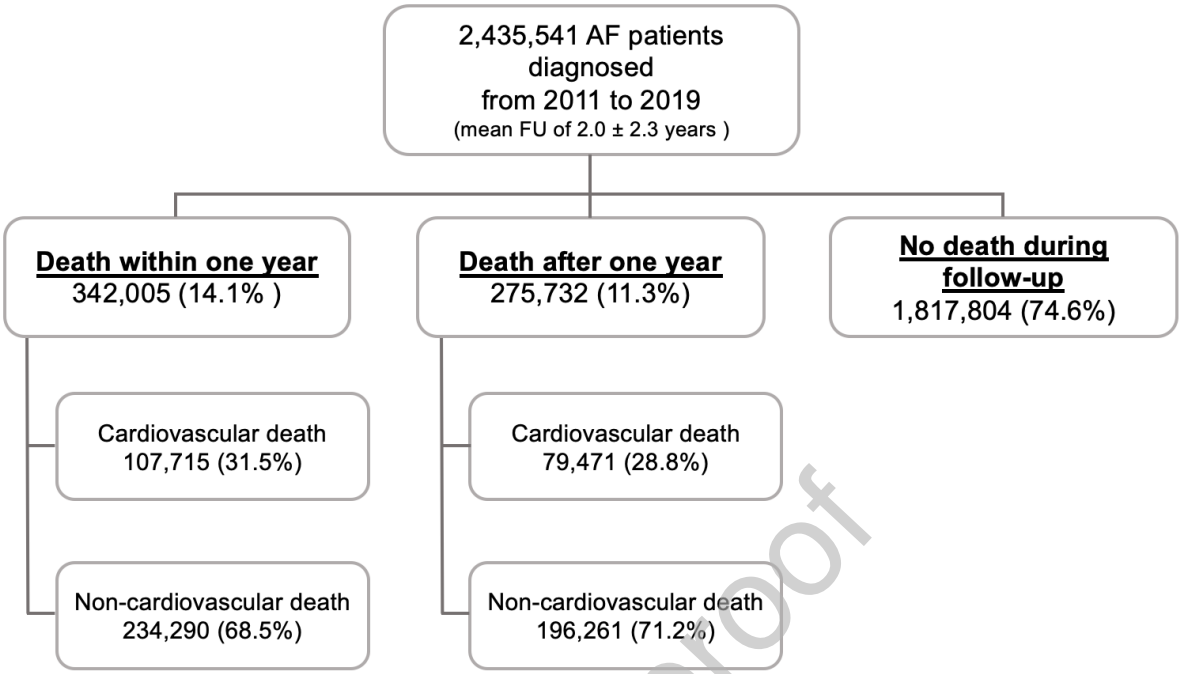


Figure 1. Flow chart for the training and validation of models.

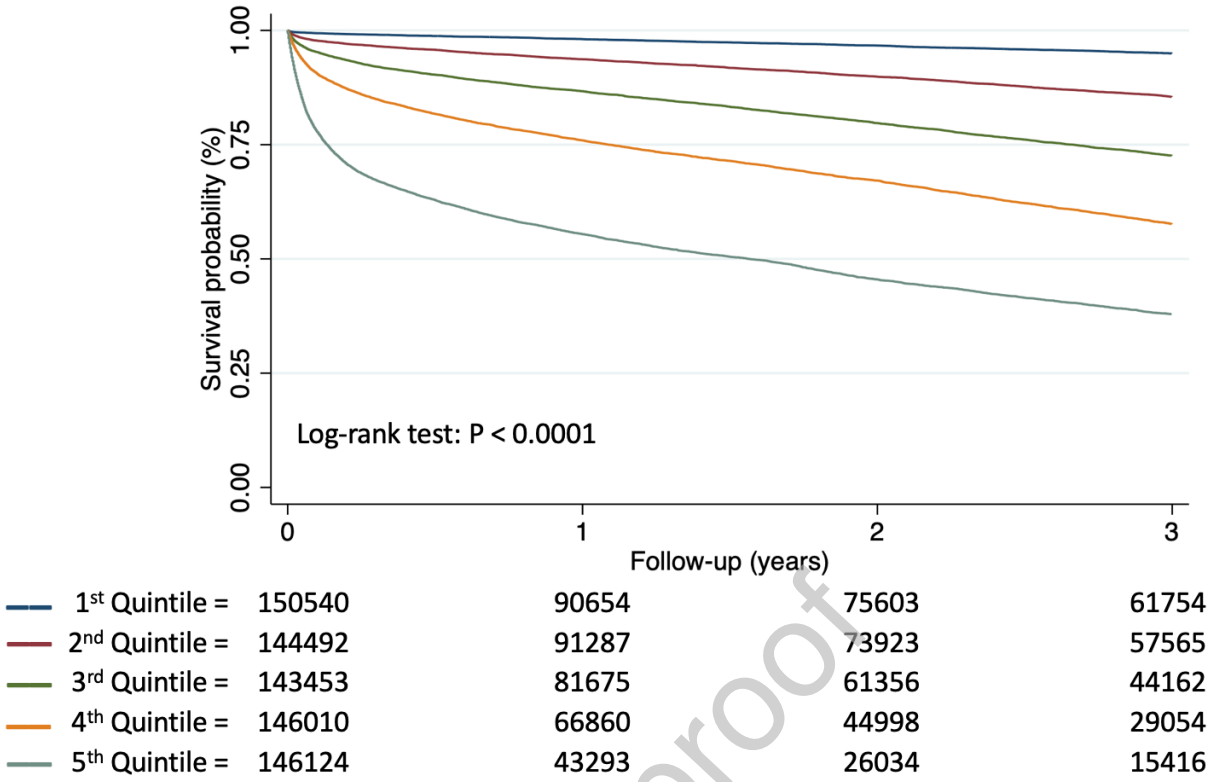


Figure 2. Kaplan-Meier curves of the prediction all cause death during follow-up.

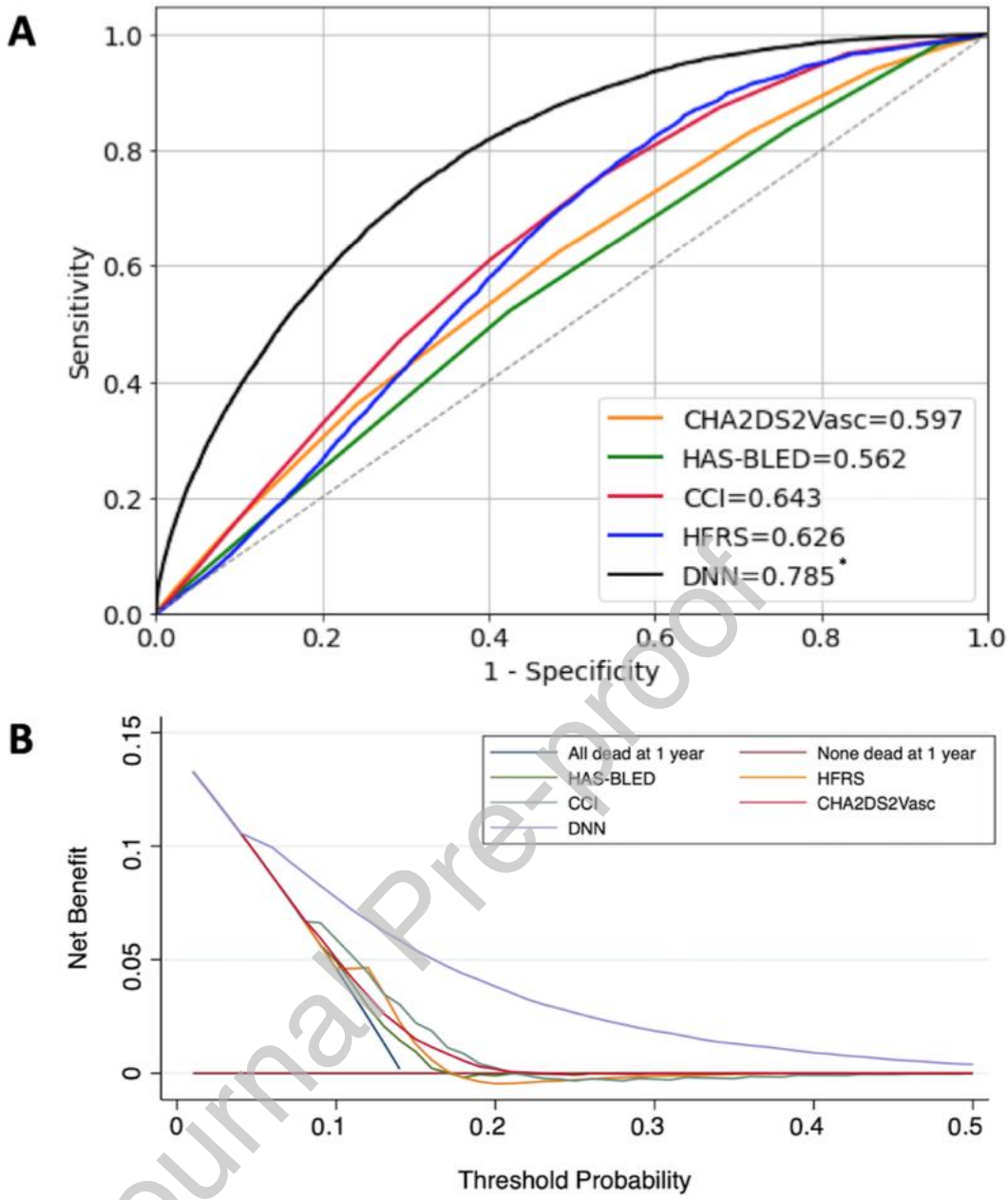


Figure 3. Panel A: Receiver operating characteristic curves of occurrence of all cause death during the year following atrial fibrillation diagnosis.

Panel B: Decision curve analyses for the deep neural network algorithm and CHA_2DS_2-VASc score, HAS-BLED score, Charlson Comorbidity Index and Hospital Frailty Risk Score.

* DNN (Deep Neural Network) P<0.0001 vs. CHA_2DS_2VASc score, HAS-BLED score, CCI (Charlson Comorbidity Index) and HFRS (Hospital Frailty Risk Score).

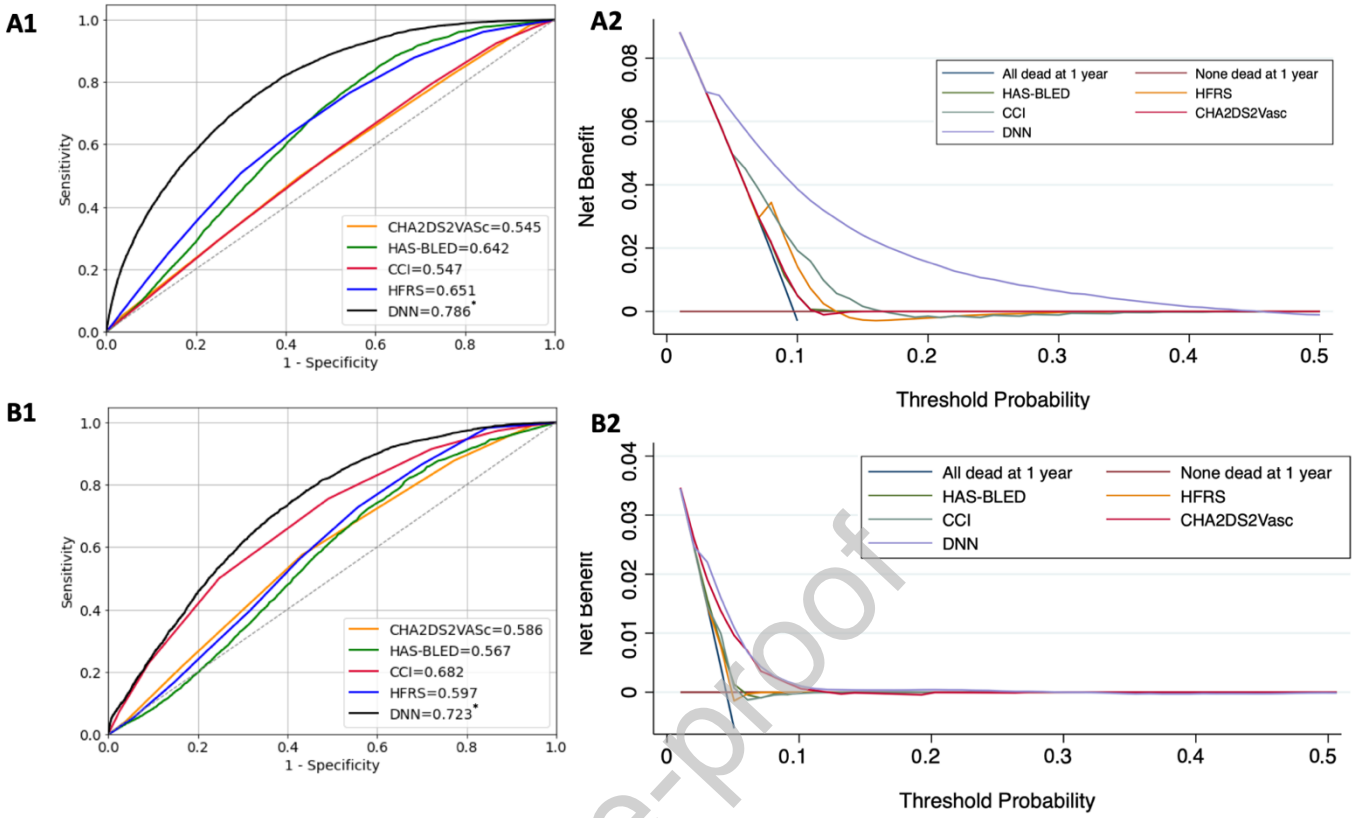


Figure 4. Panel A1 and A2: Receiver operating characteristic curves and Decision curve analyses for non-cardiovascular death within the year following AF diagnosis.

Panel B1 and B2: Receiver operating characteristic curves and Decision curve analyses for cardiovascular death within the year following AF diagnosis.

* DNN: Deep Neural Network, P<0.0001 vs. CHA_2DS_2VASc score, HAS-BLED score, CCI (Charlson Comorbidity Index) and HFRS (Hospital Frailty Risk Score).

Table 1. Baseline characteristics of the AF population according to death before or after one year.

	Total	Alive after one year	Dead within the first year	P[a]
	(n=2435541)	(n=2093536)	(n=342005)	
Clinical characteristics				
Age, mean±SD	77.2±12.1	76.53±12.23	81.29±10.28	<0.0001
CHA_2DS_2VASc score, mean±SD	3.5±1.6	3.38±1.62	3.96±1.53	<0.0001
HASBLED score, mean±SD	2.4±1.2	2.34±1.19	2.61±1.12	<0.0001
Charlson comorbidity index, mean±SD	3.5±2.8	3.28±2.78	4.56±2.67	<0.0001
Frailty index, mean±SD	9.3±9.2	8.88±9.19	11.69±8.57	<0.0001
Gender (male), n (%)	1286313 (52.8)	1103154(52.6)	183,159(53.6)	<0.0001
Hypertension, n (%)	1459065 (59.9)	1245027 (59.5)	214038 (62.6)	<0.0001
Diabetes mellitus, n (%)	509617 (20.9)	426980 (20.4)	82919 (24.2)	<0.0001
Heart failure, n (%)	882430 (36.2)	708360 (33.8)	174070 (50.9)	<0.0001
Valve disease, n (%)	334730 (13.7)	283937 (13.6)	50793 (14.9)	<0.0001
Dilated cardiomyopathy, n (%)	169108 (6.9)	142331 (6.8)	26777 (7.8)	<0.0001
Coronary artery disease, n (%)	596709 (24.5)	500199 (23.9)	96510 (28.2)	<0.0001
Previous MI, n (%)	119230 (4.9)	96876 (4.6)	23084 (6.7)	<0.0001
Previous PCI, n (%)	97241 (4.0)	83207 (4)	14034 (4.1)	0.0004
Previous CABG, n (%)	79822 (3.3)	67744 (3.2)	12078 (3.5)	<0.0001
Vascular disease, n (%)	428526 (17.6)	349961 (16.7)	78565 (23)	<0.0001
Previous pacemaker or ICD, n (%)	94691 (3.9)	77622 (3.7)	17069 (5)	<0.0001
Ischemic stroke, n (%)	173563 (7.1)	141315 (6.8)	32248 (9.4)	<0.0001
Previous major bleeding, n (%)	187806 (7.7)	144263 (6.9)	43543 (12.7)	<0.0001
Smoker, n (%)	162715 (6.7)	135364 (6.5)	27351 (8)	<0.0001
Dyslipidemia, n (%)	524489 (21.5)	458680 (21.9)	65809 (19.2)	<0.0001
Obesity, n (%)	346996 (14.2)	304846 (14.6)	42150 (12.3)	<0.0001
Alcohol related diagnoses, n (%)	122218 (5.0)	98136 (4.7)	24082 (7)	<0.0001
Abnormal renal function, n (%)	166930 (6.9)	127027 (6.1)	39903 (11.7)	<0.0001
Lung disease, n (%)	403259 (16.6)	310776 (14.8)	92483 (27)	<0.0001
Sleep apnea syndrome, n (%)	127100 (5.2)	111998 (5.3)	15102 (4.4)	<0.0001
Liver disease, n (%)	88742 (3.6)	63429 (3)	25313 (7.4)	<0.0001
Gastroesophageal reflux, n (%)	55201 (2.3)	48477 (2.3)	6724 (2)	<0.0001
Thyroid diseases, n (%)	233230 (9.6)	199187 (9.5)	34043 (10)	<0.0001
Inflammatory disease, n (%)	145531 (6.0)	119309 (5.7)	26222 (7.7)	<0.0001
Anaemia, n (%)	414210 (17.0)	315096 (15.1)	99114 (29)	<0.0001
Previous cancer, n (%)	428273 (17.6)	311607 (14.9)	116666 (34.1)	<0.0001
AF therapeutic strategy				
Medical treatment only, n (%)	2181323 (89.6)	1844118 (88.1)	337205 (98.6)	<0.0001
Electrical cardioversion, n (%)	206153 (8.5)	201911 (9.6)	4242 (1.2)	<0.0001
Atrial fibrillation ablation, n (%)	62069 (2.6)	61889 (3)	180 (0.1)	<0.0001
AV node ablation, n (%)	13784 (0.6)	13280 (0.6)	504 (0.1)	<0.0001
Left atrial appendage occlusion, n (%)	2699 (0.1)	2656 (0.1)	43 (<0.1)	<0.0001

*Patients alive *versus* dead at one year after AF diagnosis

AF: Atrial Fibrillation; CABG: Coronary Artery Bypass Graft; ICD: Implantable Cardiac Defibrillator; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; PM: Pacemaker.

Table 2. Baseline characteristics of the AF patients dead within the first year following diagnosis of AF according to the cause of death.

	Dead within the first year (n=342005)	Non-CV death (n=234290)	CV death (n=107715)	p*
Clinical characteristics				
Age	81.29±10.28	80.66±10.44	82.66±9.78	<0.0001
CHA_2DS_2VASc score, mean±SD	3.96±1.53	3.74±1.51	4.45±1.46	<0.0001
HASBLED score, mean±SD	2.61±1.12	2.57±1.14	2.71±1.07	<0.0001
Charlson comorbidity index, mean±SD	4.56±2.67	4.75±2.75	4.14±2.45	<0.0001
Frailty index, mean±SD	11.69±8.57	12.32±8.72	10.34±8.05	<0.0001
Gender (male), n (%)	183,159(53.6)	131,264(56)	51,895(48.2)	<0.0001
Hypertension, n (%)	214038 (62.6)	144197 (61.5)	69841 (64.8)	<0.0001
Diabetes mellitus, n (%)	82919 (24.2)	56164 (24)	26755 (24.8)	<0.0001
Heart failure, n (%)	174070 (50.9)	105237 (44.9)	68833 (63.9)	<0.0001
Valve disease, n (%)	50793 (14.9)	27286 (11.6)	23507 (21.8)	<0.0001
Dilated cardiomyopathy, n (%)	26777 (7.8)	15375 (6.6)	11402 (10.6)	<0.0001
Coronary artery disease, n (%)	96510 (28.2)	57702 (24.6)	38808 (36)	<0.0001
Previous MI, n (%)	23084 (6.7)	10805 (4.6)	12279 (11.4)	<0.0001
Previous PCI, n (%)	14034 (4.1)	7855 (3.4)	6179 (5.7)	<0.0001
Previous CABG, n (%)	12078 (3.5)	7081 (3)	4997 (4.6)	<0.0001
Vascular disease, n (%)	78565 (23)	46771 (20)	31794 (29.5)	<0.0001
Previous pacemaker or ICD, n (%)	17069 (5)	10676 (4.6)	6393 (5.9)	<0.0001
Ischemic stroke, n (%)	32248 (9.4)	14313 (6.1)	17935 (16.7)	<0.0001
Previous major bleeding, n (%)	43543 (12.7)	32989 (14.1)	10554 (9.8)	<0.0001
Smoker, n (%)	27351 (8)	20708 (8.8)	6643 (6.2)	<0.0001
Dyslipidemia, n (%)	65809 (19.2)	43344 (18.5)	22465 (20.9)	<0.0001
Obesity, n (%)	42150 (12.3)	28988 (12.4)	13162 (12.2)	0.2
Alcohol related diagnoses, n (%)	24082 (7)	18606 (7.9)	5476 (5.1)	<0.0001
Abnormal renal function, n (%)	39903 (11.7)	26662 (11.4)	13241 (12.3)	<0.0001
Lung disease, n (%)	92483 (27)	66907 (28.6)	25576 (23.7)	<0.0001
Sleep apnea syndrome, n (%)	15102 (4.4)	10659 (4.5)	4443 (4.1)	<0.0001
Liver disease, n (%)	25313 (7.4)	18965 (8.1)	6348 (5.9)	<0.0001
Gastroesophageal reflux, n (%)	6724 (2)	4989 (2.1)	1735 (1.6)	<0.0001
Thyroid diseases, n (%)	34043 (10)	23364 (10)	10679 (9.9)	0.6
Inflammatory disease, n (%)	26222 (7.7)	19143 (8.2)	7079 (6.6)	<0.0001
Anaemia, n (%)	99114 (29)	76301 (32.6)	22813 (21.2)	<0.0001
Previous cancer, n (%)	116666 (34.1)	98778 (42.2)	17888 (16.6)	<0.0001
AF therapeutic strategy				
Medical treatment only, n (%)	337205 (98.6)	231659 (98.9)	105546 (98)	<0.0001
Electrical cardioversion, n (%)	4242 (1.2)	2341 (1)	1901 (1.8)	<0.0001
Atrial fibrillation ablation, n (%)	180 (0.1)	91 (<0.1)	89 (0.1)	<0.0001
AV node ablation, n (%)	504 (0.1)	251 (0.1)	253 (0.2)	<0.0001
Left atrial appendage occlusion, n (%)	43 (<0.1)	22 (<0.1)	21 (<0.1)	0.01

*CV *versus* non-CV death

AF: Atrial Fibrillation; CABG: Coronary Artery Bypass Graft; CV: Cardiovascular; ICD: Implantable Cardiac Defibrillator; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; PM: Pacemaker.

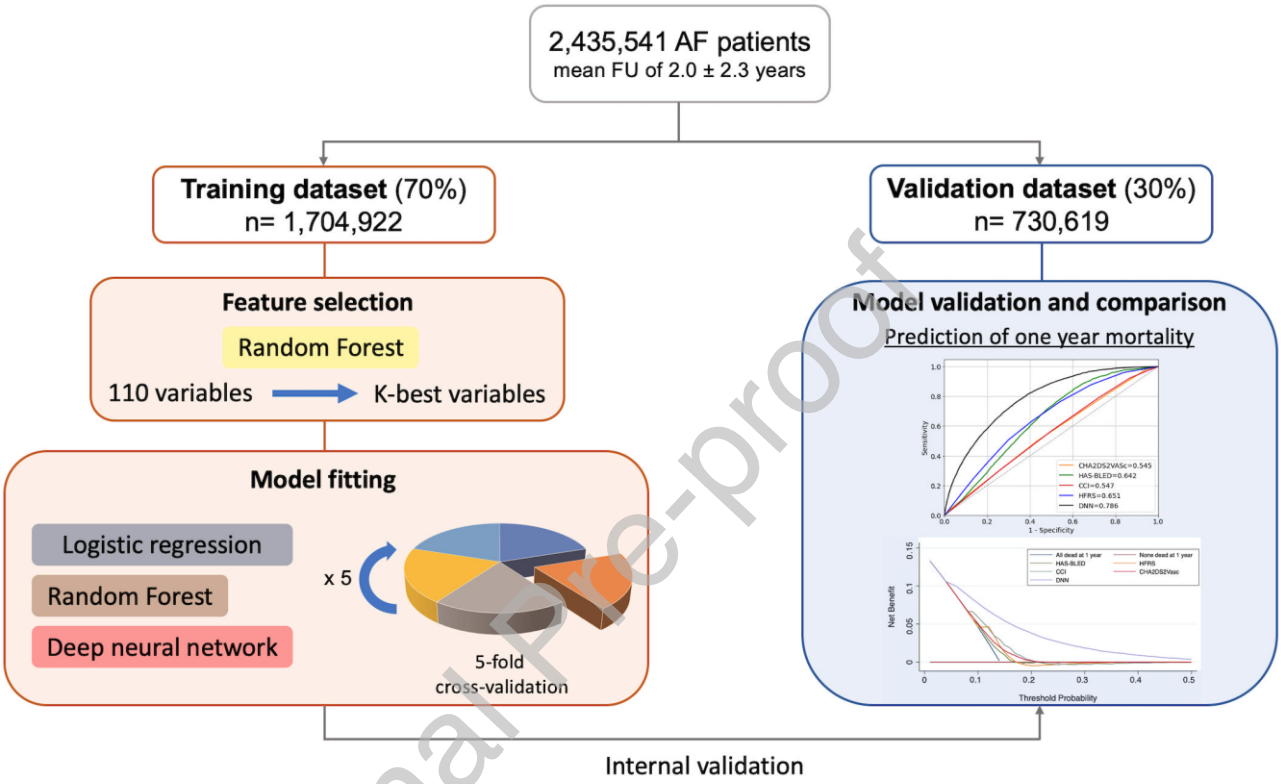
Table 3. Logistic regression analysis for clinical risk scores and occurrence of death within one year.

	Univariate analysis		**Multivariable analysis***	
	OR (95% CI)	p	OR (95% CI)	p
All-Cause Death				
DNN (for each decile)	1.52 (1.50-1.53)	<0.0001	1.56 (1.54-1.58)	<0.0001
DNN ≥ 0.16 (vs. <0.16)	6.09 (5.84-6.35)	<0.0001	4.00 (3.78-4.22)	<0.0001
CCI (for each point)	1.16 (1.15-1.17)	<0.0001	1.15 (1.14-1.16)	<0.0001
CCI ≥4 (vs. <4)	2.33 (2.24-2.42)	<0.0001	1.88 (1.79-1.99)	<0.0001
HFRS (for each point)	1.03 (1.03-1.03)	<0.0001	1.00 (1.00-1.01)	0.001
HFRS ≥15 (vs. <15)	1.50 (1.44-1.56)	<0.0001	0.94 (0.90-0.99)	0.015
Non-CV Death				
DNN (for each decile)	1.53 (1.51-1.55)	<0.0001	1.57 (1.55-1.59)	<0.0001
DNN ≥ 0.16 (vs. <0.16)	6.23 (5.92-6.55)	<0.0001	4.50 (4.21-4.80)	<0.0001
CCI (for each point)	1.17 (1.16-1.18)	<0.0001	1.19 (1.18-1.21)	<0.0001
CCI ≥4 (vs. <4)	2.49 (2.38-2.61)	<0.0001	2.22 (2.09-2.35)	<0.0001
HFRS (for each point)	1.03 (1.03-1.04)	<0.0001	1.01 (1.01-1.02)	<0.0001
HFRS ≥15 (vs. <15)	1.70 (1.62-1.78)	<0.0001	1.12 (1.06-1.18)	<0.0001
CV Death				
DNN (for each decile)	1.35 (1.34-1.37)	<0.0001	1.34 (1.31-1.37)	<0.0001
DNN ≥ 0.16 (vs. <0.16)	3.99 (3.72-4.27)	<0.0001	2.26 (2.05-2.47)	<0.0001
CCI (for each point)	1.09 (1.08- 1.10)	<0.0001	0.99 (0 .97-1.01)	0.412
CCI ≥4 (vs. <4)	1.72 (1.61-1.83)	<0.0001	1.10 (1.01-1.19)	0.025
HFRS (for each point)	1.01 (1.01-1.02)	<0.0001	0 .98 (0.98-0.99)	<0.0001
HFRS ≥15 (vs. <15)	1.03 (0.95- 1.11)	0.453	0.68 (0 .62-0 .74)	<0.0001

*adjusted on all clinical characteristics displayed Table 1

CCI: Charlson Comorbidity Index; CI: Confidence Interval; CV: Cardiovascular; DNN: Deep Neural Network; HFRS: Hospital Frailty Risk Score; OR: Odds Ratio

Graphical abstract.



CCI: Charlson Comorbidity Index; DNN: Deep Neural Network; HFRS: Hospital Frailty Risk Score.