**SUPPLEMENTARY MATERIAL**

**METHODS**

*Baseline Investigation*

 At baseline, demographic and clinical data from patients were obtained by reviewing medical records and conducting an interview using a structured questionnaire containing the variables under study. Investigators underwent training and worked together for a period to achieve consensus on assigning values to variables. Baseline investigation included factors thought to be associated with anticoagulation instability as suggested by previous studies [1, 2]. The data set included age, sex, educational status, New York Heart Association (NHYA) functional class, indications for warfarin, duration of warfarin therapy, comorbidities (heart failure, hypertension, diabetes mellitus, renal failure, depression), current medications, adherence to warfarin, consumption of alcoholic beverages, smoking status, routine laboratory tests, any prior hemorrhage diagnosis due to warfarin, and the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score [3]. Alcohol regular use was defined as alcohol intake 1-< 8 units per week. Anemia was defined as hemoglobin <13 g/dl in men and <12 g/dl in women. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula.

*Assessment of patients’ adherence to warfarin*

 Patient-reported adherence was evaluated by using the eight-item Morisky Medication Adherence Scale (MMAS) [4]. The 8-MMAS evaluates items addressing the circumstances surrounding adherence behavior [4]. Each item measures a specific medication-taking behavior and is not a determinant of adherence behavior [4]. The MMAS scores can range from 0–8 and have been classified into three levels of adherence: high adherence (score 8); medium adherence (score 6–7.75); and low adherence (score <6) [4].

*Echocardiographic examination*

 Echocardiographic examinations were performed by experienced operators. Patients were imaged in the left lateral decubitus position with commercially available systems (Vivid systems, GE Healthcare, Wauwatosa, USA). Left ventricular (LV) dimensions, volumes and ejection fraction (EF) [by modified Simpson’s method] were measured according to European Association of Echocardiography (EAE)/American Society of Echocardiography (ASE) recommendations [5]. LV diastolic functions were evaluated according to EAE/ASE standards [6]. The diagnosis of LV HF with reduced EF (HFrEF) and LV HF with preserved EF (HFpEF) were made according to guidelines [5-7]. Right heart dimensions and RV systolic-diastolic functions were evaluated according to EAE/ASE recommendations [6,8]. Tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode echocardiography with the cursor optimally aligned along the direction of the tricuspid lateral annulus in the apical four-chamber view [8]. The diagnosis of RV systolic dysfunction was considered in the presence of TAPSE<16 mm and RV diastolic dysfunction in the presence of E/E’≥4 [8].

**RESULTS**

|  |
| --- |
| Supplementary Table 1. Post-hoc analyses of Table 1 |
|  | Group 1avsgroup 2b | Group 1avsgroup 3c | Group 1avsgroup 4d | Group 2bvsgroup 3c | Group 2bvsgroup 4d | Group 3cvsgroup 4d |
| NYHA class III-IV, % | 0.008 | <0.001 | <0.001 | <0.001 | <0.001 | 0.996 |
| Hypertension, % | 0.995 | 0.016 | 0.971 | 0.023 | 0.998 | 0.039 |
| Hyperlipidemia, % | 0.913 | <0.001 | 0.511 | <0.001 | 0.271 | 0.032 |
| Coronary artery disease, % | <0.001 | 0.631 | <0.001 | <0.001 | 0.646 | <0.001 |
| Prior MI, % | 0.008 | 0.855 | <0.001 | 0.005 | <0.001 | <0.001 |
| Any prior hemorrhage diagnosis, % | 0.462 | 0.193 | 0.044 | 0.858 | 0.710 | 1.0 |
| Pulmonary disease, % | 0.816 | <0.001 | 0.003 | <0.001 | 0.087 | <0.001 |
| AST, U/L | 0.952 | 0.003 | <0.001 | 0.001 | <0.001 | 0.948 |
| ALT, U/L | 0.489 | 0.036 | 0.010 | 0.002 | <0.001 | 0.909 |
| GGT, U/L | 0.340 | <0.001 | <0.001 | <0.001 | <0.001 | 0.978 |
| Total bilirubin, mg/dL | 0.958 | <0.001 | <0.001 | <0.001 | <0.001 | 0.467 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infraction, NYHA, New York Heart Association; PAD, peripheral arterial disease; RVD, right ventricular dysfunction. a Group 1: HFpEF without RVD; b Group 2: HFrEF without RVD; c Group 3: HFpEF with RVD; dHFrEF with RVD.

|  |
| --- |
| Supplementary Table 2. Post-hoc analyses of Table 2 |
|  | Group 1avsgroup 2b | Group 1avsgroup 3c | Group 1avsgroup 4d | Group 2bvsgroup 3c | Group 2bvsgroup 4d | Group 3cvsgroup 4d |
| AF (valvular and non-valvular),% | 0.512 | <0.001 | 0.368 | <0.001 | 0.995 | <0.001 |
| Mechanical heart valves, %  | 0.075 | <0.001 | 0.007 | <0.001 | 0.860 | <0.001 |
| ATRIA score | 0.279 | 0.454 | 0.043 | 0.999 | 0.829 | 0.949 |
| Warfarin treatment |  |  |  |  |  |  |
| Duration, years | 0.191 | <0.001 | 0.053 | 0.077 | 0.952 | 0.201 |
| Total weekly dose, mg | 0.113 | <0.001 | <0.001 | <0.001 | <0.001 | 0.606 |
| Number of INR test during index period | 0.529 | <0.001 | <0.001 | <0.001 | <0.001 | 0.325 |
| Any INR test ≥ 6 during index period, % | 0.391 | <0.001 | <0.001 | <0.001 | <0.001 | 0.986 |
| TTR, % | 1.0 | <0.001 | <0.001 | <0.001 | <0.001 | 0.927 |
| TTR ≥66%, % | 0.999 | <0.001 | <0.001 | <0.001 | <0.001 | 0.909 |

AF, atrial fibrillation; ATRIA, the Anticoagulation and Risk Factors in Atrial Fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; INR, international normalized ratio; RVD, right ventricular dysfunction; TTR, time in therapeutic range.a Group 1: HFpEF without RVD; b Group 2: HFrEF without RVD; c Group 3: HFpEF with RVD; dHFrEF with RVD.

|  |
| --- |
| Supplementary Table 3. Baseline characteristics of study participants according to quality of anticoagulation control |
|  | TTR<66%(n =548) | TTR≥66%(n =345) | *P*-value |
| *Sociodemographic* |  |  |  |
| Age, years | 58±13 | 57±13 | 0.776 |
| Male gender, % | 52. | 49.6 | 0.356 |
| College education, % | 15.3 | 16.5 | 0.634 |
| Current smoker, % | 31.0 | 21.7 | 0.002 |
| Alcohol use (regular), % | 5.8 | 4.1 | 0.241 |
| NYHA class III-IV, % | 35.6 | 17.4 | <0.001 |
| *Comorbidity* |  |  |  |
| Hypertension, % | 72.6 | 64.6 | 0.012 |
| Diabetes mellitus, % | 32.5 | 25.2 | 0.021 |
| Hyperlipidemia, % | 63.0 | 66.7 | 0.260 |
| Obesity, % | 29.4 | 27.0 | 0.450 |
| Coronary artery disease, % | 51.8 | 48.4 | 0.320 |
| Prior myocardial infraction, % | 18.8 | 12.8 | 0.018 |
| Prior TIA or stroke, % | 19.3 | 13.6 | 0.027 |
| Any prior hemorrhage diagnosis, % | 19.7 | 13.9 | 0.026 |
| Peripheral arterial disease, % | 14.8 | 9.9 | 0.032 |
| Pulmonary disease, % | 29.4 | 15.7 | <0.001 |
| Depression, % | 18.6 | 17.4 | 0.645 |
| Anemia, % | 19.5 | 17.4 | 0.426 |
| CKD stage 3, % | 38.9 | 31.3 | 0.022 |
| CKD stage 4-5, %  | 21.2 | 14.2 | 0.009 |
| Presence of RVD, % | 56.8 | 80.3 | <0.001 |
| Absence of RVD, % | 43.2 | 19.7 |  |
| HFpEF, % | 48.4 | 43.2 | 0.131 |
| HFrEF, % | 51.6 | 56.8 |  |
| *Liver function tests* |  |  |  |
| AST, U/L | 27 (21-40) | 25 (21-39) | 0.667 |
| ALT, U/L | 24 (19-34) | 24 (19-35) | 0.859 |
| GGT, U/L | 43 (28-84) | 39 (27-77) | 0.356 |
| Total bilirubin, mg/dL | 0.7 (0.6-1.0) | 0.7 (0.6-1.0) | 0.908 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; GGT, gamma glutamyl transferase; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; RVD, right ventricular dysfunction; TIA, transient ischemic attack; TTR, time in therapeutic range.

|  |
| --- |
| Supplementary Table 4. Characteristics of the warfarin therapy of study participants according to quality of anticoagulation control |
|  | TTR<66%(n =548) | TTR≥66%(n =345) | *P*-value |
| Indications for warfarin |  |  |  |
| AF (valvular and non-valvular),% | 66.4 | 66.7 | 0.940 |
| Mechanical heart valves, %  | 11.3 | 11.0 | 0.890 |
| Venous thromboembolism, % | 10.2 | 9.3 | 0.645 |
| Others\*, % | 12.0 | 13.0 | 0.659 |
| 8-MMAS of warfarin adherence |  |  |  |
| High (>8), % | 27.6 | 23.8 | 0.210 |
| Medium (6-<8), % | 42.8 | 44.6 | 0.607 |
| Low (<6), % | 29.6 | 31.6 | 0.520 |
| ATRIA score | 1 (1-3) | 1 (1-2) | 0.003 |
| Warfarin treatment |  |  |  |
| Duration, years | 3 (1-5) | 3 (1-5) | 0.822 |
| Total weekly dose, mg | 28 (20-35) | 28 (23-35) | 0.077 |
| Number of INR test during index period | 4 (3-5) | 4 (3-5) | 0.596 |

AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; INR, international normalized ratio; 8-MMAS,eight-item Morisky Medication Adherence Scale; RVD, right ventricular dysfunction; TTR, time in therapeutic range.

\*Cerebrovascular thromboembolism, peripheral arterial thrombosis, presence of left heart thrombus and prophylactic treatment.

**References**

1. Demirkan K, Stephens MA, Newman KP, Self TH. Response to warfarin and other oral anticoagulants: effects of disease states. South Med J 2000;93:448-454.
2. White PJ. Patient factors that influence warfarin dose response. J Pharm Pract 2010;23:194-204.
3. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol 2011;58:395-401.
4. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008;10:348–354.
5. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233-270.
6. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165-193.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016: ehw128; DOI: 10.1093/eurheartj/ehw128.
8. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.