JAMA Network Open

Original Investigation | Cardiology

Assessment of Outcomes Among Patients With Venous Thromboembolism With and Without Chronic Kidney Disease

Shinya Goto, MD, PhD; Sylvia Haas, MD, PhD; Walter Ageno, MD; Samuel Z. Goldhaber, MD; Alexander G. G. Turpie, MD; Jeffrey I. Weitz, MD; Pantep Angchaisuksiri, MD; Joern Dalsgaard Nielsen, MD; Gloria Kayani, BSc; Alfredo Farjat, PhD; Sebastian Schellong, MD; Henri Bounameaux, MD; Lorenzo G. Mantovani, DSc; Paolo Prandoni, PhD; Ajay K. Kakkar, PhD; for the GARFIELD-VTE Investigators

Abstract

IMPORTANCE Patients with venous thromboembolism (VTE) and concomitant chronic kidney disease (CKD) have been reported to have a higher risk of thrombosis and major bleeding complications compared with patients without concomitant CKD. The use of anticoagulation therapy is challenging, as many anticoagulant medications are excreted by the kidney. Large-scale data are needed to clarify the impact of CKD for anticoagulant treatment strategies and clinical outcomes of patients with VTE.

OBJECTIVE To compare clinical characteristics, treatment patterns, and 12-month outcomes among patients with VTE and concomitant moderate to severe CKD (stages 3-5) vs patients with VTE and mild to no CKD (stages 1-2) in a contemporary international registry.

DESIGN, SETTING, AND PARTICIPANTS The Global Anticoagulant Registry in the Field–Venous Thromboembolism (GARFIELD-VTE) study is a prospective noninterventional investigation of real-world treatment practices. A total of 10 684 patients from 415 sites in 28 countries were enrolled in the GARFIELD-VTE between May 2014 and January 2017. This cohort study included 8979 patients (6924 patients with mild to no CKD and 2055 patients with moderate to severe CKD) who had objectively confirmed VTE within 30 days before entry in the registry. Chronic kidney disease stages were defined by estimated glomerular filtration rates. Data were extracted from the study database on December 8, 2018, and analyzed between May 1, 2019, and July 30, 2020.

EXPOSURE Moderate to severe CKD vs mild to no CKD.

MAIN OUTCOMES AND MEASURES The primary outcomes were all-cause mortality, recurrent VTE, and major bleeding. Event rates and 95% CIs were calculated and expressed per 100 person-years. Hazard ratios (HRs) were estimated with Cox proportional hazards regression models and adjusted for relevant confounding variables. All-cause mortality was considered a competing risk for other clinical outcomes in the estimation of cumulative incidences.

RESULTS Of the 10 684 patients with objectively confirmed VTE, serum creatinine data were available for 8979 patients (84.0%). Of those, 4432 patients (49.4%) were female and 5912 patients (65.8%) were White; 6924 patients (77.1%; median age, 57 years; interquartile range [IQR], 44-69 years) were classified as having mild to no CKD, and 2055 patients (22.9%; median age, 70 years; IQR, 59-78 years) were classified as having moderate to severe CKD. Calculations using the equation from the Modification of Diet in Renal Disease study indicated that, among the 6924 patients with mild to no CKD, 2991 patients had stage 1 CKD, and 3933 patients had stage 2 CKD; among the 2055 patients with moderate to severe CKD, 1650 patients had stage 3 CKD, 190 patients had stage 4 CKD, and 215 patients had stage 5 CKD. The distribution of VTE presentation was comparable between

(continued)

Key Points

Question Do outcomes differ in patients with venous thromboembolism with or without concomitant moderate to severe chronic kidney disease?

Findings In this cohort study of 8979 adult patients with venous thromboembolism, the presence of concomitant moderate to severe chronic kidney disease was associated with increases in the risk of death, recurrent venous thromboembolism, and major bleeding compared with mild to no chronic kidney disease.

Meaning The study's findings suggest that patients with venous thromboembolism and concomitant moderate to severe chronic kidney disease had worse prognoses, and further investigation is warranted to evaluate options for anticoagulation therapy in patients with venous thromboembolism who have advanced chronic kidney disease.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

groups. In total, 1171 patients (57.0%) with moderate to severe CKD and 4079 patients (58.9%) with mild to no CKD presented with deep vein thrombosis alone, 547 patients (26.6%) with moderate to severe CKD and 1723 patients (24.9%) with mild to no CKD presented with pulmonary embolism alone, and 337 patients (16.4%) with moderate to severe CKD and 1122 patients (16.2%) with mild to no CKD presented with both pulmonary embolism and deep vein thrombosis. Compared with patients with mild to no CKD, patients with moderate to severe CKD were more likely to be female (3259 women [47.1%] vs 1173 women [57.1%]) and older than 65 years (2313 patients [33.4%] vs 1278 patients [62.2%]). At baseline, the receipt of parenteral therapy alone was comparable between the 2 groups (355 patients [17.3%] with moderate to severe CKD vs 1253 patients [18.1%] with mild to no CKD). Patients with moderate to severe CKD compared with those with mild to no CKD were less likely to be receiving direct oral anticoagulant therapy, either alone (557 patients [27.1%] vs 2139 patients [30.9%]) or in combination with parenteral therapy (319 patients [15.5%] vs 1239 patients [17.9%]). Patients with moderate to severe CKD had a higher risk of all-cause mortality (adjusted hazard ratio [aHR], 1.44; 95% CI, 1.21-1.73), major bleeding (aHR, 1.40; 95% CI, 1.03-1.90), and recurrent VTE (aHR, 1.40; 95% CI, 1.10-1.77) than patients with mild to no CKD.

CONCLUSIONS AND RELEVANCE In this study of patients with VTE, the presence of moderate to severe CKD was associated with increases in the risk of death, VTE recurrence, and major bleeding compared with the presence of mild to no CKD.

JAMA Network Open. 2020;3(10):e2022886. doi:10.1001/jamanetworkopen.2020.22886

Introduction

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common factor associated with cardiovascular death.[1] Patients with chronic kidney disease (CKD) have a higher risk of developing VTE than those with normal kidney function.[2] In addition, decreased kidney function after PE has been found to be a short-term and long-term independent factor associated with increased mortality rates.[3] The prevalence of both CKD and VTE increases with age and the accumulation of risk factors, including type 2 diabetes and hypertension.[4,5] Furthermore, the choice of therapy can be more limited in patients with severe CKD owing to the clearance of direct oral anticoagulant (DOAC) medications by the kidneys.[6]

Randomized clinical trials support the use of DOAC therapy for the treatment of patients with VTE and mild to moderate CKD.[7,8] A meta-analysis indicated that DOAC therapy has a benefit-risk profile superior to that of vitamin K antagonist (VKA) therapy in patients with early-stage CKD.[9] The DOAC medications have varying degrees of kidney excretion; therefore, in one of the clinical trials, doses were adjusted for each patient,[7] although this adjustment was not performed in the other clinical trial.[8]

Data on the efficacy and safety of DOAC therapy for the treatment of patients with advanced CKD are limited. Phase 3 randomized clinical trials investigating the receipt of DOAC therapy among patients with VTE have excluded patients with severe kidney impairment (defined as a creatinine clearance level <25-30 mL/min).[7,8,10,11] Certain DOAC medications are approved for the treatment of VTE in patients with moderate to severe CKD and are licensed for use in patients with creatinine clearance levels as low as 15 mL/min.[12] Large-scale data are needed to clarify the impact of CKD for anticoagulant treatment strategies and clinical outcomes of patients with VTE.

The Global Anticoagulant Registry in the Field–Venous Thromboembolism (GARFIELD-VTE) study is an ongoing worldwide prospective noninterventional registry designed to observe initial and extended therapeutic strategies and clinical outcomes in patients with VTE who are receiving treatment according to local standard practices. In the present analysis, baseline characteristics,

treatment patterns, and 12-month outcomes were compared between patients with moderate to severe CKD (stages 3-5) and mild to no CKD (stages 1-2) who were enrolled in the GARFIELD-VTE.

Methods

A detailed description of the rationale and design of the GARFIELD-VTE (ClinicalTrials.gov identifier: NCT02155491) has been published previously.[13] The registry is conducted in accordance with the Declaration of Helsinki,[30] the International Council for Harmonization *Guideline for Good Clinical Practice*,[31] and the International Society of Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiological Practice*[32] and adheres to all applicable national laws and regulations. Independent ethics committees for each participating country and hospital-based institutional review boards approved the design of the registry. All patients provided written informed consent to participate. The confidentiality and anonymity of patients recruited for this registry are maintained. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.

Patient data relevant to VTE were collected through review of clinical records and patient notes. Data were captured using an electronic case report form designed by eClinicalHealth Services (Stirling, UK) and submitted electronically via a secure website to the registry coordinating center at the Thrombosis Research Institute (London, UK). The GARFIELD-VTE protocol requires that 10% of all electronic case report forms be monitored against source documentation, that there be an electronic audit trail for all data modifications, and that critical variables be subjected to additional audit. The data were extracted from the study database on December 8, 2018.

Design, Setting, and Participants

The GARFIELD-VTE enrolled patients 18 years and older who received diagnoses and treatment across a range of care settings at 415 sites in 28 countries between May 2014 and January 2017. Race and ethnicity data were collected from all participants via self-reporting. A previous study[14] suggested that variation exists among different races and ethnicities regarding the risk of developing venous thrombosis, and information about race and ethnicity was necessary to clarify the association between CKD stage and clinical outcome among patients with VTE. Eligible patients were required to have an objective diagnosis of VTE (excluding superficial vein thrombosis) within 30 days before they were entered in the registry. Patients with recurrent VTE must have completed their treatment for the previous event. Patients were excluded if long-term follow-up was not planned or if they were participating in other studies that required clinical visits, diagnostic procedures, or receipt of treatments. The aim of the registry was to record local treatment practices; therefore, no specific treatments or procedures were mandated by the study protocol. Decisions to initiate, continue, or change treatment were made solely at the discretion of the treating physicians and their patients.

The national coordinating investigators identified the care settings they believed most accurately represented the management of patients with VTE in their country, including vascular medicine, internal medicine, and general practice settings. Sites that agreed to participate were recruited after a qualification telephone conversation. The relevant investigator was required to complete a program that provided guidance on patient screening, enrollment, and follow-up in the registry.

Clinical Outcomes and CKD Stage

The primary clinical outcomes were all-cause mortality, recurrent VTE, and major bleeding. Major bleeding was defined as clinically overt bleeding associated with a critical site (eg, intracranial, intraspinal, or intraocular), decrease in hemoglobin of 2 g/dL or more, transfusion of 2 or more units of packed red blood cells, hemorrhagic stroke, or death. Nonmajor bleeding was defined as any overt bleeding that did not meet the criteria for major bleeding. The rates of cancer, nonhemorrhagic stroke or transient ischemic attack, and myocardial infarction were also recorded. In addition,

information was collected regarding the recorded cause of death and site of bleeding. Cancer events that were diagnosed more than 30 days after the VTE diagnosis date were considered cancer end points.

The severity of CKD was centrally adjudicated according to the Kidney Disease Outcomes Quality Initiative guidelines of the National Foundation.[15] The estimated glomerular filtration rate (GFR; expressed in milliliters per minute per 1.73 m squared) was calculated using the equation from the Modification of Diet in Renal Disease (MDRD) study, in which a constant of 175 is multiplied by the patient's standardized serum creatinine level (in mg/dL) to the −1.154 power multiplied by the patient's age (in years) to the −0.203 power; the product is then multiplied by 0.742 if the patient is female and by 1.212 if the patient is Black. Patients were classified as having mild to no CKD (stages 1-2) if their estimated GFR was 60 mL/min/1.73 m^2 or higher.

Patients were classified as having moderate to severe CKD (stages 3-5) if their estimated GFR was 59 mL/min/1.73 m^2 or lower (eTable 2 in the Supplement). Kidney function was confirmed by measuring creatinine clearance rate (in mL/min) using the Cockcroft Gault formula. For men, the patient's age (in years) is subtracted from a constant of 140, then multiplied by the patient's weight (in kg); this value is then divided by the product of the patient's serum creatinine level (in mg/L) multiplied by a constant of 72. For women, the resulting creatinine clearance rate is multiplied by 0.85.

Statistical Analysis

Continuous variables were summarized as median and interquartile range (IQR), and categorical variables were reported as frequency and percentage. Event rates and the associated 95% CIs were estimated using Poisson regression analysis and were expressed per 100 person-years.

Time to event analyses of outcomes were performed using Cox proportional hazards models. Hazard ratios (HRs) and associated 95% CIs were calculated. All variables that were identified as potential confounders by expert clinical judgment and through literature review were included in the adjustment models (eTable 1 in the Supplement). The proportional hazards assumption was evaluated with scaled Schoenfeld residuals. Missing values were imputed using the multivariate imputation by chained equations (MICE) method.[16] A sensitivity analysis was performed to assess the impact of excluded patients for the estimated HR. Cumulative incidence plots were estimated with cumulative incidence functions (CIFs) accounting for the competing risk of mortality for recurrent VTE episodes and major bleeding events.[17] Spearman rank correlation coefficients were used to compare creatinine clearance and GFR.

All statistical analyses were performed using R software (R Foundation for Statistical Computing)[18] and SAS software, version 9.4 (SAS Institute).[19] Throughout the study, 2-sided tests were used, and the threshold for statistical significance was $P = .05$. Data were analyzed from May 1, 2019, to July 30, 2020.

Results

Of the 10 684 patients with objectively confirmed VTE, serum creatinine data were available for 8979 patients (84.0%). Of those, 4432 patients (49.4%) were female and 5912 patients (65.8%) were White (**Table**). Overall, 6924 eligible patients (77.1%) were classified as having mild to no CKD (2991 patients with stage 1 CKD and 3933 patients with stage 2 CKD), and 2055 patients (22.9%) were classified as having moderate to severe CKD (1650 patients with stage 3 CKD, 190 patients with stage 4 CKD, and 215 patients with stage 5 CKD), as calculated using the MDRD (**Figure 1**). The Cockcroft Gault formula revealed a similar pattern for kidney function (eTable 2 in the Supplement). Patients with moderate to severe CKD compared with those with mild to no CKD were more likely to be female (1173 women [57.1%] vs 3259 women [47.1%]) and older than 65 years (1278 patients [62.2%] vs 2313 patients [33.4%]). The Spearman correlation coefficient for estimated GFR and

Table. Baseline Participant Characteristics

Characteristic	No. (%)	
	Mild to no CKD	Moderate to severe CKD
Total participants, No.	**6924**	**2055**
Female sex	3259 (47.1)	1173 (57.1)
Age, y		
Median (IQR)	57 (44-69)	70 (59-78)
Category		
<50	2482 (35.8)	271 (13.2)
50-65	2129 (30.7)	506 (24.6)
>65-75	1379 (19.9)	549 (26.7)
>75-85	774 (11.2)	548 (26.7)
>85	160 (2.3)	181 (8.8)
Race/ethnicity		
White	4485 (64.8)	1427 (69.4)
Asian	1344 (19.4)	363 (17.7)
Black	335 (4.8)	85 (4.1)
Other	389 (5.6)	99 (4.8)
Missing	371 (5.4)	81 (3.9)
BMI		
Median (IQR)	27.1 (23.9-31.2)	28.1 (24.7-32.4)
Category		
Underweight (<18.5)	161 (2.3)	34 (1.7)
Normal (18.5-24.9)	2001 (28.9)	476 (23.2)
Overweight (25.0-29.9)	2163 (31.2)	674 (32.8)
Obese (≥30.0)	1932 (27.9)	702 (34.2)
Missing	667 (9.6)	169 (8.2)
Type of VTE		
DVT alone	4079 (58.9)	1171 (57.0)
PE alone	1723 (24.9)	547 (26.6)
PE and DVT	1122 (16.2)	337 (16.4)
Site of DVT		
Lower limb	4774 (68.9)	1423 (69.2)
Upper limb	308 (4.4)	58 (2.8)
Caval vein	116 (1.7)	24 (1.2)
No DVT	1723 (24.9)	547 (26.6)
Missing	3 (0.04)	3 (0.1)
Type of lower limb DVT		
Proximal	1752 (25.3)	557 (27.1)
Distal	1651 (23.8)	419 (20.4)
Both	1319 (19.0)	428 (20.8)
Missing	2202 (31.8)	651 (31.7)
Care setting		
Hospital	5315 (76.8)	1597 (77.7)
Outpatient setting	1609 (23.2)	458 (22.3)
Specialty		
Internal medicine (hematology and intensive care)	3311 (47.8)	869 (42.3)
Vascular medicine	2858 (41.3)	952 (46.3)
Cardiology	306 (4.4)	100 (4.9)
General practitioner	241 (3.5)	92 (4.5)
Emergency medicine	205 (3.0)	42 (2.0)
Missing	3 (0.04)	0

(continued)

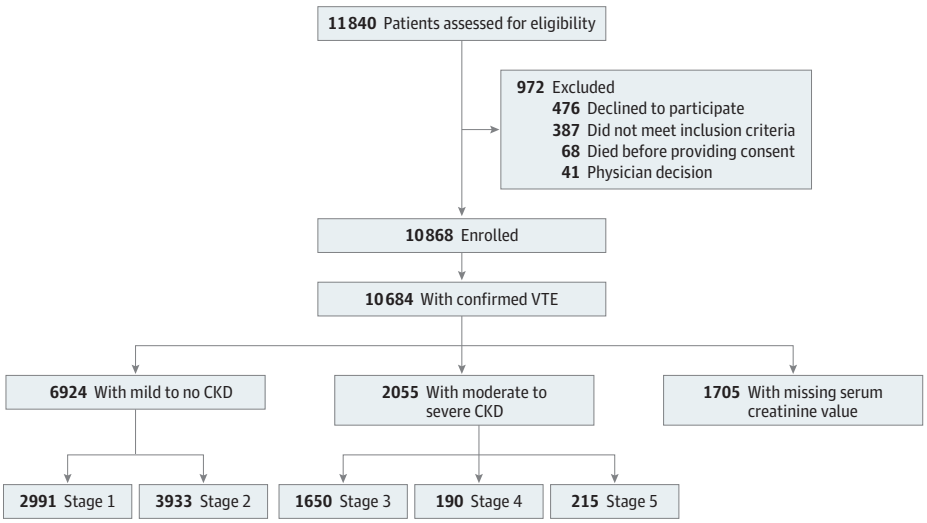
Table. Baseline Participant Characteristics (continued)

Characteristic	No. (%)	
	Mild to no CKD	Moderate to severe CKD
Region		
Europe	3856 (55.7)	1212 (59.0)
Asia	1237 (17.9)	342 (16.6)
North America and Australia	1046 (15.1)	264 (12.8)
Africa and Middle East	574 (8.3)	165 (8.0)
Latin America	211 (3.0)	72 (3.5)
Provoking risk factors[a]		
Persistent		
Active cancer	744 (10.7)	236 (11.5)
Transient		
Surgery	911 (13.2)	219 (10.7)
Hospitalization	865 (12.5)	289 (14.1)
Trauma to lower limb	548 (7.9)	103 (5.0)
Oral contraception	400 (5.8)	49 (2.4)
Acute medical illness	398 (5.7)	145 (7.1)
Long traveling	375 (5.4)	71 (3.5)
Hormone replacement therapy	98 (1.4)	46 (2.2)
Predisposing risk factors		
Previous VTE	1035 (14.9)	325 (15.8)
History of cancer	901 (13.0)	358 (17.4)
Family history of VTE	459 (6.6)	87 (4.2)
Chronic immobilization	371 (5.4)	144 (7.0)
Recent bleeding or anemia	242 (3.5)	100 (4.9)
Known thrombophilia	214 (3.1)	43 (2.1)
Chronic heart failure	154 (2.2)	138 (6.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CKD, chronic kidney disease; DVT, deep vein thrombosis; IQR, interquartile range; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Persistent and transient provoking risk factors that occurred within 3 months before VTE diagnosis.

Figure 1. Study Population Flowchart



CKD indicates chronic kidney disease and VTE, venous thromboembolism.

creatinine clearance was 0.75 (eFigure 1 in the Supplement). A full description of baseline participant characteristics is provided in the Table.

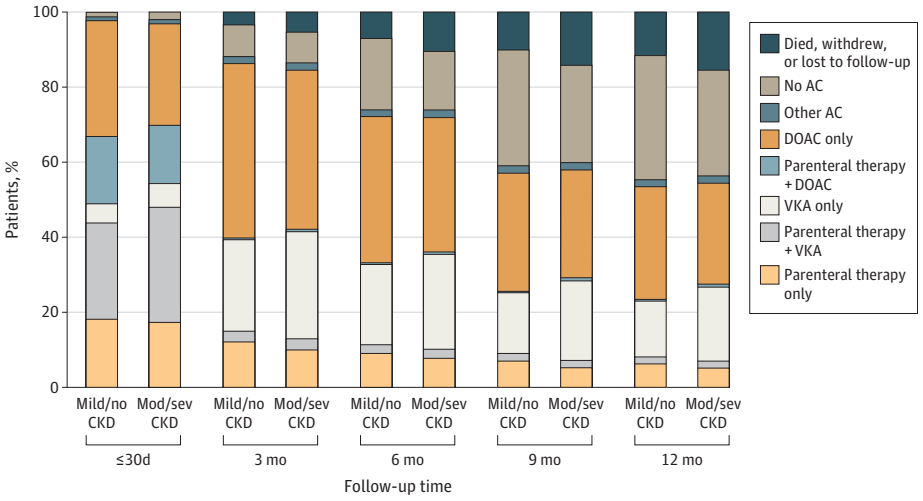
At baseline, the distribution of VTE events was comparable between groups (Table). Among patients with moderate to severe CKD, 1171 patients (57.0%) presented with DVT alone, 547 patients (26.6%) presented with PE alone, and 337 patients (16.4%) presented with PE and DVT; among

patients with mild to no CKD, 4079 patients (58.9%) presented with DVT alone, 1723 patients (24.9%) presented with PE alone, and 1122 patients (16.2%) presented with PE and DVT. The most frequent site of DVT in patients with moderate to severe CKD and those with mild to no CKD was the lower limb (1423 patients [69.2%] and 4774 patients [68.9%]). The type of lower limb DVT was comparable among patients with moderate to severe CKD and those with mild to no CKD (for proximal DVT, 557 patients [27.1%] vs 1752 patients [25.3%]; for distal DVT, 419 patients [20.4%] vs 1651 [23.8%]; and for distal and proximal DVT, 428 patients [20.8%] vs 1319 patients [19.0%]). Patients with moderate to severe CKD compared with those with mild to no CKD were older (median age, 70 years [IQR, 59-78 years] vs 57 years [IQR, 44-69 years]) and more likely to be female (1173 women [57.1%] vs 3259 women [47.1%]). Other characteristics, such as race/ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), and care setting, were similar among groups.

The prevalence of provoking risk factors, both persistent and transient, was comparable between patients with moderate to severe CKD and patients with mild to no CKD (Table). Compared with patients with mild to no CKD, patients with moderate to severe CKD were more likely to have predisposing risk factors, including chronic heart failure (154 patients [2.2%] vs 138 patients [6.7%]), chronic immobilization (371 patients [5.4%] vs 144 patients [7.0%]), and a history of cancer (901 patients [13.0%] vs 358 patients [17.4%]).

At baseline, patients with moderate to severe CKD compared with those with mild to no CKD were more likely to be receiving a VKA medication, either alone (129 patients [6.3%] vs 353 patients [5.1%]) or in combination with parenteral therapy (631 patients [30.7%] vs 1779 patients [25.7%]) and less likely to be receiving a DOAC medication, either alone (557 patients [27.1%] vs 2139 patients [30.9%]) or in combination with parenteral therapy (319 patients [15.5%] vs 1239 patients [17.9%]) (**Figure 2**). The receipt of parenteral therapy alone was comparable between groups (355 patients [17.3%] with moderate to severe CKD vs 1253 patients [18.1%] with mild to no CKD). Over time, a similar proportion of patients with moderate to severe CKD and mild to no CKD continued to receive anticoagulant therapy at 3 months (1778 patients [86.5%] vs 6100 patients [88.1%]), 6 months (1519 patients [73.9%] vs 5117 patients [73.9%]), 9 months (1231 patients [59.9%] vs 4085 patients [59.0%]), and 12 months (1136 patients [55.3%] vs 3829 patients [55.3%]).

Figure 2. Anticoagulant Treatment in Patients Over 12-Month Follow-Up



Data unavailable for 13 patients with moderate to severe chronic kidney disease and 47 patients with mild to no chronic kidney disease. AC indicates anticoagulant medication; DOAC, direct oral anticoagulant medication; mild/no CKD, mild to no chronic kidney disease; mod/sev CKD, moderate to severe chronic kidney disease; and VKA, vitamin K antagonist medication.

Clinical Outcomes

The unadjusted rate of all-cause mortality at 12 months in patients with moderate to severe CKD was higher than that of patients with mild to no CKD (12.8 deaths per 100 person-years [95% CI, 11.3-14.6 deaths per 100 person-years] vs 6.7 deaths per 100 person-years [95% CI, 6.1-7.3 deaths per 100 person-years]) (eTable 3 in the Supplement). Patients with moderate to severe CKD were more likely than patients with mild to no CKD to die of cardiac-associated conditions (185 patients [9.0%] vs 339 patients [4.9%]) but less likely to die of cancer (912 patients [44.4%] vs 4141 patients [59.8%]) and VTE-associated conditions (80 patients [3.9%] vs 346 patients [5.0%]) (eTable 4 in the Supplement). The rate of recurrent VTE was higher in patients with moderate to severe CKD compared with patients with mild to no CKD (6.6 events per 100 person-years [95% CI, 5.5-7.9 events per 100 person-years] vs 5.0 events per 100 person-years [95% CI, 4.5-5.6 events per 100 person-years]). A greater proportion of PE recurrences (with or without DVT) was found in patients with moderate to severe CKD (3102 patients [44.8%]) vs patients with mild to no CKD (2285 patients [33.0%]).

Patients with moderate to severe CKD also experienced major bleeding more frequently than patients with mild to no CKD (4.6 events per 100 person-years [95% CI, 3.7-5.7 events per 100 person-years] vs 2.4 events per 100 person-years [95% CI, 2.1-2.8 events per 100 person-years]). The most frequent sites of bleeding in patients with both moderate to severe CKD and mild to no CKD were the upper gastrointestinal tract (477 patients [23.2%] and 907 patients [13.1%]) and the lower gastrointestinal tract (376 patients [18.3%] and 907 patients [13.1%]) (eTable 5 in the Supplement).

Among patients with mild to no CKD, the unadjusted rates of myocardial infarction or acute coronary syndrome (0.7 events per 100 person-years [95% CI, 0.5-0.9 events per 100 person-years]) and stroke (0.6 events per 100 person-years [95%CI, 0.4-0.8 events per 100 person-years]) did not differ from those with moderate to severe CKD (1.3 events per 100 person-years [95% CI, 0.8-1.9 events per 100 person-years] and 0.9 events per 100 person-years [95% CI, 0.6-1.5 events per 100 person-years]) (eTable 3 in the Supplement). **Figure 3** shows the cumulative incidence curves for the primary end points of all-cause mortality, recurrent VTE, and major bleeding.

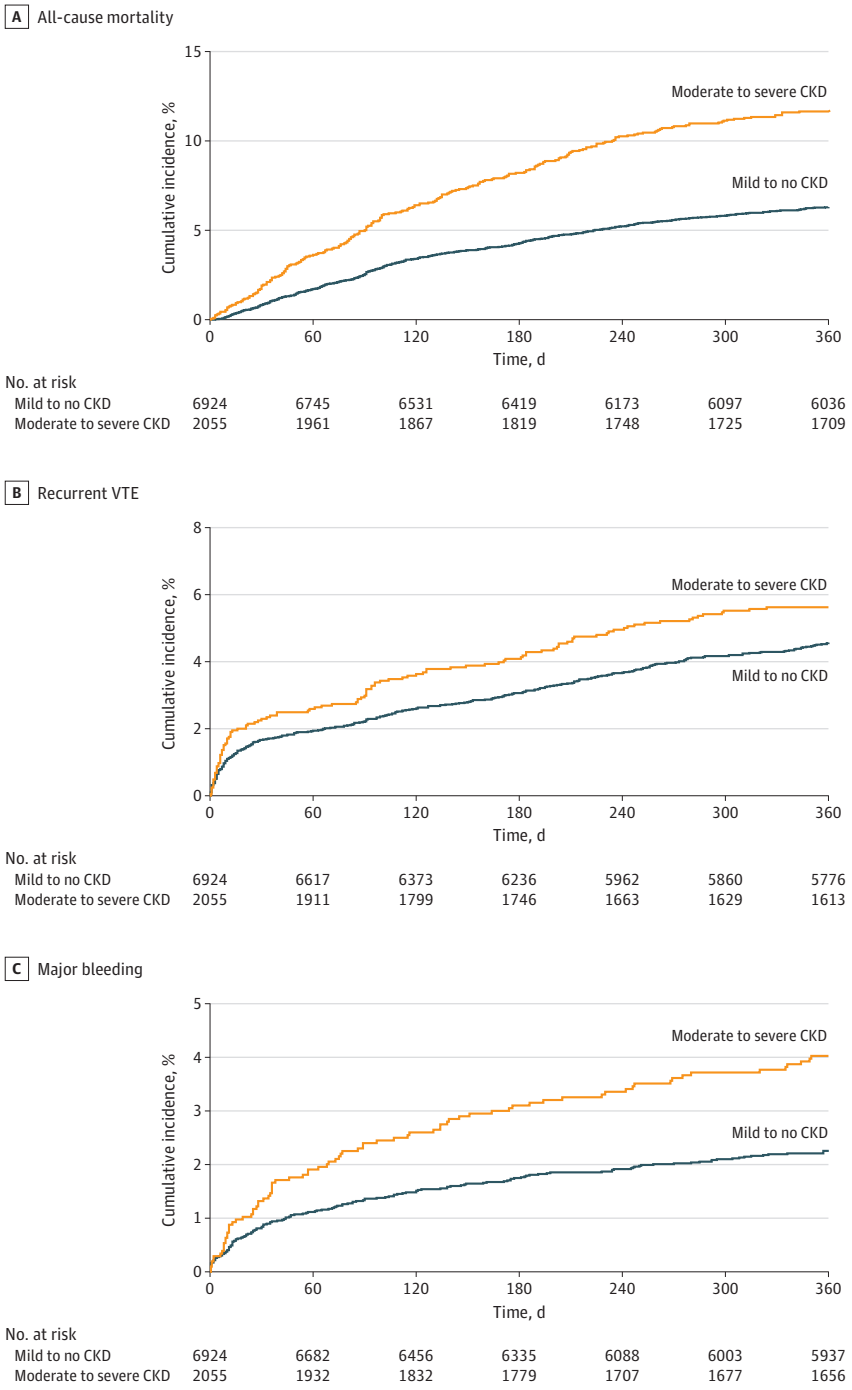
After adjustment for potential confounders (eTable 1 in the Supplement), the incidence of all-cause mortality at 12 months remained higher in patients with moderate to severe CKD (adjusted HR [aHR], 1.44; 95% CI, 1.21-1.73). The incidence of recurrent VTE (aHR, 1.40; 95% CI, 1.10-1.77) and major bleeding (aHR, 1.40; 95% CI, 1.03-1.90) at 12 months was also higher in patients with moderate to severe CKD (**Figure 4**). The incidence of cancer did not differ between patients with mild to no CKD and moderate to severe CKD (aHR, 1.15; 95% CI, 0.83-1.60).

A comparison of baseline characteristics between the patients included in the analysis and the 1705 patients (16.0%) omitted from the analysis owing to missing creatinine levels revealed distribution differences in VTE type (eFigure 2 in the Supplement). A sensitivity analysis estimating the HRs for the main clinical outcomes using imputed creatinine values for the excluded patients revealed comparable outcome rates.

A subanalysis of outcomes according to the type of lower limb DVT indicated that patients with proximal DVT compared with patients with distal DVT had a higher rate of all-cause mortality in those with mild to no CKD (7.9 deaths per 100 person-years [95% CI, 6.7-9.4 deaths per 100 person-years] vs 4.6 deaths per 100 person-years [95% CI, 3.6-5.8 deaths per 100 person-years]) and moderate to severe CKD (16.7 deaths per 100 person-years [95% CI, 13.4-20.7 deaths per 100 person-years] vs 10.2 deaths per 100 person-years [95% CI, 7.5-14.0 deaths per 100 person-years]). Patients with proximal DVT compared with distal DVT more frequently experienced recurrent VTE (for patients with mild to no CKD, 6.3 events per 100 person-years [95% CI, 5.2-7.7 events per 100 person-years] vs 5.3 events per 100 person-years [95% CI, 4.3-6.6 events per 100 person-years]; for patients with moderate to severe CKD, 8.9 events per 100 person-years [95% CI, 6.5-12.1 events per 100 person-years] vs 4.6 events per 100 person-years [95% CI, 2.9-7.4 events per 100 person-years]) and major bleeding (for patients with mild to no CKD, 2.6 events per 100 person-years [95% CI,

1.9-3.5 events per 100 person-years] vs 1.6 events per 100 person-years [95% CI, 1.1-2.4 events per 100 person-years]; for patients with moderate to severe CKD, 4.4 events per 100 person-years [95% CI, 2.9-6.8 events per 100 person-years] vs 3.2 events per 100 person-years [95% CI, 1.8-5.6 events per 100 person-years]) (eTable 6 in the Supplement).

Figure 3. Cumulative Incidence Stratified by Stage of Chronic Kidney Disease



Data are shown as percentages of patients experiencing event and 95% CIs. CKD indicates chronic kidney disease and VTE, venous thromboembolism. A, All-cause mortality. B, Recurrent VTE. C, Major bleeding.

Discussion

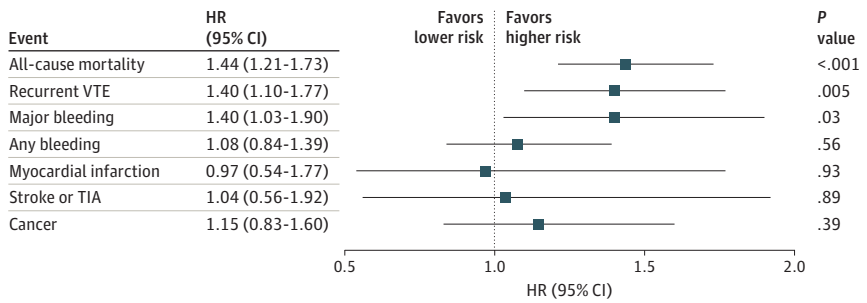
The clinical characteristics, treatment patterns, and 12-month outcomes of patients with moderate to severe CKD (stages 3-5) and mild to no CKD (stages 1-2) were evaluated using data from the large contemporary international registry of the GARFIELD-VTE. The patient's CKD stage was determined using the MDRD equation for estimated GFR levels, and kidney function was confirmed using the Cockcroft Gault formula for creatinine clearance measurement, indicating a Spearman correlation coefficient of 0.75 for the sample. The MDRD equation is typically used to calculate estimated GFR, which is the recommended measurement for establishing the stage and progression of CKD. The Cockcroft Gault formula is often used to analyze creatinine clearance as an indication of kidney function and as a means of calculating dosage requirements. The MDRD equation provides a greater level of accuracy for calculating kidney function than the Cockcroft Gault formula in patients with advanced CKD and in patients with impaired kidney function.[20,21] Both estimations are widely used to classify the progress of the patient's CKD stage, and the MDRD and Cockcroft Gault estimations did not differ substantially in our analysis.

Patients with moderate to severe CKD had higher rates of all-cause mortality, recurrent VTE, and major bleeding than those with mild to no CKD over a 12-month period after diagnosis with VTE, despite comparable use of anticoagulant therapy. It is of note that the cumulative incidences were diverse over time between patients with moderate to severe CKD and patients with mild to no CKD for both all-cause mortality and major bleeding. Differences in the cumulative incidence of VTE recurrence between the 2 groups were calculated at an early point after recruitment and maintained throughout the 12 months of follow-up.

Patients with moderate to severe CKD were older than those with mild to no CKD, confirming the association between older age and the prevalence of CKD[5]; patients with moderate to severe CKD were also more likely to be female.[22] In addition, patients with moderate to severe CKD had a higher prevalence of predisposing factors, including chronic heart failure. Heart failure and CKD share many common risk factors, such as older age, hypertension, and type 2 diabetes, with more than one-half of patients with heart failure having moderate to severe CKD.[23] A higher risk of mortality and bleeding in patients with VTE and concomitant moderate to severe CKD has been reported previously;[24-26] however, unlike the GARFIELD-VTE registry, these studies did not include a substantial number of patients who were receiving DOAC therapy,[24] and they were conducted over a shorter period of 3 months.[24-26]

In the contemporary international GARFIELD-VTE registry, inclusion of a substantial number of Asian patients indicated that, among those with moderate to severe CKD, mortality was primarily associated with cancer followed by cardiac conditions.[27] At baseline, the choice of parenteral anticoagulation treatment alone was comparable between patients with moderate to severe CKD and those with mild to no CKD. Patients with moderate to severe CKD were more likely to receive VKA therapy (alone or in combination with parenteral therapy) and less likely to receive DOAC therapy (alone or in combination with parenteral therapy) than patients with mild to no CKD.

Figure 4. Adjusted Hazard Ratios for 12-Month Outcomes



Reference group was patients with mild to no chronic kidney disease. eTable 1 in the Supplement lists variables used in the adjustment. HR indicates hazard ratio; TIA, transient ischemic attack; and VTE, venous thromboembolism.

Chronic kidney disease is recognized as an important factor in future cardiovascular events owing to the associated hypercoagulable state.[28] Even after accounting for the competing risk of death, subdistribution HRs illustrated an increased incidence of recurrent VTE and major bleeding in patients with moderate to severe CKD. A higher incidence of bleeding events in patients with moderate to severe CKD raises the question of whether the intensity of anticoagulant medication currently being used is too high. These results are consistent with those observed in the GARFIELD–Atrial Fibrillation study,[29] in which patients with moderate to severe CKD had a higher incidence of mortality and bleeding complications. A comparative effectiveness analysis detailing the impact of differing anticoagulation strategies is warranted to investigate safer treatment choices for patients with VTE and concomitant moderate to severe CKD in the future.

Limitations

This study has several limitations. The absence of creatinine clearance measurements in 16.0% of patients with objectively confirmed VTE is a major limitation. Another limitation is the heterogeneous distribution of patients' CKD stages, with only a small number of patients in the GARFIELD-VTE having advanced CKD (190 patients with stage 4 CKD and 215 patients with stage 5 CKD).

Conclusions

In this study, the presence of concomitant moderate to severe CKD among patients with VTE was associated with increases in the risk of death, recurrent VTE, and major bleeding within 12 months of VTE diagnosis compared with the presence of mild to no CKD, even after adjustment for baseline participant characteristics. Improving the quality of care for patients with VTE and concomitant moderate to severe CKD remains an important challenge. Future work within the GARFIELD-VTE will assess the impact of both the dose and the duration of anticoagulant treatment for VTE recurrence and bleeding up to 3 years after VTE diagnosis.

ARTICLE INFORMATION

Accepted for Publication: August 10, 2020.

Published: October 28, 2020. doi:10.1001/jamanetworkopen.2020.22886

Corresponding Author: Shinya Goto, MD, PhD, Professor, Department of Medicine (Cardiology), Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan (shinichi@is.icc.u-tokai.ac.jp).

Author Affiliations: Department of Medicine (Cardiology), Tokai University School of Medicine, Isehara, Kanagawa, Japan (Goto); Technical University of Munich, Munich, Germany (Haas); Department of Medicine and Surgery, University of Insubria, Varese, Italy (Ageno); Harvard Medical School, Boston, Massachusetts (Goldhaber); McMaster University, Hamilton, Ontario, Canada (Turpie); Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, Ontario, Canada (Weitz); Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (Angchaisuksiri); Copenhagen University Hospital, Frederiksberg, Denmark (Nielsen); Thrombosis Research Institute, London, United Kingdom (Kayani, Farjat); Medical Department 2, Municipal Hospital Dresden, Dresden, Germany (Schellong); Faculty of Medicine, University of Geneva, Geneva, Switzerland (Bounameaux); IRCCS Multimedica, Milan, Italy (Mantovani); University of Milano, Bicocca, Milan, Italy (Mantovani); Arianna Foundation on Anticoagulation, Bologna, Italy (Prandoni); University College London, London, United Kingdom (Kakkar).

Author Contributions: Dr Goto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Haas, Ageno, Turpie, Angchaisuksiri, Kayani, Farjat, Bounameaux, Mantovani, Prandoni, Kakkar.

Acquisition, analysis, or interpretation of data: Goto, Haas, Ageno, Goldhaber, Weitz, Angchaisuksiri, Nielsen, Farjat, Schellong, Bounameaux, Mantovani.

Drafting of the manuscript: Goto, Haas.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Farjat, Mantovani.

Obtained funding: Goto, Kakkar.

Administrative, technical, or material support: Weitz, Kayani.

Supervision: Haas, Ageno, Angchaisuksiri, Kayani, Bounameaux, Mantovani, Prandoni.

Conflict of Interest Disclosures: Dr Goto reported receiving personal fees from the Thrombosis Research Institute during the conduct of the study; grants from Bristol Myers Squibb, Ono Pharmaceutical, Pfizer, and Sanofi outside the submitted work; and personal fees from the American Heart Association outside the submitted work. Dr Haas reported receiving personal fees from Aspen Pharmacare, Bayer Pharma AG, Bristol Myers Squibb, Daiichi Sankyo, Pfizer, Portola Pharmaceuticals, and Sanofi outside the submitted work. Dr Ageno reported receiving personal fees from the Thrombosis Research Institute during the conduct of the study; grants from Bayer Pharma AG and Boehringer Ingelheim outside the submitted work; and personal fees from Aspen Pharmacare, Bayer Pharma AG, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen Pharmaceutica, Pfizer, Portola Pharmaceuticals, and Sanofi outside the submitted work. Dr Goldhaber reported receiving grants from Bayer Pharma AG, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Daiichi Sankyo, Janssen Pharmaceutica, the National Heart, Lung, and Blood Institute, and the Thrombosis Research Institute and personal fees from Bayer Pharma AG and Boehringer Ingelheim outside the submitted work. Dr Turpie reported receiving personal fees from Bayer Pharma AG and Janssen Pharmaceutica outside the submitted work. Dr Weitz reported receiving research support from the Canadian Fund for Innovation, the Canadian Institutes of Health Research, the Heart and Stroke Foundation and personal fees from Anthos Therapeutics, Bayer Pharma AG, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Ionis Pharmaceuticals, Janssen Pharmaceutica, Merck, Novartis, Pfizer, Portola Pharmaceuticals, Servier Pharmaceuticals, and Tetherex Pharmaceuticals outside the submitted work. Dr Nielsen reported receiving personal fees from Bayer Pharma AG, Boehringer Ingelheim, Bristol Myers Squibb, Leo Pharma, Merck Sharp & Dohme, Pfizer, and Roche Diagnostics outside the submitted work. Dr Kayani reported receiving grants from Bayer Pharma AG during the conduct of the study. Dr Schellong reported receiving grants from Bristol Myers Squibb and personal fees from Aspen Pharmacare, Bayer Pharma AG, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Pfizer, and Sanofi-Aventis outside the submitted work. Dr Bounameaux reported receiving grants from the Thrombosis Research Institute during the conduct of the study and personal fees from Bayer Pharma AG outside the submitted work. Dr Mantovani reported receiving grants from the Italian Ministry of Health Ricerca Corrente–IRCCS MultiMedica during the conduct of the study and grants and personal fees from Bayer Pharma AG, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer outside the submitted work. Dr Prandoni reported receiving personal fees from Bayer Pharma AG, Daiichi Sankyo, Pfizer, and Sanofi outside the submitted work. Dr Kakkar reported receiving personal fees from Bayer Pharma AG and Sanofi during the conduct of the study; grants from Bayer Pharma AG outside the submitted work; and personal fees from Anthos Therapeutics, Bayer Pharma AG, Janssen Pharmaceutica, Pfizer, Sanofi, and Verseon outside the submitted work. No other disclosures were reported.

Funding/Support: The GARFIELD-VTE study is an independent academic research initiative sponsored by the Thrombosis Research Institute (London, UK) and supported by an unrestricted research grant from Bayer Pharma AG (Berlin, Germany).

Role of the Funder/Sponsor: The Thrombosis Research Institute contributed to the design and conduct of the study under the supervision of the scientific steering committee members of the GARFIELD-VTE study. Data collection and management were carried out electronically by the Thrombosis Research Institute. Statistical analysis was performed by an academic statistician at the Thrombosis Research Institute. The manuscript was critically reviewed, approved, and prepared for submission by all coauthors and the Thrombosis Research Institute. Bayer Pharma AG provided grant support for the Thrombosis Research Institute and had an opportunity to review the manuscript before submission but did not contribute in any way to the final version of the manuscript.

Group Information: GARFIELD-VTE Principle Investigators: Ab Loualidi, MD, Ommelander Ziekenhuisgroep; Abbey Wilcox, FRACP, and Abdul Parwani, MD, Charite–Campus Virchow-Klinikum; Abdurrahim Colak, MD, Ataturk University Medical Faculty; Abraham Bezuidenhout, MD, Steve Biko Academic Hospital, Department of Surgery; Abu Abdool-Carrim, MD, Vascular Centre Milpark Hospital; Addala Azeddine, MD, private practice, Lyon, France; Adriaan Beyers, MD, Beyers AJ; Adriaan Dees, MD, PhD, Ikazia Ziekenhuis; Ahmed Mohamed, private clinic; Ahmet Aksoy, Corlu State Hospital; Akihiko Abiko, MD, Iwate Medical University Hospital; Akinori Watanabe, MD, Fujieda Municipal General Hospital; Alan Krichell, NHS Ayshire and Arran; Alberto Tosetto, MD, Ospedale San Bortolo di

Vicenza; Alberto Alfredo Fernandez, MD, Sanatorio Modelo Quilmes SA; Alexander Tsaregorodtsev, SBI of Ryazan region, Regional Clinical Cardiological Dispensary; Alexey Khotuntsov, SPb SBIH City Hospital #26; Alisha Oropallo, MD, North Shore–LIJ Heath System; Alison Slocombe, Box Hill Hospital; Allan Kelly, MD, ALTA Clinical Research; Amanda Clark, University Hospitals Bristol NHS Foundation Trust; Amr Gad, MD, private clinic; Amy Arouni, VA Medical Center–Omaha, Nebraska; Andor Schmidt, MD, Praxis; Andrea Berni, MD, Azienda Ospedaliera Sant'Andrea-Università di Roma La Sapienza; Andrei D. Vishniagov, Lomonosov Interdistrict Hospital NA I.N. Yudchenko; Andres Javier Kleiban, MD, Instituto Medico CENICLAR-C de Investigaciones Clinicas Argentina; Andrew Machowski, MD, PhD, Polokwane Hospital Surgery Department; Andrew Rapule Ratsela, MD, Polokwane Mankweng Hospital Internal Medicine Dept; Andrey Kazakov, SHI Regional Clinical Hospital; Andrey L. Komarov, MD, FSBI Russian Cardiological Scientific and Industrial Complex of the MoH of the RF; Angel Galvez, MD, PhD, Oncology Specialists; Ann Lockman, MD, Newcastle upon Tyne Hospitals NHS Foundation Trust; Anna Falanga, MD, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Presidio Papa Giovanni XXIII; Anoop Chauhan, PhD, Oxford University Hospitals NHS Trust; Antoni Riera-Mestre, PhD, Hospital Universitari de Bellvitgel; Antonino Mazzone, MD, Ospedale Civile di Legnano; Armando D'Angelo, Ospedale San Raffaele; Artur Herdy, MD, ICSC–Instituto de Cardiologia de Santa Catarina; Atsushi Kato, MD, Sendai Open Hospital; Attilia Pizzini, Arcispedale S. Maria Nuova Azienda Ospedaliera di Reggio Emilia; Ayman Abd Elhamid Ebrahim Mahmoud Salem, MD, private clinic; Azlan Husin, MD, Mmed, Hospital Universiti Sains Malaysia; Barbara Erdelyi, MD, private practice; Barry Jacobson, PhD, FRCS, Charlotte Maxeke Johannesburg Academic Hospital Haematology Department; Beatrice Amann-Vesti, MD, and Bektas Battaloglu, MD, Inonu University Medical Faculty; Benedicte Wilson, MD, Nykøbing F Sygehus; Benilde Cosmi, MD, PhD, Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi; Bergmann Jean Francois, MD, Lariboisière Hospital; Berremeli Toufek, MD, Centre Hospitalier, Annecy Genevois; Beverley Hunt, MD, University Hospital of South Manchester NHS Foundation Trust; Bhavesh Natha, FCS(SA), Matley & Partners; Binali Mavitaş, MD, Dicle University Medical Faculty; Bisher Mustafa, MD, Sheikh Khalifa Medical City; Bonnie Chi Shan Kho, Pamela Youde Nethersole Eastern Hospital; Boulon Carine, MD, CHU Bordeaux; Brian Zidel, MD, Malton Medical Center; Brisot Dominique, MD, private practice, Montpellier, France; Brousse Christophe, MD, private practice, Montpellier, France; Bruno Trimarco, MD, PhD, Azienda Ospedaliera Universitaria Federico II; Canhua Luo, The First People's Hospital of Foshan; Carlos Alberto Cuneo, MD, Prevencion Cardiovascular Salta; Carlos Jerjes Sanchez Diaz, MD, Unidad de Investigacion Clinica en Medicina SC; Carsten Schwencke, MD, Medizinisches Versorgungszentrum Prof Mathey, Prof Schofer GmbH; Cas Cader, MD, Crystal Coast Family Practice; Celal Yavuz, MD, Dicle University Medical Faculty; Cesar Javier Zaidman, CIPREC; Charles Lunn, MD, Oklahoma City Clinic–Central; Charlotte Bomken, MD, and Chau-Chung Wu, MD, PhD, National Taiwan University Hospital; Cheng Hock Toh, MD, GSTT NHS Foundation Trust; Chern-En Chiang, MD, Taipei Veterans General Hospital; Chevrier Elisa, GHICL Lille; Chien-Hsun Hsia, MD, Changhua Christian Hospital Chien-Lung Huang, MD, Cheng-Hsin Rehabilitation Medical Center; Chi-Hang Kevin Kwok, MD, Princess Margaret Hospital; Chih-Cheng Wu, MD, National Taiwan University Hospital Hsin-Chu Branch; Chi-Hung Huang, MD, PhD, Cathay General Hospital; Chooi Kheng Chiew, MRCP, Hospital Seri Manjung; Chris Ward, PhD, Royal North Shore Hospital; Christian Opitz, MD, DRK Kliniken Berlin Koepenick-PS; Christina Jeanneret-Gris, MD, Kantonsspital Bruderholz; Chung Yin Ha, MRCP, Tuen Mun Hospital; Chun-Yao Huang, MD, Taipei Medical University Hospital; Claude Luyeye Bidi, Centre Hospitalier de Jolimont-Lobbes; Clifford Smith and Cornelia Brauer, MD, Praxis; Corrado Lodigiani, MD, Istituto Clinico Humanitas; Couturaud Francis, MD, PhD, L'hôpital De La Cavale Blanche Du Chru De Brest; Cynthia Wu, University of Alberta Hospital; Daniel Staub, MD, Universitaetsspital Basel; Daniel Theodoro, MD, Washington University at St. Louis; Daniela Poli, MD, Azienda Ospedaliera Universitaria Careggi; David Adler, MD, Kopano Clinical Trials; David Jimenez, MD, PhD, Respiratory Department and Medicine Department, Ramón y Cajal Hospital; David Keeling, MD, NHS Lothian; David Scott, MD, New York Hospital of Queens; David-Riesco Acevedo, MD, PhD, Hospital El Vendrell/Xarxa Santa Tecla; Davide Imberti, MD, AUSL Piacenza–Ospedale Guglielmo da Saliceto; Desmond Creagh, MD, Royal Cornwall Hospitals NHS Trust; Desmurs-Clavel Helene, MD, Centre Hospitalier Universitaire Lyon; Dirk Hagemann, MD, Gemeinschaftspraxis Dres Hagemann, Duerfeld und Breiderhoff; Dirk Le Roux, FCS(SA), Dr Dirk le Roux, Inc; Dirk Skowasch, MD, Universitaetsklinikum Bonn AoeR; Dmitry Belenky, MD, SBIH of Novosibirsk Region Clinical Emergency Hospital #2; Dmitry Dorokhov, DCH on Station Chelyabinsk of JSC Russian Railways; Dmitry Petrov, MD, SBEI HPE Yaroslavl State Medical University of the MoH of the RF; Dmitry Zateyshchikov, DO, SBIH of Moscow City Clinical Hospital # 51; Domenico Prisco, MD, AOUC Azienda Ospedaliero-Universitaria Careggi; Dorthe Møller, PhD, Regionshospitalet Viborg; Dusan Kucera, PhD, Kardiologicka a Angiologicka Ambulance; Ehab M. Esheiba, MRCPUK, Gulf Medical University Hospital; Elena Kochmareva, SBIH of Moscow City Clinical Hospital # 15 NA OM Filatov; Elena N. Dankovtseva, SBIH of Moscow City Clinical Hospital # 51; Elizaveta Panchenko, MD, FSBI Russian Cardiological Scientific and Industrial Complex of the MoH of the RF; Elkouri Dominique, Centre Hospitalier Universitaire Nantes; Emre Dogan, Op Dr, Trabzon Ahi Evren Kalp ve Damar Cerrahisi Egitim Arastirma Hastanesi; Emre Kubat, MD, and Enrique Diaz, Health Pharma Professional Research SA de CV; Eric Wai Choi Tse, PhD, Queen Mary Hospital; Erik Yeo, MD, University Health Network; Erman Hashas, and Ernst Grochenig, MD, Kantonsspital Aarau AG; Eros Tiraferri, MD, Ospedale Degli Infermi; Erwin Blessing, MD, Klinikum Karlsbad-Langensteinbach; Escande Orthlieb Michèle, Hopital Prive

Marseille; Esther Usandizaga, MD, Hospital Sant Joan Despí-Moisés Broggi; Ettore Porreca,, Ospedale Clinicizzato SS Annunziata; Eva Lichnerova and Fabian Ferroni, MD, Hospital Universitario Austral; Falvo Nicolas, MD, Centre Hospitalier Universitaire Dijon; Félix Ayala-Paredes, MD, CHUS–Hôpital Fleurimont; Firas Koura, MD, Kentucky Lung Clinic; Fitjerald Henry, MD, Hospital Selayang; Franco Cosmi, MD, Ospedale della Val di Chiana Santa Margherita; Frans Erdkamp, MD, Zuyderland Medisch Centrum–Sittard-Geleen; Frederic Baumann, MD, and Gadel Kamalov, MD, SAIH Republican Clinical Hospital # 2; Gaetano Paparella, MD, and Garcia-Bragado Dalmau, Hospital Josep Trueta; Garrigues Damien, Clinique Monié, Villefranche de Lauragais; Garry Klein, Murmansk Regional Clinical Hospital; Gaurand Shah, MD, and Geert Hollanders, private practice in cardiology; Geno Merli, MD, Jefferson University Medical Center; Georg Plassmann, MD, UHZ Klinische Forschung; George Platt, MD and Georgy V. Smirnov, MD, SBHI of Yaroslavl region clinical hospital #10; Germain Poirier, MD, Centre de Santé et de Services Sociaux Champlain-Charles-Le Moyne; German Sokurenko, MD, FFSBI The Nikiforov Russian Center of Emergency and Radiation Medicine; Ghassan Haddad, MD, South Miami Hospital; Gholam Ali, MD, Tulane University Heart and Vascular Institute; Giancarlo Agnelli, MD, Azienda Ospedaliera di Perugia Ospedale S. Maria della Misericordia; Gin Gan, University Malaya Medical Centre; Grace Kaye-Eddie, SA, Helen Joseph Hospital Pulmonology Division; Gregoire Le Gal, MD, PhD, Montfort Hospital; Gregory Allen, PhD, NECCR IMCA; Guillermo Antonio Llamas Esperón, Hospital Cardiologica Aguascalientes; Guillot Jean-Paul, Centre Hospitalier De Bayeux; Hagen Gerofke, MD, Basildon and Thurrock University Hospitals NHS Trust; Hallah Elali, Clinique Saint-Pierre; Hana Burianova, MD, and Hans-Juergen Ohler, MD, Vivantes Klinikum Spandau; Haofu Wang, MD, The Affiliated Hospital of Qingdao University; Harald Darius, MD, PhD, Vivantes Klinikum Neukoelln; Harinder S. Gogia, MD, Chest and Critical Care Consultants; Harry Gibbs, MD, The Alfred Hospital; Harry Striekwold, Heilig Hart Ziekenhuis; Hatice Hasanoglu, MD, FCCP, Ankara Diskapı Yildirim Beyazit Training Hospital; Hatice Turker, MD, Sureyyapasa Pulmonary Diseases and Cardiothoracic Surgery Education and Research Hospital; Hendrik Franow, Regionshospitalet Horsens; Henri Bounameaux, MD, Faculty of Medicine, Geneva, Switzerland; Herbert De Raedt, MD, O.L.V Ziekenhuis; Herman Schroe, MD, Ziekenhuis Oost Limburg; Herman Sung Yu Liu, FRCP, and Hesham Salah ElDin, MD, Hesham Salah ElDin; Hesham Zidan, private clinic; Hiroaki Nakamura, MD, PhD, Kakogawa Central City Hospital; Ho Young Kim, PhD, Hallym University Sacred Heart Hospital; Holger Lawall, MD, Prof. Dr. Med. Curt Diehm; Hong Zhu, PhD, Peking University Third Hospital; Hongyan Tian, PhD, First Affiliated Hospital of Xi'an Jiaotong University; Ho-Young Yhim, MD, PhD, Chonbuk National University Hospital; Hugo ten Cate, MD, PhD, Maastricht University Medical Center; Hun Gyu Hwang, MD, PhD, Soon Chun Hyang University Hospital Gumi; Hyeok Shim, MD, Wonkwang University Hospital; Igor Kim, RSHI State Novosibirsk Regional Clinical Hospital; Igor Libov, MD, City Clinical Hospital NA Botkin; Igor Sonkin, nonstate health care institution Roadway Clinical Hospital of OJSC Russian Railways; Igor Suchkov, MD, PhD, DSc, SBI of Ryazan region Regional Clinical Cardiological Dispensary; Ik-Chan Song, MD, Chungnam National University Hospital; Ilker Kiris, MD; private Medifema Hospital; Ilya Staroverov, MD, PhD, SBIH of Yaroslavl region Regional Clinical Hospital; Irene Looi, MRCP, Hospital Seberang Jaya; Isabel M De La Azuela Tenorio, Hospital Universitario Madrid Norte Sanchinarro; Ismail Savas, MD, and Ivan Gordeev, MD, PhD, SBIH of Moscow City Clinical Hospital # 15 NA O.M. Filatov; Ivo Podpera, MD, Oblastni Nemocnice Kladno, AS Emocnice Stredoces Kraje; Jae Hoon Lee, MD, PhD, Gachon University Gil Medical Center; Jameela Sathar, MD, Hospital Ampang; James Welker, DO, Anne Arundel Health System; Jan Beyer-Westendorf, MD, GWT-TUD GmbH Dresden; Jan Kvasnicka, MD, Kardiologicka ambulance; Jan Van Meerbeeck, MD, PhD, UZ Antwerpen; Jan Vanwelden, ZNA Jan Palfijn; Jang Yong Kim, MD, The Catholic University of Korea, Seoul St. Mary's Hospital; Jaromira Svobodova, MD, Nemocnice Cesky Krumlov; Jaspal Gujral, MD, Georgia Regents University; Javier Tristan Galvar, Winsett Rethman SA de CV; Javier Claudio Marino, MD, Centro Medico Consultan Salud; Jeannine Kassis, MD, Hopital Maisonneuve-Rosemont d/b/a CIUSSS de l'Est-de-l'Île-de-Montréal; Jen-Yuan Kuo, MD, Mackay Memorial Hospital; Jhih-Yuan Shih, MD, Chi Mei Medical Center, Yung Kang Branch; JiHyun Kwon, MD, Chungbuk National University Hospital; Jin Hyun Joh, Kyung Hee University Hospital at Gangdong; Jin Hyun Park, Seoul Metropolitan Government, Seoul National University Boramae Medical Center; Jin Seok Kim, MD, Severance Hospital, Yonsei University; Jinghua Yang, MD, Beijing Anzhen Hospital; Jiri Krupicka, PhD, Medicus Services; Jiri Lastuvka, MD, Krajska Zdravotni AS–Masarykova Nemocnice v Usti nad Labem OZ; Jiri Pumprla, MD, PreventaMed SRO; Jiri Vesely, MD, Oblastni Nemocnice Nachod AS; Joan Carlos Souto, MD, PhD, Hospital Santa Creu I Sant Pau; João Antônio Correa, Centro Multidisciplinar de Estudos Clínicos, CEMEC; Johan Duchateau, AZ Sint-Maarten; John Perry Fletcher, FRACS, Westmead Hospital; Jorge del Toro, MD, Hospital Gregorio Marañón; Jorge Guillermo Chavez Paez, Instituto de Diagnostico e Investigaciones Medicas; Jørn Nielsen, MD, Frederiksberg Hospital; Jose Maria Surinach, MD, PhD, Hospital Vall D'hebron; Jose Antonio Diaz Peromingo, MD, Hospital Clinico Universitarios de Santiago Compostela; Jose Gomez Lara, Antiguo Hospital Civil de Guadalajara Fray Antonio Alcalde; Jose Dalmo Araujo Filho, MD, Instituto de Molestias Cardiovasculares, IMC; Jose Saraiva, MD, PhD, Hospital e Maternidade Celso Pierro-HMCP/PUC–Campinas; Jose Luis Fedele, Hospital Privado de Rosario; Joseph Chacko, MD, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust; Juan Carlos Álvarez Benitez, MD, Hospital Virgen de la Macarena; Juan Moreno Hoyos Abril, MD, Universidad Autonoma de Nuevo Leon, Hospital Universitario Dr. Jose Eleuterio Gonzalez; Juan Antonio Muntaner, MD, Centro Modelo de Cardiologia; Julian Humphrey, FRCEM, Barnsley Hospital NHS Foundation Trust; Julio Bono, MD, Sanatorio Allende; Julio Alberto Perez Sanchez and Junji

Kanda, MD, Asahi General Hospital; Juree Boondumrongsagoon, MD, Maharat Nakhon Ratchasima Hospital; Kai Hang Yiu, MD, Queen Mary Hospital; Kanchana Chansung, MD, Srinagarind Hospital; Karin Boomars, MD, PhD, Erasmus Medisch Centrum; Kate Burbury, FRACP, FRCPA, Peter MacCallum Cancer Centre–East Melbourne; Katsuhiro Kondo, MD, Kitakyusyu General Hospital; Kemal Karaarslan, Izmir Tepecik Training and Research Hospital; Kensuke Takeuchi, MD, Fukuoka Rehabilitation Hospital; Knut Kroeger, MD, Helios Kinikum Krefeld; Konstantin Andreichuk, MD, PhD, FFSBI The Nikiforov Russian Center of Emergency and Radiation Medicine; Konstantin Zrazhevskiy, MD, SPb SBIH City Hospital # 38 NA Semashko; Koscál Svatopluk, Angiologická ambulance; Kou-Gi Shy, MD, Shin Kong Wu Ho-Su Memorial Hospital; Kristel Vandenbosch, MD, CHU de Liege; Kuan-Cheng Chang, MD, PhD, China Medical University Hospital; Kuan-Ming Chiu, MD, Far Eastern Memorial Hospital; Kubina Jean-Manuel, Centre Hospitalier Départemental Vendée; Kwan Jing Wern, MRCP, Hospital Seri Manjung; Kwo-Chang Ueng, MD, PhD, Chung-Shan Medical University Hospital; Lalita Norasetthada, MD, Maharaj Nakorn Chiang Mai Hospital; Laure Binet, MD, CHU Ambroise Paré; Lee Ping Chew, MD, Sarawak General Hospital; Lei Zhang, MD, PhD, The 1st Affiliated Hospital of Hebei Medical University; Lidwine Tick, MD, PhD, Maxima Medisch Centrum, Eindhoven; Lilia Beatriz Schiavi, MD, Clinica del Prado; Lily Lee Wong, MRCP, Hospital Queen Elizabeth; Lisbeth Andersen, MD, and Louis Botha, Medicross City Bowl; Luc Timmermans, MD, Dokter Luc Timmermans; Luc Capiau, MD, BVBA Dr. Luc Capiau; Luciano Eduardo López, MD, Hospital Universitario Reina Sofia de Cordoba; Luigi Ria, MD, Presidio Ospedaliero Sacro Cuore di Gesù; Luis Flota Cervera, Sociedad de Cirugia Vascular Plastica Reconstructiva de Angiologia y Cardiologia SCP; Luis Manuel Hernandez Blasco, MSc, Hospital General Universitario de Alicante; Luis Alberto Guzman, MD, Instituto Medico DAMIC; Magnus Thorsen Jensen, PhD, Holbæk Sygehus; Mahe Isabelle, Hopital Louis-Mourie, Colombes; Manuel de los Rios Ibarra, Centro para el Desarrollo de la Medicina y de Asistencia Medica Especializada SC; Manuel Núñez Fernandez, MD, Complejo Hospitalario de Pontevedra; Manuel Monreal Bosch, MD, PhD, Hospital Germans Trias I Pujol; Marc Carrier, MD, The Ottawa Hospital–General Campus; Marc Righini, MD, Marcelo Raul Barrionuevo, MD, Sanatorio Mayo Privado SA; Marco Cattaneo, MD, Azienda Socio Sanitaria Territoriale Santi Paolo e Carlo, San Paolo-Polo Universitario; Marco Moia, MD, Fondazione IRCCS CA Granda Ospedale Maggiore Policlinico; Marco Antonio Alcocer Gamba, MD, Centro de Estudios Clínicos de Queretaro SC; Margaret Bowers, MD, South Eastern Health and Social Care Trust; Mariam Chetanachan, MD, Prapokklao Hospital; Mario Alberto Berli, Hospital Dr. Jose Maria Cullen; Mark Fixley, MD, Oklahoma Heart Hospital; Markus Faghih, MD, Studienzentrum Bocholderstrasse; Markus Stuecker, MD, St. Maria-Hilf-Krankenhaus; Marlin Schul, MD, Lafayette Regional Vein Center; Martin Banyai, MD, Cantonal Hospital Lucerne; Martin Koretzky, MD, CCBR-Buenos Aires AR; Martin Myriam, private practice, Annecy; Mary Elizabeth Gaffney, DO, Diversified Clinical Research/Gaffney Health Services; Masao Hirano, MD, PhD, National Hospital Organization Chiba Medical Center; Masashi Kanemoto, MD, PhD, Yamaguchi Prefectural Grand Medical Center; Mashio Nakamura, MD, PhD, Murase Hospital; Meng Lee Chang, MD, and Mersel Tahar, Centre Apolline, private practice, Narbonne; Messas Emmanuel, MD, PhD, Hôpital HEGP; Michael Kovacs, MD, LHSC–Victoria Hospital; Michael Leahy, MD, Fremantle Hospital; Michael Levy, MD, Lahey Clinic; Michael Munch, MD, Roskilde Sygehus; Michael Olsen, PhD, MD, Holbæk Sygehus; Michel Gustin, MD, CHR de la Citadelle; Michel De Pauw, MD, and Mikhail Boyarkin, MD, Lomonosov Interdistrict Hospital NA IN Yudchenko; Miroslav Homza, MD, PhD, and Modise Koto, Medunsa Clinical Research Unit (MeCRU); Mohamed Abdool-Gaffar, MD, Kingsway Clinical Trial Centre; Mohamed Ayman Fakhry Nagib, MD, private clinic; Mohamed El-Dessoki, MD, FRCSI, and Mohamed Khan, MD, Ladysmith Provincial Hospital; Monniaty Mohamed, Hospital Raja Perempuan Zainab II; Moo Hyun Kim, MD, Dong-A University Hospital; Moon-Hee Lee, MD, Inha University Hospital; Mosaad Soliman, MD, private clinic; Mostafa Shawky Ahmed, MD, private clinic; Mostafa Soliman Abd el Bary, private clinic; Moustafa A. Moustafa, MD, SC Nephrology and Hypertension Center; Muhammad Hameed, MD, Clinteam; Muhip Kanko, MD, Kocaeli Universitesi Tip Fakultesi; Mujibur Majumder, MD, Smart Medical Research; Nadezhda Zubareva, MD, PhD, SAI of Perm region City Clinical Hospital #4; Natasha Roseva-Nielsen Ngyuen Dang, and Nicola Mumoli, MD, Azienda USL6 Livorno; Nik Azim Nik Abdullah, MMed, Sarawak General Hospital; Nisa Makruasi, MD, HRH Princess Maha Chakri Sirindhorn Medical Center; Nishen Paruk, Nonglak Kanitsap, MD, Thammasat University Hospital; Norberto Duda, PhD, Hospital São Vicente de Paulo; Nordiana Nordin, MD, Hospital Sungai Buloh; Oksana A. Zemlianskaia, SBI Russian Cardiological Scientific and Industrial Complex of the MoH of the RF; Ole Nyvad, MD, Sydvestjyds Sygehus Esbjerg; Olga Barbarash, MD, PhD, FSBI Scientific Research Institute for Complex Problems of Cardiovascular Disease; Orcun Gurbuz, MD, Balikesir University Educational Research Hospital; Oscar Gomez Vilamajo, MD, Sanatorio San Martin; Oscar Nandayapa Flores, Oscar Sanz Peláez, Oscar Martin Lopez Ruiz, and Ozcan Gur, MD, Namik Kemal University; Pablo Javier Marchena, MD, Parc Sanitari Sant Joan de Déu–Hospital General; Pantep Angchaisuksiri, MD, Ramathibodi Hospital; Patrick Carroll, MPH, Redcliffe Hospital; Paul Coughlin and Pavel Lang, MD, PhD, Krajska nemocnice Liberec AS; Peter Baron von Bilderling, MD, Gefaesspraxis im Tal; Peter Blombery, MD, Masada Private Hospital; Peter MacCallum, MD, Barts Health NHS Trust; Peter Verhamme, MD, UZ Leuven; Petr Jansky, MD, Fakultni Nemocnice v Motole; Peuch Bernadette, private practice, Castelnau le Lez; Philippe Hainaut, PR, Cliniques Universitaires Saint-Luc; Philippe De Vleeschauwer, MD, H. Hartziekenhuis; Piera Maria Ferrini, Azienda Ospedaliero Universitaria di Parma; Piriyaporn Iamsai, Lampang Hospital; Ponchaux Christian, private practice, Hazebrouck; Pongtep Viboonjuntra, MD, Songklanagarind Hospital; Ponlapat

Rojnuckarin, MD, PhD, King Chulalongkorn Memorial Hospital; Prahlad Ho, The Northern Hospital; Pramook Mutirangura, MD, PhD, Siriraj Hospital; Rachel Wells, BMS, Northumbria Healthcare NHS Foundation Trust; Rafael Martinez, MD, FCCP, Pulmonary and Sleep of Tampa Bay; Raimundo Tirado Miranda, Hospital Infanta Margarita; Ralf Kroening, MD, St. Josefs-Krankenhaus; Raquel Lopez Reyes, MD, PhD, Hospital Universitario de La Fe; Raul Franco Diaz de Leon, Universidad Autonoma de Aguascalientes; Raymond Siu Ming Wong, MD, Prince of Wales Hospital; Raz Alikhan, MD, University Hospital of Wales; Reinhold Jerwan-Keim, MD, Gemeinschaftspraxis Dr. Med. Reinhold Jerwan-Keim, Renate Metz; Remedios Otero, MD, PhD, Hospital Virgen del Rocio; Renate Murena-Schmidt, MD, Schmidt Praxis für Gefäßkrankheiten; Reto Canevascini, MD, Ospedale Regionale di Lugano; Richard Ferkl, MD, Interni ambulance; Richard White, MD, University of California–Davis; Rika Van Herreweghe, Algemeen Stedelijk Ziekenhuis–Campus Aalst; Rita Santoro, MSc, Azienda Ospedaliera Pugliese Ciaccio; Robert Klamroth, MD, Vivantes Klinikum im Friedrichshain; Robert Prosecky, MD, Fakultni Nemocnice u SV Anny v Brne; Robert Mendes, MD, Wake Heart and Vascular Associates; Roberto Cappelli, MD, AOU Senese Policlinico Santa Maria alle Scotte; Rudolf Spacek, MD, CSc, Nemocnice na Frantisku; Rupesh Singh, MD, DM, Zulekha Hospital; Sam Griffin, PhD, Head to Toe Research and Wellness; Sang Hoon Na, PhD, Seoul National University Hospital; Sanjeev Chunilal, FRACP, FRCPA, Monash Medical Centre Clayton; Saskia Middeldorp, MD, PhD, Academisch Medisch Centrum; Satoshi Nakazawa, MD, Niigata City General Hospital; Sebastian Schellong, MD, Staedtisches Klinikum Dresden Standort Dresden–Friedrichstadt; See Guan Toh, Hospital Sultanah Aminah; Seinturier Christophe, MD, Centre Hospitalier Universitaire de Grenoble; Selim Isbir, MD, Marmara University Pendik Training and Research Hospital; Selma Raymundo, MD, PhD, Fundação Faculdade Regional de Medicina de São Jose do Rio Preto; Serge Motte, PR, ULB Hopital Erasme; Sergey Gryaznov, SBI of Ryazan region Regional Clinical Cardiological Dispensary; Serhat Erol, MD, and Serir Ozkan Aktogu, MD, Dr.Suat Seren Pulmonary Disease and Surgical Education and Respiratory Hospital; Servaas Donders, MD, Martini Ziekenhuis; Seung Ick Cha, MD, Kyungpook National University Hospital; Seung-Hyun Nam, MD, VHS Medical Center; Sevestre Pietri Marie-Antoinette, MD, NCI Centre Hospitalier Universitaire Amiens; Shaun Maasdorp, FCP(SA), Maasdorp SD; Shenghua Sun, MD, PhD, The Third Xiangya Hospital of Central South University; Shenming Wang, MD, The First Affiliated Hospital Sun Yat-sen University; Sherif Mohamed Essameldin, private clinic; Sherif Mohamed Sholkamy, private clinic; Shintaro Kuki, Wakayama Rosai Hospital; Shuichi Yoshida, Sendai Tokushukai Hospital; Shunzo Matsuoka, MD, Uji Tokushukai Hospital; Simon McRae, FRCPA, FRACP, Royal Adelaide Hospital; Simon Watt, Portsmouth Hospitals NHS Trust; Siong Leng Hon, and Siriwimon Patanasing, Suratthani Hospital; Siwe-Nana Jean-Léopold, private practice, Angouleme; Somchai Insiripong, MD, and Somchai Wongkhantee, MD, Khon Kaen Hospital; Soo-Mee Bang, MD, PhD, Seoul National University Bundang Hospital; Sophie Testa, MD, Azienda Socio Sanitaria Territoriale di Cremona, Istituti Ospitalieri di Cremona; Stanislav Zemek, MD, Interni ambulance; Steffen Behrens, MD, Vivantes Humboldt-Klinikum; Stephan Dominique, MD, CHU Strasbourg; Stuart Mellor, MD, East Lancashire Hospitals NHS Trust; Suaran Singh Gurcharan Singh, MD, Hospital Pulau Pinang; Sudip Datta, MD, Aviva Clinical Trial Group; Sunee Chayangsu, MD, Surin Hospital; Susan Solymoss, MD, Montreal General Hospital; Tamara Everington, PhD, Hampshire Hospitals NHS Foundation Trust; Tarek Ahmed Adel Abdel-Azim, PhD, private clinic; Tawatchai Suwanban, MD, Rajavithi Hospital; Taylan Adademir, MD, Kartal Kosuyolu Yuksek Ihtisas Egitim ve Arastirma Hastanesi; Terence Hart, MD, and Terriat Béatrice, MD, Centre Hospitalier Universitaire Le Bocage; Thifhelimbilu Luvhengo, FCS(SA), GIBS, Charlotte Maxeke Johannesburg Academic Hospital Surgery Department; Thomas Bieri, MD, Cantonal Hospital Lucerne; Thomas Horacek, MD, Forschungszentrum Ruhr; Thomas Zeller, MD, PhD, Universitaetsklinikum Freiburg; Tim Boussy, AZ Groeninge–Campus Kennedylaan; Tim Reynolds, MD, Burton Hospitals NHS Trust; Tina Biss, MD, Royal Liverpool and Broadgreen University Hospitals NHS Trust; Ting-Hsing Chao, MD, National Cheng Kung University Hospital; Tomas Smith Casabella, MD, CORDIS SA; Tomoya Onodera, MD, Shizuoka City Shizuoka Hospitel; Tontanai Numbenjapon, MD, Phramongkutklao Hospital; Victor Gerdes, MD, Slotervaartziekenhuis; Vladimir Cech, MD, Antonin Dufka; Vladimir Krasavin, SBHI of Yaroslavl region Clinical hospital #10; Vladimir Tolstikhin, TSBIH Krasnoyarsk Interdistrict Clinical Hospital of Emergency Medical Care NA NS Karpovich; W.A. Bax, MD, Noordwest Ziekenhuisgroep; Wagih Fawzy Abdel Malek, MD, private clinic; Wai Khoon Ho, FRACP, FRCPA, Austin Hospital; Walter Ageno, MD, Azienda Socio Sanitaria Territoriale Sette Laghi, Presidio Ospedale di Circolo e Fondazione Macchil; Walter Pharr, MD, Medication Management; Weihong Jiang, MD, The Third Xiangya Hospital of Central South University; Wei-Hsiang Lin, MD, Tri-Service General Hospital; Weihua Zhang, MD, The First Hospital of Jilin University; Wei-Kung Tseng, MD, PhD, E-Da Hospital; Weimar Kunz Sebba Barroso de Souza, MD, PhD, Centro de Pesquisa em Cardiometabolismo Via Médica Centro Clínico–VTE; Wen-Ter Lai, MD, PhD, Kaohsiung Medical University Chung-Ho Memorial Hospital; Wilfried De Backer, MD, PhD, Wilhelm Haverkamp, MD, PhD, and Winston Yoshida, MD, PhD, Unidade de Pesquisa Clinica da Faculdade de Medicina de Botucatu–Unesp; Wolfgang Korte, MD, Kantonsspital St. Gallen; Won Il Choi, MD, PhD, Keimyung University Dongsan Hospital; Yana Kazachek, FSBI Scientific Research Institute for Complex Problems of Cardiovascular Disease; Yang-Ki Kim, MD, PhD, Soonchunhyang University Seoul Hospital; Yasuhiro Tanabe, MD, St Marianna University; Yasushi Ohnuma, Yamagata Tokushukai Hospital; Yeung-Chul Mun, MD, Ewha Womans University Mokdong Hospital; Yohan Balthazar, Balthazar, Yohan; Yong Park, MD, Korea University Anam Hospital; Yoshisato Shibata, MD, Mohamed El-Dessoki; Yulia N. Moiseeva, PhD, City Clinical Hospital NA Botkin; Zdenek

Coufal, MD, Krajska Nemocnice T. Bati AS; Zhenwen Yang, MD, Tianjin Medical University General Hospital; Zhicheng Jing, MD, PhD, Fuwai Hospital; Zhicheng Jing, MD, PhD, The Baoding Long March Institute of Heart, Lung and Vascular Disease; Zhongqi Yang, PhD, First Affiliated Hospital of Guangzhou University of TMC; Bárbara Pagán, MD, Hyeon-Gyu Yi MD, PhD, and Michiel Van Betsbrugge, MD, GZA Ziekenhuizen–Campus Sint-Augustinus; and Ove Østergaard, MD, Pol Ravez, MD, and Shinya Goto, PhD, MD, Tokai University Educational System.

Additional Contributions: Nick Burnley-Hall, PhD, and Rebecca Watkin, PhD, provided editorial assistance for the manuscript initially drafted by the first author. Programming support was provided by Madhusudana Rao, MS, and Uma Maheshwari, BS, and statistical support was provided by Karen Pieper, MS, Alfredo Farjat, PhD, and Henrik Fryk, BS. All contributors are employed by the Thrombosis Research Institute and did not receive compensation for their assistance outside of their regular salaries. We thank the physicians, nurses, and patients involved in the GARFIELD-VTE registry.

REFERENCES

1. Heit JA. The epidemiology of venous thromboembolism in the community. *Arterioscler Thromb Vasc Biol*. 2008;28(3):370-372. doi:10.1161/ATVBAHA.108.162545

2. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol*. 2008;19(1):135-140. doi:10.1681/ASN.2007030308

3. Ģibietis V, Kigitoviča D, Vītola B, Strautmane S, Skride A. Glomerular filtration rate as a prognostic factor for long-term mortality after acute pulmonary embolism. *Med Princ Pract*. 2019;28(3):264-272. doi:10.1159/000497436

4. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-2047. doi:10.1001/jama.298.17.2038

5. Stevens LA, Levey AS. Chronic kidney disease in the elderly—how to assess risk. *N Engl J Med*. 2005;352(20):2122-2124. doi:10.1056/NEJMe058035

6. Lutz J, Menke J, Sollinger D, Schinzel H, Thürmel K. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant*. 2014;29(1):29-40. doi:10.1093/ndt/gft209

7. Büller HR, Décousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415. doi:10.1056/NEJMoa1306638

8. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi:10.1056/NEJMoa1007903

9. Ha JT, Neuen BL, Cheng LP, et al. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2019;171(3):181-189. doi:10.7326/M19-0087

10. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352. doi:10.1056/NEJMoa0906598

11. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808. doi:10.1056/NEJMoa1302507

12. Aursulesei V, Costache II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice. *Clin Cardiol*. 2019;42(8):774-782. doi:10.1002/clc.23196

13. Weitz JI, Haas S, Ageno W, et al. Global Anticoagulant Registry in the Field - Venous Thromboembolism (GARFIELD-VTE). Rationale and design. *Thromb Haemost*. 2016;116(6):1172-1179.

14. Liew NC, Alemany GV, Angchaisuksiri P, et al. Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism. *Int Angiol*. 2017;36(1):1-20.

15. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2)(suppl 1):S1-S266.

16. van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. *J Stat Soft*. 2011;45(3):1-67. doi:10.18637/jss.v045.i03

17. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133(6):601-609. doi:10.1161/CIRCULATIONAHA.115.017719

18. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing; 2018. Accessed January 24, 2019. https://www.R-project.org/

19. SAS Institute. Base SAS 9.4 Procedures Guide, Seventh Edition. SAS Institute; 2017. Updated August 20, 2020. http://documentation.sas.com/api/docsets/proc/9.4/content/proc.pdf?locale=en#nameddest=titlepage

20. Kuan Y, Hossain M, Surman J, El Nahas AM, Haylor J. GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end-stage renal disease. *Nephrol Dial Transplant*. 2005;20(11):2394-2401. doi:10.1093/ndt/gfi076

21. Schwandt A, Denkinger M, Fasching P, et al. Comparison of MDRD, CKD-EPI, and Cockcroft-Gault equation in relation to measured glomerular filtration rate among a large cohort with diabetes. *J Diabetes Complications*. 2017;31(9):1376-1383. doi:10.1016/j.jdiacomp.2017.06.016

22. Carrero JJ. Gender differences in chronic kidney disease: underpinnings and therapeutic implications. *Kidney Blood Press Res*. 2010;33(5):383-392. doi:10.1159/000320389

23. Ahmed A, Campbell RC. Epidemiology of chronic kidney disease in heart failure. *Heart Fail Clin*. 2008;4(4):387-399. doi:10.1016/j.hfc.2008.03.008

24. Falgá C, Capdevila JA, Soler S, et al; RIETE Investigators. Clinical outcome of patients with venous thromboembolism and renal insufficiency. Findings from the RIETE registry. *Thromb Haemost*. 2007;98(4):771-776. doi:10.1160/TH07-02-0132

25. Spirk D, Sebastian T, Banyai M, et al. Venous thromboembolism and renal impairment: insights from the Swiss Venous Thromboembolism Registry (SWIVTER). *Semin Thromb Hemost*. 2019;45(8):851-858. doi:10.1055/s-0039-1698770

26. Catella J, Bertoletti L, Mismetti P, et al; investigators of the RIETE registry. Severe renal impairment and risk of bleeding during anticoagulation for venous thromboembolism. *J Thromb Haemost*. 2020;18(7):1728-1737. doi:10.1111/jth.14837

27. Yang Y, Li H-Y, Zhou Q, et al. Renal function and all-cause mortality risk among cancer patients. *Medicine (Baltimore)*. 2016;95(20):e3728. doi:10.1097/MD.0000000000003728

28. Rattazzi M, Villalta S, De Lucchi L, et al. Chronic kidney disease is associated with increased risk of venous thromboembolism recurrence. *Thromb Res*. 2017;160:32-37. doi:10.1016/j.thromres.2017.10.011

29. Goto S, Angchaisuksiri P, Bassand J-P, et al; GARFIELD-AF Investigators. GARFIELD-AF Investigators. Management and 1-year outcomes of patients with newly diagnosed atrial fibrillation and chronic kidney disease: results from the prospective GARFIELD-AF Registry. *J Am Heart Assoc*. 2019;8(3):e010510. doi:10.1161/JAHA.118.010510

30. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

31. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6 (R1). June 10, 1996. Accessed September 28, 2020. https://ichgcp.net/

32. Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf*. 2016;25(1):2-10. doi:10.1002/pds.3891

SUPPLEMENT.

eTable 1. Covariates Considered for the Adjustment of 12-Month Outcomes
eTable 2. Chronic Kidney Disease Classification Using the Modification of Diet in Renal Disease Equation and the Cockcroft Gault Calculation of Renal Function
eTable 3. Unadjusted 12-Month Clinical Outcomes
eTable 4. Cause of Death Over 12 Months of Follow-Up
eTable 5. Site of Major Bleeding in Patients With Moderate to Severe Chronic Kidney Disease and Mild to No Chronic Kidney Disease
eTable 6. Incidence Rates of Outcomes at 12 Months in Patients With Mild to No Chronic Kidney Disease and Moderate to Severe Chronic Kidney Disease According to Type of Lower Limb Deep Vein Thrombosis
eFigure 1. Spearman Correlation for Association Between Glomerular Filtration Rate and Creatinine Clearance Among Patients With Mild to No Chronic Kidney Disease and Moderate to Severe Chronic Kidney Disease
eFigure 2. Sensitivity Analysis for Standardized Differences Between Baseline Characteristics for Missing Patients and Patients Included in the Study