Bleeding risk in elderly patients with venous thromboembolism who would have been excluded from anticoagulation trials

Running title: Bleeding risk in elderly patients

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KEY POINTS

- About a third of older patients would be excluded from key VTE anticoagulation trials and such patients have a higher bleeding risk
- Results from such trials may not be generalizable to older, multimorbid, and co-medicated patients

ABSTRACT

Older patients with venous thromboembolism (VTE) are underrepresented in clinical anticoagulation trials. We examined to which extent elderly patients with VTE would be excluded from such trials and compared the bleeding risk between hypothetically excluded and enrolled patients. We studied 991 patients aged ≥65 years with acute VTE in a prospective multicenter cohort. We identified 12 landmark VTE oral anticoagulation trials from the 8th and updated 9th American College of Chest Physician Guidelines. For each trial, we abstracted the exclusion criteria and calculated the proportion of our study patients who would have been excluded from trial participation. We examined the association between five common exclusion criteria (hemodynamic instability, high bleeding risk, comorbidity, co-medication, invasive treatments) and major bleeding (MB) within 36 months using competing risk regression, adjusting for age, sex, and periods of anticoagulation. A median of 31% (range 20-52%) of our patients would have been excluded from participation in the landmark trials. Hemodynamic instability (sub-hazard ratio [SHR] 2.2, 95%CI 1.1-4.7), comorbidity (SHR 1.5, 95%CI 1.1-2.2), and co-medication (SHR 1.5, 95%CI 1.0-2.3) were associated with MB. Compared to eligible patients, those with ≥2 exclusion criteria had a 2-fold (SHR 2.16, 95%CI 1.38-3.39) increased risk of MB. Overall, about one third of older patients would not be eligible for participation in guideline-defining VTE anticoagulation trials. The bleeding risk increases significantly with the number of exclusion criteria present. Thus, results from such trials may not be generalizable to older, multimorbid, and co-medicated patients.

KEYWORDS

Venous thromboembolism; anticoagulation; bleeding risk; exclusion criteria; elderly

INTRODUCTION

Venous thromboembolism (VTE) usually requires anticoagulant treatment with direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) for at least three months to prevent recurrence and pulmonary embolism (PE)-related death.[1] Patients aged ≥65 years not only represent the majority (55%) of patients with VTE, they also have a 2- to 3-fold increased risk of major (MB) and fatal bleeding.[2,3] Randomized controlled trials exert a major influence on guideline recommendations with respect to indication, type, and duration of oral anticoagulant therapy.[1,4,5] However, due to strict eligibility criteria, older patients who carry an increased bleeding risk are often excluded from trial participation and thus may be underrepresented in landmark trials of VTE treatment.[6] Hence, whether guideline recommendations are extrapolable to older patients with VTE remains uncertain.

Evidence suggests that 19-41% of patients with VTE would be excluded from clinical anticoagulation trials and that such patients may have an increased risk of MB.[7-9] The proportion of elderly patients with VTE who are not eligible for trial participation and the risk of bleeding of these patients has never been quantified. We therefore aimed to assess to which extent elderly patients with VTE would be potentially excluded from landmark VTE randomized controlled treatment trials and to compare the risk of bleeding between hypothetically excluded and enrolled patients in a prospective multicenter cohort study of patients aged ≥65 years with acute VTE. We hypothesized that a substantial proportion of older patients with VTE would not be eligible for trial participation and that such patients carry a higher risk of bleeding.

METHODS

Study design, setting and participants

We analyzed data from the SWIss venous Thromboembolism COhort study 65+ (SWITCO65+), a prospective multicenter cohort study that assessed long-term medical outcomes in older patients with a diagnosis of acute symptomatic VTE. Consecutive patients aged ≥65 years with acute, objectively confirmed symptomatic deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were identified in the in- and outpatient services of nine Swiss university and non-university hospitals between 09/2009 and 03/2012 and followed for up to four years. Exclusion criteria were catheter-related thrombosis, thrombosis at a different site than lower limb, conditions incompatible with follow-up (i.e., life expectancy <3 months), inability to provide informed consent (i.e., severe dementia), or insufficient French- or German-speaking ability. Study design and methods have been reported previously.[10] The institutional review board approved the study at each participating site and all participants provided written informed consent.

Baseline data collection

Trained study nurses collected baseline demographic characteristics (age, sex, body weight), systolic blood pressure, comorbid conditions (history of stroke, prior major bleeding events, cancer, liver disease, heart failure, myocardial infarction, severe infection/sepsis, thrombophilia), location of index VTE (PE ± DVT, DVT only), laboratory findings (hemoglobin, platelet count, serum creatinine), co-medication with antiplatelet or non-steroidal anti-inflammatory drugs, and VTE-related treatments (anticoagulants, thrombolysis, surgical thrombembolectomy, insertion of an inferior vena cava filter, cardiopulmonary resuscitation, and administration of catecholamines)

from all enrolled patients. All data were recorded using standardized data collection forms.

Identification of landmark VTE treatment studies

We defined a landmark VTE treatment study as a multicenter randomized controlled clinical trial on which treatment recommendations were based in two major international, interdisciplinary guidelines: the 8th Edition of the American College of Chest Physicians (ACCP) Guidelines from 2008 (VKA era)[1] and the updated 9th Edition of the ACCP Guidelines from 2016 (DOAC era).[4] We considered only studies that compared oral anticoagulation strategies using VKAs or DOACs (VKAs vs. DOACs or comparisons of different durations or intensities of VKA treatment). We did not include studies that used study drugs that are not widely available or were withdrawn from the market (e.g., fluindione, ximelagatran),[11-13] examined short-duration anticoagulation (1 month),[14-16] or compared parenteral vs. oral anticoagulant regimen.[17-33] In study series with identical or almost identical eligibility criteria,[34-36] we considered only the first published study for our analysis. By applying these selection criteria, we identified 12 landmark VTE treatment studies, six from the VKA[37-42] and six from the DOAC[43-48] era (Table 1). The mean age of participating patients ranged from 53 to 67 years in these studies. In 5 of 12 trials (all from the VKA era) the number of screened patients was reported.[37,39-42] Overall, 8% to 50% of screened patients were non-eligible for study participation.

Abstraction of patient exclusion criteria

For each selected landmark study, we ascertained all study exclusion criteria described in the original publication, methods paper, and/or the study protocol if available. If the exact definition of a given exclusion criterion was not available in our

dataset, we used the best possible proxy variable. Exclusion criteria that were not documented in our database were assumed to be absent. We did not consider exclusion criteria that were used to exclude specific types of VTE (i.e., provoked or recurrent VTE, immobilization for >72 hours, surgery, trauma prior to index VTE, or history of prior VTE) because studies from the VKA-era often selectively enrolled patients with an unprovoked or first VTE only.[37,39-41] Moreover, we did not include drug-specific exclusion criteria (e.g., contraindication to a specific drug), criteria that are not meaningful in older patients (pregnancy, breast-feeding), and criteria that cannot be reliably reproduced (e.g., any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk, would preclude compliance, or successful completion of the study). The main exclusion criteria of all landmark trials and their definitions used in our database are shown in the Supplement.

Study outcomes

The primary outcome was the proportion of patients enrolled in the SWITCO65+ cohort who would have been excluded from participation in the landmark studies. Secondary outcomes were major bleeding (MB) based on the International Society of Thrombosis and Haemostasis definition[49] and clinically relevant bleeding (CRB), a composite outcome of MB and clinically relevant non-MB. Clinical relevant non-MB was defined as any bleeding not meeting the definition of MB but requiring medical attention (e.g., a physician consultation or emergency department visit).[50] Tertiary outcomes were recurrent, symptomatic, objectively confirmed VTE, defined as new fatal or nonfatal PE or new DVT (proximal or distal) based on previously published criteria,[51] and overall mortality.

Follow-up included one telephone interview and two surveillance face-to-face evaluations during the first year of study participation and then semi-annual contacts,

alternating between face-to-face evaluations (clinic or home visits in housebound patients) and telephone calls, as well as periodic reviews of the patient's hospital chart. If bleeding or death occurred, the information was complemented by reviewing hospital discharge letters, medical charts, and autopsy reports and interviewing patients' primary care physicians and/or family members. Outcomes were adjudicated by three independent blinded clinical experts, who reviewed all available patient information and determined the cause of death. Death was considered bleeding-related if it followed an intracranial hemorrhage or a bleeding leading to hemodynamic deterioration.[52] Final classification of the cause of death was based on full consensus of the committee.

Statistical analyses

We applied the trial-specific exclusion criteria (Supplementary Table S1) to all patients in our study for each landmark VTE treatment trial and calculated the proportion of hypothetically excluded vs. enrolled patients for each trial. For each landmark trial, we examined the association between patient trial enrolment status (excluded vs. enrolled) and the time to a first MB and CRB up to 36 months using competing risk regression,[53] accounting for non-bleeding-related death as a competing event. The strength of the association was expressed as the sub-hazard ratio (SHR) with corresponding 95% confidence intervals (CI). Patients who withdrew their consent or were lost to follow-up were censored at the time of the last contact. The models were adjusted for age, sex, and periods of anticoagulation as a time varying co-variate to minimize the risk of confounding by differing treatment durations. We have chosen bleedings within 36 months rather than bleedings during initial anticoagulation as our primary analysis because patients who suffer recurrent VTE after stopping initial anticoagulation are likely to receive anticoagulant treatment again. These analyses were repeated in patients aged >75 vs. ≥75 years and in women vs. men.

As the number and exact definitions of exclusion criteria differed across landmark trials, we established five major trial exclusion criteria: hemodynamic instability, high-risk of bleeding, comorbidity, co-medication, and invasive treatment (Table 2) and applied these criteria to all patients in our study. Using the same competing risk regression models, we assessed the relationship between the presence of these five major trial exclusion criteria and bleeding. First, we examined the association between individual major trial exclusion criteria and the time to a first MB and CRB within 36 months. Second, we assessed the association between the number of major trial exclusion criteria present and the time to a first MB and CRB up to 36 months, during the period of initial anticoagulation only, and during the period after stopping initial anticoagulation. We performed two separate sensitivity analyses. First, we excluded patients with hemodynamic instability because such patients may require thrombolysis. Second, we excluded patients with cancer because therapy with low-molecular-weight heparins rather than oral anticoagulants used to be the standard of care for patients with VTE who have active cancer until recently.

We examined the association between the number of major trial exclusion criteria and the time to a first recurrent VTE using competing risk regression, accounting for non-VTE-related death as a competing event. Finally, we assessed the association between the number of major trial exclusion criteria and the time to death from all causes using a Cox proportional hazard model. The models were adjusted for age, sex, and periods of anticoagulation as a time varying co-variate when appropriate. All analyses were done using Stata 17 (Stata Corporation, College Station, Texas).

RESULTS

Study sample and bleeding events

The SWITCO65+ study screened 1863 patients. Of these, 860 were initially excluded because they had catheter-related thrombosis, thrombosis at a different site than lower limb, conditions incompatible with follow-up, insufficient French- or German-speaking ability, inability to provide informed consent, or they refused study participation.[10] Of the 1003 enrolled patients, 12 patients were further excluded due to denial of data use or early withdrawal, leaving a final study sample of 991 older patients with acute VTE. Patients had a median age of 75 years (interquartile range [IQR] 69-81 years), 510 (51%) were aged ≥75 years, 528 (53%) were men, 687 (69%) presented with PE±DVT and 304 (31%) with DVT only. Most patients were treated with VKAs (87%). The median duration of initial anticoagulation was 7.5 months (IQR 4.0-24.0 months) and the median follow-up duration 29.6 months (IQR 18.6-36.2 months). Overall, 130 (13.1%) patients developed a first MB (including 23 intracranial and 13 fatal bleeds), 281 (28.4%) a first CRB, 114 (11.5%) a first recurrent VTE (106 PE±DVTs [19 were fatal] and 8 isolated DVTs), and 206 (20.8%) died during follow-up. Patients with a first MB were slightly older (median 77 vs. 75 years) and more likely to have hemodynamic instability (6% vs. 3%), a creatinine clearance <30 ml/min. (11% vs. 5%), or to receive co-medication (22% vs. 15%) than those without MB.

Patients excluded from landmark VTE treatment trials and risk of bleeding

When we applied the trial-specific exclusion criteria to our study sample for each of the 12 landmark trials independently (Table 1), the median number of trial exclusion criteria was 7 (range 3-18). The median proportion of patients who would have been excluded from trial participation was 31% (range 20-52%). The median number of exclusion criteria was higher in the six DOAC (14, range 8-18) than in the six VKA trials

(5, range 3-6). Thus, the median proportion of potentially excluded patients was greater in DOAC (43%, range 28-52%) than VKA trials (25%, range 20-34%). We found comparable proportions of potentially excluded patients among those aged <75 vs. ≥75 years and women vs. men (Supplementary Table S2 and S3). After the exclusion of patients with cancer in a sensitivity analysis, the median proportion of potentially excluded patients was 24% (range 3-47%) (15%, range 3-20% for VKA trials; 31%, range 27-47% for DOAC trials).

When we applied the individual exclusion criteria of each trial to our study population, patients with at least one exclusion criterion (i.e., hypothetically excluded patients) had a significantly increased risk of MB with 36 months in 8 of 12 trials compared to patients with no exclusion criterion (i.e., hypothetically eligible patients) (adjusted SHR range 1.4-1.5; Table 1). In 7 of 12 trials, the risk of CRB was also significantly higher among potentially excluded patients (adjusted SHR range 1.2-1.4; Table 1). In our subgroup analyses stratified age and sex, we found similar bleeding risks among patients aged <75 vs. ≥75 years (Table S2) and women vs. men (Table S3). After exclusion of patients with cancer in a sensitivity analysis, there was no significant impact on MB, but patients with at least one exclusion criterion had a significantly increased risk of CRB in 4 of 12 trials compared to patients with no exclusion criteria (adjusted SHR range 1.3-1.4).

Major trial exclusion criteria and risk of bleeding

When we applied five commonly described major trial exclusion criteria (hemodynamic instability, high-risk of bleeding, comorbidity, co-medication, and invasive treatment) to our sample, 55% of patients had at least one exclusion criterion (Table 2). The prevalence of major trial exclusion criteria varied from 3% (hemodynamic instability) to 38% (comorbidity). Patients with hemodynamic instability

(adjusted SHR 2.2, 95% CI 1.1-4.7), comorbidity (adjusted SHR 1.5, 95% CI 1.1-2.2, especially active cancer or a creatinine clearance <30 ml/min.), or co-medication (adjusted SHR 1.5, 95% CI 1.0-2.3) had a significantly increased risk of MB within 36 months compared to those without these exclusion criteria (Table 3). Patients with a comorbidity (adjusted SHR 1.3, 95% CI 1.1-1.7) or those with co-medication (adjusted SHR 1.3, 95% CI 1.0-1.8) had also a higher risk of CRB (Table 3). Other major trial exclusion criteria were not associated with an increased risk of MB or CRB.

Overall, the number of major trial exclusion criteria was associated with an increasing risk of bleeding. Compared to patients without exclusion criterion, the presence of ≥2 exclusion criteria doubled (adjusted SHR 2.16, 95% CI 1.38-3.39) the risk of MB within 36 months (Table 4). Patients with ≥2 exclusion criteria had also a significantly greater risk of CRB (adjusted SHR 1.63, 95% CI 1.17-2.25) (Table 4). When only the period of initial anticoagulation or the period after stopping initial anticoagulation was considered, the results did not change markedly (Table 4).

After exclusion of hemodynamically unstable patients in a sensitivity analysis, the results remained very similar. When we excluded patients with active cancer in another sensitivity analysis, the risk of MB (adjusted SHR 1.97, 95% CI 1.16-3.35) and CRB (adjusted SHR 1.56, 95% CI 1.07-2.27) within 36 months remained elevated in patients presenting with ≥2 exclusion criteria.

We did not find a relationship between the number of major trial exclusion criteria and recurrent VTE. However, patients with ≥1 and ≥2 exclusion criteria had a 4- and 5-fold increased risk of overall mortality within 36 months, respectively (Table 4).

DISCUSSION

Our results demonstrate that 31% of elderly patients receiving anticoagulants for acute VTE would have been excluded from participation in guideline-defining landmark VTE treatment trials, with a substantially higher proportion of excluded patients in DOAC trials than in trials from the VKA era (43% vs. 25%). In two thirds of the examined landmark trials, excluded older patients would have had a significantly increased risk of MB (relative risk increase 40-50%) and CRB (relative risk increase 20-40%). Overall, more than half of older patients enrolled in our cohort had at least one major trial exclusion criterion, such as hemodynamic instability, comorbidity, or co-medications, and the presence of such criteria was associated with a higher risk of MB.

Compared to the elderly without major exclusion criteria, those with ≥2 exclusion criteria had a 2-fold increased risk of MB and a 5-fold increased risk of death. Thus, whether results from randomized controlled anticoagulation trials and corresponding guideline recommendations are generalizable to elderly patients with VTE who are multimorbid or receive antiplatelet co-medication, must be questioned. As oral anticoagulants are commonly used in older patients who would not have been eligible for clinical trials, the bleeding risk of extended anticoagulation should be carefully weighed against potential benefits, and a closer monitoring may be required. Interestingly, the number of exclusion criteria was almost twice as high in the more recent DOAC studies indicating that DOACs, even more than VKAs, may have been evaluated in rather selected, low-risk patient populations.

Our results are consistent with the findings from a case-control study of younger patients with VTE (mean age 60 years) demonstrating that patients with two exclusion criteria based on six pivotal clinical VKA trials had a 4-fold greater risk of bleeding-related hospitalizations than those without exclusion criteria.[8] Overall, 29% of screened patients were excluded from these VTE treatment trials.[8] In a Portuguese registry,

exclusion criteria of four randomized controlled trials evaluating DOACs for acute VTE were determined in 68 patients (mean age 69 years) admitted for PE. Most patients (59-84%) would have been excluded in the trials, mainly due to the presence of comorbidities.[7] In the RIETE registry, 19% of patients with VTE (mean age 65 years) had at least 1 of 6 predefined study exclusion criteria of landmark DOAC trials.[9] Excluded patients were significantly older than enrolled patients (70 vs. 63 years), and had a 4-fold increased risk of MB and a 6-fold increased risk of fatal bleeding.[9]

The underrepresentation of older patients in clinical trials has been reported across a broad range of cardiovascular diseases and other conditions.[54] Importantly, while only 1 of the 12 landmark anticoagulation studies for VTE excluded older patients based on an upper age limit (85 years),[37] many elderly patients would have been excluded based on the presence of comorbidities and antiplatelet co-medication, presumably, because such conditions may convey an increased risk of bleeding and/or recurrence. This justified concern should be balanced against the right of the rapidly increasing older population to access evidence-based treatments.[55] Guidance statements from the European Medicine Agency and the Federal Drug Administration underline the importance of an adequate representation of older patients in clinical trials and suggest to design studies with eligibility criteria that allow participation of older patients and to enroll at least 100 older participants.[56,57] Randomized controlled trials and guidelines should also state to which patient population they apply.[8,58]

Commonly used age-sensitive exclusion criteria that preclude study participation in anticoagulation trials are rather subjective, such as a limited life expectancy or “any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol”.[43,44,47] Moreover, many comorbidities, including anemia, non-severe thrombocytopenia, previous bleeding events, or metastatic cancer do not represent

absolute contraindications to therapeutic anticoagulation. Although we acknowledge the merits of efficacy trials including their high internal validity, we believe that the use of more objective and less restrictive eligibility criteria would increase trial participation of older patients and broaden the generalizability of study results.

As we only considered trials comparing oral anticoagulation strategies, cancer-related VTE-specific trials were not represented in our analysis. Moreover, 4 of 6 trials from the VKA era (but none of the DOAC trials) explicitly focused on “idiopathic” VTE[37,39-41] and naturally did not enroll patients with cancer. However, after excluding patients with cancer in a sensitivity analysis, we still found a high proportion of potentially excluded patients who had a higher bleeding risk than potentially enrolled patients.

Our study has several limitations. First, our sample may not reflect the full prognostic range of older persons with VTE because patients with a limited life expectancy and those with severe cognitive impairment were not enrolled in the prospective SWITCO65+ cohort. As such patients are also likely to be excluded from clinical trials, our analysis may underestimate the true proportion of older patients who would be ineligible for trial participation. Thus, it would be interesting to estimate the proportion of non-eligible elderly patients using data from a registry with broad eligibility criteria/wide age range and to compare the proportion of non-eligible older vs. younger patients. Second, exact definitions of exclusion criteria differed across landmark trials, and the variable definitions may have slightly differed in our study. Third, several exclusion criteria were not documented in our study (positive hepatitis B antigen or C antibody, elevated liver enzymes, gastrointestinal ulcer, and aspirin dosage) and were assumed to absent. Fourth, we did not consider study drug-specific (e.g., intolerance or allergy) and subjective exclusion criteria such as a limited life expectancy or the investigator’s opinion that a subject would have an unacceptable risk from study

participation, a suboptimal compliance, or any condition precluding successful study completion. Given that we could not capture the entire spectrum of exclusion criteria in our study, it is likely that the true proportions of older patients who are excluded from trial participation are even higher. Fifth, most patients of our study population were treated with VKAs and thus may have had a higher bleeding risk than if DOACs had been used.[59] For the same reason, we could not compare the bleeding risk in patients treated with VKAs vs. DOACs. Limited evidence suggests that treatment with DOACs may significantly reduce the risk of bleeding compared to VKAs in the elderly with VTE.[59] Finally, our study focused on risk only and did not compare the clinical net benefit of anticoagulation in potentially excluded vs. enrolled patients.

In conclusion, about a third of elderly patients receiving anticoagulants for VTE are not eligible for participation in landmark VTE treatment trials and have an increased risk of bleeding complications and death. The bleeding and mortality risk increases with the number of exclusion criteria present. Our results indicate that the results from randomized controlled anticoagulation trials may not be generalizable to older, multimorbid, and co-medicated patients with VTE. The bleeding risk of extended anticoagulation must be weighed against potential benefits in such patients. The use of less restrictive eligibility criteria has the potential to increase trial participation of older patients and the generalizability of study results.

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AUTHOR CONTRIBUTIONS

Concept and design: Carla Schenker, Odile Stalder, Marie Méan, Drahomir Aujesky. Data acquisition: Marie Méan, Marc Righini, Nicolas Rodondi, Drahomir Aujesky. Statistical analysis: Odile Stalder. Drafting of the manuscript: Carla Schenker, Drahomir Aujesky. Critical revision of the manuscript for important intellectual content: all authors. Final approval of the manuscript: all authors.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

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Table 1. Exclusion from landmark VTE treatment trials and bleeding risk among hypothetically excluded vs. enrolled patients

	First author, study acronym, publication year, citation	Mean patient age, years	Trial exclusion criteria, n	Hypothetically excluded patients*, n (%)	Major bleeding, n/N		Adjusted† SHR (95% CI)	Clinically relevant bleeding, n/N		Adjusted† SHR (95% CI)
					Excluded	Enrolled		Excluded	Enrolled	
VKA era	Schulman, DURAC, 1995[42]	61	4	200 (20)	32/200	98/791	1.4 (0.9 - 2.1)	60/200	221/791	1.1 (0.8 - 1.5)
	Kearon, LAFIT, 1999[39]	59	5	319 (32)	52/319	78/672	1.5 (1.0 - 2.1)	103/319	178/672	1.3 (1.0 - 1.6)
	Agnelli, WODIT-DVT, 2001[37]	67	3	200 (20)	32/200	98/791	1.4 (0.9 – 2.1)	60/200	221/791	1.1 (0.8 - 1.5)
	Ridker, PREVENT, 2003[41]	53	6	230 (23)	38/230	92/761	1.5 (1.0 - 2.1)	72/230	209/761	1.2 (0.9 - 1.6)
	Kearon, ELATE, 2003[40]	57	4	279 (28)	43/279	87/712	1.3 (0.9 - 1.9)	84/279	197/712	1.1 (0.9 - 1.5)
	Campbell, n/a, 2007[38]	59	5	338 (34)	47/338	83/653	1.2 (0.8 - 1.7)	91/338	190/653	1.0 (0.8 - 1.3)
DOAC era	Schulman, RE-COVER, 2009[46]	54	9	291 (29)	47/291	83/700	1.4 (1.0 - 2.0)	95/291	186/700	1.3 (1.0 - 1.6)
	Bauersachs, EINSTEIN, 2010[48]	57	8	280 (28)	46/280	84/711	1.4 (1.0 - 2.1)	95/280	186/711	1.4 (1.1 - 1.8)
	Agnelli, AMPLIFY-EXT, 2012[44]	57	16	422 (43)	65/422	65/569	1.4 (1.0 - 2.0)	134/422	147/569	1.3 (1.0 - 1.6)
	Agnelli, AMPLIFY, 2013[43]	57	18	442 (45)	68/442	62/549	1.4 (1.0 - 2.0)	140/442	141/549	1.3 (1.0 - 1.7)
	Büller, Hokusai-VTE, 2013[45]	56	11	472 (48)	71/472	59/519	1.4 (1.0 - 1.9)	146/472	135/519	1.2 (1.0 - 1.6)
	Schulman, RE-MEDY/RE-SONATE, 2013[47]	55	16	520 (52)	79/520	51/471	1.4 (1.0 - 2.0)	168/520	113/471	1.4 (1.1 - 1.8)

Abbreviations: VKA, vitamin K antagonist; DOAC, direct oral anticoagulants; n/a, not available; SHR, sub-hazard ratio; CI, confidence interval.

*Based on the SWITCO65+ cohort.

†Adjusted for age, sex, and periods of anticoagulation as a time-varying covariate.

Table 2. Prevalence of major exclusion criteria in the SWITCO65+ study (n=991)

Major exclusion criteria	Prevalence, n (%)
Hemodynamic instability*	30 (3)
High risk of bleeding†	111 (11)
Any comorbidity‡	376 (38)
- Active cancer§	178 (18)
- Chronic liver disease¶	14 (1)
- Cardiovascular disease#	63 (6)
- Uncontrolled hypertension**	24 (2)
- History of thrombophilia††	13 (1)
- Anemia‡‡	113 (11)
- Thrombocytopenia§§	35 (4)
- Creatinine clearance <30 ml/min.¶¶	58 (6)
Co-medication##	158 (16)
Invasive treatment***	41 (4)
Number of criteria present	
0	446 (45)
1	396 (40)
2	128 (13)
≥3	20 (2)

Data were missing for uncontrolled hypertension (n=18), anemia (n=63), thrombocytopenia (n=63), and creatinine clearance <30 ml/min. (n=79). Missing data were assumed to be absent.

*Systolic blood pressure <90 mm Hg, cardiopulmonary resuscitation, or use of catecholamines.

†History of major bleeding.

‡Presence of at least one of the comorbid conditions listed below.

§Cancer that required therapy (surgery, chemotherapy, and/or radiotherapy) during the last 3 months.

¶Known liver cirrhosis, chronic hepatitis (B, C, autoimmune, etc.), chronic liver failure or hemochromatosis.

#Acute heart failure or myocardial infarction during the last 3 months.

**Systolic blood pressure >180 mm Hg.

††Factor V Leiden mutation, activated protein C resistance, prothrombin gene mutation, deficiency of natural anticoagulants (protein C, protein S, or antithrombin), positive lupus anticoagulant, anticardiolipin antibodies, anti-beta 2-glycoprotein antibodies, hyperhomocysteinemia, or elevated levels of fibrinogen, factor VIII, factor IX, or factor XI.

‡‡Hemoglobin <10 g/dL.

§§Platelet count <100 G/L.

¶¶Based on the Cockcroft-Gault formula.

##Antiplatelet monotherapy with clopidogrel or prasugrel, dual antiplatelet therapy, or concomitant treatment with non-steroidal anti-inflammatory drugs (see definitions in the Supplement).

***Thrombolysis, surgical thrombembolectomy, or insertion of an inferior vena cava filter.

Table 3. Association between individual major exclusion criteria and bleeding

	Major bleeding, n/N		Adjusted* SHR (95% CI)	Clinically relevant bleeding, n/N		Adjusted* SHR (95% CI)
Major trial exclusion criteria	**Criterion present**	**Criterion absent**		**Criterion present**	**Criterion absent**	
Hemodynamic instability	8/30	122/961	2.2 (1.1 - 4.7)	11/30	270/961	1.3 (0.7 - 2.5)
High risk of bleeding	17/111	113/880	1.3 (0.8 - 2.1)	34/111	247/880	1.2 (0.8 - 1.7)
Any comorbidity†	62/376	68/615	1.5 (1.1 - 2.2)	124/376	157/615	1.3 (1.1 - 1.7)
Active cancer	30/178	100/813	1.5 (1.0 - 2.3)	56/178	225/813	1.2 (0.9 - 1.6)
Chronic liver disease	3/14	127/977	1.7 (0.5 - 5.6)	4/14	277/977	1.1 (0.4 - 3.4)
Cardiovascular disease	10/63	120/928	1.2 (0.6 - 2.3)	23/63	258/928	1.2 (0.8 - 1.9)
Uncontrolled hypertension	2/24	128/967	0.6 (0.2 - 2.6)	9/24	272/967	1.4 (0.8 - 2.6)
History of thrombophilia	1/13	129/978	0.6 (0.1 - 4.3)	2/13	279/978	0.5 (0.1 - 1.9)
Anemia	19/113	111/878	1.4 (0.8 - 2.3)	39/113	242/878	1.4 (1.0 - 2.0)
Thrombocytopenia	6/35	124/956	1.3 (0.6 - 2.9)	13/35	268/956	1.4 (0.8 - 2.5)
Creatinine clearance <30 ml/min.	15/58	115/933	2.2 (1.2 - 3.9)	24/58	257/933	1.6 (1.0 - 2.6)
Co-medication	29/158	101/833	1.5 (1.0 - 2.3)	56/158	225/833	1.3 (1.0 - 1.8)
Invasive treatment	4/41	126/950	0.8 (0.3 - 2.1)	9/41	272/950	0.8 (0.4 - 1.7)

Abbreviations: SHR, sub-hazard ratio; CI, confidence interval.

*Adjusted for age, sex, and periods of anticoagulation as a time-varying co-variate.

†Presence of at least one of the comorbid conditions listed below.

Table 4. Association between major exclusion criteria, bleeding, recurrent VTE, and overall mortality

	Within 36 months	During initial AC only	After stopping initial AC only
Number of exclusion criteria	**Adjusted SHR[*] (95% CI)**	**Adjusted SHR[†] (95% CI)**	**Adjusted SHR[*] (95% CI)**
Major bleeding			
0	Reference	Reference	Reference
1	1.08 (0.72 - 1.62)	1.02 (0.64 - 1.62)	1.29 (0.60 - 2.78)
≥2	2.16 (1.38 - 3.39)	2.05 (1.21 - 3.47)	3.05 (1.43 - 6.51)
Per 1 criterion	1.41 (1.12 - 1.78)	1.38 (1.05 - 1.81)	1.57 (1.10 - 2.23)
Clinically relevant bleeding			
0	Reference	Reference	Reference
1	1.15 (0.88 - 1.50)	1.12 (0.83 - 1.51)	1.30 (0.80 - 2.11)
≥2	1.63 (1.17 - 2.25)	1.58 (1.10 - 2.29)	1.87 (1.06 - 3.27)
Per 1 criterion	1.24 (1.07 - 1.45)	1.22 (1.02 - 1.45)	1.34 (1.03 - 1.74)
Recurrent VTE			
0	Reference	Reference	Reference
1	0.77 (0.50 - 1.18)	0.76 (0.34 - 1.70)	0.78 (0.47 - 1.29)
≥2	1.07 (0.64 - 1.81)	1.62 (0.65 - 4.03)	1.16 (0.64 - 2.10)
Per 1 criterion	0.97 (0.75 - 1.26)	1.18 (0.72 - 1.92)	0.99 (0.74 - 1.32)
	Adjusted HR[*] (95% CI)	**Adjusted HR[†] (95% CI)**	**Adjusted HR[*] (95% CI)**
Overall mortality			
0	Reference	Reference	Reference
1	4.34 (2.92 - 6.46)	3.45 (2.02 - 5.87)	5.54 (2.99 - 10.27)
≥2	5.46 (3.50 - 8.52)	4.56 (2.47 - 8.41)	7.04 (3.59 - 13.80)
Per 1 criterion	1.97 (1.67 - 2.31)	1.86 (1.49 - 2.33)	2.05 (1.62 - 2.59)

Abbreviations: AC, anticoagulation; SHR, sub-hazard ratio; CI, confidence interval; VTE, venous thromboembolism; HR, hazard ratio.

*Adjusted for age, sex, and periods of anticoagulation as a time-varying co-variate.

†Adjusted for age and sex.