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Age-dependent clinical outcomes in primary versus oral anticoagulation-related intracerebral hemorrhage

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Abstract

Aims: This study determined the influence of age on bleeding characteristics and clinical outcomes in primary spontaneous (non-OAC), vitamin K antagonist-related (VKA-) and non-vitamin K antagonist oral anticoagulant-related (NOAC-) ICH.

Methods: Pooled individual patient data of multicenter cohort studies were analyzed by logistic regression modelling and propensity-score-matching (PSM) to explore the influence of advanced age on clinical outcomes among non-OAC-, VKA-, and NOAC-ICH. Primary outcome measure was functional outcome at three months assessed by the modified Rankin Scale, dichotomized into favorable (mRS = 0–3) and unfavorable (mRS = 4–6) functional outcome. Secondary outcome measures included mortality, hematoma characteristics, and frequency of invasive interventions.

Results: In VKA-ICH 33.5% (670/2001), in NOAC-ICH 44.2% (69/156) and in non-OAC-ICH 25.2% (254/1009) of the patients were ≥80 years. After adjustment for treatment interventions and relevant parameters, elderly ICH patients comprised worse functional outcome at three months (adjusted odds ratio (aOR) in VKA-ICH: 1.49 (1.21–1.84); $p < 0.001$; NOAC-ICH: 2.01 (0.95–4.26); $p = 0.069$; non-OAC-ICH: 3.54 (2.50–5.03); $p < 0.001$). Anticoagulation was significantly associated with worse functional outcome below the age of 70 years, (aOR: 2.38 (1.78–3.16); $p < 0.001$), but not in patients of ≥70 years (aOR: 1.21 (0.89–1.65); $p = 0.217$). The differences in initial ICH volume and extent of ICH enlargement between OAC-ICH and non-OAC-ICH gradually decreased with increasing patient age.

Conclusions: As compared to elderly ICH-patients, in patients <70 years OAC-ICH showed worse clinical outcomes compared to non-OAC-ICH because of larger baseline ICH-volumes and extent of hematoma enlargement. Treatment strategies aiming at neutralizing altered coagulation should be aware of these findings.

Keyword

Intracerebral hemorrhage, intracranial hemorrhage, age, anticoagulation

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Introduction

The demographic trend towards an aging population will lead to dramatic changes for health care systems in industrialized countries.[1] The proportion of elderly people increased considerably during the past decades and will further rise in the future.[2] Latter suffer more frequently from cerebrovascular disease including primary spontaneous ICH (non-OAC-ICH). Alongside, comorbidities such as atrial fibrillation will also increase, why the rate of elderly people requiring oral anticoagulation (OAC) will likewise intensify in the future leading also to a higher incidence of OAC-associated ICH (OAC-ICH).[1,3–5]

In non-OAC-ICH advanced age is linked to more frequent lobar ICH, larger ICH volumes and worse functional outcome.[2,6,7] In OAC-ICH, given altered coagulation with larger bleedings and more frequent hematoma enlargement, clinical outcome is generally

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worse as compared to non-OAC-ICH, however the specific impact of age on hematoma characteristics and outcomes is not established.[2,6,8,9] Age-dependent differences are likely to exist, given recent findings that antiplatelet treatment and oral anticoagulation seem to exert stronger effects in younger patients.[10–13] Therefore, patients' age may influence hematoma characteristics and clinical outcomes in OAC-ICH in a similar manner as in non-OAC-ICH.

Aim and hypothesis

The present study explored the hypothesis that OAC-related ICH, similar to primary spontaneous ICH, reveals an age-dependent impact on ICH-characteristics and thus clinical outcomes.

Methods

Detailed information and methods of the multicenter RETRACE program (part 1 recruited patients from 1 January 2006 until 31 December 2010 (NCT01829581) and part 2 from 1 January 2011 until 31 December 2015 (NCT03093233)) and the prospective UKER-ICH registry (NCT03183167) have been published previously.[14–18] The study was approved by the local ethics committees and institutional review boards based on the central vote from Friedrich-Alexander-University Erlangen-Nuremberg, Germany (Re.No-4409 & 30_16B, 115_17B). Written consent was obtained by patients or legal representatives.

Definitions

ICH classifications and age. Intracerebral bleedings with secondary etiologies such as aneurysms, arteriovenous malformations or tumorous lesions were excluded. Non-OAC-ICH was defined as ICH not associated with secondary etiologies or anticoagulation. VKA-ICH was defined as ICH on effective treatment with vitamin K antagonists (INR value greater than 1.5 on hospital admission) and NOAC-ICH when patients were known to be on treatment with NOAC at ICH-onset.[16] We defined ICH of older age as ICH patients aged 80 years or older and ICH of younger age as ICH patients younger than 80 years at hospital admission.[8] Early care limitations were defined as care limitation employed during the first 24 h after hospital admission.[19] Any care limitations were defined as any care limitation employed during hospital stay ($\leq$24 h and $>$24 h after hospital admission).

Primary and secondary outcomes. Primary outcome measure was functional outcome at three months among patients with non-OAC-ICH and OAC-ICH in a dichotomized age-dependent analysis ($<$80 versus $\geq$80 years of age) using the modified Rankin Scale (mRS)[20] categorized into favorable (mRS = 0–3) and unfavorable (mRS = 4–6) outcome.[14,21] Secondary outcomes comprised (i) mortality at three months, (ii) and hematoma characteristics, and (iii) frequency of invasive interventions.

Data acquisition

Demographic, clinical, and laboratory parameters. Demographic, clinical, and laboratory data were collected as previously described.[18] Medical history of arterial hypertension, diabetes mellitus, prior stroke, congestive heart failure, abnormal kidney, and premorbid modified Rankin Scale[20] were assessed. Laboratory and clinical parameters on admission and during hospital stay were obtained by institutional databases and medical charts.

Imaging. Hematoma characteristics (ICH location, intraventricular hemorrhage; primary intraventricular hemorrhage (IVH) was rated as deep ICH) were assessed as previously described.[14] ICH volume was calculated according to the ABC methods and hematoma enlargement was defined as ICH volume increase of more than 33% (relative) or $\geq$12.5 ml (absolute) from initial to follow-up imaging.[14,22]

Primary and secondary outcomes. Data on mortality and functional outcome (modified Rankin Scale (mRS)) were assessed by standardized mailed questionnaires or semi-structured telephone-interviews at three months.[14]

Statistical analysis

We performed statistical analyses using the statistical package SPSS 21.0 (www.spss.com) and R 2.12.0 (www.r-project.org). Two-sided statistical tests were performed with a significance level of $\alpha = 0.05$. Categorical data are presented as counts (percentage in brackets) and analyzed using the Pearsons-χ^2 and the Fisher's exact test. Normally distributed data are presented as mean ($\pm$SD) and compared using the Student-T-test. Non-normally distributed data are presented as median ($\pm$interquartile range) and analyzed using the Mann–Whitney U-test.

Propensity score matching (PSM) was performed using a balanced, parallel, fixed ratio (1:1) nearest-neighbor approach at a calliper of 0.2, based on significant and relevant differences in baseline characteristics between non-OAC-ICH and OAC-ICH patients (i.e. age, female sex, arterial hypertension and premorbid functional status (mRS)).[23] PSM was performed

separately for patients of younger age (<80 years) and older age (≥80 years).Clinical outcomes (mortality and unfavorable functional outcome) between non-OAC-ICH and OAC-ICH patients were compared in the PSM cohort by multivariable analyses additionally adjusted for therapeutic interventions (mechanical ventilation, surgical hematoma evacuation, external ventricular drain, early care limitation), and deep hematoma location. Multivariable regression analyses in the non-PSM-cohort were adjusted for the same parameters (i.e. age, female sex, arterial hypertension, mRS, therapeutic interventions (mechanical ventilation, surgical hematoma evacuation, external ventricular drain, early care limitation) and deep hematoma location) except for ICH volume, because analyses suggested ICH volume mediating the differences in clinical outcomes between non-OAC-ICH and OAC-ICH. Analyses for the association between older age and clinical outcome were performed as shift of functional outcome towards death or dependence (all categories of the mRS) in the non-PSM-cohorts of non-OAC-ICH, VKA-ICH and NOAC-ICH and adjusted for the same above mentioned parameters including ICH volume and any care limitation.

Specific associations between anticoagulation and unfavorable functional outcome (mRS = 4–6) were determined in the non-PSM-cohort by regression analysis in strata of specific age periods with five-year intervals (±10 years). The last significant OR estimate of the specific strata revealed the cut-off age beyond which OAC was no longer related to worse clinical outcome. The regression of odds ratio estimates were corrected for overestimation by the method of moving averages.[24] Differences in initial hematoma volume and extent of hematoma enlargement between OAC-ICH and non-OAC-ICH were calculated in the above mentioned strata of specific age periods and compared between patients at younger age (<80 years) and older age (≥80 years) using the Mann–Whitney U-test.

Results

Study population and clinical characteristics

We pooled individual patient data of 3580 ICH patients—2314 VKA-ICH and 190 NOAC-ICH patients of the multicenter RETRACE I and II study, each including 19 tertiary care centers, and 1076 non-OAC-ICH patients of the prospective UKER-ICH registry (Figure 1). After exclusion of 414 (11.6%) patients because of missing data, 3166 ICH patients remained for the present analysis. In VKA-ICH 33.5% (670/2001), in NOAC-ICH 44.2% (69/156) and in non-OAC-ICH 25.2% (254/1009) of the patients were ≥80 years ($p < 0.001$). Patients ≥80 years presented with worse premorbid functional status (OAC-ICH: 1 (0–2) vs. 0 (0–1), $p < 0.001$; non-OAC-ICH: 2 (1–3) vs. 0 (0–2), $p < 0.001$; Table 1).

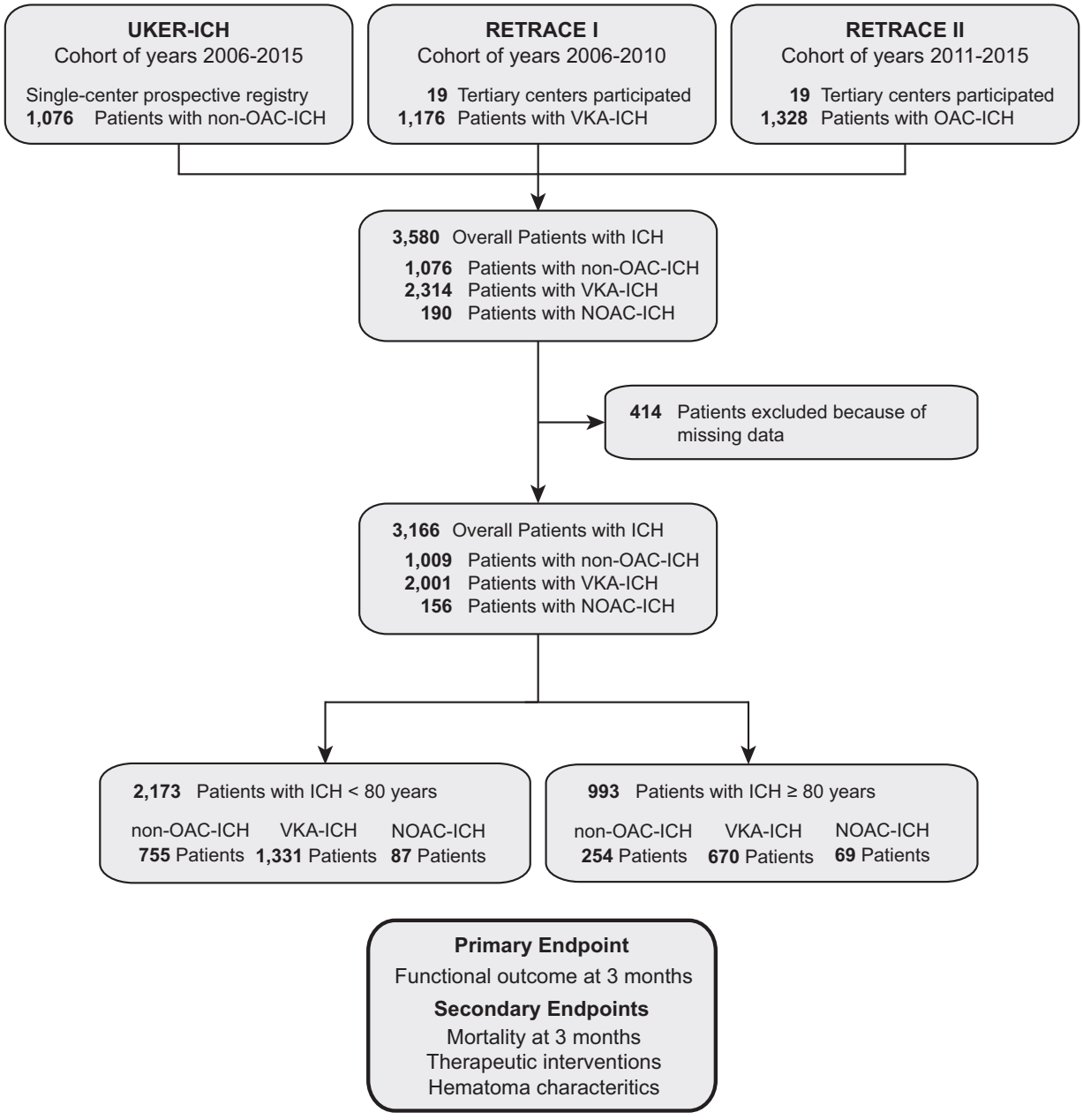
Regarding frequency of invasive interventions, there were significant imbalances in disfavor of older patients among all three ICH groups (Table 1). Patients ≥80 years received mechanical ventilation, hematoma evacuation surgery and placement of ventricular drains less often compared to younger individuals (mechanical ventilation: OAC-ICH: 229/739 (31.0%) vs. 641/1418 (45.2%); $p < 0.001$; non-OACH-ICH: ≥80 years: 58/254 (22.8%) vs. <80 years: 348/755 (46.1%); $p < 0.001$), whereas rates of early care limitations were higher (OAC-ICH: 177/739 (24.0%) vs. 203/1418 (14.3%); $p < 0.001$; non-OACH-ICH: ≥80 years: 67/254 (26.4%) vs. <80 years: 83/755 (11.0%); $p < 0.001$).

Age-dependent hematoma characteristics according to anticoagulation status

To explore the influence of anticoagulation status on hemorrhage characteristics, we performed propensity score matching between the groups of OAC-ICH and non-OAC-ICH patients of older age (≥80 years) and younger age (<80 years) for imbalances in age, female sex, arterial hypertension and premorbid functional status (Supplemental Table 1). Table 2 shows that in patients of younger age, there were significant differences in baseline hematoma volume, occurrence and extent of hematoma enlargement between OAC and non-OAC-ICH (ICH volume: 20.3 (7.1–54.3) ml in OAC vs. non-OAC: 13.1 (4.4–34.4) ml; $p < 0.001$; hematoma enlargement: 198/510 (38.8%) vs. 57/566 (10.1%); $p < 0.001$; volume of ICH enlargement: 16.3 (6.0–34.6) ml vs. 9.7 (2.6–28.4) ml; $p = 0.037$), whereas there were no significant differences in hematoma location (Table 2). Contrary, in elderly patients there were no significant differences in baseline hematoma volume and extent of hematoma enlargement between OAC and non-OAC-ICH (ICH volume: 17.2 (6.0–57.0) ml in OAC vs. non-OAC: 19.2 (5.0–53.3) ml; $p = 0.548$; volume of ICH enlargement: 12.8 (4.3–30.5) ml vs. 11.5 (3.2–20.4) ml; $p = 0.607$), but significant differences in hematoma enlargement and hematoma location (hematoma enlargement: 54/150 (36.0%) vs. 18/160 (11.3%); $p < 0.001$; lobar ICH location: 93/249 (37.3%) vs. 135/249 (54.2%); $p < 0.001$).

Figure 2(a) illustrates the age-dependent differences in initial ICH volume and in extent of hematoma expansion between non-OAC-ICH and OAC-ICH. There was a gradual decrease of both hematoma volume parameters with increasing patient age and a significant difference between patents of younger and older age regarding the difference in initial hematoma

Figure 1. Flow chart of study participants. Overall, 1076 patients with non-OAC-ICH and 2504 patients with OAC-ICH (years 2006–2010: 1176 patients; years 2011–2015: 1328 patients) were eligible for data analysis including 2314 VKA-ICH and 190 NOAC-ICH patients. After Exclusion of 414 patients because of missing data, 3166 ICH patients—2173 patients at younger age (i.e. <80 years) and 993 patients at older age (i.e. ≥80 years)—remained for study analyses. ICH: intracerebral hemorrhage; non-OAC-ICH: not oral anticoagulation associated ICH (i.e. primary spontaneous ICH); VKA: vitamin K antagonists; OAC: oral anticoagulation; NOAC: non-vitamin K antagonist oral anticoagulant.



volume (<80 years: 5.5 (5.0–9.8) ml vs. ≥80 years: 2.0 (1.0–3.0) ml; p = 0.010) and extent of hematoma enlargement (7.0 (4.3–11.0) ml vs. 1.5 (0.3–2.8) ml; p = 0.013) associated with anticoagulation.

Age-dependent clinical outcomes

To determine the relevance of anticoagulation on functional outcome according to age, we performed multivariable regression analyses in the PSM cohort adjusted

Table 1. Clinical characteristics of non-OAC-ICH and OAC-ICH patients at younger (<80 years) and older age (≥80 years)

	Non-OAC-ICH (n = 1009)			OAC-ICH (n = 2157)		
	Age < 80 years (n = 755)	Age ≥ 80 years (n = 254)	p value	Age < 80 years (n = 1418)	Age ≥ 80 years (n = 739)	p value
Age, years (IQR)	68 (58–74)	84 (82–87)	<0.001	73 (67–76)	83 (81–86)	<0.001
Female sex	310 (41.1%)	158 (62.2%)	<0.001	562 (39.6%)	362 (49.0%)	<0.001
Prior comorbidities						
Hypertension	616 (81.6%)	219 (86.2%)	0.091	1202 (84.8%)	652 (88.2%)	0.028
Diabetes mellitus	204 (27.0%)	56 (22.0%)	0.117	434 (30.6%)	187 (25.3%)	0.010
Prior ischemic stroke/TIA	123 (16.3%)	53 (20.9%)	0.097	381 (26.9%)	203 (27.5%)	0.766
Congestive heart failure	69 (9.1%)	37 (14.6%)	0.015	251 (17.7%)	159 (21.5%)	0.032
Abnormal kidney function	87 (11.5%)	39 (15.4%)	0.110	330 (23.3%)	202 (27.3%)	0.038
Premorbid mRS (IQR)	0 (0–2)	2 (1–3)	<0.001	0 (0–1)	1 (0–2)	<0.001
Treatment measures						
Mechanical ventilation	348 (46.1%)	58 (22.8%)	<0.001	641 (45.2%)	229 (31.0%)	<0.001
Surgical hematoma evacuation	56 (7.4%)	3 (1.2%)	<0.001	231 (16.3%)	47 (6.4%)	<0.001
External ventricular drain	246 (32.6%)	18 (7.1%)	<0.001	290 (20.5%)	80 (10.8%)	<0.001
Early care limitation	83 (11.0%)	67 (26.4%)	<0.001	203 (14.3%)	177 (24.0%)	<0.001
Symptom onset to admission, h (IQR)	4.52 (1.93–12.38)	4.50 (1.80–9.85)	0.369	1.70 (1.00–4.03)	1.83 (1.03–4.30)	0.176
Admission to reversal, min (IQR)	NA	NA	NA	101 (62–180)	105 (63–202)	0.578

ICH: intracerebral hemorrhage; OAC: oral anticoagulation; OAC-ICH: OAC-associated ICH; non-OAC-ICH: not OAC-associated ICH (i.e. primary spontaneous ICH); IQR: interquartile range; TIA: transient ischemic attack; mRS: modified Rankin scale.

Table 2. Hematoma characteristics of propensity score matched non-OAC-ICH and OAC-ICH patients at younger (<80 years) and older age (≥80 years)

	Age < 80 years (n = 1406)			Age ≥ 80 years (n = 498)		
	Non-OAC-ICH (n = 703)	OAC-ICH (n = 703)	p value	Non-OAC-ICH (n = 249)	OAC-ICH (n = 249)	p value
Deep	328 (46.7%)	327 (46.5%)	0.957	87 (34.9%)	116 (46.6%)	0.008
Lobar	290 (41.3%)	279 (39.7%)	0.550	135 (54.2%)	93 (37.3%)	<0.001
Infratentorial	85 (12.1%)	97 (13.8%)	0.340	27 (10.8%)	40 (16.1%)	0.088
Intraventricular hemorrhage	353 (50.2%)	329 (46.8%)	0.200	123 (49.4%)	130 (52.2%)	0.530
ICH volume, ml (IQR)	13.1 (4.4–34.4)	20.3 (7.1–54.3)	<0.001	19.2 (5.0–53.3)	17.2 (6.0–57.0)	0.548
Hematoma enlargement[a]	57/566 (10.1%)	198/510 (38.8%)	<0.001	18/160 (11.3%)	54/150 (36.0%)	<0.001
Volume of hematoma enlargement, ml (IQR)	9.7 (2.6–28.4)	16.3 (6.0–34.6)	0.037	11.5 (3.2–20.4)	12.8 (4.3–30.5)	0.607

ICH: intracerebral hemorrhage; OAC: oral anticoagulation; OAC-ICH: OAC-associated ICH; non-OAC-ICH: not oral anticoagulation associated ICH (i.e. primary spontaneous ICH); IQR: interquartile range.

[a]Hematoma enlargement was defined as increase of volume >33% or ≥12.5 ml on follow-up imaging. non-OAC-ICH and OAC-ICH patients <80 years and ≥ 80 years were separately matched according to propensity scores calculated from age, female sex, arterial hypertension, and premorbid functional status (1:1 ratio, caliper 0.2, nearest-neighbor approach).

for therapeutic interventions and deep hematoma location. Regarding patients of younger age, there were significant differences in mortality (OAC-ICH: 292/703 (41.5%) vs. non-OAC-ICH: 177/703 (25.2%), adjusted odds ratio (aOR): 2.98 (2.20–4.03); $p < 0.001$; Figure 3(a)) and functional outcome at three months in favor of primary spontaneous ICH (unfavorable functional outcome (mRS = 4–6) OAC-ICH: 498/703 (70.8%) vs. non-OAC-ICH: 398/703 (56.6%), aOR: 2.29 (1.75–3.00); $p < 0.001$). Regarding elderly patients, there were no significant differences in mortality (OAC-ICH: 147/249 (59.0%) vs. non-OAC-ICH: 133/249 (53.4%), aOR: 1.39 (0.89–2.17); $p = 0.146$) and functional outcome (OAC-ICH: 202/249 (81.1%) vs. non-OAC-ICH: 193/249 (77.5%), aOR: 1.08 (0.67–1.74); $p = 0.749$) between the two groups (Figure 3(b)).

To titrate a cut-off age beyond which OAC was no longer related to worse clinical outcomes, we performed multivariable regression analyses in the non-PSM-cohort among strata of specific age periods with five-year intervals (±10 years). Figure 2(b) revealed that below the age of 70 years, anticoagulation is significantly associated with worse functional outcome (aOR: 2.38 (1.78–3.16); $p < 0.001$), whereas in patients of 70 years or older there was no significant association with functional outcome (aOR: 1.21 (0.89–1.65); $p = 0.217$). Subgroup analysis revealed similar associations in VKA-ICH (age < 70 years: 2.50 (1.86–3.36); $p < 0.001$ vs. age > 70 years: 1.19 (0.87–1.63); $p = 0.277$; Figure 2(d)), but no significant associations with functional outcome for NOAC-ICH (Figure 2(c)).

Multivariable regression analyses verified age-dependent outcome associations (for age ≥ 80 years) in the overall, non-PSM-cohorts of VKA-ICH (adjusted OR (aOR) for death or dependence: 1.49 (1.21–1.84); $p < 0.001$), NOAC-ICH (aOR: 2.01 (0.95–4.26); $p = 0.069$) and non-OAC-ICH (aOR: 3.54 (2.50–5.03); $p < 0.001$).

Discussion

In this study we demonstrate that elderly ICH patients show worse clinical outcomes independently of treatment interventions and premorbid functional status in all ICH-subsets, i.e. non-OAC-ICH, VKA-ICH, and NOAC-ICH. Oral anticoagulation impacts functional outcome specifically in ICH patients <70 years, driven by larger hematoma volumes and extent of hematoma enlargement, however, does not influence hemorrhage characteristics and functional outcome of

Figure 2. Impact of anticoagulation on hematoma volume and functional outcome. (a) Age-dependent differences in volume of hematoma enlargement and in initial ICH volume between non-OAC-ICH and OAC-ICH are illustrated for the non-PSM-cohort. The gray dots show the difference in initial hematoma volume between OAC-ICH and non-OAC-ICH in specific age periods with five-year intervals (±10 years). The black triangles show the corresponding extent of hematoma enlargement between OAC-ICH and non-OAC-ICH. (b–d) Age-dependent impact of anticoagulation on functional outcome at three months is shown for patients with (b) OAC-ICH, (c) NOAC-ICH and (d) VKA-ICH. Multivariable regression analyses (adjusted for age, female sex, arterial hypertension, premorbid functional status, therapeutic interventions (mechanical ventilation, surgical hematoma evacuation, external ventricular drain, early care limitation) and deep hematoma location) were performed in the non-PSM-cohort among strata of specific age periods with five-year intervals (±10 years). The thick lines represent a regression of odds ratio estimates for unfavorable functional outcome (mRS = 4–6) generated for these stratified intervals of patients' age. The thin lines indicate the 95% confidence intervals and the vertical dashed line the last significant OR estimate of the specific strata. OAC: oral anticoagulation; ICH: intracerebral hemorrhage; NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonists; aOR: adjusted odds ratio; CI: confidence intervals.

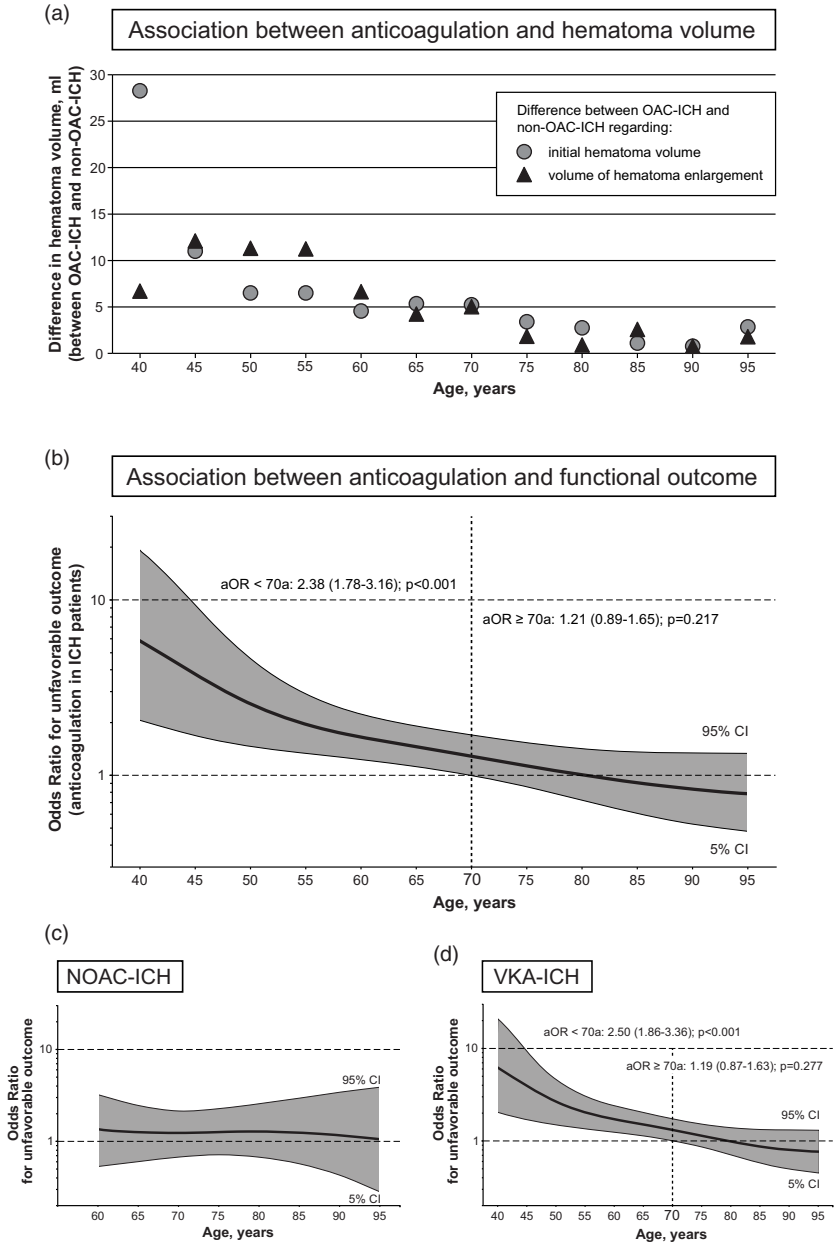
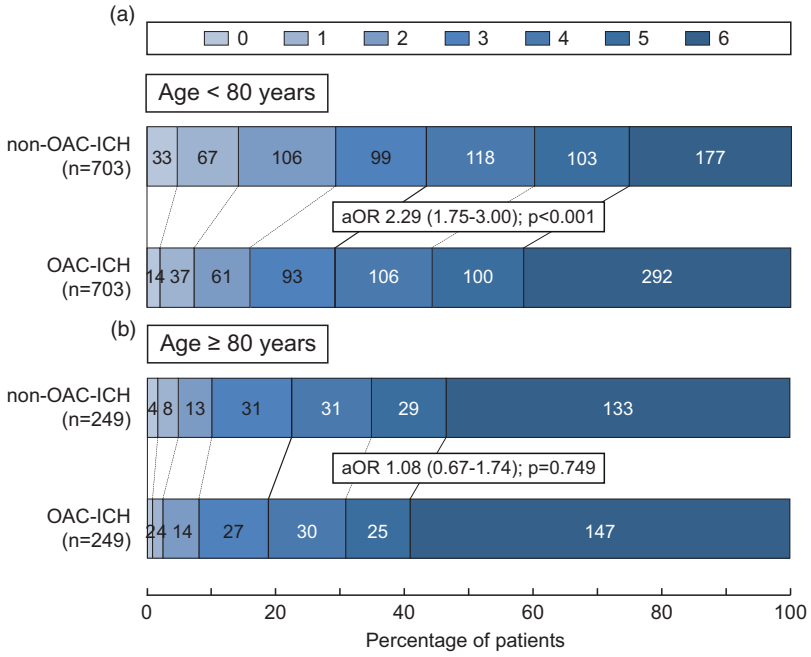


Figure 3. Functional outcome at three months. Distribution of functional outcome (modified Rankin Scale) at three months between non-OAC-ICH and OAC-ICH patients of (a) younger age (i.e. < 80 years) and (b) older age (i.e. ≥ 80 years). Odds Ratios were calculated for the association of unfavorable outcome (mRS = 4–6) between OAC-ICH and non-OAC-ICH and adjusted for therapeutic interventions (mechanical ventilation, surgical hematoma evacuation, external ventricular drain, early care limitation), and deep hematoma location in the propensity scores matched cohorts (for details see methods section and Supplemental Table 1). ICH: intracerebral hemorrhage; OAC: oral anticoagulation; non-OAC-ICH: not oral anticoagulation associated ICH (i.e. primary spontaneous ICH); mRS: modified Rankin scale; aOR: adjusted odds ratio.



ICH patients in the elderly. These findings have important implications for clinical routine.

The hemostatic system in elderly people is induced by complex changes in platelet function, coagulation system, and vascular endothelium, which leads to pronounced hemostatic state in elderly patients.[25] This physiological pro-coagulatory condition may explain that anticoagulation does not lead to larger ICH volume or extent of hematoma enlargement, and does therefore not impact functional outcome, in elderly ICH-patients. Furthermore, worse clinical outcome in older patients may per se reduce the clinical relevance of additional anticoagulation. Of note, oral anticoagulation leads to worse functional outcome in younger ICH patients by gradually increasing extent of hematoma enlargement and hematoma volume. Thus, reversal strategies must be initiated immediately specifically in younger ICH-patients to increase chances of more favorable outcomes.

Elderly patients more frequently require oral anticoagulation therapy due to cerebrovascular diseases such as atrial fibrillation.[1,4] However anticoagulation is often withheld in fear of higher incidence and severity of bleeding complications with increasing patient age.[5] A recent nationwide study of over 25,000 elderly patients found no increased incidence of ICH among patients with OAC therapy.[13] Our study results demonstrate that severity of ICH is not influenced by OAC-pretreatment in elderly patients, which serves as an additional argument to not withhold OAC for secondary prevention in elderly patients.[4,13]

Conflicting results existed about hematoma characteristics in OAC-ICH, partly suggesting more frequent intraventricular hemorrhage or lobar hemorrhage location.[26] We here clarify that anticoagulation at symptom onset is not associated with specific bleeding location in younger ICH patients, whereas in elderly patients deep hematoma location was more frequent in OAC-ICH. Our findings emphasize that small vessel disease may not only expose to lobar bleeding under oral anticoagulation, but also to bleeding of the deep perforating arteries resulting in deep hematoma location.[27,28] Our findings are in contrast to another study of 77 OAC-ICH patients,[26] but in line with post-hoc analysis of the SMART and ESPRIT

trials.[29] ICH bleeding risk assessment and stratification should therefore include severity of this small vessel disease entity.

There are some limitations in our study. Of note, OAC-ICH patients were recruited in a multicenter retrospective study design, whereas non-OAC-ICH patients in a prospective single-center study, all of which may have led to potential center effects and confounding. ICH volumes were calculated by ABC-method, not by volumetric assessment and residual bias of treatment restrictions may have influenced clinical outcomes in elderly patients.[30] In addition, patients with missing data were excluded from analyses leaving room for residual uncertainties. Further, the numbers of NOAC-ICH patients were limited.

Conclusion

Older age is associated with worse functional outcome in non-OAC-ICH, VKA-ICH, and NOAC-ICH patients. Oral anticoagulation does not affect hematoma volumes and clinical outcomes in elderly ICH-patients >80 years of age, whereas OAC influences outcome specifically in ICH-patients <70 years of age, mainly driven by larger baseline ICH volume and increased extent of hematoma enlargement.

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Supplemental material

Supplemental material for this article is available online.

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