Intracerebral hemorrhage and antithrombotic drugs - clinical aspects and prognostic outcomes

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– Clinical aspects and prognostic outcomes

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Trine Apostolaki-Hansson

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Abstract

Background: Intracerebral hemorrhage (ICH) holds the highest lethality amongst all stroke subtypes and is associated with a high risk of functional dependency amongst survivors. This thesis aims to advance knowledge regarding functional and survival outcomes related to ICH and antithrombotic drugs. It also aims to delineate the effect of oral anticoagulant (OAC) reversal therapy on prognosis, using patient data from Riksstroke, the Swedish Stroke Register. Patient outcome following antithrombotic-related ICH based on data from Riksstroke has not been studied prior to this thesis.

Methods: This thesis describes patients registered in Riksstroke between 2012 and 2019, including data from Riksstroke's acute survey and 3-month follow-up survey. Data on mortality and prescribed drugs were obtained from the Swedish Causes of Death Register and the Swedish Prescribed Drug Register, respectively. The modified Rankin Scale was used to evaluate functional outcome. Multivariable models used in this thesis were Cox regression and logistic regression analysis. Multiple imputation was used in Paper I to minimize attrition bias.

Results:

Paper I included 2 483 patients registered in Riksstroke between 2012 and 2016 who had taken oral anticoagulants prior to their ICH (OAC-ICH). Of these, 300 had taken non-vitamin K oral anticoagulants (NOAC) and 2 183 had taken vitamin K antagonists (VKA). In both groups, mean age was 79 years, and 58% were male. We found no significant difference in all-cause 90-day mortality between NOAC-ICH (44.3%) and VKA-ICH (42.6%) (NOAC-ICH Hazard Ratio (HR) = 0.93; 95% CI: 0.78 – 1.12) or 90-day functional outcome. Patient factors associated with an increased death rate in both groups were increased age and a decreased level of consciousness (LOC) at hospital admission.

Paper II included 572 patients with OAC-ICH registered in Riksstroke during 2017, whereof 369 received OAC reversal treatment and 203 patients did not. Patients who received reversal treatment were more often younger, pre-stroke independent and had a more favorable LOC at hospital admission. Withholding reversal treatment was associated with an increased death rate at 90 days (HR = 1.47; 95% CI: 1.08 – 2.01) in a Cox regression model stratified for LOC. Additional factors associated with an increased death rate were male sex, age, and intraventricular hemorrhage.

Paper III included 13 291 patients with ICH registered in Riksstroke between 2012 and 2016 and compared 90-day mortality and functional outcome in patients with OAC-ICH (n = 2 300), antiplatelet-related ICH (n = 3 637), and nonantithrombotic ICH (n = 7 354). Patients undergoing antithrombotic treatment with either OAC or antiplatelets were more often older, more often prestroke dependent, and had a larger comorbidity burden compared to patients with nonantithrombotic ICH. In a multivariable analysis, antiplatelet-ICH and OAC-ICH were associated with an increased death rate at 90 days compared to nonantithrombotic ICH, and a higher risk of early mortality (≤24h). From a logistic regression analysis, patients with antiplatelet-ICH and OAC-ICH were not found to have increased functional dependency at 90 days compared to patients without antithrombotic treatment.

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Conclusion: This thesis confirms the poor prognosis associated with ICH. Both antiplatelet and OAC treatment are associated with increased 90-day fatality compared to patients not taking antithrombotic drugs prior to their ICH. NOAC-ICH and VKA-ICH had similar patient outcomes. We identified that receiving OAC reversal treatment was associated with a more favorable prognosis, yet less than half of patients with NOAC-ICH received this treatment despite representing a greater number of OAC-ICH cases today.

Key words Intracerebral hemorrhage, prognosis, survival, functional status, oral anticoagulant drug, antiplatelet drug, reversal treatment, antidote

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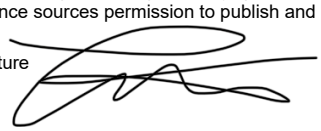
Signature  Date 2023-03-30

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To Dad,

Life is a gift

Contents

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List of publications

I Apostolaki-Hansson T, Ullberg T, Norrving B, Petersson J. Prognosis for intracerebral hemorrhage during ongoing oral anticoagulant treatment. Acta Neurol Scand. 2019;139:415-421

II Apostolaki-Hansson T, Ullberg T, Pihlsgard M, Norrving B, Petersson J. Reversal treatment in oral anticoagulant-related intracerebral hemorrhage-an observational study based on the Swedish Stroke Register. Front Neurol. 2020;11:760

III Apostolaki-Hansson T, Ullberg T, Pihlsgard M, Norrving B, Petersson J. Prognosis of intracerebral hemorrhage-related to antithrombotic use: An observational study from the Swedish Stroke Register (Riksstroke). Stroke. 2021;52:966-974

IV Apostolaki-Hansson T, Ullberg, T, Norrving, B & Petersson, J (2022). Patient factors associated with receiving reversal therapy in oral anticoagulant-related intracerebral hemorrhage. Acta Neurologica Scandinavica, 00, 1–8. https://doi.org/10.1111/ane.13685

Abbreviations

ADL	Activities of daily living
AF	Atrial fibrillation
AP	Antiplatelet
AP-ICH	Antiplatelet-related intracerebral hemorrhage
APOE	Apolipoprotein E
APP	Amyloid precursor protein
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AT	Antithrombotic
ATC	Anatomical therapeutic chemical
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CMB	Cerebral microbleed
cSS	Cortical superficial siderosis
CT	Computed tomography
DALYs	Disability adjusted life years
DNR	Do not resuscitate
EMA	European Medicines Agency
ESO	European Stroke Organisation
FCS	Fully conditional specification
FUNC	Functional outcome in patients with primary intracerebral hemorrhage
GCS	Glasgow coma scale
HE	Hematoma expansion
HR	Hazard ratio

ICD-11	Statistical Classification of Diseases and Health Related Problems, eleventh revision
ICH	Intracerebral hemorrhage
ICU	Intensive care unit
INR	International normalized ratio
IVH	Intraventricular hemorrhage
LAD	Large artery disease
LOC	Level of consciousness
MI	Multiple imputation
mRS	Modified Rankin Scale
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
NOAC	Non-vitamin K oral anticoagulant
NOAC-ICH	Non-vitamin K oral anticoagulant-related intracerebral hemorrhage
OAC	Oral anticoagulant
OAC-ICH	Oral anticoagulant-related intracerebral hemorrhage
OR	Odds ratio
PCC	Prothrombin complex concentrate
PH	Proportional Hazards
PT	Prothrombin time
RCT	Randomized controlled trial
RLS-85	Reaction Level Scale 85
RR	Relative risk
SAD	Small artery disease
SVD	Small vessel disease
TIA	Transient ischemic attack
TOAST	Trial of Org. 10172 in Acute Stroke Treatment
VKA	Vitamin K antagonist
VKA-ICH	Vitamin K antagonist-related intracerebral hemorrhage
WML	White matter lesions

Introduction

Intracerebral hemorrhage (ICH) is the second most common cause of stroke, accounting for 10 – 15% of all stroke cases in high-income countries, and having the highest death rate of all strokes[1]. The proportion of ICH constituting all stroke cases is nearly double in low-income to upper-middle-income countries compared to high-income countries (29.5% vs 15.8%)[2]. The one-month case fatality for ICH ranges between 30 to 40% and only 20% reclaim independence[3]. The implications of ICH are many and can be devastating due its high risk of death and disability[4]. Despite several advances in acute ischemic stroke care, such as intravenous thrombolysis and thrombectomy, driven by numerous randomized controlled trials (RCT), the development of new treatment options for ICH in the acute stage has not progressed as rapidly. Through primary and secondary prevention, the risk of ICH can be lowered. Nonetheless the increasing prescription rate of antithrombotic drugs poses a threat to patients who are vulnerable to this condition.

Stroke definition and classification

Stroke is defined as:

> "Rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin." [5]

According to the newest version of the International Classification of Diseases (ICD) 11th Revision, ICD-11, stroke is included in diseases of the nervous system and is defined as a cerebrovascular disease relating to a group of brain dysfunctions related to disease of the blood vessels supplying the brain[6]. The ICD-11 categorizes stroke into the following categories: cerebral ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and stroke not known if ischemic or hemorrhagic.

Ischemic stroke accounts for approximately 85% of stroke cases and is subclassified into five major subtypes according to the TOAST (Trial of Org. 10172 in Acute Stroke Treatment) classification system including: cardioembolic, large artery disease (LAD), small artery disease (SAD), other determined causes, and

cryptogenic stroke[7]. Hemorrhagic stroke accounts for the remaining 15% of stroke cases, with subarachnoid hemorrhage representing approximately 5% of these cases commonly caused by a ruptured intracranial aneurysm[8].

Intracerebral hemorrhage

Intracerebral hemorrhage represents approximately 10% of stroke cases[9]. The overall incidence of ICH is 24.6 per 100 000 person-years[3]. Spontaneous ICH is defined as bleeding into the parenchyma of the brain in the absence of trauma or surgery, sometimes extending into the ventricles and, seldomly, into the subarachnoid or subdural space[1 10]. Figure 1 depicts the most common locations in the brain parenchyma affected by spontaneous ICH. Spontaneous ICH includes patients treated with antithrombotic medications. Depending on the etiology, intracerebral hemorrhage has historically been classified as primary or secondary hemorrhage. Although this type of classification is commonly used, it is disparaged as it discourages an adequate investigation of etiology and should therefore be avoided[11]. Instead, it is encouraged to recognize spontaneous ICH according to hemorrhage location[11].

The most common cause of spontaneous intracerebral hemorrhage is cerebral small vessel disease (SVD), as it accounts for approximately 85% of ICH cases[11-13]. In the instance of ICH, cerebral SVD incorporates common pathologies such as hypertensive vasculopathy and cerebral amyloid angiopathy (CAA). Hypertensive vasculopathy results in alterations of the vessel wall, including degeneration of the smooth muscle cells of the middle and distal portions of the lenticulostriate arteries, as well as lipohyalinosis, and microaneurysms[14]. These pathologic changes may eventually lead to small vessel rupture and consequent ICH. Non-lobar intracerebral hemorrhage accounts for the majority of spontaneous ICH cases and is related to hypertensive vasculopathy, with hemorrhage predominantly occurring in the deep structures of the brain, specifically, the basal ganglia, thalamus, brainstem (commonly pons), or cerebellum[1,15]. On the other hand, lobar ICH is commonly located at the junction of the cortical gray matter and subcortical white matter[16]. A significant proportion of spontaneous lobar ICH results from a process termed cerebral amyloid angiopathy. Cerebral amyloid angiopathy primarily affects the elderly and is a pathologic process of amyloid beta depositing in the media and adventitia of small arteries and capillaries in the brain and leptomeninges showing cortical predominance, namely, in the temporal and occipital regions[17,18]. Cerebral amyloid angiopathy may be associated with apolipoprotein E (APOE) ε2 or ε4 genotypes[15,17,19].

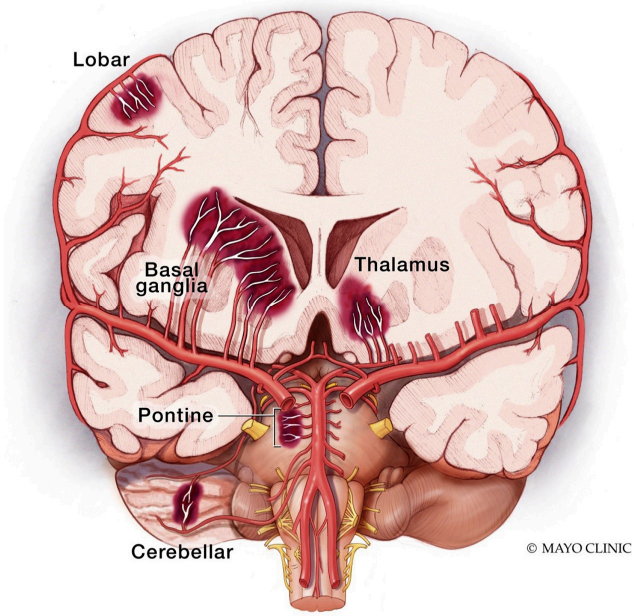


Figure 1 Hemorrhage location.
The most common spontaneous intracerebral hemorrhage locations presented in a coronal section of the brain. Reprinted from O'Carroll CB, Brown BL, Freeman WD. Intracerebral Hemorrhage: A Common yet Disproportionately Deadly Stroke Subtype. Mayo Clin Proc. 2021;96:1639-1654. doi: 10.1016/j.mayocp.2020.10.034, with permission from Elsevier.

According to the modified Boston Criteria, a definitive diagnosis of CAA is made through post-mortem examination of brain tissue revealing lobar, cortical, or corticosubcortical hemorrhage with pathological evidence of severe CAA with vasculopathy[20]. In living persons, a probable diagnosis of CAA is made through imaging-based criteria (magnetic resonance imaging (MRI) or computed tomography (CT)) and clinical data (age $\geq$ 55 years). The diagnosis includes hemorrhages $\geq$ 2 (ICH or cerebral microbleeds) in the lobar, cortical or corticosubcortical regions, or a cerebellar hemorrhage, or the presence of a single lobar, cortical, corticosubcortical hemorrhage and cortical superficial siderosis (cSS) (either focal or disseminated)[21]. The absence of secondary causes of hemorrhage must be excluded.

Table 1 displays the modified Boston Criteria for CAA. Updated Boston Criteria v2.0 have been proposed and incorporate emerging MRI markers of CAA to improve diagnosis sensitivity[22]. In a recent study, the v2.0 for the diagnosis of probable CAA had superior accuracy compared to the current Boston criteria, although future studies are needed to determine generalizability of the criteria[23]. Furthermore, the Edinburgh CT and genetic diagnostic criteria, a prediction model for the identification of CAA-related ICH, incorporates CT features (subarachnoid hemorrhage and finger-like projections from intracerebral hemorrhage) and APOE

genotype to predict the risk and estimate diagnostic accuracy of this type of lobar hemorrhage[24]. A Dutch validation study suggested that the prediction model had high sensitivity, especially in patients with larger hemorrhage volumes[25].

Table 1. Modified Boston Criteria for cerebral amyloid angiopathy.

Definite CAA
Full postmortem examination demonstrating:
Lobar, cortical, or cortical–subcortical hemorrhage
Severe CAA with vasculopathy
Absence of other diagnostic lesion
Probable CAA with supporting pathology
Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating:
Lobar, cortical, or cortical–subcortical hemorrhage (including ICH, CMB, or cSS)
Some degree of CAA in specimen
Absence of other diagnostic lesion
Probable CAA
Clinical data and MRI or CT demonstrating:
Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical, or cortical–subcortical regions (cerebellar hemorrhage allowed), or single lobar, cortical, or cortical–subcortical hemorrhage and cSS (focal or disseminated)
Age ≥55 y
Absence of other cause of hemorrhage*
Possible CAA
Clinical data and MRI or CT demonstrating:
Single lobar, cortical, or cortical–subcortical ICH, CMB, or cSS (focal or disseminated)
Age ≥55 y
Absence of other cause of hemorrhage*
CAA indicates cerebral amyloid angiopathy; CMB, cerebral microbleed; cSS, cortical superficial siderosis; CT, computed tomography; ICH, intracerebral hemorrhage; and MRI, magnetic resonance imaging.
*Other causes of hemorrhage (differential diagnosis of lobar hemorrhages): antecedent head trauma, hemorrhagic transformation of an ischemic stroke, arteriovenous malformation, hemorrhagic tumor, warfarin therapy with international normalization ratio >3, and vasculitis.

Reproduced from S. M. Greenberg, A. Charidimou. Diagnosis of Cerebral Amyloid Angiopathy: Evolution of the Boston Criteria. Stroke 2018. Vol 49. Issue 2. Page 492. https://www.ahajournals.org/doi/10.1161/STROKEAHA.117.016990, with permission from Wolters Kluwer Health, Inc.

Several imaging markers of cerebral SVD exist. These include white matter lesions (WML), which may be prominent in both non-lobar and lobar ICH[16]. Microbleeds, perivascular spaces located in centrum semiovale, and WMLs are prominent findings in CAA[26,27]. The extent of the WML burden in patients with CAA is said to be associated with cognitive impairment[28]. Contrary to a CAA diagnosis, the diagnostic criteria for non-lobar ICH attributable to hypertension are not well established, although the total cerebral SVD score, originally developed in patients with lacunar ischemic stroke[29], has been reported to be significantly correlated with non-lobar ICH[27]. This score includes MRI imaging findings characteristic of lacunes, cerebral microbleeds (CMB), the presence of perivascular spaces in the basal ganglia, and deep WMLs based on the Fazekas scale[29].

Other etiologies of intracerebral hemorrhage which occur in both lobar and non-lobar locations include pathologies such as arteriovenous malformations, cerebral venous thrombosis, hemostatic disease, vasculitis, or hemorrhagic tumours. An

underlying etiology could remain cryptogenic despite a substantial diagnostic evaluation.

Risk factors

Primary intracerebral hemorrhage is not typically caused by a single risk factor, but instead through an interaction of multiple individual patient risk factors contributing to an increased risk of ICH[30] (Figure 2). Therefore, distinguishing ICH based on any one specific risk factor may dissuade the identification of further important risk factors. Hence the terminology primary and secondary ICH should be discouraged. As several modifiable risk factors for ICH are related to lifestyle and cardiovascular disease and can be reduced through specific lifestyle modifications or prescription medications, it is important to extensively evaluate patient history to reduce the risk of ICH in patients susceptible to a first ever or repeat ICH. Contrarily, non-modifiable risk factors including sex, age, and genetic profile cannot be altered. The following paragraphs present a brief overview of important risk factors.

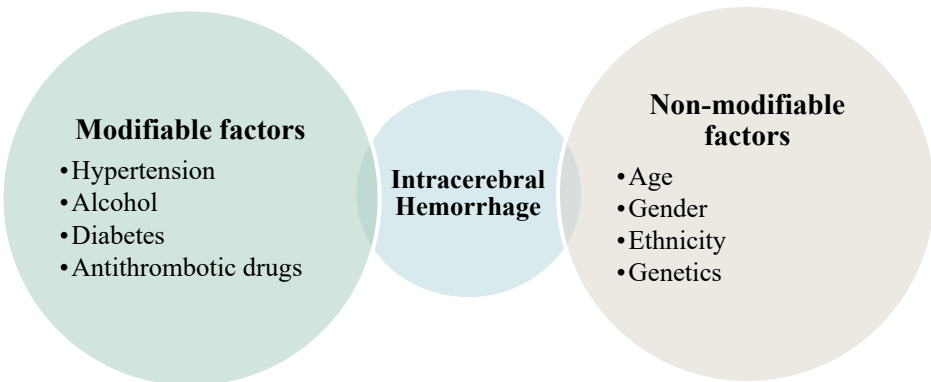


Figure 2. Modifiable and non-modifiable risk factors for intracerebral hemorrhage

The single most important modifiable risk factor associated with ICH is chronic hypertension[31]. Hypertension accounts for approximately three quarters of non-lobar ICH cases[32]. A history of hypertension is associated with a crude odds ratio (OR) of 3.68 (95% confidence interval (CI): 2.52 – 5.38)[33], and it is suggested that the risk of ICH is greater with increased levels of blood pressure[34,35].

Antithrombotic medications, including antiplatelet and oral anticoagulant drugs, increase the risk of ICH. The risk of ICH and the implications of antithrombotic drugs are discussed in a separate section of this thesis below.

Alcohol consumption is another significant modifiable risk factor related to hemorrhagic stroke. Alcohol intake (g/day) has been reported to be associated with an increased risk of ICH in a dose-dependent manner[33]. Based on eight case-control studies, Ariesen et al. reported that moderate alcohol consumption (≤56 g/d) and high alcohol consumption (>56 g/d) were associated with a crude OR of 2.05 (95% CI: 1.35 – 3.11) and 4.11 (95% CI: 2.54 – 6.65), respectively. In addition, smoking (ever smoked and current smoker) has been proposed to be directly associated with an increased risk of hemorrhagic stroke[30,36]. However a large systematic review did not find an association between ICH and smoking to be significant[33].

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial reported an increased risk of ICH in patients treated with lipid-lowering agents, particularly statin treatment[37]. However, large studies are lacking that can confirm a statistically significant association between statin treatment and an increased risk of ICH[38]. Conversely, physical activity, compared to an inactive lifestyle, has not been found to be associated with a lower risk of ICH[39].

The incidence of ICH increases with age; individuals older than 85 years have a reported incidence ratio of 9.6 compared to a reference group of persons aged 45 – 54 years, and the incidence ratio for persons below 45 is 0.1[3]. Older patients are most often affected by ICH related to arteriosclerosis or CAA, and ruptured vascular malformations are reported to be more representative of the younger ICH population[40]. Male sex is directly associated with ICH risk (risk ratio (RR) = 3.73 (95% CI: 3.28 to 4.25)[33], and is thought to be more frequently associated with non-lobar hemorrhages[13]. Asian ethnicity is known to be associated with a higher incidence of ICH compared to Caucasian, African American, and Hispanic origins (51.8 per 100 000 person-years, 95% CI: 38.8 – 69.3)[3]. A family history of a first-degree relative with ICH has been shown to be associated with an increased risk of ICH[32]. This has encouraged the search for genes associated with ICH. Gene variants that are currently known to contribute to ICH risk include APOE[32] and β-amyloid precursor protein (APP) related CAA[16].

The risk for a recurrent ICH is higher than a first-ever spontaneous ICH, with an estimated recurrence rate of around 2% per year[41,42]. The highest recurrence rate is reported within the first year following initial ICH[43]. The risk of recurrent ICH is higher in patients with lobar hemorrhage and CAA compared to those with non-lobar ICH, aggravated by the presence of multiple lobar cerebral microbleeds and cortical superficial siderosis [44-46]. Several other patient factors increase the risk of both lobar and non-lobar hemorrhage recurrence including uncontrolled hypertension[47], age[41], and ethnicity (African American and Asian population)[48].

Lifestyle modification after initial ICH is encouraged for decreasing risk of recurrence.

Oral anticoagulant drugs

The overall incidence of ICH is 24.6 per 100 000 person-years and it has not decreased over the last decades[3,49]. Primary and secondary prevention of ICH has improved, and this is reflected by the decreased incidence of hypertensive ICH in younger patients (<75 years) in high-income countries[50,51]. However, this reduction has been offset by the increased incidence of ICH related to the greater use of oral anticoagulant drugs (OAC), including vitamin-K antagonists (VKA) and non-vitamin K oral anticoagulants (NOAC)[50], especially in high-income countries and in aging populations[52-54]. Currently, the overall global trend shows that NOAC is used more frequently than VKA (60% vs 40%), and that this proportion is larger in high income countries[55].

The shift of OAC choice from VKA to NOAC is well-documented in the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) study[55]. This study aimed to prospectively determine choice of OAC treatment in patients with newly diagnosed atrial fibrillation in 35 countries. The study was undertaken to analyze changes in the physician's primary choice of OAC drug since the introduction of NOAC. Since its introduction, treatment with NOAC drugs has augmented dramatically due to ease of administration, fewer food and drug interactions and a more favorable side effect profile compared to VKA[55,56]. However, severe renal dysfunction and certain cardiac conditions, including mechanical valves, still favor VKA treatment.

Ischemic stroke prevention with OAC drugs is the mainstay of treatment in patients with non-valvular atrial fibrillation. As previously mentioned, the use of NOAC over VKA is increasing at a rapid pace. The paradigm shift of OAC choice is supported by the findings of a meta-analysis[57] that included patients with atrial fibrillation from the following trials: the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY)[58], The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)[59], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[60], and The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF–TIMI 48)[61] trials. The meta-analysis demonstrated a significant reduction in the number of strokes in patients treated with NOAC compared to VKA[57]. The decrease in strokes was mainly attributed to a reduction in hemorrhagic stroke cases (RR = 0.49), as NOAC was non-inferior to VKA in the reduction of ischemic stroke cases. Several

subsequent studies have demonstrated a similar reduction in ICH risk in patients taking NOAC compared to VKA[62-64].

Treatment with oral anticoagulant drugs is effective in reducing the risk of ischemic stroke in patients with non-valvular atrial fibrillation[65]. However, treatment with oral anticoagulant therapy is in itself a risk factor for ICH, especially in the elderly population[66-68]. The mechanism behind the increased rate of ICH related to OAC treatment is rather ambiguous as it is doubtful that oral anticoagulants induce vascular injury or inhibit vascular repair. It is postulated that OAC may exacerbate subclinical hemorrhages (including CMBs) leading to clinically significant bleeds, especially in elderly persons with extensive WMLs, other degenerative vasculopathies and significant risk factors[66].

The absolute risk of ICH associated with OAC use is approximately 0.1 – 0.6% per patient-year of OAC treatment, constituting the most devastating side effect of OAC use[58,69,70]. Oral anticoagulant therapy is associated with larger hemorrhage volumes, hematoma expansion (HE) (≥33% from baseline), and worse clinical outcomes compared to spontaneous ICH without anticoagulant treatment[71-74]. Purrucker et al. reported that the frequency of HE in NOAC patients is 38%[72]. A recent meta-analysis showed a similar HE frequency for ICH related to VKA[75]. In spontaneous ICH, hematoma expansion most commonly occurs within the first 3 hours following hemorrhage[76]. However, in OAC-related ICH, the time window for hematoma expansion is considered greater as hemostasis is altered[66]. It is therefore pertinent to normalize anticoagulant activity as soon as possible following ICH to diminish hematoma expansion. Figure 3 illustrates hematoma expansion following spontaneous intracerebral hemorrhage.

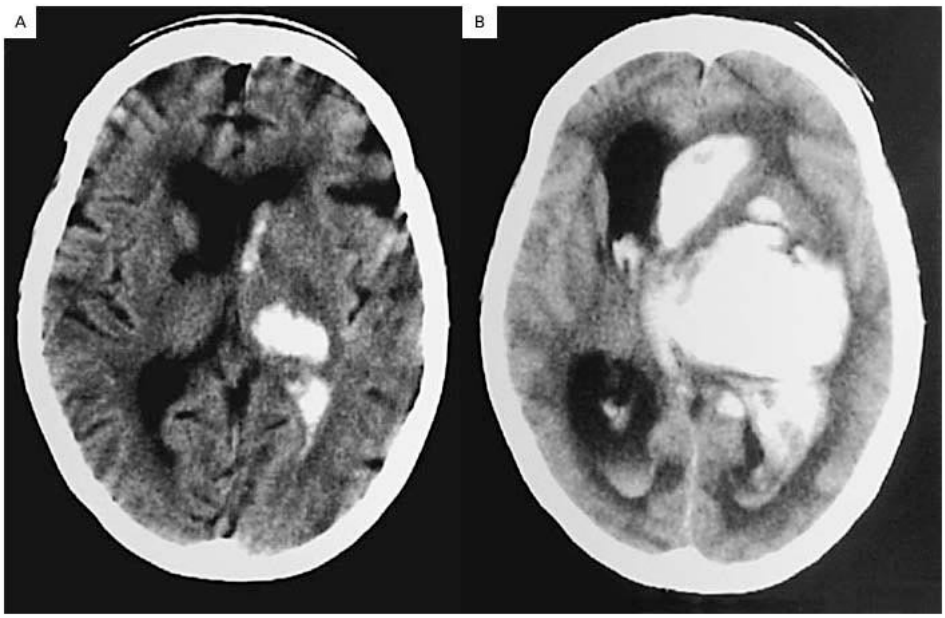


Figure 3. Computed tomography (CT) images illustrating hematoma expansion following spontaneous intracerebral hemorrhage.
The first CT scan (A) was obtained 1 hour after the patient presented with neurological symptoms. Scan B was obtained 6 hours after symptom presentation showing substantial expansion of the hematoma. Reprinted from A. I. Qureshi, et al. N Engl J Med. 2001 May 10; 344 (19): 1450-60. doi: 10.1056/NEJM200105103441907., with permission from Massachusetts Medical Society.

In clinical practice, monitoring the international normalized ratio (INR) serum levels in an outpatient or inpatient setting in patients taking VKA is straightforward as this blood test is readily available. Treatment with VKA requires frequent monitoring of INR levels to maintain a therapeutic target range. Unlike VKA drugs, NOACs do not require regular blood tests to determine serum drug levels. In the vast majority of emergency rooms, testing for anticoagulant activity in patients taking NOAC is not as straightforward or readily available as is testing for VKA activity. For those taking NOACs, time of last drug intake may be unknown and obtaining specific drug levels may be necessary in certain circumstances. Several acute situations could potentially occur that would require the assessment of NOAC plasma levels, for example, in determining whether a patient with acute ischemic stroke could be eligible for intravenous thrombolysis, or when considering NOAC reversal in patients with ICH or other major bleedings. Non-specific routine coagulation tests (Prothrombin time (PT), INR, activated partial thromboplastin time (aPTT)) can be employed in the acute setting but will only provide qualitative information on NOAC activity and does not entirely reflect the extent of anticoagulation[77]. To determine quantitative plasma levels of dabigatran, diluted

thrombin time, ecarin clotting time, or ecarin chromogenic assay can be employed[77]. In addition, chromogenic anti-Xa assays determine plasma levels of factor Xa inhibitors[78], although these specialized assays may be time consuming if they are not routinely analyzed in acute settings. Table 2 displays suggestions for laboratory measurements of NOACs depending on the availability of specialized assays.

As previously mentioned, it is known that OAC-ICH is associated with more severe strokes and worse patient outcome compared to non-OAC-ICH. However, there are conflicting reports on whether NOAC-ICH and VKA-ICH have similar hemorrhage volumes, frequency of hematoma expansion, mortality, and neurological functional outcome.

Table 2. Suggestions for laboratory measurement of non-vitamin K oral anticoagulants

Drug	Clinical objective			
	Exclude clinically relevant* drug levels		Exclude clinically relevant* drug levels when specialized assays are available	
	Suggested Test	Interpretation	Suggested Test	Interpretation
Dabigatran	TT, aPTT	Normal TT excludes clinically relevant levels Prolonged TT does not discriminate between clinically important and insignificant levels Normal aPTT usually excludes clinically relevant levels, if a sensitive reagent is used.	Dilute TT, ECT, ECA	Normal result probably excludes clinically relevant levels
Apixaban, edoxaban, or rivaroxaban	None	Normal PT and aPTT do not exclude clinically relevant levels	Anti-Xa	Absent chromogenic anti-Xa assay activity probably excludes clinically relevant levels

Anti-Xa = anti–factor Xa; aPTT = activated partial thromboplastin time; PT = prothrombin time; TT = thrombin time.
* "Clinically relevant" refers to NOAC levels that may contribute to bleeding or surgical bleeding risk. The International Society on Thrombosis and Hemostasis recommends consideration of anticoagulant reversal for patients with serious bleeding and a NOAC level >50 ng/mL, and for patients requiring an invasive procedure with high bleeding risk and a NOAC level >30 ng/mL. The minimum NOAC level that may contribute to bleeding or surgical bleeding risk is unknown[79].

Modified from Tomaselli et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants, Journal of the American College of Cardiology 2017. Vol 70. Issue 24. Page 3042 – 3067, with permission from Elsevier, and, from Steiner et al. Non-vitamin K Oral Anticoagulants Associated Bleeding and Its Antidotes. Journal of Stroke 2018;20(3):292-301 with permission from Korean Stroke Society under the terms of the Creative Commons Attribution Non-Commercial License.

Oral anticoagulant reversal therapy

In 2019, the European stroke organisation (ESO) issued new guidelines regarding hemostatic treatment following OAC-ICH[80]. The guidelines have strongly recommended the use of vitamin-K and prothrombin complex concentrate (PCC) for the reversal of vitamin-K antagonist (VKA) activity. The use of direct antidotes

for non-vitamin K oral anticoagulant (NOAC) related ICH is strongly recommended with idarucizumab for dabigatran-related hemorrhages and with andexanet alfa for factor Xa inhibitor (apixaban and rivaroxaban) related hemorrhages. A weak recommendation was given for the use of high-dose PCC (50 IU/kg) for edoxaban-related hemorrhages as well as for apixaban and rivaroxaban if direct antidotes are unavailable. These recommendations are based on low quality of evidence due to the absence of RCTs comparing different reversal strategies, partly due to ethical reasons. Figure 4 summarizes ESO's recommendations on the reversal of OAC drugs.

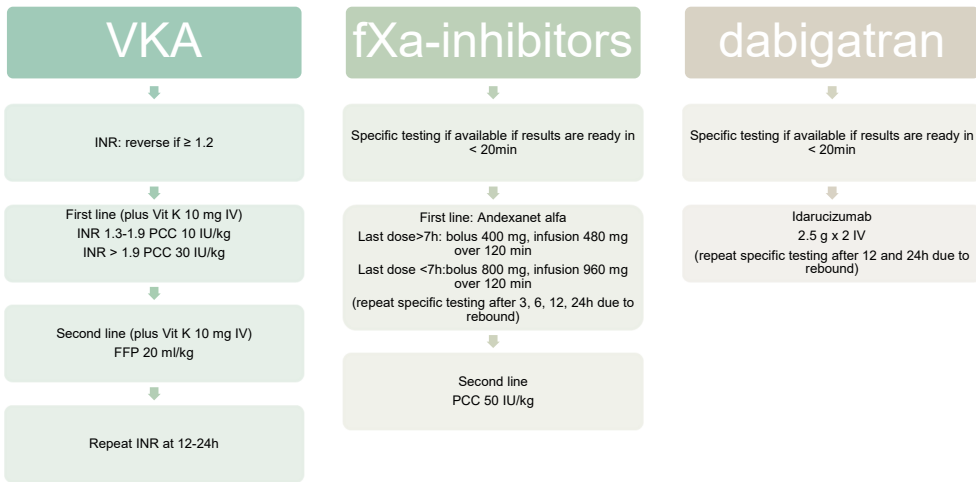


Figure 4. European Stroke Organisation guidelines on reversal of oral anticoagulants in acute intracerebral hemorrhage.
Reproduced and reprinted from Christensen H, et al. European Stroke Journal. 2019; Vol. 4(4):294-306. under the terms of the Creative Commons CC-BY license, with permission from SAGE Publications.

Early administration of hemostatic therapy could inhibit HE, but the benefit of this measure on clinical outcome is uncertain[81,82]. In addition, the effect of PCC on attenuating hematoma growth in OAC-ICH is not well established and few publications exist regarding PCC use in OAC-ICH related to NOAC drugs[72,83,84].

Outcome studies comparing PCC with no treatment following VKA-ICH are scarce, and previous studies report that reversal with PCC is not associated with a more favorable outcome[85]. However, these results are conflicting as another publication demonstrated lower case-fatality in patients receiving PCC compared to no reversal treatment following VKA-ICH[86].

Reversal of the anticoagulant effect of dabigatran with idarucizumab first gained European approval by the European Medicines Agency (EMA) in 2015[87]. Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran and reverses its anticoagulant effect within minutes[88]. To reverse the effect of dabigatran, two doses of 2.5 g (total 5 g) of idarucizumab are administered no more than 15 minutes apart. The Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE-AD) trial reported a 30-day mortality rate of 16.4% in patients with intracranial hemorrhage (53 ICH, 39 subdural, and 26 subarachnoid hemorrhages)[88]. Data on HE in ICH patients were unavailable. Studies on mortality and functional outcome comparing the use of idarucizumab to PCC are non-existent. Studies on the effect of idarucizumab on outcome following ICH are restricted to smaller retrospective studies and reports on bleeding complications in general, including few patients with intracranial hemorrhage and even fewer with ICH[88-90].

Published in 2017, the Unactivated Prothrombin Complex Concentrates for the Reversal of Anti-Factor Ten Inhibitors (UPRATE) trial evaluated hemostasis rates following administration of four factor (4F)-PCC in patients who had been taking factor Xa inhibitors (rivaroxaban or apixaban) and had major bleeding (70% ICH)[91]. A hemostasis rate of 69.1% was found. The German-Wide Multicenter Analysis of Oral Anticoagulation-Associated Intracerebral Hemorrhage II (RETRACE-II) study and an additional study compared observational data on PCC vs no PCC but found no significant effect on HE or outcome in patients with NOAC-ICH[72,92]. Despite these results, studies have shown normalization of coagulation parameters after the administration of 37.5 – 50 IU/kg 4F-PCC in healthy individuals treated with factor Xa inhibitors and edoxaban, but not dabigatran[93-95]. Importantly, however, a recent study published in 2020 demonstrated that 4F-PCC did not normalize thrombin generation in vitro at inhibitor levels ≥ 75 ng/ml and that andexanet alfa allowed for immediate restoration of thrombin generation to normal levels over a broad range of factor Xa inhibitor concentrations[96].

Treatment with andexanet alfa reduces factor Xa inhibitor activity. In the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) trial, 82% of patients received good or excellent hemostatic effect following treatment with andexanet alfa[97]. Patients treated with andexanet received a bolus dose over a period of 15 – 30 minutes, followed by a 2-hour infusion. The dosing protocol in the ANNEXA-4 trial consisted of low dose (rivaroxaban >7h since last drug intake or apixaban: 400 mg bolus and 480 mg infusion) and high dose (rivaroxaban ≤7h since last drug intake or edoxaban or enoxaparin: 800 mg bolus and 960 mg infusion) approaches depending on specific NOAC drug and/or last known drug intake. A recent retrospective study compared HE and clinical outcomes using data on ICH patients from the ANNEXA-4 trial and RETRACE-II, that compared ANNEXA-4 patients receiving andexanet alfa with RETRACE-II patients who were treated with usual care (PCC). This study reported that HE was less frequent in patients treated with andexanet compared to patients treated with

usual care (ICH vol change 7 ml less in the ANNEXA-4 group) despite having similar initial ICH volume (13.6 cm^3 vs 16.1 cm^3, respectively). However, clinical outcomes (in-hospital mortality and 30-day mRS) were similar[98].

As previously mentioned, guidelines concerning OAC reversal therapy after OAC-ICH are based on weak evidence and further studies are required to evaluate the effects on prognosis this treatment intervention may provide.

Antiplatelet drugs

Antiplatelet agents refer to different drugs possessing similar antithrombotic and anti-aggregative properties, including, but not limited to, acetylsalicylic acid, clopidogrel, ticagrelor, and dipyridamole. The most commonly prescribed antiplatelet agent, acetylsalicylic acid, also known as aspirin, effectively reduces the risk of cardiovascular disease, including stroke, when used as secondary prevention. It also reduces the risk of stroke in select patients at high risk of cardiovascular disease, who coincidingly have a low bleeding risk profile[99]. Historically, healthy individuals above the age of 70 were prescribed aspirin as a means of primary prevention of cardiovascular disease, a practice which is discredited today following the results of the Aspirin in Reducing Events in the Elderly (ASPREE) trial[100]. Supported by the A Study of Cardiovascular Events in Diabetes (ASCEND) trial, the use of aspirin as a means of primary prevention of cardiovascular disease in patients with or without diabetes mellitus is discouraged as the risk for major bleeding outweighs the cardiovascular benefits of aspirin[99,101]. Instead, it is recommended that treating physicians identify other means of decreasing cardiovascular risk, for example blood pressure control, smoking cessation, daily exercise, diet modifications, or the use of statins.

Patients treated with antiplatelet drugs are at increased risk of ICH[102], with an absolute risk increase of 12 events per 10 000 persons[103]. The risk of ICH associated with antiplatelet use is far from negligible also considering the vast number of patients treated with these drugs and the resultant implications of stroke[104]. Elevated cardiovascular risk necessitating the reinstatement of an antiplatelet drug after an ICH event is often discussed after the acute event has unfolded. This prompted the Restart or Stop Antithrombotics Randomized Trial (RESTART) that investigated the ICH recurrence rate in patients who were reintroduced to aspirin versus avoidance. The RESTART trial showed that the reinstatement of antiplatelet therapy was not associated with increased risk of repeat ICH that could surpass the benefit of reinstating the drug[105]. As participants were more commonly prescribed monotherapy with an antiplatelet, the risk of ICH recurrence in patients requiring dual antiplatelet treatment was not reported.

There is currently no hemostatic therapy proven to be clinically effective in patients with antiplatelet-related ICH. The Platelet transfusion versus standard care after acute intracerebral hemorrhage associated with antiplatelet therapy (PATCH) trial was designed to determine whether platelet transfusions would benefit this patient group. However, results from this trial showed that platelet transfusions are harmful in patients with antiplatelet-ICH who are not undergoing emergency surgery and should be avoided[106]. The Tranexamic acid for hyperacute primary intracerebral hemorrhage (TICH-2) study was a phase III, prospective, double-blind, randomised placebo-controlled trial designed to determine whether the administration of tranexamic acid following ICH was associated with a more favourable outcome compared to a placebo. The TICH-2 trial found that tranexamic acid given within 8 hours of symptom onset was not associated with improved functional outcome at 3 months following spontaneous ICH[107]. A separate analysis was performed to determine the effects of tranexamic acid on antiplatelet-related ICH. Tranexamic acid significantly reduced hematoma expansion in both patients with and without antiplatelet treatment prior to ICH compared to placebo (HE 27.2% vs 34.5%, respectively), but outcome was unchanged[108]. The TICH-3 trial is currently ongoing and aims to randomize the use of tranexamic acid and placebo and shorten the inclusion time of symptom onset to baseline imaging from 8h to 4.5h. It will also study the effect of tranexamic acid on early death and 6 month functional outcome[109]. The Factor Seven for Acute Hemorrhagic Stroke (FAST) trial investigated the effectiveness of recombinant factor VIIa on outcome and HE after spontaneous ICH. This trial included a small proportion of patients with antiplatelet-related ICH and found no outcome benefit of factor VIIa despite reduced hematoma growth in patients receiving the intervention drug[110]. Since then, the Recombinant Factor VIIa (rFVIIa) for Hemorrhagic Stroke Trial (FASTEST) has been developed that aims to administer recombinant factor VIIa more rapidly than the FAST trial, within 120 minutes, to determine whether 180-day patient outcome can improve versus placebo and standard therapy alone[111]. Desmopressin has previously been studied as a hemostatic treatment in patients with antiplatelet-related ICH, although these studies were small, non-randomized, and did not have a placebo-controlled arm. Thus, the safety of desmopressin in this patient group and its treatment benefit are uncertain[112-115]. The Desmopressin for reversal of Antiplatelet drugs in Stroke due to Haemorrhage (DASH) trial is a phase II double-blind randomised controlled feasibility trial investigating the effect of administering desmopressin to patients with antiplatelet-associated ICH to attenuate HE[116]. This trial is currently ongoing as greater interest has developed in the pro-hemostatic effect of desmopressin when used as hemostatic treatment for other medical conditions.

Outcome after intracerebral hemorrhage

Stroke is a leading cause of global death and disability. Since the World Health Organization (WHO) began classifying stroke as a disease of the nervous system rather than a disease of the of the circulatory system, neurological disorders have become the leading main group of disability adjusted life years (DALYs) and the second largest group in terms of global death[117]. Stroke accounts for nearly two thirds of all deaths related to neurological disease[117], and the latest WHO ICD-11 terminology recognizing stroke as its own entity emphasizes the burden of stroke as a major disease[118].

Amongst all stroke subtypes, intracerebral hemorrhage has the highest lethality both in the short-term and long-term[119]. The reported 30-day mortality rate for spontaneous intracerebral hemorrhage is 40% (range 13.1 – 61)[3]. Previous studies show that approximately half of the total ICH population will die within the first year after ICH[119,120]. In surviving patients, approximately 12 – 39% are functionally independent after ICH[3]. Survivors of ICH more often than not report unmet rehabilitation needs one year post stroke regarding dependency on activities of daily life (ADL), depression, pain, and self-perceived health[121]. Compared to ICH unrelated to antithrombotic drugs, intracerebral hemorrhage associated with OAC use in particular is associated with increased death and dependency[72,122]. In contrast, several studies show that antiplatelet-related ICH is thought to have similar outcomes to patients who are not taking antithrombotic medication prior to ICH[73,123-126], although other studies have demonstrated worse outcomes[122,127,128]. Given that antiplatelet drugs are associated with higher risk of ICH compared to the general population, it is important to delineate outcome in this patient group considering the liberal use of these drugs in clinical practice.

Several prognostic factors are associated with poor outcome following ICH. Hemorrhage volume has a strong correlation with death and disability[129]. Higher mortality rates are observed with hemorrhage volumes on baseline CT that are equal to or greater than 30 cm^3. In patients with hematoma volumes greater than 60 cm^3, a 93% mortality rate is reported along with an OR of 4.5 as an independent predictor of severe disability or death[129,130]. Other predictors of increased death rate and functional dependency related to ICH are presenting level of consciousness after acute stroke[129,131], intraventricular hemorrhage (IVH)[130], and hematoma expansion[71]. In addition, a number of other radiological signs have been found to predict hematoma expansion and/or poor functional outcome including spot sign, blend sign, black hole sign, island sign, and hypodensities[132].

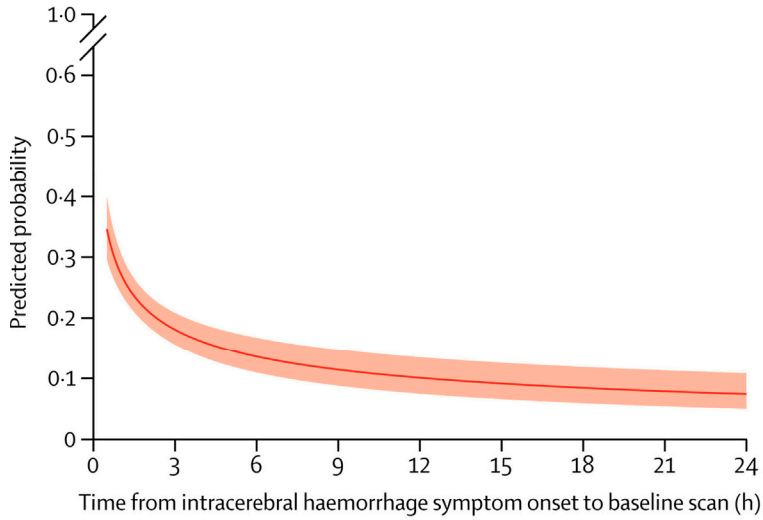


Figure 5. Predicted probability of intracerebral hemorrhage growth > 6ml.
Predicted probability by time from symptom onset to baseline imaging. Reprinted from Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, et al. The Lancet Neurology. 2018;17:885-894. doi: 10.1016/S1474-4422(18)30253-9, under the terms of the Creative Commons CC-BY license, with permission from Elsevier.

A prediction model for the growth of spontaneous ICH was recently published by Al-Shahi Salman et al. Predictors of hematoma expansion, defined as a >6 ml absolute volume increase on repeat imaging, were OAC and antiplatelet use, time from symptom onset to baseline imaging (growth declined after 0.5 – 3 h, Figure 5), ICH volume at baseline imaging (growth plateaued at 75 ml), and CT angiography spot sign (Figure 6)[76]. Spot sign on CT angiography only slightly improved the C-index of the prediction model. As hematoma expansion is directly associated with an increased risk of death in all ICH patients, identifying patients at risk for hemorrhage expansion is pertinent so as to allow for the swift implementation of relevant interventions, including treatment with an OAC reversal agent and other acute care measures.

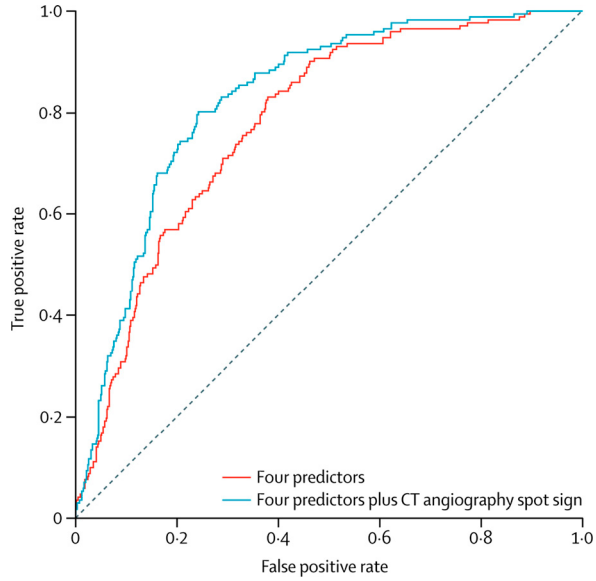


Figure 6. Predicted probability of intracerebral hemorrhage growth > 6ml.
Receiver operating characteristic curves used the four predictors outlined in the previous paragraph, and four predictors plus CT angiography spot sign. Reprinted from Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, et al. The Lancet Neurology. 2018;17:885-894. doi: 10.1016/S1474-4422(18)30253-9, under the terms of the Creative Commons CC-BY license, with permission from Elsevier.

Treatment recommendations aiming to decrease mortality and morbidity exist for the management of acute ICH. These include, but are not limited to, acute blood pressure lowering, OAC reversal, general inpatient care measures (including for example glucose and temperature management, thromboprophylaxis, treatment of acute seizures), and neurosurgical interventions (including neuroinvasive monitoring, external ventricular drainage, hematoma evacuation, decompressive craniotomy)[133]. The Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial and the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) were designed to determine whether early intensive blood pressure lowering following ICH would be associated with better outcome. However, both trials failed to show an improved outcome[134,135]. Since then, several meta-analyses[136,137] and post-hoc analyses[138,139] based on these two trials have emerged that have helped guide current recommendations to include early initiation of systolic blood pressure lowering to a target range of 130 – 140 mmHg with careful titration to ensure smooth and continuous blood pressure control[133]. Studies also found that acute systolic blood pressure lowering below 130 mmHg may be detrimental to a favourable outcome[135,140].

An acute care bundle (the ABC care bundle) was recently proposed in an intervention study to improve speed of delivery, access to acute care, and decrease case fatality following ICH[141]. The ABC care bundle includes the following

treatment strategies: rapid anticoagulant reversal within 90 minutes of hospital admission, early intensive systolic blood pressure lowering to a target of 130 to 140 mmHg (within 60 minutes after hospital admission) for patients arriving within 6 h of symptom onset, and immediate neurosurgical referral for those patients who meet the criteria for such an intervention. Despite certain limitations, including study design, in order to test for a causal relationship between the care bundle and lower case fatality, this study demonstrated significantly lower mortality rates in patients receiving the care bundle versus care before implementation of the bundle.

Recent focus has been placed on novel treatment strategies for improving outcome following ICH. One of such interventions presented in the CLEAR III trial is intraventricular fibrinolysis aimed at removing IVH with alteplase in patients with severe intraventricular involvement and a routine external ventricular drain, as IVH is a direct predictor of mortality and functional dependency[142]. Unfortunately, the CLEAR III trial did not manage to show any substantial improvement in functional outcome in patients receiving this intervention, although mortality was improved. Yet, a recent meta-analysis based on pooled data from two RCTs and seven observational studies showed that intraventricular fibrinolysis was significantly associated with improved functional outcome at 6 months, especially in patients receiving treatment within 48 hours[143].

Another intervention aimed at improving functional outcome was whether minimally invasive catheter hematoma evacuation followed by thrombolysis could reduce the intracerebral hemorrhage clot size (the MISTIE III trial)[144]. This trial, however, did not show any improvement in functional outcome.

Prognostic models on patient outcome have attempted to identify patients at the highest risk of a poor prognosis, the most common model being the ICH score that allows risk stratification on presentation with ICH (Table 3)[145,146]. Prognostication early after ICH is often desired by physicians and families. Existing prognostic models may be useful tools for prognostication purposes but are biased since they do not account for the influence of withdrawal of support and early limitation-of-care decisions. Applying prognostic models for withdrawal of care may therefore lead to a self-fulfilling prophecy of a poor outcome[147-149]. Withdrawal of care orders have been identified as the most potent predictors of death following ICH. This is presumed to be due to an overestimation of poor outcome based on information present at the time of patient admission, which in the case of ICH, are usually neurologically devastating features[149-151]. Current guidelines therefore recommend an early aggressive treatment approach in ICH patients without limitation-of-care orders, and to postpone care limitations in patients without a limitation-of-care order until at least 48 hours after hospitalization for ICH regardless of results derived from prognostic models[152]. The functional outcome in patients with primary intracerebral hemorrhage (FUNC) score is another valid acute clinical score based on risk stratification that was developed to predict the likelihood of functional independence after ICH[153]. This score can help provide guidance in clinical

decision-making but may also be subject to withdrawal of care bias and should thus be used with this knowledge in mind.

Table 3. Determination of the intracerebral hemorrhage (ICH) Score.
In the University of California, San Francisco (UCSF) cohort, 30-day mortality rates for patients with ICH Scores of 0, 1, 2, 3, 4, and 5 were 0%, 13%, 26%, 72%, 97%, and 100% respectively. No patient with an infratentorial ICH had a hematoma volume ≥30 cm, and thus a score of 6, though the authors assume 100% mortality.[146]

Component	ICH Score Points
GCS score	
3–4	2
5–12	1
13–15	0
ICH volume, cm^3	
≥30	1
<30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age, y	
≥80	1
<80	0
Total ICH Score	**0–6**

GCS score indicates GCS score on initial presentation (or after resuscitation); ICH volume, volume on initial CT calculated using *ABC*/2 method; and IVH, presence of any IVH on initial CT.

Intracerebral hemorrhage in Sweden

The Swedish Stroke Register, Riksstroke, provides yearly reports on stroke in Sweden (see separate section in Subjects and methods for more details regarding this register). In 2020, approximately 2 800 ICH cases were registered in Riksstroke, accounting for nearly 13% of stroke cases in Sweden. The absolute number of ICH in Sweden has been stable since 2011 for reasons similar to those mentioned in other sections in the introduction of this thesis. Similar to international trends, the number of OAC-ICH are increasing and are beginning to represent a larger proportion of ICH cases. In 2020, OAC-ICH represented 26% of ICH cases, whereof 71% were associated with use of NOAC and the remainder were related to VKA use (Figure 7)[154].

In 2020, 52% (353/669) of all OAC-ICH patients received reversal treatment. Remarkably, only 44% of patients with factor Xa inhibitors received treatment with a reversal agent[154]. Current Swedish guidelines published in 2019 by the Swedish National Board of Social Affairs and Health include recommendations similar to ESO guidelines for the reversal of VKA-ICH and dabigatran-ICH with 4F-PCC and vitamin-K, and idarucizumab, respectively[154]. The reversal of factor Xa inhibitor activity with direct antidote andexanet alfa is given research priority. A further recommendation for the use of 4F-PCC is not specified for the reversal of factor Xa inhibitor activity if andexanet alfa is not given.

To date, patient characteristics, outcome after antithrombotic-related ICH, including OAC and antiplatelet drugs, and the treatment effect of OAC reversal therapy on prognosis has not been studied in the Swedish population, and few international publications exist.

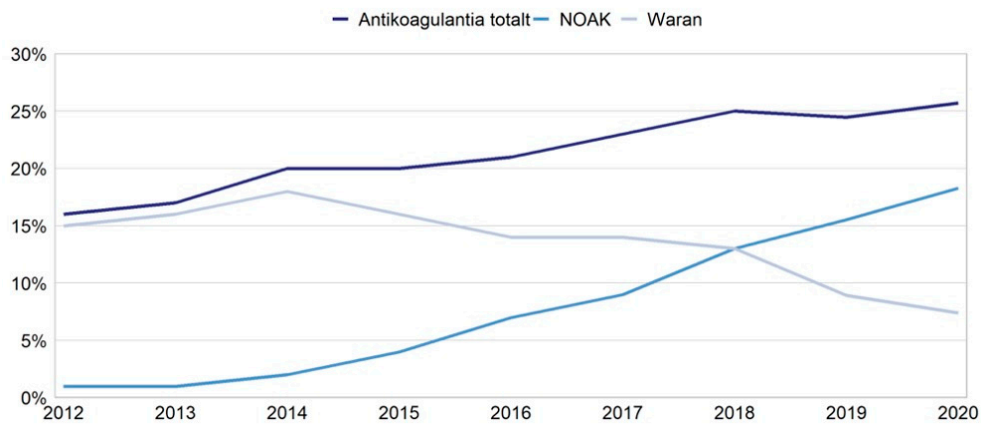


Figure 7. Percentage of patients with intracerebral hemorrhage related to oral anticoagulant drugs between 2012 and 2020. Antikoagulantia totalt = total anticoagulant, NOAK = Non-vitamin K oral anticoagulant (NOAC), Waran = Warfarin. Reprinted with permission from Riksstroke.

Aim of the thesis

The overall aim of this thesis is to advance knowledge regarding functional and survival outcomes related to intracerebral hemorrhage in a large unselected Swedish stroke cohort. Furthermore, we aim to identify patient factors associated with receiving oral anticoagulant reversal therapy and to delineate the effect of this treatment on prognosis. Patient outcome following antithrombotic-related ICH based on data from the Swedish Stroke Register (Riksstroke) has not been studied prior to this thesis.

The specific aims were:

Paper I	To describe patient characteristics related to survival and functional outcome at 90 days following OAC-ICH in patients with ongoing VKA treatment compared to patients taking NOAC drugs.
Paper II	To delineate mortality and functional outcome at 90 days following OAC-ICH in patients who received OAC reversal therapy compared to patients who did not receive reversal therapy.
Paper III	To analyse patient characteristics in those affected by ICH during ongoing treatment with antiplatelet drugs, OAC drugs, and without antithrombotic treatment, and to compare functional outcome and all-cause mortality at 90 days between drug categories.
Paper IV	To define patient factors related to receiving OAC reversal treatment following OAC-ICH, and to recognize temporal changes in the proportion of patients receiving OAC reversal treatment.

Subjects and methods

Study materials

The studies included in this thesis are all observational in nature and are primarily based on data derived from the Swedish Stroke Register, Riksstroke.

The Swedish Stroke Register (Riksstroke)

Founded in 1994, Riksstroke is a hospital-based quality register for stroke care in Sweden[155]. Riksstroke provides an approximate 90% nationwide coverage of all stroke cases in Sweden with approximately 25 000 new stroke cases registered per year. Riksstroke provides a unique source of data on acute stroke and follow-up after stroke. The primary intention of Riksstroke is to ensure continuous quality improvement in the management of stroke patients, both acute and long-term, in Sweden. Considering Riksstroke's broad coverage of stroke cases, it serves as a valuable source of research data. To date, several research projects have incorporated data from Riksstroke both in Sweden and internationally[156].

Riksstroke provides data on patient demographics, acute stroke care management and processes, as well as outcome data including ADL function at discharge. All patients registered in Riksstroke in the acute setting are contacted at 3-months and 12-months post stroke and are invited to complete a follow-up questionnaire covering aspects such as their perceived expectations and experience of their healthcare, functional status and living conditions post stroke.

Riksstroke provides yearly reports summarizing important aspects of stroke characteristics and care throughout Sweden with the aim of supporting consistent quality of healthcare in both inpatient and outpatient settings. Riksstroke aims to serve as a follow-up instrument for the stroke care guidelines provided by the National Board of Health and Welfare in Sweden.

The Swedish Causes of Death Register

Mortality status and date of death were provided by the Swedish Causes of Death Register, a register regulated by the National Board of Health and Welfare in Sweden. The register provides almost complete coverage of deaths of Swedish citizens[157].

The Swedish Prescribed Drug Register

Paper III used data from the Swedish Prescribed Drug Register, a register founded in 2005 by the Swedish government[158]. This register contains data on the following: age, sex, prescription dates, and information on dispensed drugs (date, item, amount, dosage, and more). Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system[159]. In Paper III, data on whether a drug was dispensed to a patient or relative was obtained for the following ATC codes, provided that the drug was dispensed from a Swedish pharmacy up to 12 months prior to the ICH event: B01AC06 acetylsalicylsyra, B01AC04 clopidogrel besilate, B01AC07 dipyridamol, B01AC24 ticagrelor, B01AA03 warfarin, B01AE07 dabigatran, B01AF01 rivaroxaban, and B01AF02 apixaban.

Study participants and outcome assessments

All study participants in this thesis were ≥ 18 years of age and were registered in Riksstroke during their hospital stay with the diagnosis of spontaneous intracerebral hemorrhage (ICD-I61). In all studies, data on baseline and stroke characteristics were obtained from Riksstroke's acute stroke questionnaire. Data from Riksstroke's 3-month follow-up questionnaire were acquired to analyse patient functional status in Papers I, II, and III. In all studies, mortality status was obtained from the Swedish Causes of Death register. Table 4 provides a brief overview of the design of the individual studies presented in this thesis.

Table 4. Overview of intracerebral hemorrhage study design for each of the papers included in this thesis.

	N*	Year			Drug			Main outcome		
		2012-2016	2017	2017-2019	All ICH	OAC	Reversal	Mortality	Functional	Predictors
Paper I	2 483	■				■		■	■	
Paper II	572		■			■	■	■	■	
Paper III	13 291	■			■			■	■	
Paper IV	1 902			■		■	■			■

Table includes number of participants (n), cohort year, specific drug included in study, and main outcomes (mortality outcome, functional outcome, predictors of OAC reversal treatment). * = number of participants. ICH = intracerebral hemorrhage, OAC = oral anticoagulant. Table inspired by Sennält S, Stroke in the Long Term, page 43. Lund University, Faculty of Medicine Doctoral Dissertation Series 2020:89.

Paper I

Paper I included patients with either VKA-ICH or NOAC-ICH registered in Riksstroke between 2012 and 2016. Prior to analysis, we excluded six ICH patients who were registered as simultaneously taking both VKA and NOAC (assumed registration error), 124 patients who were concurrently taking OAC and anti-platelets, and 10 patients where data on NOAC type were missing. The NOAC drugs

taken by patients in this study prior to their ICH event were apixaban, rivaroxaban, or dabigatran.

The primary outcome variables were functional status at 90 days and all-cause mortality status at 7, 30 and 90 days for patients with NOAC-ICH or VKA-ICH.

Paper II

Paper II included patients with OAC-ICH registered in Riksstroke between 1 January 2017 and 31 December 2017. Patients were anticoagulated with either VKA, apixaban, rivaroxaban or dabigatran prior to their ICH event. Data on the method of OAC reversal treatment were obtained from Riksstroke acute stroke questionnaire.

Primary outcome variables were all-cause mortality and functional status at 90 days. Prognosis in patients who received OAC reversal treatment was compared to prognosis in patients who did not receive OAC reversal treatment.

Paper III

All patients with ICH registered in Riksstroke between 1 January 2012 and 31 December 2016 were included in this study. Patients were categorized according to antithrombotic drug treatment prior to ICH event. Three categories were defined according to antithrombotic drug status: 1) OAC, including NOAC (apixaban, rivaroxaban, dabigatran) and VKA drugs 2) Antiplatelet, including acetylsalicylic acid (ASA), clopidogrel, dipyridamole, and ticagrelor 3) No antithrombotic treatment. Primary drug adherence was defined as a patient filling a prescription within 100 days of the index ICH. The Swedish Board of Health and Welfare linked patient-specific data from Riksstroke and the Swedish Prescribed Drug Register using Swedish personal identification numbers. This provided information on drug adherence according to the inclusion criteria and predefined drug categories.

The primary outcomes in this study were early all-cause mortality (≤24 h and 1 – 7 days), late all-cause mortality (8 – 90 days), and functional status at 90 days following ICH. Three defined patient categories (OAC, AP, no antithrombotic treatment) were compared.

Paper IV

Paper IV included patients registered in Riksstroke between 1 January 2017 and 31 December 2019, who had an oral anticoagulant-related ICH. Patients included in this study were taking an anticoagulant drug prior to their ICH event, and the following OAC drugs were included in this study: VKA, apixaban, rivaroxaban, dabigatran and edoxaban. Data on the method of oral anticoagulant reversal treatment were obtained from Riksstroke's acute stroke questionnaire.

Paper IV aimed to define baseline characteristics of patients with oral anticoagulant-related intracerebral hemorrhage, temporal changes regarding the use of OAC

reversal treatment during the study period, and to determine predictive factors associated with receiving OAC reversal treatment following ICH.

Definitions and measures

Stroke severity

The patient's presenting level of consciousness (LOC) at hospital admission based on the reaction level scale (RLS-85) was used as a proxy for stroke severity. The RLS-85 is an 8 grade LOC assessment tool that correlates well with the Glasgow Coma Scale (GCS)[160]. RLS-85 is commonly used in Sweden to assess LOC in hospital-based settings. Riksstroke refers to the RLS-85 by grouping scores into three separate categories: alert (RLS 1), drowsy (RLS 2 – 3), and comatose (RLS 4 – 8).

Prestroke functional status

Defining prestroke functional status was pertinent in all studies reported in this thesis as prestroke mRS status is unavailable in Riksstroke's acute stroke questionnaire. All studies included in this thesis define prestroke independency as a patient living independently without homecare, who is independently able to attend to dressing, toileting, and walking unassisted both indoors and outdoors. Prestroke dependency is outlined as a patient with one or more of the following characteristics: living in their own residence with homecare, residing at an assisted living facility (or comparable institution), or who is dependent on assistance with dressing, toileting, and/or mobility.

Modified Rankin Scale score

In Papers I, II, and III a validated Riksstroke algorithm was used to translate self-reported outcome variables found in Riksstroke's 3-month follow-up questionnaire into a modified Rankin Scale (mRS) score to study 90-day functional outcome[161]. The mRS score was translated by incorporating the following variables into the algorithm: dressing and toileting (independent or dependent), living conditions (living independently, living independently with home care, assisted living facility, or in-patient care), mobility (fully mobile, only mobile indoors, or fully dependent on assistance for mobility), and dependency on next of kin for support (fully dependent, partially dependent, or independent).

The final mRS scores achieved through this translation were subsequently catalogued into three separate categories: mRS score 0 to 2 were defined as functionally independent, mRS 3 to 5 were defined as functionally dependent, and mRS 6 was defined as deceased. The Modified Rankin Scale score is depicted in Table 5.

Table 5. The Modified Rankin Scale[162]

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms: able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately secere disability: unable to walk without assistance, and unable to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Reproduced from J.C. van Swieten, P.J. Koudstaal, M.C. Visser, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988. Vol 19. Issue 5. Pages 604-607, https://doi.org/10.1161/01.STR.19.5.604, with permission from Wolters Kluwer Health, Inc.

Lost to follow-up

Patients lost to follow-up were defined as those who were alive but had not returned the follow-up questionnaire, or where variables on functional status were missing to the extent that it was not possible to determine an mRS score.

Statistical Methods

All statistical analyses were performed using IBM SPSS Statistics for Mac version 24.0, 26.0, and 27.0 (IBM Corp, Armonk, New York, United States). In all studies, baseline characteristics were analysed and presented as proportions, means and medians. Independent samples t-tests and Mann-Whitney U tests were used to analyse continuous variables. In Paper III, a Kruskal-Wallis test was used to compare non-parametric data between groups. In all papers, a Chi-squared test was used to determine differences between categorical variables. A p-value of < 0.05 was considered statistically significant in all studies. The following sections describe fundamental statistical methods employed in this thesis.

Survival analysis

The incorporation of survival analysis, also known as time-to-event analysis, was performed in all studies presented in this thesis. Time-to-event analyses refer to specific methods that can be used to determine the length of time taken to the occurrence of a predefined event. All survival analyses presented in this thesis had a binary outcome defined as all-cause death over time following intracerebral hemorrhage. As survival times generally do not assume a normal distribution pattern, we applied non-parametric and semi-parametric tests including the log-rank test and the Cox proportional hazards (PH) model in our data analysis. Survival curves based on these models were plotted using the Kaplan-Meier method.

The Kaplan-Meier survival curves displayed in Papers I, II, and III plot estimated survival probabilities against time between the patient groups specified in each paper. In all studies, hypothesis testing was performed using the log-rank test to compare the survival event between the specified patient groups. The log-rank test is used for identifying significant differences in observed survival. However, it is unable to provide estimates of the differences in effect size between groups. Therefore, Cox regression was applied in Papers I, II, and III to estimate the effect size of an individual covariate by adjusting for potential confounders that are known to affect prognosis following intracerebral hemorrhage. In this way, hazard ratios (HR) could be calculated. The HR is a ratio of the hazard rates between compared groups i.e., the HR demonstrates the ratio between the chance of an event, in this case death, occurring in one patient group compared to the same event occurring in another patient group.

As the Cox PH model assumes that all patients have a similar baseline hazard function[163], Paper II required a different approach to the regression analysis as baseline hazards differed significantly between the studied groups. Stratification was used in Paper II to account for the different baseline hazards associated with OAC reversal treatment in patients who presented with different levels of consciousness at hospital admission. We assumed that the effect of the LOC covariate would differ over time considering the relationship between stroke severity and presenting LOC, and therefore the effectiveness of OAC reversal therapy would differ among different LOC categories. Thus, due to the indication of non-proportionality in mortality rates corresponding to different LOC categories, a stratified model was applied to the multivariable Cox PH model using LOC category as the stratification variable.

The fundamental assumption in the Cox PH model is that hazards are proportional across different covariates[164]. In order to determine and cope with non-proportionality the assumption of proportional hazards can be assessed by visualizing individual log-log plots of survival.

Logistic Regression

Logistic regression was applied in Papers III and IV. This method was used to model the effect of various covariates on a binary outcome. In Paper III, logistic regression was used to model the effect of several covariates on functional status 90 days following ICH. This was achieved by determining the odds ratio as an estimate of the association between the different antithrombotic treatment groups and functional dependency, based on the mRS score, by controlling for confounding factors. In Paper IV, logistic regression was used in predictive analysis to identify factors associated with increased odds of patients receiving reversal treatment as opposed to patients not receiving reversal treatment.

Multiple Imputation

In Paper I, approximately 13.5% of data regarding 90-day functional status based on estimated mRS scores were unavailable due to patients lost to 90-day follow-up. Lost to follow-up consisted of patients who were alive and had not returned the follow-up questionnaire or where variables on functional status were missing. Multiple imputation (MI) was therefore applied to estimate mRS score in patients who were lost to 90-day follow-up.

Since data on functional status were missing at random in patients lost to follow-up, data were imputed using a fully conditional specification (FCS) imputation method, which is an iterative Markov chain Monte Carlo method. Several known predictive variables available in our data that were related to functional status were included in this analysis since MI will avoid bias only if a sufficient number of variables predictive of missing values are included in the model[165]. These predictive variables included age, gender, diabetes, hypertension, previous stroke, previous transient ischemic attack (TIA), atrial fibrillation, prestroke dependency, living alone prior to ICH, and level of consciousness at hospital admission. Additionally, the predictive and imputed variables included in the MI model were mobility, dressing, toileting, living conditions prior to ICH, and dependency on next of kin for support. In this way, imputed variables required for translation into an mRS score were acquired.

Ethical considerations

Papers I, II and III were approved by the local Research Ethics Committee in Lund, Sweden (dnr 2017/529). Paper IV was approved by the Swedish Ethical Review Authority (dnr 2020-04680). The Swedish Ethical Review Authority is a public agency that serves under the Ministry of Education and began operations on the 1 January 2019, thus replacing the previous regional ethical review committees[166].

The Swedish Stroke Register (Riksstroke) employs strict ethical practices. All patients, and when necessary, next of kin, are informed of registering patient data in Riksstroke. Participation is voluntary and patients are able to opt out at any time. All studies used anonymized data and individual consent was not warranted since patients or their next of kin were informed and acknowledged that once patient data are entered into the Riksstroke register, they may be used for research purposes.

Results

Prognosis for intracerebral hemorrhage during ongoing oral anticoagulant treatment (Paper I)

Patient characteristics

Paper I included 2 483 patients with OAC-ICH registered in Riksstroke between 1 January 2012 and 31 December 2016. Patients were categorized into two groups according to prescribed OAC treatment used leading up to the ICH event. This study included 300 patients taking NOAC and 2 183 patients taking VKA prior to their ICH. Baseline characteristics were similar in both groups (Table 6). Mean age was 79 years and male sex represented 58% of the patient cohort. Patients with NOAC treatment were more often prestroke ADL dependent (37.7%) and had more often suffered a previous stroke (35.3%) compared to patients on VKA. The proportion of missing data in the entire patient cohort varied between 0 and 2% for all variables except prestroke dependency (3.6%) and smoking (20.3%). The National Institutes of Health Stroke Scale (NIHSS) score was not included in the baseline data due a substantial number of missing cases.

Table 6. Baseline characteristics of 2 483 patients with non-vitamin K oral anticoagulant-related intracerebral hemorrhage or vitamin K antagonist-related intracerebral hemorrhage.

Variables	NOAC-ICH (n=300) n (%)	VKA-ICH (n=2183) n (%)	p-value
Demographics			
Mean age	79.0 (8.4)*	79.1 (8.8)*	0.85
Sex (male)	175 (58.3)	1270 (58.2)	0.96
Living alone	146 (48.7)	954 (43.7)	0.11
Prestroke dependent	113 (37.7)	651 (29.8)	0.003
Vascular risk factors			
Diabetes	61 (20.3)	467 (21.4)	0.69
Hypertension	228 (76.0)	1655 (75.8)	0.96
Atrial fibrillation	254 (84.7)	1798 (82.4)	0.32
Previous stroke	106 (35.3)	571 (26.3)	0.001
Previous TIA	22 (7.3)	182 (8.3)	0.57
Smoker	12 (4.0)	78 (3.6)	0.03
Statins	112 (37.3)	693 (31.7)	0.10
Stroke characteristics			
Admitted to stroke unit	245 (81.7)	1743 (79.8)	0.46
Admitted to intensive care unit	40 (13.3)	220 (10.1)	0.08
Median duration of acute care (days)	8	8	0.51
Level of consciousness			0.08
Alert	161 (54.0)	1297 (60.2)	
Drowsy	80 (26.8)	465 (21.6)	
Comatose	57 (19.1)	394 (18.3)	
Discharge location			0.39
Own residence	70 (23.3)	609 (27.9)	
Assisted living facility	68 (22.7)	409 (18.7)	
Geriatric/rehab ward	37 (12.3)	291 (13.3)	
Other	9 (3.0)	51 (2.3)	
Death during hospital stay	116 (38.7)	823 (37.7)	

*Standard deviation of the mean. ICH = intracerebral hemorrhage, NOAC = non-vitamin K oral anticoagulant, TIA = transient ischemic attack, VKA = vitamin-K antagonist.

Survival

All patients were included in the survival analysis. The cumulative all-cause mortality at 7, 30, and 90 days in patients with NOAC-ICH was 31.3% (n = 94), 40.7% (n = 122), and 44.3% (n = 133), respectively. The corresponding proportions in patients with VKA-ICH was 29.1% (n = 636), 38.3% (n = 836), and 42.6% (n = 930), respectively. There was no significant difference between NOAC-ICH and VKA-ICH in all-cause mortality at 7 days (p = 0.46), 30 days (p = 0.43), or 90 days (p = 0.54) in the univariable analysis (Figure 8a).

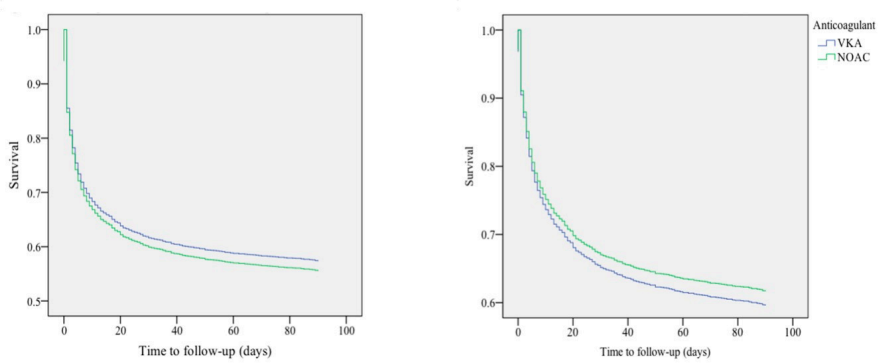


Figure 8. Kaplan Meier curves showing 90-day cumulative survival following non-vitamin K oral anticoagulant-related intracerebral hemorrhage (n = 300), and vitamin K antagonist-related intracerebral hemorrhage (n = 2 183). a) Crude model for 90-day survival (left) b) Adjusted model for 90-day survival (right). ICH = intracerebral hemorrhage, NOAC = non-vitamin K oral anticoagulant, VKA = vitamin K antagonist.

Cox regression analysis was used to determine the death rate at 90 days for patients with NOAC-ICH compared to VKA-ICH. In the crude analysis, the HR for death in patients with NOAC-ICH was 1.06 (95% CI: 0.88 – 1.27) compared to VKA-ICH patients. After adjusting for age, sex, previous stroke, and level of consciousness (stroke severity), the HR for death remained insignificant with a trend towards a more favorable survival outcome following NOAC-ICH than VKA-ICH (HR = 0.93; 95% CI: 0.78 – 1.12) (Figure 8b). Patient factors associated with a higher mortality rate following OAC-ICH were age, LOC, and previous stroke (Table 7).

Table 7. Cox regression analysis showing hazard ratios for 90-day mortality in 2 483 patients with oral anticoagulant-related intracerebral hemorrhage.

Variable	HR	95% CI		P-value
		upper	lower	
Crude model				
NOAC (VKA ref.)	1.06	0.88	1.27	0.55
Adjusted model				
NOAC (VKA ref.)	0.93	0.78	1.12	0.47
Female sex	0.91	0.80	1.03	0.14
Age	1.03	1.03	1.04	< 0.001
Level of consciousness on admission				
alert	1			
drowsy	3.50	2.99	4.09	< 0.001
comatose	12.15	10.40	14.19	< 0.001
Previous stroke	1.21	1.06	1.38	0.006

CI = confidence interval, HR = hazard ratio, ICH = intracerebral hemorrhage, NOAC = non-vitamin K oral anticoagulant, ref = reference, VKA = vitamin K antagonist

Functional status

At 90 days, 1 420 patients had survived (57.2%). At 90 days, 13.7% of NOAC-ICH patients were functionally independent (mRS 0 – 2), 27.3% were functionally dependent (mRS 3 – 5), and 44.3% were deceased (mRS 6). This was compared with VKA-ICH patients whose functional status was as follows: 15.3% were functionally independent (mRS 0 – 2, n = 334), 28.9% were functionally dependent (mRS 3 – 5, n = 630), and 42.6% were deceased (mRS 6, n = 930). There was no significant difference in 90-day functional status between NOAC-ICH and VKA-ICH patients (p = 0.52) (Figure 9a).

Figure 9a. Functional status at 90 days following oral anticoagulant-related intracerebral hemorrhage in patients with vitamin K antagonist-related intracerebral hemorrhage and non-vitamin K oral anticoagulant-related intracerebral hemorrhage, including patients lost to follow-up (n = 333).

mRS = modified Rankin Scale, NOAC = non-vitamin K oral anticoagulant, VKA = vitamin K antagonist.

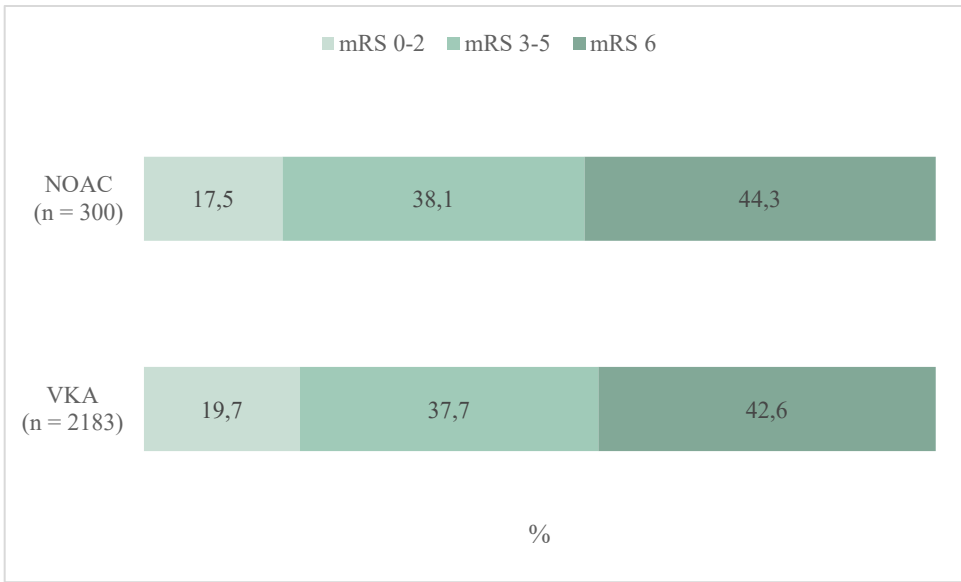


Figure 9b. Imputed data estimating 90-day functional outcome in patients lost to follow-up n = 333. mRS = modified Rankin Scale, NOAC = non-vitamin K oral anticoagulant, VKA = vitamin K antagonist.

Lost to follow-up

The number of patients who were lost to follow-up was 333 (289 VKA vs 44 NOAC, p = 0.30). These patients had all survived but had not returned the 3-month follow-up questionnaire, or data on variables related to mRS status were missing. Patients who were not included in the functional status analysis were more often prestroke dependent, had a greater comorbidity burden (diabetes and hypertension), had a less favorable presenting LOC at hospital admission, and were more likely to be discharged to an assisted living facility compared to patients who were followed-up. Multiple imputation was used to estimate functional outcome in patients who were missing at random. After data imputation, 17.5% of NOAC-ICH patients had an mRS status of 0 – 2 and 38.1% were mRS 3 – 5. Corresponding proportions for VKA-ICH were 19.7% and 37.7%, respectively (Figure 9b).

Reversal treatment in oral anticoagulant-related intracerebral hemorrhage (Paper II)

Study population and reversal therapy

This study included 572 patients with OAC-ICH registered in Riksstroke between 1 January 2017 and 31 December 2017. Oral anticoagulant treatment prior to their ICH event was with either VKA or NOAC (apixaban, rivaroxaban or dabigatran). Patients were categorized into the following two groups: 1) patients who received OAC reversal treatment following ICH event and 2) patients who did not receive any OAC reversal treatment. Baseline characteristics were compared between both groups (Table 8).

Patients who had received reversal treatment were younger (79 vs 81 years old; $p = 0.003$), more often ADL independent prior to the stroke event ($p < 0.001$) and had less often suffered a previous stroke ($p = 0.02$) compared to patients who did not receive reversal treatment. Stroke characteristics differed between the two groups. Patients who did not receive reversal treatment presented more frequently with an unfavourable LOC at hospital admission (comatose 30.7% vs 9.0%; $p < 0.001$), they more often had a supratentorial hemorrhage versus an infratentorial location (91.0% vs 85.2%; $p = 0.05$), had shorter hospital stays (5 vs 11 days; $p < 0.001$), and were less often treated in a stroke care unit or intensive care unit (ICU) compared to patients who received reversal treatment (80.8% vs 90.1%; $p < 0.001$). Time delay from symptom onset to hospital admission did not differ between groups ($p = 0.49$).

Table 8. Baseline characteristics of 572 patients with oral anticoagulant-related intracerebral hemorrhage comparing patients that received reversal treatment to patients who did not receive reversal treatment.

Variables	reversal (n=369) n (%)	non-reversal (n=203) n (%)	p-value
Demographics			
Mean age	79.0 (+/-9.2)*	81.4 (+/-8.9)*	0.003
Sex (male)	205 (55.6)	104 (51.2)	0.32
Prestroke dependent	116 (32.7)	94 (46.3)	<0.001
Vascular risk factors			
Hypertension	296 (80.2)	167 (82.3)	0.79
Atrial fibrillation	319 (86.4)	182 (89.7)	0.18
Diabetes	80 (21.7)	36 (17.8)	0.27
Previous stroke	98 (26.6)	73 (36.0)	0.02
Previous TIA	42 (11.4)	21 (10.3)	0.84
Clinical characteristics			
Symptom onset to hospital arrival (time)			0.49
0 – 3 h	141 (38.2)	88 (43.3)	
3 – 6 h	110 (29.8)	50 (24.6)	
> 6 h	88 (23.8)	46 (22.7)	
Admitted to stroke unit or ICU	364 (90.1)	164 (80.8)	0.001
Length of hospital stay (median days)	11	5	<0.001
Level of consciousness at hospital admission			<0.001
Alert	238 (65.0)	92 (45.5)	
Drowsy	95 (26.0)	48 (23.8)	
Comatose	33 (9.0)	62 (30.7)	
Hemorrhage location			
Supratentorial	311 (85.2)	183 (91.0)	0.05
Intraventricular hemorrhage	*140/311 (45.8)*	*85/183 (47.5)*	0.71
Neurosurgery	*9/311 (2.9)*	*2/183 (1.1)*	0.19
Infratentorial	54 (14.8)	18 (9.0)	0.05
Intraventricular hemorrhage	*14/54 (26.9)*	*5/18 (27.8)*	0.94
Neurosurgery	*7/54 (13.0)*	*0/18 (0.0)*	0.11
Anticoagulant			
NOAC	118 (32.0)	117 (57.6)	
Apixaban	*78 (66.1)*	*83 (70.9)*	0.64
Rivaroxaban	*31 (26.3)*	*28 (23.9)*	
Dabigatran	*9 (7.6)*	*6 (5.1)*	
VKA	251 (68.0)	86 (42.4)	
INR < 1.7	*16 (6.4)*	*10 (11.6)*	0.17
INR 1.7 – 3	*149 (59.4)*	*43 (50.0)*	
INR > 3	*86 (34.3)*	*33 (38.4)*	

*Standard deviation of the mean. ICH = intracerebral hemorrhage, ICU = intensive care unit, INR = international normalized ratio, NOAC = non-vitamin K oral anticoagulant, TIA = transient ischemic attack, VKA = vitamin-K antagonist.

Patients with VKA-ICH who received reversal therapy (251/337) were treated with 4F-PCC and vitamin K in 85.7% of cases and received PCC only in 11.6% of cases. For patients with NOAC-ICH who received OAC reversal treatment (118/235), 82.2% received PCC, 5.9% received idarucizumab only, and one patient received both PCC and idarucizumab. The mode of reversal treatment was unknown in 2.3% of VKA and 11% of NOAC patients.

The proportion of missing data in Paper II varied between 0 and 1.0% for all variables except for VKA reversal type (2.3%), intraventricular hemorrhage (2.5%), prestroke dependency (4.5%), NOAC reversal type (11%), and time interval between symptom onset to hospital arrival (8.6%).

Survival outcome and level of consciousness

All patients were included in the survival analysis. All-cause mortality at 7, 30, and 90 days in patients receiving reversal treatment was 19.2%, 30.1%, and 33.6%, respectively. The corresponding proportions for patients who did not receive reversal treatment was 41.9%, 48.8%, and 52.7%, respectively. Mortality differed significantly at all endpoints (7, 30, and 90 days) comparing treatment groups when a simple Cox regression analysis was applied (Figure 10a). Using a univariable analysis, the HR for death at 90 days in patients who did not receive reversal treatment was 1.92 (95% CI: 1.48 – 2.49).

Survival outcome in relation to presenting level of consciousness at hospital arrival differed between patients receiving reversal treatment compared to those who did not. These differences can best be visualized with the help of Kaplan-Meier survival curves displayed in Figure 10b-d. Total all-cause mortality in both groups was 18.4% if patients presented as alert, 53.1% if drowsy, and 89.0% if comatose at hospital admission.

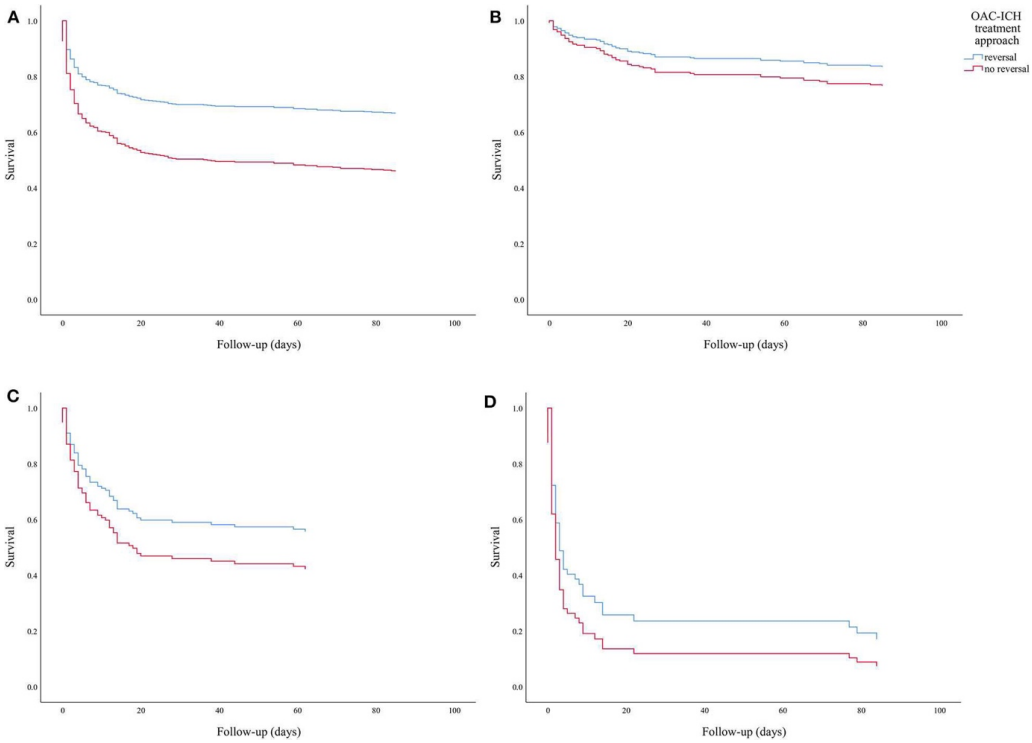


Figure 10. Kaplan-Meier survival curves illustrating 90-day cumulative survival following oral anticoagulant-related intracerebral hemorrhage comparing patients with reversal treatment versus no reversal treatment.
(A) Univariable analysis (n = 572). (B–D) Survival curves based on multivariable analysis stratified for level of consciousness. State of consciousness according to graph is as follows: (B) alert (n = 316), (C) drowsy (n = 128), (D) comatose (n = 78). ICH = intracerebral hemorrhage, OAC = oral anticoagulant.

The multivariable Cox regression analysis was stratified for LOC because of the different baseline hazards associated with presenting LOC, as depicted in Figure 10b-d. After adjusting for relevant confounders found in Table 9, the HR for death for patients who did not receive OAC reversal treatment was 1.47 (95% CI: 1.08 – 2.01).

Two additional Cox regression analyses were modelled for patients with VKA-ICH and NOAC-ICH, respectively. The death rate in patients with VKA-ICH who did not receive OAC reversal treatment was 1.49 (95% CI: 0.94 – 2.37). An HR of 1.96 was reported for patients who had an elevated INR of between 1.7 and 3, while the HR for patients who had an INR level greater than 3 was 2.16. The death rate for patients with NOAC-ICH who did not receive reversal treatment was 1.41 (95% CI: 0.88 – 2.24). An additional subgroup Cox regression analysis comparing patients with VKA-ICH to NOAC-ICH showed no significant difference in 90-day survival (NOAC HR = 0.95; 95% CI: 0.70 – 1.28), this was similar to the findings in Paper I.

Table 9. Cox regression analysis stratified for level of consciousness showing hazard ratios for 90-day mortality in 572 patients with oral anticoagulant-related intracerebral hemorrhage. Simple analysis is displayed as a crude model.

Variable	HR	95% CI		P-value
		lower	upper	
Crude model				
No OAC-reversal	1.92	1.48	2.49	<0.001
Adjusted model*				
No OAC-reversal	1.47	1.08	2.01	0.02
Male sex	1.42	1.06	1.92	0.02
Age	1.05	1.02	1.07	<0.001
Diabetes	1.03	0.70	1.50	0.89
Hypertension	0.80	0.57	1.14	0.22
Atrial fibrillation	0.74	0.48	1.14	0.17
Prestroke dependency	1.02	0.74	1.40	0.92
Intraventricular hemorrhage	2.41	1.77	3.29	<0.001
Neurosurgery not performed	2.13	0.91	5.02	0.08
Infratentorial hemorrhage	1.47	0.96	2.24	0.08

*Stratified for level of consciousness (alert, drowsy and comatose). CI = confidence interval, HR = hazard ratio, OAC = oral anticoagulant.

Functional status

The follow-up rate provided for the 90-day functional outcome analysis was 86%. A crude analysis of data at 90 days revealed a more favorable outcome (mRS 0 – 2) in patients receiving OAC reversal treatment compared to those who did not (Figure 11). Similar results were observed for all three categories of presenting LOC at hospital admission in patients receiving OAC reversal treatment (Figure 12a-c). Patients taking VKA prior to ICH had a superior functional outcome if reversal treatment was received, although a favorable outcome remained less apparent in patients with NOAC-ICH who received reversal treatment (Figure 13). For prestroke ADL independent patients, a more favorable functional outcome was observed in those who had received reversal treatment compared to those who did not receive reversal treatment. However, this difference was less apparent in patients who were prestroke dependent prior to their ICH event (Figure 14a-b).

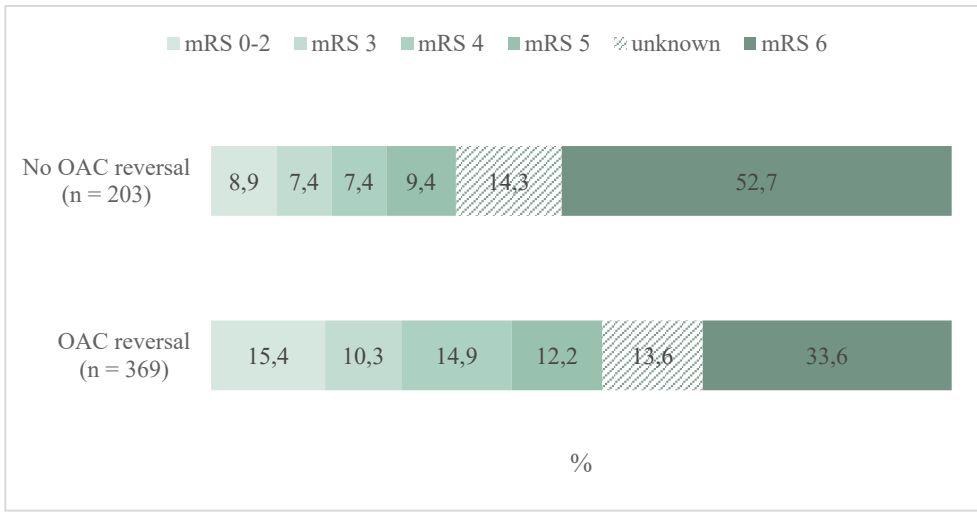
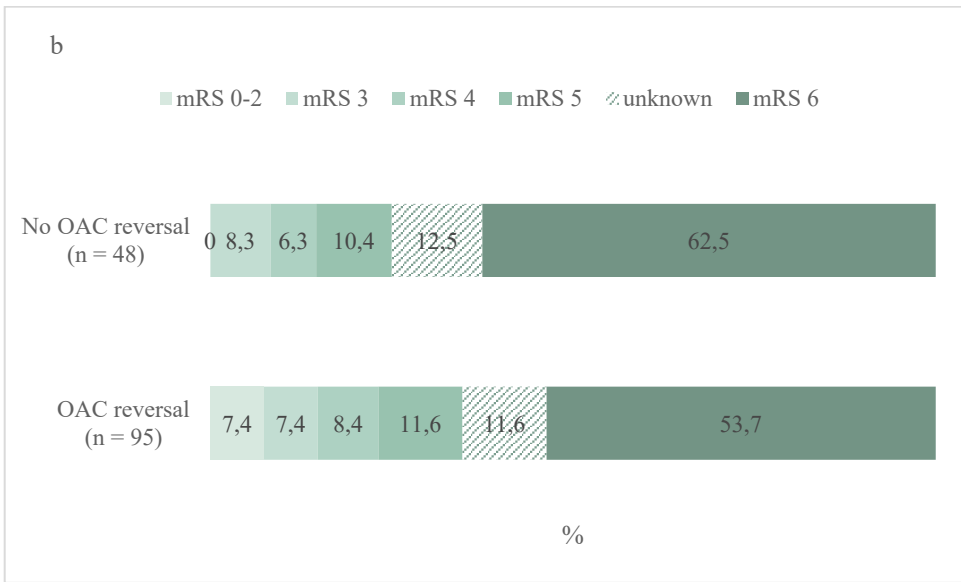


Figure 11. Crude data comparing 90-day functional outcome following oral anticoagulant-related intracerebral hemorrhage in patients who received oral anticoagulant reversal treatment (n = 369) versus no treatment (n = 203). Figure includes patients lost to follow-up. mRS = modified Rankin Scale, OAC = oral anticoagulant.


a
mRS 0-2
mRS 3
mRS 4
mRS 5
unknown
mRS 6
No OAC reversal (n = 92)
18,5
10,9
12,0
15,2
25,0
18,5
OAC reversal (n = 238)
20,6
12,6
18,9
12,2
16,4
19,3
%


b
mRS 0-2
mRS 3
mRS 4
mRS 5
unknown
mRS 6
No OAC reversal (n = 48)
0
8,3
6,3
10,4
12,5
62,5
OAC reversal (n = 95)
7,4
7,4
8,4
11,6
11,6
53,7
%

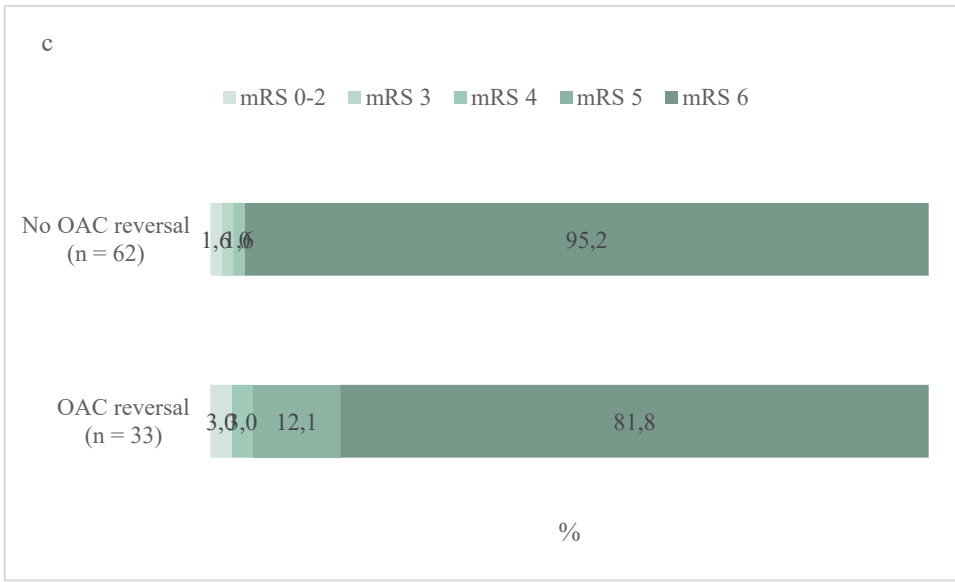


Figure 12. Data comparing 90-day functional outcome following oral anticoagulant-related intracerebral hemorrhage based on presenting level of consciousness (a = alert, b = drowsy, c = comatose). Figure includes patients lost to follow-up. mRS = modified Rankin Scale, OAC = oral anticoagulant.

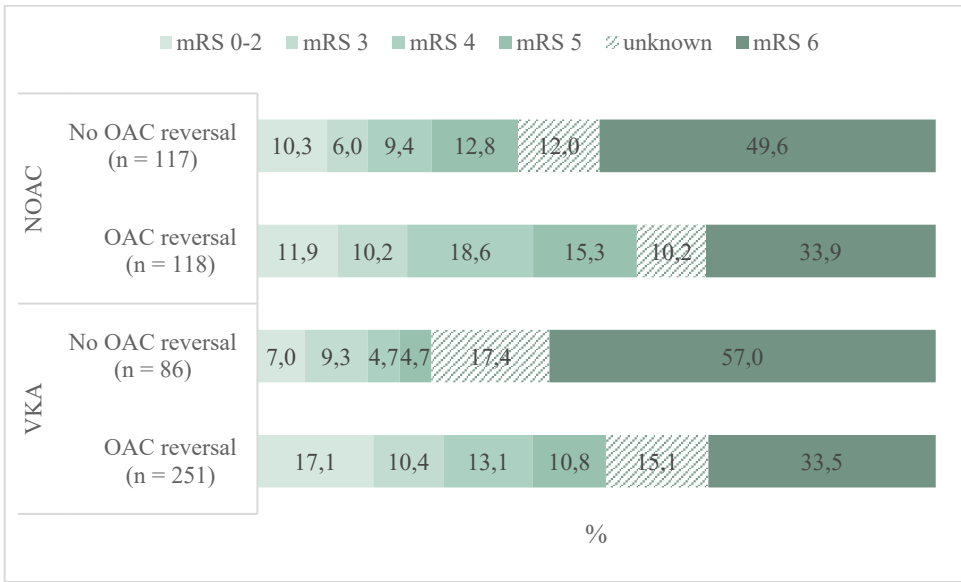


Figure 13. Crude data comparing 90-day functional outcome following oral anticoagulant-related intracerebral hemorrhage. Figure includes patients lost to follow-up. mRS = modified Rankin Scale, OAC = oral anticoagulant.

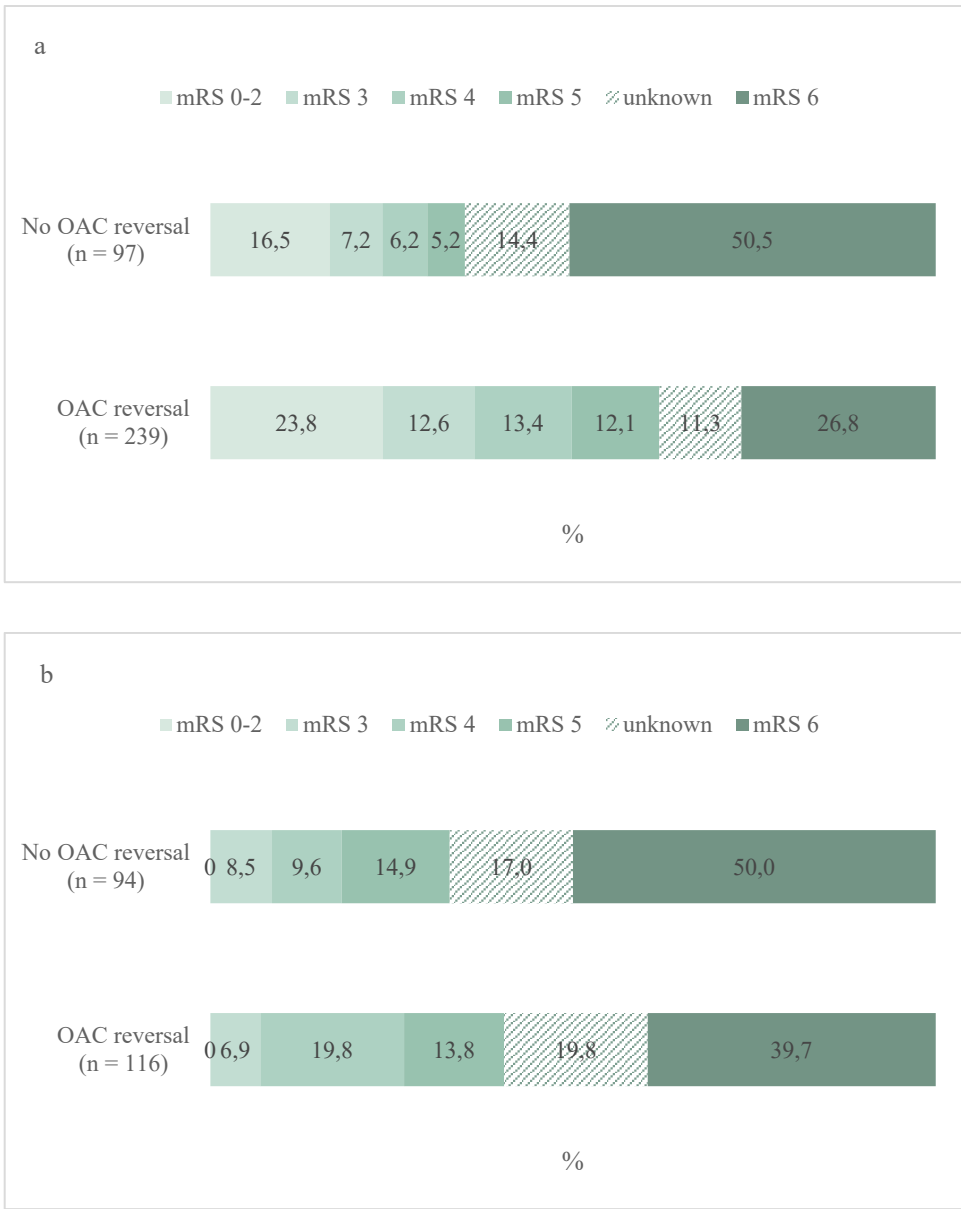


Figure 14. Data comparing 90-day functional outcome following oral anticoagulant-related intracerebral hemorrhage in a) prestroke independent patients b) prestroke dependent patients. Figure includes patients lost to follow-up. mRS = modified Rankin Scale, OAC = oral anticoagulant.

Prognosis of intracerebral hemorrhage related to antithrombotic use (Paper III)

Study population

Paper III included 13 291 patients with ICH recorded in Riksstroke between 1 January 2012 and 31 December 2016. Patients were categorized into three groups according to the presence of ongoing treatment with an antithrombotic agent up until the index ICH. At baseline, 2 300 patients with OAC-ICH, 3 637 with antiplatelet-related ICH and 7 354 patients without antithrombotic treatment prior to ICH were included in this study. Prior to inclusion, 1 094 patients were excluded due to missing data on drug adherence, and 336 patients were excluded due to faulty registration in Riksstroke's database. Patients who had concomitant treatment with an antiplatelet and an oral anticoagulant were only included in the OAC-ICH group (8.0%). Drug adherence was determined from the Swedish Prescribed Drug Register and was defined as a patient, or next of kin, filling a prescription within 100 days of the ICH event.

Baseline patient characteristics can be seen in Table 10. Patients with antithrombotic treatment (antiplatelet or OAC) were older, more likely to be prestroke dependent, had a greater proportion of premorbid comorbidity (diabetes, hypertension, previous stroke/TIA, atrial fibrillation, hypercholesterolemia), and had a less favorable LOC at hospital admission (drowsy/comatose) compared to patients without antithrombotic treatment. Patients were more often male in the OAC-ICH group compared to the two other groups.

The amount of missing data in Paper III was low and ranged between 0 and 2% for all variables except prestroke dependency (2.5%).

Table 10. Baseline characteristics of 13 291 participants with non-traumatic intracerebral hemorrhage.

Variables	Non-AT-ICH (n = 7354)	AP-ICH (n = 3637)	OAC-ICH (n = 2300)	P-value
Demographics				
Mean Age	68.9 (+/-14.7)*	78.9 (+/-9.9)*	78.6 (+/-8.7)*	<0.001
Sex (male)	3815 (51.9)	1886 (51.9)	1366 (59.4)	< 0.001
Living independently	3139 (42.7)	1957 (53.8)	977 (42.5)	<0.001
Prestroke dependent	1477 (20.4)	1520 (43.0)	675 (30.5)	<0.001
Vascular risk factors				
Diabetes	780 (10.6)	825 (22.7)	495 (21.5)	<0.001
Hypertension	2930 (39.8)	2532 (69.6)	1750 (76.1)	<0.001
Atrial Fibrillation	369 (5.0)	50 (13.9)	1890 (82.2)	<0.001
Previous stroke	1022 (13.9)	1265 (34.8)	661 (28.7)	<0.001
Previous TIA	144 (2.0)	447 (12.3)	210 (9.1)	<0.001
Statins	748 (10.2)	1559 (42.9)	744 (32.3)	<0.001
Antiplatelet treatment	-	-	183 (8.0)	-
Stroke characteristics				
Stroke unit/ICU admission	5549 (75.5)	2698 (74.2)	1731 (75.3)	0.34
Median duration of acute care (days)	9	7	8	<0.001
Level of consciousness				<0.001
Alert	4638 (63.1)	2043 (56.2)	1333 (58.0)	
Drowsy	1477 (20.1)	867 (23.8)	505 (22.0)	
Comatose	1087 (14.8)	661 (18.2)	431 (18.7)	

*Standard deviation of the mean, AP = antiplatelet, ICH = intracerebral hemorrhage, ICU = intensive care unit, OAC = oral anticoagulant, AT = antithrombotic , TIA = transient ischemic attack.

Cumulative mortality

All patients were included in the mortality analysis. At 90 days, all-cause mortality in the total ICH patient cohort (n = 13 291) was 34%. From the multivariable analysis, patient factors that were associated with an increased death rate included age (HR = 1.04; 95% CI: 1.03 – 1.04), male sex (HR = 1.13; 95% CI: 1.06 – 1.20), prestroke dependency (HR = 1.33; 95% CI: 1.24 – 1.43), and an unfavourable LOC at hospital admission ((drowsy HR = 3.70; 95% CI 3.42 – 4.01) (comatose HR = 12.51; 95% CI: 11.56 – 13.54)). Antiplatelet therapy was associated with an HR of 1.23 (95% CI: 1.14 – 1.33) for death following ICH and the HR for oral anticoagulant therapy was 1.40 (95% CI: 1.26 – 1.57).

The Cox regression subgroup analysis of early (≤24 h and 1 – 7 days) and late mortality (8 – 90 days) was performed to determine whether an increased mortality rate associated with antithrombotic drug use was present in both early and late phases following the ICH event (Table 11). There was a significant association with increased mortality related to the use of antiplatelet or OAC drugs at all follow-up time points except for OAC users during the 8 – 90-day period. This period was no longer associated with a significant increased death rate in patients with OAC treatment prior to ICH event.

Table 11. Cox regression analysis showing hazard ratios for ≤24 h, 7-day, 8 – 90-day, and 90-day mortality in all intracerebral hemorrhage patients (n = 13291). Adjusted for age, sex, prestroke dependency, diabetes, atrial fibrillation, hypertension, and living alone. Reference = No antithrombotic treatment.

	Antiplatelet		Oral Anticoagulant	
	HR (95% CI)	P-value	HR (95% CI)	P-value
0 – 90 days				
Crude model	1.82 (1.70 – 1.94)	< 0.001	1.87 (1.73 – 2.01)	< 0.001
Adjusted model	1.23 (1.14 – 1.33)	< 0.001	1.40 (1.26 – 1.57)	< 0.001
≤ 24h				
Crude model	1.65 (1.45 – 1.88)	< 0.001	2.28 (1.99 – 2.61)	< 0.001
Adjusted model	1.32 (1.13 – 1.54)	< 0.001	1.93 (1.57 – 2.38)	< 0.001
1 – 7 days				
Crude model	1.75 (1.61 – 1.91)	<0.001	1.98 (1.80 – 2.17)	< 0.001
Adjusted model	1.24 (1.09 – 1.41)	0.001	1.30 (1.08 – 1.57)	0.005
8 – 90 days				
Crude model	1.94 (1.74 – 2.16)	< 0.001	1.66 (1.45 – 1.89)	< 0.001
Adjusted model	1.19 (1.05 – 1.34)	0.006	1.12 (0.93 – 1.35)	0.22

CI = confidence interval, HR = hazard ratio

Functional outcome

In Paper III, the 90-day follow-up rate was 84.8%. The remaining 15.2% of patients were alive but of unknown functional status. Lost to follow-up accounted for 2016 patients. These patients were younger, had more severe strokes and had a higher rate of prestroke dependency compared to patients who were included in follow-up analysis. At 90 days (Figure 15), the analysis of crude follow-up data revealed the following functional outcomes in patients without antithrombotic treatment: 27.7% mRS 0 – 2, 28.6% mRS 3 – 5, and 26.3% mRS 6 (17.4% lost to follow-up). Corresponding proportions for patients with AP-ICH were as follows: 15.0% mRS 0 – 2, 29.3% mRS 3 – 5, and 43.1% mRS 6 (12.6% lost to follow-up). In patients with OAC-ICH the corresponding mRS scores were the following: 15.7% mRS 0 – 2, 29% mRS 3 – 5, and 43.1% mRS 6 (12.2% lost to follow-up). Univariate analysis using logistic regression revealed that antithrombotic treatment was associated with a higher odds of functional dependency (mRS 3 – 5) at 90 days following ICH. In univariable logistic regression analysis, the odds ratio (OR) for functional dependency related to AP treatment was 1.89 (95% CI: 1.67 – 2.13) and the OR for functional dependency related to OAC treatment was 1.78 (95% CI: 1.55 – 2.05).

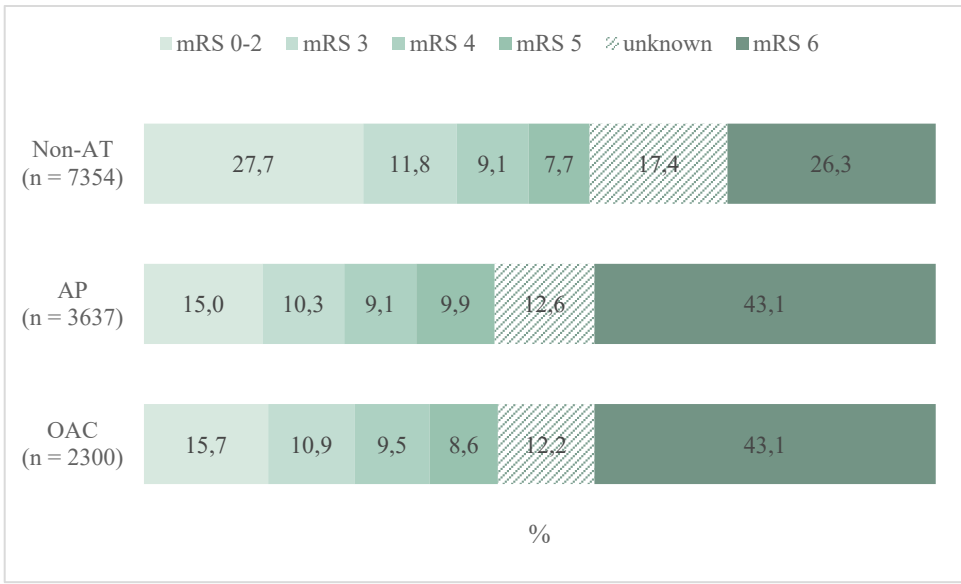


Figure 15. Crude data showing 90-day functional outcome in patients following oral anticoagulant-related intracerebral hemorrhage, antiplatelet-related intracerebral hemorrhage, and non-antithrombotic intracerebral hemorrhage. Figure includes patients lost to follow-up. AP = antiplatelet, AT = antithrombotic, mRS = modified Rankin Scale, OAC = oral anticoagulant.

From the multivariable logistic regression analysis, factors found to be associated with a significantly higher odds of functional dependency (mRS 3 – 5) at 90 days following ICH were female sex (OR = 1.36), age (OR = 1.05), living alone prior to index ICH (OR = 1.95), diabetes (OR = 1.58), previous stroke (OR = 2.04), and an unfavourable LOC at hospital admission (drowsy OR = 4.61; comatose OR = 6.41). Antithrombotic treatment, both OAC and AP drugs, was no longer associated with functional dependency at 90 days after adjusting for relevant confounders in a logistic regression analysis (Table 12).

Table 12. Logistic regression analysis showing odds ratios (OR) for 90-day functional outcome depicted as mRS 3-5 in all surviving patients with known mRS status (n = 7 284).

Variable	OR	95% CI		P-value
		lower	upper	
Crude Model				
Antithrombotic treatment				
No antithrombotic (ref)	1			
Antiplatelet	1.89	1.67	2.13	<0.001
Oral anticoagulant	1.78	1.55	2.05	<0.001
Adjusted Model				
Female sex	1.36	1.21	1.52	<0.001
Age	1.05	1.04	1.05	<0.001
Living alone	1.95	1.74	2.19	<0.001
Previous stroke	2.04	1.77	2.37	<0.001
Previous TIA	0.99	0.77	1.26	0.92
Diabetes	1.58	1.35	1.85	<0.001
Atrial fibrillation	1.20	0.97	1.50	0.10
Hypertension	1.02	0.90	1.14	0.81
Antithrombotic treatment				
No antithrombotic (ref)	1			
Antiplatelet	1.07	0.92	1.24	0.39
Oral anticoagulant	0.96	0.76	1.22	0.75
Level of consciousness				
Alert (ref)	1			
Drowsy	4.61	3.89	5.48	<0.001
Comatose	6.41	4.58	8.95	<0.001

CI = confidence interval, ref = reference, TIA = transient ischemic attack.

Patient factors associated with receiving reversal treatment in oral anticoagulant-related intracerebral hemorrhage (Paper IV)

Patient characteristics

Paper IV included 1 902 patients with OAC-ICH registered in Riksstroke between 1 January 2017 and 31 December 2019. During the study period, OAC-ICH accounted for 23.0% of all ICH cases in Sweden (n = 8 256). Baseline characteristics were compared in patients with OAC-ICH reversal treatment (n = 1 146) and patients without treatment (n = 756) (Table 13). Patients receiving reversal treatment were more often younger, male, prestroke independent, and suffering their first stroke. These patients were more often treated at a university hospital, in a stroke unit/ICU setting, and had a more favorable presenting LOC compared to patients who did not receive reversal treatment. Comorbidities were similar in both groups. Unadjusted 90-day all-cause mortality was 38.2% in patients receiving

reversal treatment versus 51.9% in patients who did not receive reversal treatment. Missing data was below 1% in the patient cohort, except for hemorrhage location (1.5%), IVH (2.8%), pre-stroke ADL dependency (4.7%), and INR values (15.2%).

Table 13. Baseline characteristics of 1902 patients with oral anticoagulant-related intracerebral hemorrhage comparing patients that received reversal treatment compared to patients who did not receive reversal treatment. *Standard deviation of the mean.

Variables	reversal (n=1146) n (%)	non-reversal (n=756) n (%)	p-value
Demographics			
Mean age	79.3 (+/-8.9)*	81.6 (+/-8.7)*	<0.001
Sex (male)	688 (60.0)	394 (52.1)	0.001
Prestroke dependent	373 (33.9)	348 (48.9)	<0.001
Vascular risk factors			
Hypertension	915 (80.2)	601 (79.9)	0.82
Atrial fibrillation	1007 (87.9)	662 (87.6)	0.84
Diabetes	236 (20.6)	171 (22.7)	0.26
Previous stroke	296 (25.9)	247 (32.8)	0.001
Previous TIA	115 (10.1)	79 (10.5)	0.80
Clinical characteristics			
Type of hospital			0.03
University	283 (25.1)	162 (20.9)	
County	843 (74.9)	614 (79.1)	
Admitted to stroke unit or ICU	918 (80.1)	563 (74.5)	0.004
Length of hospital stay (median days)	10	5	<0.001
Level of consciousness at hospital admission			<0.001
Alert	709 (62.3)	394 (52.6)	
Drowsy	302 (26.5)	148 (19.8)	
Comatose	127 (11.2)	207 (27.6)	
Hemorrhage location			
Supratentorial	949	637	
Intraventricular hemorrhage	414/949	285/637	0.96
Neurosurgery	44/949	7/637	<0.001
Infratentorial	180	102	
Intraventricular hemorrhage	55/180	37/102	0.39
Neurosurgery	19/180	1/102	0.003
Anticoagulant			
NOAC	475	507	
Apixaban	314/475	360/507	0.05
Rivaroxaban	124/475	127/507	
Dabigatran	34/475	17/507	
Edoxaban	3/475	3/507	
VKA	671	249	
INR < 1.7	33/671	25/249	0.005
INR 1.7 – 3	349/671	108/249	
INR > 3	200/671	65/249	
Crude mortality			
In hospital death	366 (31.9)	320 (42.3)	<0.001
At 90 days	438 (38.2)	392 (51.9)	<0.001

ICU = intensive care unit, INR = international normalized ratio, NOAC = non-vitamin K oral anticoagulant, TIA = transient ischemic attack, VKA = vitamin-K antagonist.

Paper IV aimed to determine temporal changes in the general use of OAC reversal agents in Sweden. In 2017, 64.5% of the OAC-ICH patient population received reversal treatment. The corresponding proportions in 2018 and 2019 were 60.7% and 55.9%, respectively (p = 0.009). A decreasing proportion of patients with NOAC-ICH who received reversal treatment was observed throughout the study period. In 2017, 50.2% of all NOAC-ICH patients received reversal treatment. The corresponding proportions for 2018 and 2019 were 51.2% and 44.9%, respectively (p = 0.19). In all registered VKA-ICH patients, the proportion of those receiving reversal treatment was 74.5% in 2017, 70.2% in 2018, and 74.8% in 2019 (p = 0.34) (Figure 16).

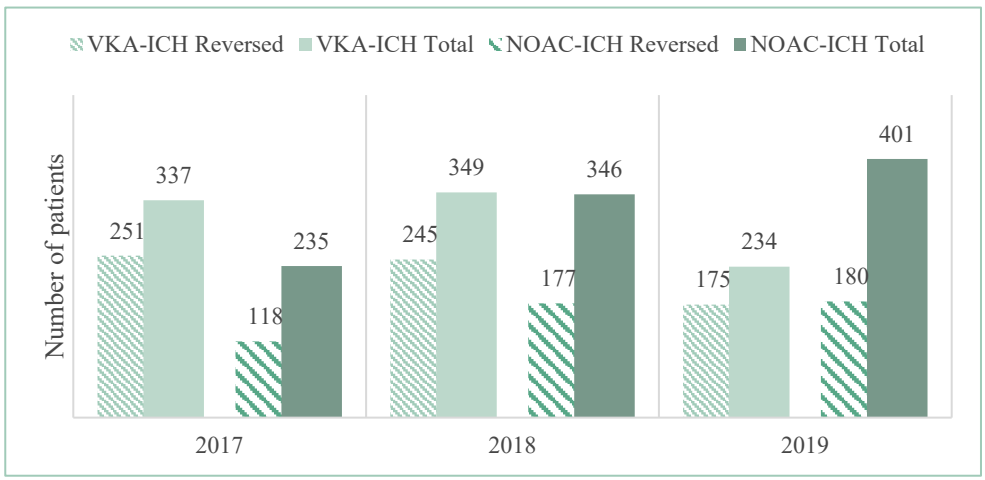


Figure 16. Total number of patients with vitamin K antagonist-related intracerebral hemorrhage compared to non-vitami K oral anticoagulant-related intracerebral hemorrhage receiving reversal treatment between 2017 and 2019. ICH = intracerebral hemorrhage, NOAC = non-vitamin K oral anticoagulant, VKA = vitamin K antagonist.

In 2017, a minority of patients (32%) receiving OAC reversal treatment had NOAC-ICH; the remaining patients who received OAC reversal treatment had VKA-ICH. The corresponding proportions of patients with NOAC-ICH in 2018 and 2019 increased to 41.9% and 50.7%, respectively. This was attributed to the decreased use of VKA in the general population.

During the study period, the majority of patients with NOAC-ICH who received OAC reversal treatment were treated with PCC (91.6%, 435/475), while 5.7% received idarucizumab (27 patients with dabigatran-ICH). Information on the type of OAC reversal treatment was missing in the remaining 2.7% of patients with NOAC-ICH who received OAC reversal treatment. In patients with VKA-ICH who received OAC reversal therapy, 99% (664/671) were treated using PCC, and 86.9% (583/671) received treatment with PCC in addition to intravenous vitamin-K.

Prediction analysis

Prediction analysis was performed to investigate patient and stroke characteristics associated with receiving OAC reversal treatment. This was realized using logistic regression with the binary outcome being treatment with OAC reversal therapy, yes/no (Table 14). Patients with NOAC-ICH had lower odds of receiving OAC reversal treatment compared to patients with VKA-ICH (OR = 0.34; 95% CI: 0.28 – 0.42). Additionally, prestroke dependent patients were less likely to receive OAC reversal treatment compared to prestroke independent patients (OR = 0.72; 95% CI: 0.58 – 0.91). Furthermore, patients who were older (OR = 0.98; 95% CI: 0.96 - 0.99), had a previous stroke (OR = 0.78; 95% CI: 0.62 – 0.98), or who presented as comatose on hospital admission (OR = 0.36; 95% CI: 0.27 - 0.48; reference = alert) had lower odds of receiving reversal treatment.

Table 14. Multivariable logistic regression analysis showing odds ratios (OR) for variables predictive of receiving reversal treatment (n = 1 902).

Variable	OR	95% CI		P-value
		lower	upper	
Male sex	1.15	0.93	1.42	0.19
Age	0.98	0.96	0.99	<0.001
Previous stroke	0.78	0.62	0.98	0.03
Prestroke dependency	0.72	0.58	0.91	0.005
Level of consciousness				
Alert (ref)	1			
Drowsy	1.31	1.02	1.69	0.03
Comatose	0.36	0.27	0.48	<0.001
NOAC (*VKA ref*)	0.34	0.28	0.42	<0.001

CI = confidence interval, NOAC = non-vitamin K oral anticoagulant, ref = reference, VKA = vitamin-K antagonist.

Methodological considerations

Study design

All papers in this thesis are based on observational data from high quality patient registers with good reliability and data accuracy. The registers used in this thesis are described in more detail in the "Subjects and methods" section. By providing large amounts of organized data, patient registries aim to improve quality of guideline-based healthcare by identifying patterns in patient care, assessing such patterns, and facilitating academic research in order to provide knowledge that will support current or future guidelines. However, despite the extensive amount of data in registry-based research, it is often difficult to account for the lack of explicit detail that could be required for a particular study. This thesis broadly includes studies that aim to determine the natural outcome of a disease rather than a specific intervention, with the exception of Paper II. In turn, an observational design could rationally be employed. Given the ethical dilemmas associated with randomization of patient groups in Paper II to treatment and no treatment groups, an observational approach remained feasible. The ethical dilemmas in Paper II are further discussed in other parts of this thesis.

Not only are register studies limited by their study design, register-based observational studies are also subject to various types of bias. The most relevant areas of bias in this thesis are discussed below.

Selection bias at study entry

Selection bias at study inclusion transpires when the chosen population sample is not representative of the target population. Riksstroke acquires data from only hospital-based stroke cases. Therefore, the total number of patients with ICH that are not admitted to a hospital remains unknown. These may be patients who were sent home from the emergency department prior to diagnosis, who succumbed at their residence as a result of ICH or who were treated palliatively through homecare or at an assisted living facility[167]. Case ascertainment of total first ever stroke patients in Sweden has been previously estimated to range between 86 – 92%[168]. Consequently, although Riksstroke has an approximate 89% coverage rate of

hospital-based stroke cases and records approximately 21 000 stroke cases per year (based on 2019 reports)[169], the register is not able to represent the entire target population as there will always be missed cases, despite best efforts as demonstrated in a recent study by Aked, et al[170]. Thus, all studies in this thesis may slightly be subject to selection bias.

Indication bias

Indication bias is a fundamentally essential aspect that can skew data in clinical observational studies. It occurs when the risk of an outcome is directly related to the indication for treatment but not by the treatment itself[171]. In Paper II, patients who received reversal treatment had superior mortality outcomes following OAC-ICH compared to patients who received no reversal treatment. The beneficial outcome for patients who received OAC reversal therapy may have been subject to indication bias, a type of selection bias. For example, patients presenting to the emergency department with unfavourable LOC (comatose) and baseline CT imaging demonstrating extensive ICH volumes may have been managed conservatively or had acute treatment withheld altogether. These patients may have been immediately directed to palliative care with the idea that their fate was determined by prognostic factors and not by the access to OAC reversal treatment. Thus, indication bias may occur when the choice of treatment is influenced by the risk of the specific outcome.

In Paper II, the Cox PH model was stratified for LOC to account for this bias. Here, confounding by indication bias could be minimized in the sense that the exposure (reversal treatment) rather than the indication (severity of bleeding based on LOC) was more likely to have caused the outcome (death). Despite taking disease severity into account through the means of stratification, this model is still subject to residual confounding external to what could be accounted for. Randomization is the ultimate means of reducing indication bias but considering strict guidelines in the management of OAC-ICH and several ethical dilemmas concerning withholding a potentially beneficial treatment, this study design is presently not feasible.

Withdrawal of care bias

Intracerebral hemorrhage is a devastating disease. Currently, guidelines for withdrawal of care following ICH in Sweden do not exist to the same extent as those provided by the American Heart Association. The American Heart Association recommends aggressive care early after ICH onset and postponement of new do not resuscitate (DNR) orders until at least 48 hours after hospitalization in order to minimize any form of a self-fulling prophecy[133]. The reason for this intervention is

to decrease mortality and functional dependence due to the presence of early prognostic uncertainty after ICH. Several studies have found that early care limitations have a direct association with death and functional dependency[149-151]. The strength of this recommendation is moderate and is based on moderate quality evidence from non-randomized studies[150,151,172]. In this thesis, DNR orders were unaccounted for, and this may have influenced results in our patient cohort related to mortality rates and functional dependency following ICH.

Residual confounding

Confounding occurs when the effect of an exposure is obscured by the effect of another variable. Without determining an appropriate relationship between exposure and outcome, there is a risk that overestimating the effect of an exposure, or that adjusting for spurious associations, may occur. Several methods exist on how to address confounding, whereby a few used in this thesis are described below.

A simple means of limiting confounding is achieved through the use of a restriction method which is carried out by selecting individuals with similar baseline characteristics (confounding variable). In Paper II, a crude analysis showed that functional outcome was more favorable in patients who received OAC reversal treatment compared to those who had not. Functional status was then subgrouped according to prestroke dependency and the effect of OAC reversal on functional outcome was studied separately in patients who were prestroke independent and prestroke dependent. In the crude data analysis, patients who were prestroke independent had a superior outcome if given reversal treatment compared to not receiving treatment. However, this benefit was undistinguishable in patients who were already prestroke dependent. While this method of placing patients into subgroups may account for confounding bias to an extent, it renders the results less generalizable to a larger population by giving room for other confounding factors to obscure the effect of the exposure, which in this case, is the effect of OAC reversal treatment on outcome.

Stratification is a type of restriction that is used as a means to control for a confounding factor. As patients presenting with different LOC following OAC-ICH had different baseline hazards related to death and hence assumed different outcomes, by using stratification in Paper II, the effect of OAC reversal would not be confounded by the presenting LOC because LOC would not vary within a given stratum.

Regression analysis was used in all papers to address confounding through modelling for multiple confounders at the same time. Thereby allowing the determination of the estimated effect of a variable of interest when other confounders are held constant. For example, in Paper III, functional outcome was

compared between categories of antithrombotic use related to ICH (OAC, AP, no antithrombotic drugs). In univariable analysis using logistic regression with functional dependency (mRS 3 – 5) denoted as the dependent variable and antithrombotic category as the independent variable, both antiplatelet and OAC use were strongly associated with significantly higher odds of dependency at 90 days compared to no antithrombotic treatment following ICH (AP: OR 1.89 95% CI 1.67 – 2.13 and OAC: OR 1.78 95% CI 1.55 – 2.05). However, after modelling for several relevant confounders using a logistic regression analysis, this effect was attenuated, and thus antithrombotic drug use was no longer associated with the outcome of interest (AP: OR 1.07 95% CI 0.92 – 1.24 and OAC: OR 0.96 95% CI 0.76 – 1.22). It is therefore essential to address potential areas of confounding that are limited to the study of interest in order to avoid this type of important bias.

Although Riksstroke includes several important variables related to stroke and its outcome, there are still several factors associated with ICH and OAC-ICH that the database does not retain. Important factors that were unable to be controlled for in our statistical models are denoted as residual confounders. Hospitals report patient cases to Riksstroke by completing forms regarding patient and stroke characteristics. It is unfortunately not feasible to overburden hospitals with extensive registrations relevant to stroke research, thus Riksstroke has limited the number of variables to those that are primarily linked to priority items in the guidelines and/or variables that are readily available in patient journals[173]. An earlier study published in 2016, however, reported that the content validity of Riksstroke's acute stroke form is very high[173]. Riksstroke's database was also found to include almost all core quality indicators identified by an international panel of stroke experts and other European registers[173,174]. Riksstroke now includes over 81 variables on acute stroke.

Considering the observational nature of the studies presented in this thesis, they are all subject to residual confounding. Despite Riksstroke's extensive content on acute stroke cases, several variables that would have improved the reporting quality of the studies were unavailable for analysis. Most importantly, information regarding diagnostic imaging to assess hematoma expansion and volumes, last known drug intake, coagulation parameters, and indication for antithrombotic use were unknown. Particularly in Paper I, NOAC had previously been reported to be associated with smaller hemorrhage volumes and possibly less hematoma expansion. In addition, in Paper II, the evaluation of hematoma expansion would have been of importance in assessing the effect of reversal treatment based on this variable. These factors were unable to be accounted for as information on both hemorrhage volume and hematoma expansion are unavailable in Riksstroke's database. Coagulation parameters, last known drug intake, time to OAC reversal treatment, and reversal agent dosages may have specifically confounded results related to Paper II as compliance issues were unaccounted for in this paper and a good outcome may therefore be overestimated if drug levels were low or negligible.

Attrition bias

Attrition bias is a type of selection bias that is due to systematic differences between study groups in the processes that define the way participants are lost from a study[175]. For example, the reason for attrition in a study determining functional status following stroke may be due to self-limiting factors including the inability to respond to a questionnaire due to functional limitations or dependency on a caregiver. Furthermore, loss to follow-up also included participants that had missing variables in the dataset essential for calculating the mRS score. Attrition leads to bias in the sense that individuals with a more favorable functional status will continue to the follow-up period. Therefore, the extent of functional dependency may be underestimated in the study population as more favorable outcomes will ultimately be demonstrated. To ascertain this type of bias, characteristics of patients lost to follow-up can be compared against those included in the follow-up analysis.

Attrition bias is a common issue in register studies. In Riksstroke, non-responders include patients who are alive but are lost to follow-up due to opting-out of the quality register or due to not responding to the follow-up questionnaire as a result of emigration or having an inaccessible residence address. A previous study found that non-responders in Riksstroke are more often women, older, living alone, and were more frequently prestroke ADL dependent[176]. Another publication based on Riksstroke data reported that demographics (older, more prestroke dependent), stroke characteristics (more severe strokes, location of stroke) and outcomes (worse functional status) significantly affected stroke patients in their ability to consent to stroke trials and follow-up[177]. Attrition bias was present in Papers I, II, and III, as all three papers studied functional outcome following ICH. In all three studies, patients who were lost to follow-up were more often pre-stroke ADL dependent. In Papers I and III, additional characteristics of patients lost to follow-up included that they more often lived alone, had more severe presenting LOC at hospital admission, and were less often admitted to a stroke care unit/ICU. In Paper III, patients who were lost to follow-up were also younger.

In Paper I, attrition bias was addressed using multiple imputations in order to estimate functional outcome in patients lost to follow-up. This analysis demonstrated that an underestimation of stroke severity and functional outcome was present. Paper III avoided attrition bias to a greater extent as a substantial study population was included in analysis.

Furthermore, survivors of ICH could retain a more favorable functional outcome since the most vulnerable patients may have succumbed prior to follow-up analysis. This would in turn pose as a form of attrition bias at follow-up. In order to avoid this bias, we included death in the presentation of functional outcome proportions.

Misclassification bias

Misclassification bias occurs when a patient is assigned to an incorrect group or category that ultimately changes the perceived relationship with the outcome of concern. In Papers I, II, and III, functional outcome analysis was based on self-reported mRS data. Patients, or those responsible for filling out the 3-month follow-up questionnaire, may have over or underestimated functional status leading to an incorrect association between stroke severity and outcome. However, a previous study found that the translation of self-reported outcome to mRS scores in Riksstroke has high precision compared to objectively assessed mRS scores, therefore lowering the risk for this type of bias[161].

External validity

External validity addresses the generalizability of a study. That is to say, how likely it is that the observed effects or outcomes would occur external to the study, i.e., the extent to which results of a study can be generalized to another patient population. The generalizability of the papers in this thesis is enhanced considering the large, unselected study sample present. Nevertheless, the patient demographics included in this study represent a population from a high-income country and generalizability to middle and low-income countries may not be entirely achievable.

General discussion and future perspectives

Prognosis for intracerebral hemorrhage during ongoing oral anticoagulant treatment (Paper I)

Paper I investigated 90-day mortality and functional outcome in patients with OAC-ICH comparing those who had taken VKA and NOAC in a large, unselected patient cohort in Sweden. At 90 days, 42.6% of VKA-ICH and 44.3% of NOAC-ICH patients had died. This is in line with data from previous studies[58,70,178]. There was no evidence to support that mortality at 90 days differed between drug categories after adjusting for relevant confounders, and we found no significant difference in 90-day functional outcome in a crude analysis comparing NOAC-ICH and VKA-ICH patients. Patients taking NOAC had a higher occurrence of prestroke dependency and previous stroke.

The similar mortality and functional outcome related to NOAC-ICH and VKA-ICH in Paper I are consistent with several publications[84,179-183]. A systematic review by Boulouis et al. that included imaging data reported similar baseline ICH volumes and hematoma growth in a group of 393 NOAC-ICH patients and a group of 3482 VKA-ICH patients. In addition, their data on mortality and functional outcome was similar to that presented in our study[179]. Tsivgoulis et al. reported smaller baseline hematoma volumes in 219 NOAC users compared to 831 VKA users (adjusted linear regression coefficient = -0.24; 95% CI: -0.47 to -0.16), though mortality and functional outcomes were similar at 3 months[180].

On the contrary, other studies have reported more favourable survival outcomes in NOAC-ICH patients[184-188]. In addition to a more favourable survival outcome associated with NOAC-ICH compared to VKA-ICH, two recent Japanese studies also reported less hematoma growth in NOAC-ICH patients[186,187]. Nonetheless, reports showing a more favorable outcome in NOAC users were often limited to small numbers. A recent cohort study based on data from the Get With The Guidelines (GWTG) Stroke registry reported that factor Xa inhibitor-related ICH was associated with a more favorable mortality outcome and functional status compared to VKA-ICH[188]. However, this study had several limitations including residual confounding and lack of radiologic data. Several studies have shown that

ICH volumes are similar or smaller in NOAC-ICH compared to VKA-ICH[182,186,187,189,190].

The overall risk of stroke is lower in patients taking NOAC, and this is mainly attributed to the decreased risk of ICH as the risk for ischemic stroke is non-inferior to VKA[57]. Considering the lower rate of ICH in patients taking NOAC, the general use of anticoagulant treatment is expected to increase given that the aging population is growing, and improved detection rates of non-valvular atrial fibrillation exist. The rapid increase in prescription of NOAC drugs seems to be associated with an increase in emergency visits for NOAC related hemorrhages[191]. With an aging population, the incidence of lobar hemorrhages related to CAA is likely to increase due to the higher risk of ICH in this patient group, exacerbated by OAC use[184,192,193]. Cerebral amyloid angiography is commonly diagnosed after a cerebrovascular event or as an accidental finding. The elderly population is not screened for CAA and thus risk/benefit evaluation prior to the prescription of OAC may be overlooked in this patient population.

In the early stages of NOAC drug use, established reversal treatment was available for VKA drugs, but there were no direct oral anticoagulant reversal agents available for treating NOAC-ICH. Thus, there was uncertainty as to whether NOAC-ICH was associated with larger hematoma volumes and hematoma expansion compared to VKA-ICH. There was also uncertainty whether NOAC-ICH was associated with worse outcomes compared to VKA-ICH given the novelty of NOACs and the lack of specific reversal agents[194-196]. While conflicting reports exist concerning whether taking VKA or NOAC results in similar outcomes following ICH, no study has shown a worse outcome following NOAC-ICH. Paper I could contribute to the unsupported reluctance of NOAC use that certain physicians may still carry given their comparative novelty to VKA since we report similar mortality and functional outcomes in NOAC-ICH and VKA-ICH patients.

In order to confirm whether a difference in outcome exists between NOAC and VKA users following ICH, further studies, with the inclusion of a large prospective patient population, are required to compare mortality and functional outcome. Future studies should include important prognostic indicators of poor outcome including, but not limited to, baseline hemorrhage volume, time to baseline imaging, hematoma growth rate, and OAC serum drug levels both at admission and after treatment with reversal agents. They should also include data on OAC reversal treatment (drug, dosage, and timing), antihypertensive therapy and blood pressure recordings. Finally, care limitations should be incorporated into future studies comparing prognosis after ICH as DNR policies and practices have been shown to be negatively related to survival. The implications of care limitations in the acute ICH setting are further discussed elsewhere in this thesis and are an important source of bias in ICH outcome studies.

Given that NOAC use is steadily increasing, the determination of prognosis comparing NOAC-ICH to VKA-ICH is of diminishing importance. This is particularly valid for high-income countries where NOAC use predominates given its superior side effect profile as previously discussed in the introduction of this thesis. Nevertheless, this study supports the knowledge that patient outcome following NOAC-ICH is non-inferior to patients with VKA related ICH and therefore supports the transition to NOAC use instead of VKA for the majority of non-valvular AF patients.

Reversal treatment in oral anticoagulant-related intracerebral hemorrhage (Paper II)

To date, there are no randomized controlled trials studying the effect of OAC reversal treatment on prognosis after OAC-ICH. Despite the absence of such trials, the use of OAC reversal treatment after acute OAC-related ICH may be of paramount importance in potentially reducing HE, and its use is strongly recommended in both European and American stroke guidelines. The lack of RCTs in this field is in part due to the strong ethical predicament on withholding a potentially beneficial treatment. However, it may also be related to the presence of large, randomized studies showing a lower hemorrhage risk in patients taking NOAC drugs compared to VKA. Thereby, the need for such studies may presumably be given less importance seeing as fewer hemorrhages occur in patients taking NOAC. Nonetheless, as previously mentioned in the introduction of this thesis, the OAC population is growing and with that an increasing number of bleeding complications in patients taking NOACs will follow. Paper II presents retrospective data comparing treatment effects related to the use of reversal therapy in a large OAC-ICH population.

The proportion of patients who died in the OAC reversal treatment group was 33.6%. The corresponding proportion of deaths in patients not receiving reversal treatment was 52.7%. After adjusting for relevant confounders, a higher all-cause fatality at 90 days was associated with not receiving OAC reversal treatment. Additional factors that were associated with a higher death rate following OAC-ICH were male sex, age, and the presence of intraventricular hemorrhage extension. The more favorable survival outcome identified in patients receiving OAC-reversal treatment is in keeping with findings from other observational studies[81,197,198]. Although, these studies were restricted to patients with VKA-ICH. The benefit of OAC reversal therapy remains more ambiguous in NOAC-ICH cases as previous studies have not demonstrated a more favorable outcome following administration of reversal agents, particularly PCC[72,92]. In Paper II, a subgroup analysis was performed on the 235 patients with NOAC-ICH. Overall, 50.2% of NOAC-ICH

patients received reversal treatment and there was no statistically significant treatment effect on the occurrence of death at 90 days in patients who were withheld OAC reversal treatment.

Since LOC is closely related to hemorrhage volume and mortality, the Cox regression model was stratified for this variable. Dramatic death rates were associated with patients who were comatose. At 90 days, 89% of all comatose patients had died. The proportion of deaths at 90 days in alert or drowsy patients at hospital admission was 18.4% and 53.1%, respectively. A recent publication found no benefit in terms of clinical outcome after the administration of PCC for patients with VKA-ICH who had a GCS ≤ 8, although this study was limited by design and sample size[199]. Paper II reports more favorable survival in patients receiving OAC reversal treatment in all LOC categories, including patients who were comatose. These data support the use of reversal agents in the event of OAC-ICH.

A crude real-world analysis of functional outcome at 90 days was also studied in Paper II. Patients receiving reversal treatment often had more favorable mRS outcomes compared to those not receiving treatment. At 90 days, 25.7% of patients receiving reversal treatment were able to walk unassisted compared to 16.3% of those not receiving reversal treatment (mRS 0 – 2, mRS 3).

Retrospective reports on patient outcome related to the administration of reversal agents after OAC-ICH exist, however they are scarce and are often limited by population size or other limitations in their study design. To date, there is no strong evidence supporting the use of OAC reversal treatment in the event of OAC-ICH. Nonetheless, its use is often strongly recommended[80,133]. This recommendation is based on retrospective studies and is strengthened by the pharmacodynamic properties of the specific reversal agents used[91,95,200]. The administration of direct NOAC antidotes, idarucizumab and andexanet alfa, is known to provide rapid reversal of anticoagulant effect in dabigatran and factor Xa inhibitors, respectively[88,97]. The primary indication that supports the use of reversal treatment is the prevention of hematoma expansion. This intervention needs to be administered promptly to patients arriving at the hospital with OAC-ICH as hematoma expansion is a time-dependent gradual process that can result in devastating neurological outcomes particularly in patients taking OAC drugs.

Approximately half (50.2%) of patients with NOAC-ICH received reversal treatment during the study period. This proportion was far higher in patients with VKA-ICH (74.4%). In patients with dabigatran-related hemorrhage, 60% (9/15) received reversal treatment with idarucizumab, and the remaining 40% received no reversal treatment. Andexanet alfa was not available during the study period. As previously mentioned in the introduction of this thesis, the ESO guidelines recommend reversal treatment to all patients with OAC-ICH. The questionable therapeutic effect of PCC in patients with NOAC-related hemorrhages, mentioned previously in this thesis, or reasons associated with indication bias, such as care

limitations or withdrawal of care, may have dissuaded clinicians from employing this treatment. Thereby, as a result of residual confounding, an overestimation of the beneficial treatment effect of OAC reversal therapy may have surfaced in this study. The subject area of OAC-ICH reversal treatment is replete with conflicting results and given the observational design of this study on the effectiveness of OAC reversal treatment, a considerable amount of bias and residual confounding that cannot be accounted for, exist. Hence, the results in this study should be interpreted with caution.

Further studies with the inclusion of prospective data are required to strengthen the current evidence on the prognostic benefit of OAC reversal treatment related to ICH. While the execution of an RCT comparing no treatment versus hemostatic treatment may be ethically questionable, a plausible comparison of treatment effect could include the comparison of andexanet alfa and PCC in a prospective study. It may be beneficial in a health economic perspective to compare the two treatments as the market price for andexanet alfa stands far higher in comparison to PCC, with a price difference of 177 777 SEK per treatment[201], yet the two drugs have previously shown similar treatment effects on outcome in factor Xa inhibitor-related ICH populations. The cost of idarucizumab is similar to PCC, thus a comparison between the two would appear futile in the perspective of health economics.

Large retrospective studies, including indicators related to prognostic outcomes, should be performed to identify potential differences in outcomes related to receiving reversal treatment after acute OAC-ICH. By providing more knowledge in this area, the proportion of patients eligible for OAC reversal treatment may increase from the numbers seen today. Future studies should include variables on time from symptom onset to intervention with a reversal agent, and hematoma volume and expansion. Data on concomitant use of other drugs affecting hemostasis and OAC serum drug levels at admission and following treatment with reversal agents are also of importance. The inclusion of data regarding care limitations is relevant as to avoid withdrawal of care bias. Given the unclear benefit of treatment with reversal agents in terms of reducing hematoma expansion, it is important to determine whether the early administration of a reversal agent could mitigate this effect or if the natural course of OAC-ICH expansion would remain unaffected despite treatment.

As previously discussed in the introduction section of this thesis, the implementation of several acute care interventions, and not just a sole intervention, is essential for approaching the acute ICH patient. Therefore, early management focusing on acute systolic blood pressure lowering, general patient care recommendations, OAC reversal, neurosurgical interventions, as well as an aggressive treatment approach and avoiding early care-limitation orders are paramount in the multifaceted management of acute ICH patients in order to improve outcome.

Prognosis of intracerebral hemorrhage related to antithrombotic use (Paper III)

This study included a large retrospective patient cohort of 13 291 patients with spontaneous ICH between 2012 and 2016 in Sweden. This study reflects patient outcome at 90 days following ICH associated with antithrombotic drug use, including both antiplatelet and oral anticoagulant drugs. We determined that 34% of all patients included in the study had died at 90 days. Ninety-day mortality was 26.3% in patients with no antithrombotic treatment, 43.1% in patients with antiplatelet-ICH, and 43.1% in patients with OAC-ICH. The adjusted 90-day fatality was significantly worse for both OAC-ICH and antiplatelet-ICH patients.

The all-cause fatality within 24 hours was most remarkable, emphasizing the severity of this condition. The death rate was attenuated, yet still significant, at 1 – 7 days. However, at 8 – 90 days the HR for death was no longer significant in patients with OAC-ICH, though still significant in patients with antiplatelet-ICH. Results from several previous studies report that antiplatelet-ICH and non-antithrombotic-related ICH have similar mortality outcomes[73,123-126]. Our data, however, show that antiplatelet-ICH is associated with higher all-cause fatality compared to patients without antithrombotic treatment prior to ICH. This may be in part explained by the age difference and the higher proportion of comorbidities seen in patients treated with antiplatelets compared to patients without antithrombotic treatment. Though, even after adjusting for these patient factors a significant difference was still found.

There are several implications from these findings. Older patients tend to have a greater comorbidity burden as well as a greater burden of cerebral SVD characterised by the presence of cerebral microbleeds, white matter hyperintensities, and enlarged perivascular spaces[202]. Individuals with cerebral SVD who are particularly at risk of ICH are those with cortical microbleeds and cortical superficial siderosis characteristic of lobar CAA[203-206]. The risk of ICH, and specifically recurrent ICH, increases based on the extent of the cerebral SVD burden. Moreover, it is suggested that a greater cerebral SVD burden, particularly cerebral microbleeds, may correlate to larger hemorrhage volumes and worse clinical outcome following ICH[204,207,208].

The presence of cerebral microbleeds has been found to be more prevalent in antiplatelet users even after adjusting for comorbidities related to cardiovascular risk[202,209]. A large meta-analysis based on observational studies including over 20 000 patients aimed to determine whether antiplatelet therapy was associated with an increased risk of cerebral microbleeds and ultimately an increased risk of ICH[209]. This study, by Qiu et al., found that antiplatelet treatment was associated with both an increased risk of cerebral microbleeds and an increased risk of ICH in patients with cerebral microbleeds. A systematic review from 2010 also indicated an

association between the frequency of microbleeds and antiplatelet-related ICH risk[210]. However, it was suggested that the result may be biased due to the heterogeneity of the cohorts included in the paper. In addition, the risk of hemorrhage related to OAC use is elevated in patients with evidence of cerebral SVD[211]. Furthermore, the risk of ICH recurrence is more common following lobar than non-lobar hemorrhage[212], particularly due to the presence of cortical SVD that may be susceptible to hemorrhage given the appropriate conditions.

A large systematic review previously determined that clinicians most often underestimate harms and overestimate benefits of interventions, possibly due to overly optimistic expectations or inadequate knowledge of potential harms[213]. Given the exceptionally high mortality rate associated with antiplatelet-related ICH shown in Paper III, comparable with OAC-ICH, it is important to identify patients who are at a higher risk of hemorrhage, or recurrent hemorrhage, and thus to assess their risk-benefit profile related to antiplatelet treatment. Aspirin itself is widely known to be associated with an increased risk of ICH[103]. Nevertheless, the beneficial effects of antiplatelet drugs in preventing cardiovascular disease in certain high risk patients, including secondary prevention in patients with prior ischemic stroke or myocardial infarction, are outweighed by the risk of ICH[103].

After an ICH event, evaluating the reinstatement of antiplatelet treatment in patients with high cardiovascular risk who require continued antithrombotic treatment is challenging. The RESTART trial studied ICH recurrence in patients reintroduced to aspirin following ICH and found that aspirin was not associated with an increased ICH recurrence risk[214]. However, this trial was subject to selection bias as patients had smaller hemorrhage volumes and the study had a limited population. The Study of Antithrombotic Treatment after Intracerebral Hemorrhage (STATICH) trial is an ongoing randomised, open, blinded end-probe clinical trial also investigating ICH risk after reinstatement of antithrombotic treatment. Results from this trial and from further studies are required to support the findings reported in the RESTART trial.

In Paper III, we found that the death rate between 8 – 90-days post ICH was no longer significant in patients with OAC-ICH compared to patients with non-antithrombotic-related ICH, the opposite was true for antiplatelet-related ICH. A possible explanation for this may be that the larger hemorrhage volumes and the imminent risk of HE associated with OAC-ICH that leads to a higher number of early deaths. This may have heralded the survival of a certain selection of individuals who were fit enough to survive the first week following hemorrhage, thus lowering the death rate between the 8 – 90-day time period. Although data on neuroimaging were unavailable for analysis in Paper III, this presumption is supported by other publications that found an association between ultra-early death and hematoma expansion in patients taking oral anticoagulant drugs[71,215].

Intracerebral hemorrhage is associated with poor functional outcome. In patients with ICH associated with both antiplatelet and OAC drugs, crude data demonstrated

that only 15% of individuals were functionally independent at 90 days (12% lost to follow-up). In comparison, 28% of patients without antithrombotic treatment were functionally independent at 90 days. However, after adjusting for confounding factors, antithrombotic use (AP and OAC) was no longer associated with an increased odds of functional dependency at 90 days compared to patients without antithrombotic treatment. A trend towards a more favorable functional outcome in patients with OAC-ICH was seen, and this may be explained by survivor bias. Factors that were strongly associated with a less favorable functional outcome at 90 days were age, female sex, living alone prior to ICH, previous stroke, diabetes, and the severity of presenting LOC at hospital admission.

The most important finding in this study was that antiplatelet-related ICH displays a significantly higher mortality compared to patients not undergoing antithrombotic treatment prior to ICH. To date, previous clinical trials have not shown positive treatment interventions following antiplatelet-related ICH[106,107,110,116]. These studies are further detailed in the introduction of this thesis. Future study designs should focus on early administration of treatment to prevent HE and ideally identify markers of HE (imaging factors or blood tests) to determine the efficacy of hemostatic treatment with recombinant factor VIIa or tranexamic acid[133]. Our study highlights the importance of evaluating the risk/benefit when initiating treatment with antithrombotic drugs for the prevention of cardiovascular disease. This is especially important in patients with an elevated risk of ICH given the high lethality associated with these agents in the event of an ICH. Further clinical trials are required to determine whether an optimal hemostatic treatment exists for patients with antiplatelet-related ICH considering the poor outcome and the substantial number of patients affected by this disease.

Patient factors associated with receiving reversal treatment in oral anticoagulant related intracerebral hemorrhage (Paper IV)

In this nationwide study on OAC reversal treatment we identified that the overall use of reversal treatment declined by 9% during the study period ($p = 0.009$). This was primarily attributed to the increasing number of NOAC-ICH cases in the total study population over time compared to VKA-ICH cases. The OR for receiving OAC reversal treatment following ICH was 2.99 in patients with VKA-ICH when compared with NOAC-ICH. Prediction analysis was performed to identify patient and stroke characteristics associated with receiving OAC reversal treatment. Patients who were younger, prestroke independent, were having their first ever stroke, and those who had a more favorable presenting LOC were at higher odds of receiving OAC reversal treatment following ICH.

As seen in Riksstroke data and in the GARFIELD trial, NOAC cases are increasing globally, and they will sequentially represent a larger number of patients eligible to receive OAC reversal treatment. However, despite an increase in the number of NOAC-ICH cases, in this study, the proportion of NOAC-ICH patients receiving reversal treatment was only 48%. In contrast, approximately 78% of VKA-ICH patients were given OAC reversal treatment. Given the severe prognosis following OAC-ICH, one might question as to why this proportion is so low. Presumable explanations for the smaller proportion of NOAC patients receiving OAC reversal treatment may exist. In particular, the effect of PCC on attenuating hematoma growth in OAC-ICH has yet to be scrupulously established. Publications regarding the effect of PCC on HE are scarce, and studies oftentimes show conflicting results. Despite the low quality of evidence regarding the prognostic benefit of this intervention, a greater majority of VKA patients still received reversal treatment compared to those taking NOAC. The following section delves into reasons why this may be so.

Several retrospective studies have failed to show an improved survival or functional outcome in patients receiving PCC versus no PCC with NOAC-ICH[72,92]. Additionally, studies on patient prognosis succeeding the administration of direct antidotes idarucizumab or andexanet alfa compared to PCC are infrequent. A recent study reported similar patient outcomes following the administration of PCC versus andexanet alfa for factor Xa inhibitor-related ICH[98], though studies comparing idarucizumab to PCC are scarce. Nevertheless, in vivo studies reporting the hemostatic effect of PCC and direct antidotes, idarucizumab and andexanet alfa, have been performed. Normalization of coagulation parameters after the administration of 37.5 – 50 IU/kg 4F-PCC in healthy individuals treated with factor Xa inhibitors has been reported[93-95]. In addition, the ANNEXA-4 Trial reported that 82% of patients achieved good or excellent hemostatic effect through the reduction of factor Xa inhibitor activity when treated with andexanet alfa[97]. Furthermore, idarucizumab reverses the anticoagulant effect of dabigatran within minutes after administration[88]. Thus, the use of reversal agents is consequently theorized to improve patient outcome by reducing HE based on these hemostatic properties.

In Paper II, we found that 90-day survival following OAC-ICH was more favorable in patients receiving reversal treatment compared to those who did not[216]. However, this outcome was no longer significant when analyzing NOAC- and VKA-ICH independently, possibly due to a loss of power. Consequently, considering conflicting results from previous studies, we presume that treatment decisions are influenced by the ambiguous prognostic benefit associated with the use of reversal treatment for OAC-ICH, and early withdrawal of care. We also consider that decisions may be linked to several other patient factors.

In Paper IV, we aimed to identify specific patient variables associated with lower odds of receiving reversal treatment in order to delineate factors that may influence treatment decisions. In a multivariable logistic regression analysis, we identified

that increasing age, patients with previous stroke, prestroke dependency, comatose presentation following ICH, and NOAC drug use were factors associated with lower odds of receiving reversal treatment. Furthermore, more patients were given OAC reversal therapy at university hospitals compared to county hospitals in Sweden. Although an association between receiving OAC reversal treatment and hospital type was not determined to be significant in the multivariable logistic regression analysis.

Paper IV highlights the importance of future studies evaluating the effect of access to early hemostatic treatment and the potential beneficial effect of OAC reversal treatment on prognosis. Riksstroke began including variables related to OAC reversal treatment in 2017, and we determined that a substantial proportion of NOAC-ICH patients have been withheld reversal treatment in Sweden. The proportion of NOAC-ICH patients receiving reversal treatment was less than 50% regardless of presenting LOC, and OAC reversal treatment was more often withheld in patients who were older. It is therefore clear that better evidence to support the use of OAC reversal agents is required to increase the number of NOAC-ICH patients eligible for this intervention. Contrary to the several advancing treatment options for patients with ischemic stroke, treatment options for ICH management have not progressed as rapidly. This highlights the importance of early and aggressive management of patients with acute ICH, including access to OAC reversal treatment. The need for future clinical trials aimed at determining novel and previously studied interventions for the management of acute ICH to improve patient outcome is paramount. It is important to be able to provide evidence-based acute treatment interventions for patients affected by OAC-ICH as treatment options are limited in this patient group and lethality is high.

Given the limited treatment options for ICH and its corresponding high case fatality, the importance of monitoring clinical practice in patients with ICH using quality registers is crucial to maintain quality control of stroke care by identifying strengths and weaknesses in patientcare at a nationwide level. The implementation and use of a stroke quality register can also provide an opportune basis for the evaluation of any deviations from national guidelines.

Conclusions

The main aim of this thesis was to improve knowledge on functional outcome and mortality outcomes following intracerebral hemorrhage using data from the Swedish Stroke Register, as well as to determine whether treatment with oral anticoagulant reversal therapy can improve patient outcome after intracerebral hemorrhage. Our conclusions are the following:

Paper I — Ninety-day mortality and functional outcome after oral anticoagulant associated intracerebral hemorrhage was similar in patients taking NOAC and VKA drugs.

Paper II — Patients who received oral anticoagulant reversal treatment following OAC-ICH had a more favorable 90-day functional outcome in crude analysis and a more favorable survival rate compared to patients who do not receive OAC reversal treatment. Presenting level of consciousness at hospital admission was strongly associated with mortality, yet the association between the beneficial effect of OAC reversal treatment on improved survival outcome was seen in all stroke severity groups based on LOC.

Paper III — Both antiplatelet and OAC treatment are significantly associated with higher fatality following ICH compared to patients without antithrombotic treatment. However, adjusted 90-day functional outcome was similar in patients with and without antithrombotic treatment. Patients with antithrombotic treatment were more often older, prestroke dependent, and had a higher comorbidity burden compared to patients without antithrombotic treatment. Patients with antithrombotic treatment prior to the ICH event had more severe strokes compared to those without.

Paper IV — Less than half of patients presenting with NOAC-related ICH received OAC reversal treatment, and a greater proportion of VKA-ICH patients received OAC reversal treatment. Patients who were younger, prestroke independent, presented with their first-ever stroke, and who had a more favorable presenting LOC had higher odds of receiving OAC reversal treatment.

Swedish summary

Populärvetenskaplig sammanfattning på svenska

Hjärnblödning är den näst vanligaste typen av stroke efter hjärnpropp (ischemisk stroke). Idag är det cirka 3000 patienter årligen som insjuknar i hjärnblödning i Sverige och cirka 25% av dessa fall inträffar under pågående behandling med ett starkt blodförtunnande läkemedel (antikoagulantia). Antikoagulantia används i allt ökande utsträckning främst för att skydda mot ischemisk stroke vid förmaksflimmer, vilket är en oregelbunden hjärtrytm som ökar risken för stroke. Behandlingen har stark evidens, men leder till ett ökat antal patienter som får hjärnblödning eller annan blödningskomplikation. Antalet patienter som behandlas med antikoagulantia ökar årligen både inom Sverige och globalt. Detta medför ett växande medicinskt problem då antalet patienter som insjuknar med hjärnblödning under denna behandling kommer sannolikt parallellt att öka. Det behövs mer kunskap om hur dessa patienter bäst skall behandlas och vilken effekt läkemedel som upphäver den antikoagulerande effekten vid hjärnblödning har. Mindre kraftfulla blodförtunnande läkemedel som påverkar blodplättarna (trombocythämmande läkemedel) är en annan läkemedelstyp som används i stor utsträckning inom befolkningen för att förebygga hjärt- och kärlsjukdomar. Det är inte helt klarlagt huruvida de lättare blodförtunnande läkemedlen är förknippade med en sämre prognos efter hjärnblödning än hos de som inte står på någon blodförtunnande behandling alls.

Ökad kunskap om förekomst, orsaker, behandlingar och prognos kan leda till bättre handläggning av patienter med hjärnblödning. Det saknas beskrivande studier av prognos efter hjärnblödningar inom Sverige, främst hos patienter som står på blodförtunnande behandling med antikoagulantia men även hos de som står på lättare blodförtunnande behandlingar med trombocythämmande läkemedel. Denna avhandling har till syfte att ge en heltäckande beskrivning av förekomst, patientfaktorer, tillgång till behandling, samt olika typer av prognoser efter hjärnblödning med särskild fokus på patienter som insjuknar under pågående antikoagulantiabehandling.

Alla studier baseras på data från Riksstroke, det svenska kvalitetsregistret för strokesjukvård, och är registerstudier. Patientinformation har uthämtats från Riksstroke för patienter som insjuknat i tidsspannet 2012 – 2019. Data har även hämtats från Läkemedelsregistret och Dödsorsaksregistret.

Delarbete I Beskriver överlevnad och funktionsförmåga tre månader efter hjärnblödning under pågående antikoagulantiabehandling och jämför patienter som står på det äldre läkemedlet Warfarin med dem som står på nyare antikoagulantiabehandlingar, så kallade Non-Vitamin K Orala Antikoagulantia (NOAK). Överlevnad och funktionsförmåga skiljde sig inte mellan patientgrupperna. Vid tre månader efter insjuknandet hade cirka 43% av patienterna avlidit och enbart 15% var oberoende av hjälp i vardagen.

Delarbete II Analyserar effekten av läkemedel som upphäver den blodförtunnande behandlingen, med avseende på prognos hos patienter som insjuknar med hjärnblödning under behandling med antikoagulantia. Behandling med läkemedel som motverkar den blodförtunnande effekten av antikoagulantia ledde till en förbättrad tremånadersöverlevnad gentemot patienter som inte fick tillgång till denna typ av behandling. Bland enskilda patientattribut var manligt kön, sänkt medvetandegrad, ålder samt blödning inom hjärnans inre hålrum associerad med en sämre prognos.

Delarbete III Beskriver skillnader avseende överlevnad samt funktionsförmåga vid tre månader hos patienter utan någon blodförtunnande behandling, hos dem som behandlas med trombocythämmandeläkemedel samt hos dem som behandlas med antikoagulantia (Warfarin eller NOAK). Både lättare blodförtunnande och antikoagulantiabehandling var förknippade med en sämre överlevnad vid tre månader, men inte en sämre funktionsförmåga hos överlevande, än hos patienter utan pågående blodförtunnande behandling.

Delarbete IV Fokuserar på patientfaktorer som är förknippade med behandling med läkemedel som upphäver den blodförtunnande effekten hos personer som insjuknar med hjärnblödning under pågående antikoagulantiabehandling. Mindre än hälften av patienterna som ingick i studien fick tillgång till denna typ av behandling trots pågående antikoagulantia vid insjuknandet. Färre behandlades med antidot i gruppen som medicinerade med nyare antikoagulantia (NOAK). Patienter som var yngre, levde ett självständigt liv före hjärnblödningen, hade sitt första strokeinsjuknande, och patienter som var vakna vid ankomst till sjukhus fick behandling som upphäver den blodförtunnande effekten i större utsträckning.

Sammanfattningsvis beskriver avhandlingen den dåliga prognosen som är förknippad med hjärnblödningar utifrån en stor patientgrupp med tillförlitligt patientmaterial. Pågående behandling med lättare blodförtunnande läkemedel eller antikoagulantiabehandling är associerat med en ökad dödlighet jämfört med

patienter som inte stod på blodförtunnande behandling vid insjuknandet i hjärnblödning. Resultaten visar också på att patienter som behandlas med läkemedel som upphäver den antikoagulantiaeffekten har bättre överlevnad gentemot dem som inte erhåller en sådan behandling. Trots detta är det under hälften av patienterna som står på de nyare antikoagulantia som erbjuds denna behandling även om man ser att denna patientgrupp ökar över tid. Detta belyser att det finns en inkonsekvent hållning mellan Socialstyrelsens riktlinjer och det som praktiseras vid sjukhusen. Anledningen till att kvalitetsregister som Riksstroke är nödvändiga och samhällsviktiga är för att kunna bevaka och påvisa brister i vården som kan leda till eventuella förbättringar inom strokevården och förbättra återhämtningen efter stroke. Våra resultat belyser även att lättare blodförtunnande behandlingar är förknippade med en hög dödlighet och att dessa läkemedel ska användas med rätt indikation för att minska risken för allvarliga blödningskomplikationer.

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About the author

TRINE APOSTOLAKI-HANSSON is a clinical neurologist at Skåne University Hospital in Sweden and a member of the Stroke Policy and Quality Register Research Group at Lund University. Intracerebral hemorrhage (ICH) is a life-threatening type of stroke that is associated with high fatality rates, and survivors often experience physical dependence in daily activities. This thesis aims to advance knowledge regarding prognostic outcomes following ICH and to define the patient characteristics of those affected by this type of stroke, based on data from the Swedish Stroke Register, Riksstroke.

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