

Cardiovascular Events after Intracerebral Hemorrhage

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Abstract

Cardiovascular events after primary intracerebral hemorrhage (ICH) have emerged as a leading cause of poor functional outcomes and mortality during the long-term recovery after an ICH. These events encompass arterial ischemic events such as ischemic stroke and myocardial infarction, arterial hemorrhagic events that include recurrent ICH, and venous thrombotic events such as venous thromboembolism. The purpose of this review is to summarize the cardiovascular complications after ICH, epidemiology and associated risk factors, and their impact on ICH outcomes. Additionally, we will highlight possible pathophysiological mechanisms to explain the short and long-term increased risks of ischemic and hemorrhagic events after ICH. Finally, we will highlight potential secondary stroke and venous thrombotic prevention strategies often not considered after ICH, balanced against the risk of ICH recurrence.

Non-Standard Abbreviations:

CAA cerebral amyloid angiopathy

DWI diffusion-weighted imaging

DVT deep venous thrombosis

ICH intracerebral hemorrhage

PE pulmonary embolism

VTE venous thromboembolism

Introduction

Intracerebral hemorrhage (ICH) is the most devastating form of stroke that affects about 2.9 million people worldwide every year.¹ For decades, ICH has remained the least treatable form of stroke with a high associated mortality and morbidity.² Over a third of patients who survive an ICH can recover in the first year.³ However, nearly one in four ICH survivors with mild to moderate disability initially, experience long-term functional decline, mainly due to acute cerebrovascular and cardiovascular events.⁴ In fact, incident and recurrent vascular events are a leading cause of readmissions in ICH patients, second only to infections.^{5,6} Major arterial events, particularly, ischemic stroke and ischemic cardiovascular disease account for nearly 15% of deaths after ICH.⁷ Despite these emerging data, secondary prevention efforts after ICH focus mainly on blood pressure control and current guidelines equivocate about the use of antithrombotic and statin medications due to concerns about ICH recurrence.⁸ This review discusses the types of major vascular events after ICH (Figure 1), their epidemiology, purported mechanisms, impact on ICH outcomes, and potential prevention strategies, in an effort to improve overall brain and systemic health.

1. ICH and arterial ischemic events

ICH is traditionally believed to mostly increase the risk of ICH recurrence⁹, but emerging data have shown that ICH survivors may also face a heightened risk of major arterial ischemic events. Large case series have reported rates of arterial ischemic events after ICH, particularly acute ischemic stroke which varies from 3-7%^{10,11} (Table 1), and myocardial infarction which may be

as high as 4%.^{12,13} A longitudinal analysis from the U.K. that pooled data from two prospective, population-based studies with 674 ICH patients evaluated the incidence of a serious vascular event defined as a composite of recurrent ICH, nonfatal ischemic stroke, non-fatal myocardial infarction, or vascular death. The pooled event rates for a serious vascular event were 15.5% (95% CI, 10.0-24.1%) and 6.8% (95% CI, 3.6-12.5%) among patients with and without atrial fibrillation, respectively.¹⁴ In a population-based record linkage study from the Netherlands comprising nearly 2,000 ICH survivors, the 1-year cumulative rate of an arterial ischemic event or vascular death was slightly higher among men compared to women, in the 55-74 years (9.2% vs. 7.4%) and 75-94 year age groups (14.6% vs. 14.1%).¹⁵ The 10-year rates reached as high as 40% in the elderly age group, suggesting that ICH survivors experience major arterial ischemic events, both short- and long-term.¹⁵ In terms of timing of arterial ischemic events after ICH, prior studies have mostly considered the time after discharge from the ICH or the first 30 days after the index ICH, with the follow-up period extending anywhere between 1 and 10 years (Table 1). Exclusion of the first few weeks after ICH was done due to the high 30-day mortality of ICH, which may yield erroneously high rates of arterial ischemic events.

However, these studies did not include a control group; consequently, the exact nature of the risk of an arterial ischemic event after ICH could not be inferred from these studies. A recent pooled analysis of patient-level data from four U.S. population-based studies with nearly 50,000 participants showed that ICH was associated with an increased risk of an arterial ischemic event (adjusted hazard ratio [aHR], 2.3; 95% CI, 1.7-3.1), compared to the general population, which corresponded to an incidence rate of 3.6% per year versus 1.1% in the general population.¹⁶ Similarly, the risks of ischemic stroke (aHR, 3.1; 95% CI, 2.1-4.5) and myocardial infarction

(aHR, 1.9; 95% CI, 1.2-2.9) were also high after ICH.¹⁶ This risk was consistently elevated both short-term (<1 year after ICH) and long-term (>1 year after ICH), regardless of vascular risk factors including atrial fibrillation and antithrombotic medication use. Although this risk is elevated long-term, there may be a higher risk short-term after the index ICH as observed in an analysis of 1.8 million Medicare beneficiaries in the U.S. where the risk of an arterial ischemic event after ICH was highest in the first 6 months, with the 1-year cumulative incidence being 5.7% (95% CI, 4.8–6.8) in patients with ICH and 1.8% (95% CI, 1.7–1.9) in patients without ICH.¹⁷ Further support for the heightened risk of a major arterial ischemic event after ICH comes from a cohort study of 988 subjects from the U.K., where patients with an ICH experienced had a 2.5 times higher risk of an ischemic stroke as compared to the general population (sub HR, 2.49; 95% CI, 1.85-3.34).¹⁸ Even among patients without atrial fibrillation, a higher risk of ischemic stroke was observed after ICH (sub HR, 2.28; 95% CI, 1.65-3.16), albeit this risk was nearly half of what was noted in ICH patients with atrial fibrillation (sub HR, 5.47; 95% CI, 2.16–13.83).¹⁸

ICH characteristics and risk of arterial ischemic events

The majority of population-based cohort studies assessing the risk of a major arterial ischemic event after ICH lack data on ICH severity characteristics such as hematoma volume, location, and presence of intraventricular hemorrhage. Given the different biological processes implicated in lobar and deep ICHs, hematoma location is of great interest¹⁹; however, studies have yielded conflicting results. For instance, a prospective observational study by Casolla and colleagues evaluated 560 ICH patients and found that the 1-year cumulative incidence of major arterial ischemic events was about twice higher after a deep ICH, compared to a lobar ICH (7.3% vs.

3.5%).²⁰ Conversely, ICH recurrence was nearly 3-fold higher in the lobar ICH group (6.1% vs. 2.6%). A deep ICH was independently associated with an increased risk of a major arterial ischemic event (sub HR, 1.85; 95% CI, 1.01-3.40), compared to a lobar ICH.²⁰ Contrary to these findings, the prospective multi-center Clinical Relevance of Microbleeds in Stroke study (CROMIS-2) study, with 1,094 ICH patients reported similar absolute event rates of about 3% for a cerebral ischemic event (ischemic stroke or transient ischemic attack) in lobar and deep ICH.²¹ Cox regression analysis did not reveal a relationship between hematoma location and a subsequent cerebral ischemic event (aHR, 1.13; 95% CI, 0.66-1.92). Notably, while only 11% of the population had atrial fibrillation in the former study (Casolla et al.)²⁰, the rate of atrial fibrillation at baseline was 37% in the CROMIS-2 study.²¹ It is therefore possible that a high rate of prevalent atrial fibrillation confounded the relationship between hematoma location and an ischemic arterial event after an index ICH. Interestingly, admission hematoma volume did not influence arterial ischemic events, but a prior history of ischemic stroke or TIA was associated with a higher risk of an arterial ischemic event in both studies.^{20,21} Lastly, a meta-analysis of population-based and hospital-based studies showed a non-significant trend toward a lower risk of major vascular events in lobar ICH (relative risk [RR], 0.8; 95% CI, 0.5-1.2).¹⁴

ICH and covert cerebral infarction

Covert cerebral infarction is nearly 4 times more common than clinically apparent strokes.²² It is therefore not surprising that acute punctate ischemic infarcts occur in about a third of all ICH patients, as seen on the diffusion-weighted imaging (DWI) sequence of a magnetic resonance imaging scan, and can be spatially in the surrounding vicinity or remote from the index hematoma (Figure 2).^{23,24} Although most studies have reported the incidence of DWI lesions in

the first week after ICH, these lesions may appear as late as 30 days after ICH.^{25,26} Factors implicated in DWI lesions include admission ICH volume, aggressive blood pressure reduction in the acute phase, and pre-existing imaging markers of cerebral small vessel disease- cerebral microbleeds and white matter hyperintensities^{25,27}, but the exact underlying mechanism has yet to be discerned. Furthermore, underlying stroke mechanisms may influence the pattern of DWI lesions after ICH. For instance, large artery atherosclerosis in conjunction with blood pressure reduction was associated with large DWI lesions after ICH, while cerebral small vessel disease burden was associated with punctate DWI lesions in a prospective study of 305 ICH patients.²⁸ DWI lesions have been shown to adversely affect long-term functional outcomes after ICH.^{25,27} Moreover, these lesions may serve as markers for future arterial ischemic risk as observed in a post hoc exploratory analysis of two large ICH trials, where the authors concluded that the presence of a DWI lesion was associated with a 6.9% (95% CI, 2.2-11.6) absolute increase in risk of all stroke that corresponded to a HR of 2.6.²⁹ There was also an increased risk of ischemic stroke (aHR, 3.5; 95% CI, 1.1-11.0). A contemporary study of ICH patients enrolled in the REstart or STop Antithrombotics Randomised Trial (RESTART), found that a DWI lesion was associated with all stroke, (aHR 2.2; 95% CI 1.1 to 4.2) and recurrent ICH (aHR, 4.8; 95% CI 1.8 to 13.2), but not ischemic stroke.³⁰ Both studies, however, were limited by few outcome events that precluded adequate adjustment of covariates. Nevertheless, DWI lesions offer an insight into the microvascular mechanisms associated with recurrent cerebrovascular disease.

Arterial ischemic events and ICH outcomes

Patients who survive the acute phase of ICH often make substantial recovery during the months and years after the event.³ Acute vascular events, mainly stroke, are the second most common

reason for readmissions after ICH, after infections.^{5,6} A longitudinal analysis of prospectively collected claims data in the U.S. showed that cardiac disease and ischemic stroke accounted for nearly 8% and 5% of deaths among ICH survivors with atrial fibrillation, respectively.⁷ In fact, even among younger ICH patients (18-55 years), recurrent stroke was the cause of death in 15% of patients.³¹ In addition to being increasingly recognized as a cause of death or readmission after ICH, arterial ischemic events have been shown to adversely affect long-term ICH recovery. For instance, a retrospective cohort study of U.S. Medicare beneficiaries reported a two-fold increased risk of death from an arterial ischemic event among ICH survivors.³² Recurrent stroke, ischemic or hemorrhagic, was associated with a 4-fold heightened risk of functional decline and disability in a single-center, prospective study of 560 ICH patients who survived at least 6 months.⁴ These data collectively suggest that new arterial ischemic events are not uncommon after ICH, and portend poor prognosis. In a registry study from Finland, patients with ICH who showed good recovery at 3 months went on to have similar outcomes as age- and sex-matched controls.³³ In the context of these findings, one may surmise that prevention of incident arterial ischemic events can potentially improve long-term recovery and clinical outcomes after ICH.

Mechanisms of arterial ischemic events after ICH

The elevated risk of ischemic stroke may be attributable to antithrombotic drug cessation after the ICH diagnosis and the lack of an optimal time frame for resumption of these medications. For example, studies have reported that fewer than 50% of patients resume antithrombotic agents in the first year after ICH despite strong indications.³⁴ However, prior studies suggested that only about 20% of patients were on antithrombotic medications prior to ICH³⁵, and rates of observed ischemic strokes among ICH survivors with atrial fibrillation exceed those of expected events for

a given CHA₂DS₂-Vasc score.³⁶ The use of statin medications has also been controversial after ICH. While observational data seem to suggest a 40% risk reduction of major cardiovascular events with the initiation or resumption of statin therapy after ICH³⁷, the presumed increased risk of ICH recurrence, particularly among patients with a lobar ICH, adds to the complexity of clinical decision making.³⁸ Taken together, these factors fail to implicate cessation of antithrombotic medications as the sole mechanism of increased thrombotic risk after ICH.

Another potential explanation is poor risk factor control after ICH. Uncontrolled blood pressure has been demonstrated in one third to half of patients after an ischemic stroke^{39,40}, and these patients have significantly worse blood pressure and risk factor control compared to patients with other cardiovascular conditions such as acute MI.⁴¹ This is further supported by the results of a U.S. population-level study, where survivors of ischemic stroke did not experience improvements in cardiovascular health due to secondary prevention efforts that included seven domains -smoking, diet, physical activity, body mass index, blood pressure, total cholesterol, and fasting glucose.⁴² Given that ICH survivors have more disability than ischemic stroke patients, risk factor control is presumably worse after ICH.

2. Recurrent ICH after primary ICH

Long-term risk of ICH recurrence

The reported annual rates of ICH recurrence range from 0.9% to 11.6% in published literature (30 studies: 8 population-based and 22 hospital-based) as shown in Table 1. Possible reasons for the wide range of recurrent ICH likely include differences in study cohorts with some being enriched with hypertensive ICH while others with a higher proportion of cerebral amyloid

angiopathy (CAA), which confers a higher risk of ICH as discussed in the section below. Interestingly, unlike the significant reduction in the recurrence of transient ischemic attack or ischemic stroke over the years,^{43,44} rates of recurrent ICH after primary ICH did not improve over the past four decades (Table 1).

Risk factors for ICH recurrence

Hematoma location has been shown to be one of the strongest risk factors for recurrent ICH. In a meta-analysis combining seven published studies looking at risks of recurrent ICH by hematoma location, Li et al. found that lobar ICH was associated with a 2-fold increased risk of recurrent ICH compared to non-lobar ICH (RR, 2.3; 95% CI 1.5-3.3).¹⁴ The annual rate of recurrent ICH was 5.1% after lobar ICH and 1.8% after non-lobar ICH in a pooled analysis of two contemporary prospective population-based studies.¹⁴ The higher risk of recurrent ICH after lobar ICH is likely explained by the high prevalence of CAA in the group. CAA is a bleeding-prone vasculopathy resulting from beta-amyloid deposition in cortical blood vessels, and a previous meta-analysis showed that CAA-related ICH was associated with a significantly higher risk of recurrent ICH (7.4%) compared to non-CAA-related ICH (1.1%).⁴⁵ A recent large cohort study of 194,290 patients with ICH also found that ICH patients with a concomitant diagnosis of CAA were three times more likely to have recurrent ICH compared to patients without CAA even after controlling for potential confounders.⁴⁶ Another contributing factor for the higher ICH recurrence after lobar ICH is worse blood pressure control compared to non-lobar ICH. In fact, less than half of lobar ICH survivors were on blood pressure lowering treatment at hospital discharge while 71% of patients with non-lobar ICH were treated with antihypertensive medication.¹⁴ Furthermore, Biffi et al.⁴⁷ showed that inadequate control of blood pressure during

follow-up was an independent risk factor (lobar ICH: aHR, 3.53; 95% CI 1.67-7.54; non-lobar ICH: aHR, 4.23; 95% CI, 1.02-17.52). Of note, 20-50% of the ICH patients have hematomas involving both lobar and deep areas and tend to share the same risk profile for ICH recurrence as that of hypertension-related deep ICH.⁴⁸⁻⁵⁰

The risk of ICH recurrence is also influenced by race. Rodriguez-Torres et al. showed that among 2,291 ICH survivors, Black (aHR, 1.98; 95% CI 1.36-2.86) and Hispanic patients (aHR, 1.51; 95% CI, 1.14-2.00) were at higher risks of recurrent ICH.⁵¹ Similarly, in a retrospective cohort analysis of 31,355 patients with ICH, a higher risk of ICH recurrence was observed among Black (aHR, 1.22; 95% CI, 1.01-1.48) and Asian patients (aHR, 1.29; 95% CI, 1.10-1.50) compared to White patients.⁵² While the mechanisms underlying these racial/ethnic differences remain unclear, emerging evidence suggest that socioeconomic factors that are more likely to disproportionately affect minorities resulting in higher premorbid blood pressure and consequently, higher burden of cerebral small vessel disease.^{47,51,53} Other proposed independent risk factors for recurrent ICH include age, prevalence of cerebral small vessel disease (i.e. disseminated cerebral superficial siderosis, enlarged perivascular space in the centrum semiovale, cerebral microbleeds and white matter changes),^{48,54-57} previous history of ischemic stroke,^{58,59} and renal impairment.⁶⁰

ICH Characteristics of recurrent ICH

Recurrent ICH often tends to involve similar regions of the brain as the index ICH. In a study of 464 ICH survivors, most recurrences were “lobar-lobar” type⁶¹, and recurrences occurred in the

same type of location (lobar vs. non-lobar) as the index ICH, although the exact location of recurrence was only the same in only 33% of the patients.⁶² However, in populations with a high incidence of hypertension-related deep ICH, the most common location of recurrent ICH was deep ganglionic, with a younger age of onset.⁵¹ In addition to the hematoma location, recurrent ICH also shares the underlying pathology as the index ICH, as observed in a prospective study of 185 patients with recurrent ICH, where the pathology between the recurrent and the index events were in agreement in 151 cases (81.6%).⁶³ In two population-based studies in the UK, recurrence after lobar ICH were all lobar whereas up to 50% of the recurrence after non-lobar ICH was also lobar.¹⁴ Recurrent ICH is usually severe, resulting in severe disability in about half of patients⁶⁴, and death in over a third of patients.^{14,62}

Timing of ICH recurrence

Very few studies reported the time-course of recurrent ICH. The risk of recurrent ICH was most marked in the first 90 days, especially for lobar ICH, although the risk was still high beyond the subacute phase.¹⁴ Hanger et al. also found that of 464 ICH survivors, recurrence rate for ICH was higher in the first year (2.1%) while overall the risk was 1.2%.⁶¹ The front-loading risk of recurrent ICH has potential clinical implications as it identifies a group of most vulnerable patients who might benefit from more effective prevention efforts. Secondary prevention trials are evaluating therapies such as intensive blood pressure control (NCT02699645 and NCT03863665), and resumption of antithrombotic and lipid lowering medications, with an eye on the safety endpoint of ICH recurrence.⁶⁵⁻⁶⁸

3. Venous thromboembolism after ICH

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), are serious complications after ICH and prior studies have focused on the risk of VTE mainly during the acute and subacute phases of ICH. The overall rate of symptomatic VTE after ICH ranges from 2-5% (Supplemental Table S1), with the incidence being higher in patients admitted to the intensive care unit.^{69,70} With routine screening, the incidence may be as high as 25% by the end of two weeks of hospitalization.⁷¹ The rate of new symptomatic VTE is 2-3 fold higher after ICH than after ischemic stroke (Supplemental Table S1).⁷²⁻⁷⁵ Furthermore, the cumulative rate of VTE in a heterogeneous U.S. cohort was 4.7% (95% CI, 4.5-4.9) at 7 years after ICH, which was similar to that after ischemic stroke (4.4%, 95% CI, 4.3-4.5).⁷⁶ The time course for the development of VTE was, however, different between ICH and ischemic stroke, with the VTE risk being higher in the first year after ICH than after ischemic stroke. The occurrence of VTE may be influenced by race and ethnicity as noted in a systemic review where the risks of DVT and PE were higher among Black and Asian patients compared to White patients (DVT: 2.0%, 7.1% and 12.5% at 3 months for White, Asian and Black patients respectively; PE: 0.8%, 1.4% and 4.2%, respectively).⁷⁷

Timing and Risk Factors for VTE after ICH

Although data on the time course of VTE after ICH are limited, it is commonly believed that the highest risk is in the acute phase of ICH. DVTs may occur as early as day 2, peaking between days 3 and 7, but could very well continue after the acute phase.⁷⁸ The majority of the studies

reported a mean/median time to symptomatic VTE diagnosis of around 5-20 days (Supplemental Table S1). Commonly recognized risk factors for VTE include age, prior history of VTE, hemiplegia, immobility, high NIHSS score at baseline, intubation, presence of IVH and prolonged length of stay.^{79,80} High D-dimer has also been shown to be associated with venous clots in some studies.^{71,81} More recently, concurrent infection was also proposed as a strong risk factor for VTE after ICH.^{82,83} Melmed et al. reported that any infection was associated with increased risk of VTE (adjusted odds ratio [aOR], 4.5; 95% CI, 1.6-12.6), which was driven predominantly by respiratory (aOR, 5.7; 95% CI, 2.8-11.7) and blood stream infections (aOR, 4.0, 95% CI, 1.3-11.0).⁸²

VTE prophylaxis and treatment after ICH

As VTE is independently associated with poor outcome in patients with ICH,⁸⁴ prophylaxis is important. One early study showed that without prophylaxis, three quarters of the ICH patients with hemiplegia developed a DVT, and PE-related death occurred in about 5% of the patients.^{78,85} Intermittent pneumatic compression (IPC) devices have been used extensively in the hyper acute phase of ICH for VTE prophylaxis, based on the results of the Clots in Legs Or sTockings after Stroke 3 (CLOTS 3) trial, with international guidelines including those from the American Heart Association/Stroke and European Stroke Organisation advocating their use (Table 2).^{8,86} Among 2876 acute stroke patients including 376 with ICH, use of IPCs was associated with a significant reduction in the risk of DVTs at 30 days (8.5% vs. 12.1%), and a significant reduction in death at 6 months (aHR, 0.86, 95% CI, 0.74-0.99).⁸⁷ Studies assessing the efficacy of pharmacological prophylaxis after ICH have yielded conflicting results with one network meta-analysis not showing any relationship between prophylaxis and incident VTE (OR,

0.93; 95% CI, 0.19-4.37)⁸⁸, while an earlier meta-analysis found that anticoagulation chemoprophylaxis initiated between 1 and 6 days after admission did result in a significant reduction in PE (1.7% vs. 2.9%, RR, 0.37; 95% CI, 0.17-0.80).⁸⁹ Several guidelines including the American Heart Association/Stroke⁸, recommend the use of low-dose chemoprophylaxis after the demonstration of hematoma stability, but their implementation in the real-world setting has been surprisingly low. In a retrospective cohort study using a large U.S. administrative database, Prabhakaran et al. showed that less than a fifth of ICH patients received anticoagulation for VTE prophylaxis, and among those where anticoagulation was initiated, less than half of the patients had a time to initiation of less than two days.⁹⁰ Should VTEs be diagnosed after ICH, treatment options include anticoagulation, inferior vena cava filter, and specifically in case of PEs, thrombolysis and mechanical thrombectomy.⁹¹ However, as patients with ICH were excluded from randomized trials on anticoagulation therapy for VTE, there is lack of high-quality evidence for the treatment of VTE after ICH, especially during the acute phase when hematoma expansion and recurrence risks may be high.

Conclusion

To summarize, 2.9 million patients experience intracerebral hemorrhage each year worldwide,¹ and many of these patients survive and can recover.³ Intracerebral hemorrhage may be a risk marker for cardiovascular disease.^{92,93} Emerging data indicate that patients with ICH are not only at risk for recurrent bleeding, but also at a higher risk of arterial ischemic events than the general population. There is, however, equipoise about the use of established strategies like antithrombotic and lipid-lowering medications after ICH.⁸ . In light of the increased risk of

arterial ischemic events, the focus should also be on de novo initiation of secondary stroke prevention and not just reinstatement of previous medications. Further research is needed to aid the careful selection of specific ICH populations (such as deep ICH) and underlying etiologies (like atrial fibrillation), where the benefit of prevention outweighs the risk of recurrent ICH. This review highlights the need for randomized clinical trials to assess the net clinical benefit of antithrombotic therapy and statin medications in this high-risk population.⁹⁴⁻⁹⁶

Disclosures

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Figure Legend

Figure 1: Schematic Diagram Highlighting Cardiovascular and Cerebrovascular Events after Intracerebral Hemorrhage.

Figure 2: Diffusion-Weighted Imaging (DWI) Lesion after Intracerebral Hemorrhage. Computed Tomography Scan (Panel A) and Magnetic Resonance Imaging Scans of the Hematoma (Panel B) and DWI lesion (Panel C).

Table 1. Annual rates (per 100 patient-years) of Recurrent Intracerebral Hemorrhage (ICH) and Ischemic Stroke (IS) in Patients with Primary Intracerebral Hemorrhage Reported in Previous Studies.

Study	Country	Study period	Total number of patients	Mean/Median follow-up	Recurrent ICH (No/annual rate)	Recurrent IS (No/annual rate)
Population-based						
Counsell ^{97,98}	UK	1981-1986	66	1.5 years	4 (4.4%)	2 (2.1%)
Inagawa ⁹⁹	Japan	1991-1998	279	3.1 years	19 (2.3%)	-
Huhtakangas ⁵⁸	Finland	1993-2008	680	3.6 years	58 (1.7%)	-
Pennlert ¹⁰⁰	Sweden	1995-2008	815	3.1 years	38 (1.5%)	63 (2.5%)
Flach ¹⁰¹	UK	1995-2018	364	3.0 years	19 (1.7%)	9 (0.8%)
Li ¹⁴	UK	2002-2018	255	2.5 years	15 (2.4%)	7 (1.1%)
Poon ¹⁴	UK	2010-2018	419	1.9 years	31 (3.9%)	18 (2.3%)
Aked ¹⁰²	Sweden	2015-2016	60	1.0 year	0 (0)	1 (1.7%)
Hospital-based						
Passero ⁶²	Italy	1978-1982	112	7.0 years	27 (3.4%)	8 (1.0%)
Vermeer ¹⁰³	Netherlands	1986-1995	243	5.5 years	30 (2.1%)	16 (1.4%)
Hill ¹⁰	Canada	1986-1996	172	3.6 years	15 (2.4%)	19 (3.0%)
Zia ¹¹	Sweden	1993-2000	353	3.0 years	20 (2.3%)	24 (2.8%)
Viswanathan ¹⁰⁴	US	1994-2004	207	1.6 years	39 (11.6%)	7 (2.1%)
Robert	UK	1994-2005	417	3.0 years	14 (0.9%)	29 (2.3%)
Biffi ⁴⁷	US	1994-2013	1,145	3.1 years	146 (4.2%)	-
Yeh ⁶³	Taiwan	1995-2013	3,785	3.9 years	185 (1.3%)	-
Hanger ⁶¹	New Zealand	1996-2004	768	4.0 years	19 (1.2%)	17 (1.3%)
Chong ¹⁰⁵	HK	1996-2010	440	5.2 years	47 (2.1%)	29 (1.3%)
Weimar ¹⁰⁶	Germany	2002-2006	496	2.0 years	11 (1.1%)	21 (2.1%)
Asberg ¹⁰⁷	Sweden	2004-2009	6,082	3.2 years	234 (1.2%)	350 (1.9%)
Casolla ²⁰	France	2004-2009	310	6.0 years	24 (1.3%)	33 (1.8%)
Skajaa ¹⁰⁸	Denmark	2004-2018	13,387	1.6 years	531 (2.5%)	534 (2.5%)
Leasure ⁵²	US	2005-2011	31,355	2.9 years	1330 (1.5%)	-
Qiu ⁵⁹	Singapore	2006-2013	1,708	3.7 years	60 (1.1%)	-
Rodriguez-Torres/MGH ⁵¹	US	2006-2013	759	4.2 years	118 (3.9%)	-
Castello/ENRICH ⁵³	US	2006-2017	329	1.5 years	49 (2.9%)	-
Kubiszewski ¹⁰⁹	US	2006-2017	1,279	4.4 years	128 (4.2%)	-
Castello/MGH ⁵³	US	2010-2017	593	3.9 years	62 (4.2%)	-
Banerjee ¹¹⁰	UK	2011-2015	1,094	3.0 years	45 (1.9%)	70 (2.9%)
Tsai ⁴⁸	Taiwan	2014-2018	300	1.9 years	36 (6.3%)	12 (2.1%)

Studies were included if they reported annual rates of recurrent intracerebral hemorrhage or ischemic stroke, or if they reported the crude numbers of recurrent stroke and patient-years of follow-up.

Table 2. Recommendations for Venous Thromboembolism Prophylaxis in Recent Guidelines for Patients with Intracerebral Hemorrhage

Guideline	Recommendation:			Recommendation:		
	Mechanical	Timing	Quality of evidence	Pharmacological	Timing	Quality of evidence
AHA/ASA 2015 ⁸	Patients with ICH should have IPC	Day of hospital admission	High	After documentation of cessation of bleeding, low-dose LMWH or UFH may be considered in patients with lack of mobility	After 1 to 4 days from onset	Moderate
Australia and New Zealand 2022 ¹¹¹	IPC may be used"	Not specified	Weak	Pharmacological prophylaxis may be considered once haematoma growth has stabilized	After 48-72 hours	Weak
ESO 2014 ⁸⁶	Recommend IPC in immobile patients.	Not specified	Moderate	No recommendation	Not specified	Low
HSFC 2020 ¹¹²	Patients should be started on IPC devices	Day of hospital admission	High	LMWH can be initiated after documentation of hematoma stabilization on neuroimaging	After 48 hours	Moderate
NICE 2018 ¹¹³	Consider IPC for people who are immobile.	Within 3 days from onset	Not mentioned	No recommendation	NR	NR

ESO=European Stroke Organisation; AHA/ASA=American Heart Association/American Stroke Association; NICE=National Institute for Health and Care Excellence; HSFC=Heart and Stroke Foundation of Canada. IPC=Intermittent Pneumatic Compression.