Journal of Population Therapeutics & Clinical Pharmacology

Review
DOI: 10.15586/jptcp.v27i2.660

Antithrombotics in intracerebral hemorrhage in the era of novel agents and antidotes: A review

Dimitrios Giakoumettis[1], Dimitrios A. Vrachatis[2], Dimitrios Panagopoulos[3], Asimina Loukina[2], Georgios Tsitsinakis[2], Katerina Apostolopoulou[3], Georgios Giannopoulos[3], Sotiria G. Giotaki[4], Spyridon Deftereos[4,5], and Marios S. Themistocleous[3]

[1]Department of Neurosurgery, Centre Hospitalier de Wallonie picarde - CHwapi A.S.B.L., Site UNION, Tournai, Belgium

[2]Department of Cardiology, General Hospital of Athens "G. Gennimatas", Athens, Greece

[3]Department of Neurosurgery, Agia Sofia Children's Hospital, Athens, Greece

[4]Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens

[5]Section of Cardiovascular Medicine, Yale University School of Medicine, CT, USA

Corresponding author: E-mail: dgiakoumettis@gmail.com

Submitted: 3 December 2019. Accepted: 17 February 2020. Published: 3 April 2020.

ABSTRACT

Intracerebral hemorrhage (ICH)1 is characterized by the pathological accumulation of blood within the brain parenchyma, most commonly associated with hypertension, arteriovenous malformations, or trauma. However, it can also present in patients receiving antithrombotic drugs, either anticoagulants such as acenocoumarol/warfarin—novel oral anticoagulants or antiplatelets, for the prevention and treatment of thromboembolic disease. The purpose of this review is to present current bibliographic data regarding ICH irrespective of the cause, as well as post-hemorrhage use of antithrombotic agents. Moreover, this review attempts to provide guidelines concerning the termination, inversion, and of course resumption of antithrombotic therapy.

We reviewed the most recently presented available data for patients who dealt with intracerebral hemorrhagic events while on antithrombotic agents (due to atrial fibrillation, prosthetic mechanical valves or recent/recurrent deep vein thrombosis). Furthermore, we examined and compared the thromboembolic risk, the bleeding risk, as well as the re-bleeding risk in two groups: patients receiving antithrombotic therapy versus patients not on antithrombotic therapy. Antithrombotic therapy is of great importance when indicated, though it does not come without crucial side-effects, such as ICH. Optimal timing of withdrawal, reversal, and resumption of antithrombotic treatment should be determined by a multidisciplinary team consisting of a stroke specialist, a cardiologist, and a neurosurgeon, who will individually approach the needs and risks of each patient.

Keywords: *ICH, antiplatelets, antithrombotic agents, anticoagulation, thromboembolism*

INTRODUCTION

Intracerebral hemorrhage (ICH) is defined as the accumulation of blood within the cerebral parenchyma and accounts for 15% of all strokes.[1–4] It is caused by a variety of factors and seems to have a more devastating effect on patients compared to ischemic strokes. In general, clinical presentations are associated with the location of the hematoma in the brain parenchyma and the size of the hemorrhagic clot. As the hemorrhage expands, it causes inflammation and edema in the surrounding regions, which lead to an increase in intracranial pressure (ICP), herniation, and neurological deterioration.

On the other hand, there are numerous conditions, like thromboembolic events including deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), as well as atrial fibrillation (AF) and the presence of mechanical heart valves, for the prevention and treatment of which antithrombotic therapy, such as acenocoumarol is absolutely indicated. Despite the benefit in lowering the mortality risk after such events, antithrombotic agents are linked to increased hemorrhagic risk, including ICH. Therefore, a protocol needs to be established in order to examine bleeding and ischemic risks and determine the optimal time point for discontinuation, reversal, and resumption of antithrombotic therapy. This review addresses the above issues according to the latest guidelines.

BACKGROUND—ICH CLASSIFICATION

ICH can be classified as either primary or secondary, on the basis of the underlying cause of bleeding. Primary ICH is usually the result of arterial hypertension and/or cerebral amyloid angiopathy (CAA), whereas secondary ICH is related to tumors or vascular malformations (such as aneurysms, cerebral cavernous malformations, arteriovenous malformations).

In the acute phase of ICH, the initial hematoma is created by the extravasation of blood from the ruptured vessel until it is controlled by pressure from the nearby tissue. A secondary hematoma is very likely to form as an expansion of the initial one, due to a mechanism quite relative to that of the primary ICH.[5,6] Secondary ICH is lesion-dependent, for example, from vascular malformations that lead to disruption of normal architecture of the vessel wall, making it thinner and more fragile even to subtle changes in haemodynamics.[7] In addition, as mentioned above, secondary ICH is also related to intracranial tumors, through the mechanism of neoangiogenesis.[8,9]

ICH represents 10–20% of all strokes and has twice the incidence of subarachnoid hemorrhage.[10,11]

The overall incidence of ICH is 24.6 cases per 100,000 person-years and has not changed since 1980, according to a large meta-analysis.[12]

ICH is divided in two main categories, lobar and deep hemorrhages.[13,14] Lobar ICH in cortical and subcortical areas accounts for 15–30% of the cases, whereas deep ICH in the internal capsule and basal ganglia is encountered in 35–70% of cases. The rest include cerebellum hemorrhage and brainstem hemorrhage in 5–10% of ICH cases.

RISK FACTORS

Hypertension seems to be one of the major risk factors for ICH, making it absolutely necessary for hypertensive patients to strictly control their blood pressure levels.[15] Hypertensive patients have 3.5-fold increased risk for ICH and more precisely, when blood pressure values are > 160/90 mmHg, the risk can be increased ninefold.[16,17] The second most important risk factor is the deposition of amyloid within the media and adventitia, mainly of cortical vessels[18,19] and is often correlated to the development of lobar ICH.[20,21] Apart from that, age seems to play an important role, as the incidence of ICH increases after 55 years, whereas after the age of 85 the overall odds are the highest.[22] Recent clinical trials have shown that low serum triglyceride levels are associated with increased risk of ICH and more particularly with deep or infratentorial cerebral minor bleedings.[17,23] Other significant risk factors include diabetes mellitus,[16,24] high LDL cholesterol and hyperuricemia,[25] previous cerebrovascular accidents of any kind, alcohol consumption,[26] smoking and recreational drug use (heroin, cocaine, amphetamine, ecstasy).[27,28] Finally, anticoagulation, with either acenocoumarol/warfarin or NOACs, is established as a high-ranking risk factor for ICH.[29–32] Moreover, while aspirin is also estimated to be a potential risk factor for ICH,[33] its beneficial effect on preventing ischemic events and improving mortality seems to be much more significant. Compared to the general population, patients receiving anticoagulants are 7–10 times more inclined to develop ICH.[34,35] As has been demonstrated in several clinical trials, risk factors for anticoagulant-associated ICH (AAICH) include: (1) older age, (2) history of ischemic ictus, (3) hypertension, (4) leukoaraiosis, and (5) aggressive anticoagulation.[34,36,37]

ANTITHROMBOTIC THERAPY

Antithrombotic drugs are subdivided into three major categories, according to the underlying mechanism of action, displayed in Table 1.

The Most Commonly Used Antiplatelet Drugs

Aspirin is the most popular antiplatelet agent. It inhibits the production of thromboxane A2 by acetylating a serine residue near the active site of platelet cyclooxygenase-1 (COX-1), and its action lasts a platelet's lifetime. Aspirin (with or without clopidogrel) is indicated for the treatment of coronary artery disease, carotid artery disease, and lower extremity artery disease[38] and has dose-related side-effects such as peptic ulcers

TABLE 1. Antithrombotic Agents and Their Use in Thrombosis

Antithrombotic Drugs	Treatment Strategy
Antiplatelet drugs	Main choice for arterial thrombosis
Anticoagulants	Prevention and treatment of venous thromboembolism Treatment of arterial thrombosis in acute setting
Fibrinolytic agents	Direct action in dissolving existing thrombus and are the preferred therapeutic regimen in selected patients for the acute treatment of thrombosis

TABLE 2. P2Y12 Receptor Antagonists

Thienopyridine	Mechanism of Action	Half-life Time	Main Adverse Effects
Clopidogrel	Irreversible inhibitor of P2Y12 receptors	6 h parent drug, 30 min active metabolite	Upper respiratory tract infection, chest pain, headache, flulike syndrome
Prasugrel	Irreversible inhibitor of P2Y12 receptors	7 h	Bleeding, anemia, atrial fibrillation, back pain, dyspnea, headache
Ticagrelor	Reversible inhibitor of P2Y12 receptors	7 h	Nausea, vomiting, diarrhea, severe agranulocytosis, thrombopenia

complicated with bleeding and perforation. Platelets contain two kinds of receptors: (1) P2Y1 which induces aggregation and shape changes and (2) P2Y12 which increases platelets adhesiveness and inhibits adenylyl cyclase causing platelet activation (Table 2).

GPIIb/IIIa is a platelet-surface integrin that undergoes transformation when platelets are activated and acts as a surface receptor for fibrinogen and von Willebrand factor. Antagonists of this glucoprotein can act as antiplatelet agents and are often used in combination with aspirin or heparin in the setting of ACS patients undergoing PCI. Bleeding is their major side-effect.

ANTICOAGULATION

The most widely used anticoagulants are: (1) warfarin, (2) heparin and derivative substances and (3) NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) since 2000.

Warfarin is a vitamin K antagonist and is usually prescribed in patients with DVT, PE, AF, and mechanical prosthetic heart valves. In order for vitamin K antagonists to be effective, international normalized ratio (INR) must be strictly maintained within a therapeutic ratio of 2.0–3.0.

Novel oral anticoagulants (NOACs) or direct oral anticoagulants (DOACs) include direct inhibitors of factor IIa, such as dabigatran and argatroban, and direct inhibitors of factor Xa, such as rivaroxaban, apixaban, and edoxaban.

Dabigatran has a reversal agent, idarucizumab, which is a humanized monoclonal antibody fragment approved in 2015 by the FDA. It has an initial and terminal half-life time of 47 min and 10.3 h respectively, and its recommended dose is 5 g of intravenous administration with no need for modification on renal or hepatic impairment. Most frequent adverse effects are hypokalemia, delirium, constipation, pyrexia, pneumonia, and headache. A recombinant modified version of human activated factor X, andexanet alpha, acts as a decoy receptor and reverses the effects of FXa inhibitors. The drug was approved as an antidote for rivaroxaban and apixaban by the FDA in 2018. It has a half-life elimination of 5–7 h, and the dose of andexanet alfa is based on the rivaroxaban or apixaban dose. The most common adverse effects are infusion-related reactions, thromboembolic events, intracranial bleeding, and gastrointestinal bleeding.

There are several studies in the international literature that support the safety of NOACs and document lower rates of ICH in comparison to warfarin. ARISTOTLE trial[39] has verified that apixaban can reduce stroke or embolism by 55% when compared to aspirin, and have comparable rates of ICH episodes.[40,41] RE-LY study has stated that dabigatran presented with 20% lower bleeding rate but with akin effect in preventing stroke or systemic embolism with warfarin.[42,43] A study for rivaroxaban, ROCKET-AF, reported annual rate for ICH at 0.8% versus 1.2% with warfarin,[44] after one daily dose for prevention of stroke and embolism in AF.

TABLE 3. Commonly Used Antithrombotic Drugs and Pharmacological Features

Antithrombotic Drug	Half Life	Duration of Action	Reversible	Treatment Strategy
Classic heparin	1.5 h	2.5–4 h	Yes	Protamine
LMHW dalteparin/ ardeparin	3–5 h	8–12 h depending on renal function	Partially	Protamine and factor VIIa
Enoxaparin	7 h	8–12 h depending on renal function	Partially	Protamine and factor VIIa
Fondaparinux	17–21 h	2–4 days depending on renal function	Limited evidence	Factor VIIa
Apixaban	8–15 h	24 h	No	No known antidote from human studies
Rivaroxaban	7–11 h	8–12 h	No	No known antidote from human studies
Dabigatran	817 h		No	(1) Prothrombin complex concentrate (2) Idarucizumab
Warfarin	40 h	2–5 days	Yes	Vitamin K,Prothrombin complex concentrate, factor VIIa, FFP
Aspirin	2–4.5 h	5–7 days	No	Platelets
Clopidogrel	6 h	5–7 days	No	Platelets
Prasugrel	7 h	5–9 days	No	Platelets
Ticlopidine	12 h	4–10 days	Yes	Methylprednisolone
Ticagrelor	7–8.5 h	24–48 h	Yes	Platelet inhibition subsides competitively. Platelets

LMWH, Low molecular weight heparins.

Heparin activates antithrombin III, which is an inhibitor of thrombin and consequently of blood clotting. It inhibits the conversion of fibrinogen to fibrin and the activation of factor VIII. Classic heparin is metabolized in the liver and the reticuloendothelial system and has a half-life time of 60'–90'. Low molecular weight heparins (LMWHs) inhibit only the clotting factor Xa by binding to antithrombin, in contrast to classical heparin that can inhibit factor IIa as well.

Fibrinolytic drugs are used for in-hospital treatment in the acute setting for: acute MI, ischemic stroke, acute peripheral arterial thrombosis, and massive PE. They consist of streptokinase, tissue-type plasminogen activator (t-PA), and recombinant plasminogen activator (r-PA).

The most commonly used antithrombotic drugs are summarized in Table 3.

ANTICOAGULANTS IN ICH AND THE RISK OF RECURRENCE

Antithrombotic therapy is employed for stroke and systemic embolism prevention in patients with AF and/or mechanical heart valve prosthesis. Furthermore, it is also used in the therapeutic strategy for DVT and PE as well as the prevention and treatment of intracardiac thrombi. The decision to initiate anticoagulation treatment is without doubt based on: (1) the relative risk of a thromboembolic episode without anticoagulants and (2) the recurrence rates of ICH on anticoagulation therapy.[45–48] The annual incidence of ICH in patients receiving anticoagulant therapy is

about 0.6–1.0%,[49] whilst the annual risk of ICH relapse in patients who survived a first episode is in the range of 2–3%. This is translated to a 10-fold increase in relative risk and an absolute annual risk increase of 2% in the general population.[18,19,50,51] In addition, after the first ictus of an ICH without anticoagulation therapy, the reported rate of 3-month recurrence ranges between 0.4 and 3%.[19,52,53] Patients with ICH associated with anticoagulation therapy usually show larger hematomas and poorer prognosis with a 3-month mortality of about 54%.[54] However, it has been documented that abrupt reversal of warfarin is of utmost importance in the effort for prevention of hematoma enlargement.[55,56]

ATRIAL FIBRILLATION AND ICH

AF presents with a prevalence of approximately 3% in patients > 20 years old.[57,58] One-year stroke risk in AF patients ranges between 1.9–18.2 and 0–15.2, as determined by two scoring systems, CHADS2 and CHA2DS2VASc scores respectively.[59,60] Another scoring system, the HAS-BLED Score, can help evaluate the annual risk of spontaneous major bleeding in AF patients, from 1.02 to 12.50 bleeds per 100 patient-years.[61] Literature has a variety of scoring systems for stratifying the bleeding risk, such as ATRIA and HEMORR2HAGE[62,63] and the most recent one, ORBIT by O'Brien et al. in 2015 (Table 4).[64]

Patients with AF can benefit the most from anticoagulant treatment. It is documented that adjusted-dose warfarin can reduce ischemic stroke by approximately 60%. Nevertheless, warfarin increases the rates of ICH recurrence by 3–5% and is commonly linked to more extensive hematomas, as well as worse prognosis with 3-month mortality at about 54%.[20,65–67] The most popular antiplatelet agent, aspirin, has been correlated with an increased relative risk of 1.4–1.8 for an initial ICH.[33,68] The combination of aspirin plus warfarin can increase the relative risk of ICH 2–4 times in comparison to monotherapy of warfarin.[69–71] Moreover, oral anticoagulation has been associated with a higher 30-day case fatality after lobar ICH, compared to no antithrombotic treatment.[72,73] Two large meta-analyses of AF patients documented decreased relative risk of ICH (RR = 0.48) on NOACs, in contradiction to warfarin.[74,75] They also supported the fact that NOACs reduced ICH incidence in patients with AF by almost 50%, compared to vitamin K antagonist users.[74]

PROPHYLACTIC OR THERAPEUTIC ANTICOAGULATION REGIMEN FOR VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) consists of two major categories: (1) DVT and (2) PE. PE is observed in 1–5% of ICH patients, 2–4 weeks after the ictus, and surprisingly enough does not accompany a clinically symptomatic DVT.[76–81] Evidence-based literature suggests the use of clinical scoring systems such as Modified Wells Scoring and Revised Geneva Scoring in order to estimate the clinical probability of PE.

TABLE 4. ORBIT Scoring System for Patient Bleeding Risk Stratification

Risk Factors	Points	Patients Risk Stratification
Age > 75 y	1	Low risk (0–2 points)
History of anemia	2	Intermediate risk (3 points)
Bleeding history	2	High risk (≥ 4 points)
Kidney dysfunction	1	
On antiplatelet agents	1	

There is no consensus regarding the most appropriate time and treatment protocol of DVT prophylaxis in neurosurgical patients. Prophylaxis includes compression stockings and/or antithrombotic therapy. When only compression stockings are used for DVT prophylaxis after neurosurgical procedures, DVT is found in 32% of patients.[82] Despite the fact that the use of classic heparin reduces DVT and PE incidence by 40–50%,[83] it also raises the ICH risk rate from 1–3.9% to 10.9%.[84–86] LMWH reduces the relative risk of VTE by 38% and presents with an ICH risk of 2.2–2.6%, whereas patients without antithrombotic treatment have an ICH risk of 0.8–2.6%.[83] Even though there are various LMWH agents available, the safety of only enoxaparin is mainly supported in neurosurgical procedures.[82] The safe administration of enoxaparin has also been documented for VTE prophylaxis without augmenting the risk of ICH deterioration after 24 h of a secondary ICH due to a head injury.[87] Prophylactic dose of LMWH or unfractionated heparin (UFH) has been considered to be safe for administration in hemiplegic patients after 3–4 days from an ICH episode and once its progression has stopped.[88,89]

Patients with mechanical heart valves must be on antithrombotic therapy despite the possibility of an ICH. A recent meta-analysis has certified that warfarin reduced the risk of thrombosis in patients with prosthetic valves from 1.8 to 0.2 per 100 patient-years, and the incidence of major embolism by 80%.[90,91] The greatest risk for a thromboembolic episode is during the first month of valve replacement, when almost 20% of all episodes are encountered. Lastly, it should be stated that NOACs have not yet been approved for patients with prosthetic valves.

RESUMING ANTITHROMBOTIC THERAPY

The risk for a thromboembolic episode as well as the risk of ICH recurrence is increasing over time. On the contrary, the risk for an ICH enlargement is documented to be higher during the first days of the event.[92,93] Oral anticoagulants reduce the risk for an ischemic episode and their reinstatement after an ICH is generally recommended. Stratified data show that the mortality risk rate of a stroke in the group of patients who resumed anticoagulant treatment was 3.6%, whereas the group that did not resume presented with a mortality risk rate of 7.6%. The risk of ICH recurrence of the first group was 3.6% in contrast to the risk of the second group, which was over 5.1%. Stratification of patients in groups revealed that patients suffering from AF who resumed therapy presented with an incidence rate for ischemic events of 8.2% whereas the non-treatment group had an incidence rate over 37.5%. However, it has been reported that AF patients who discontinued their treatment presented with a greater stroke risk of 10–48% than the risk of developing an ICH which was 0–9%.[45,94–97] It is a fact that patients with a mechanical valve have a high risk of a thromboembolic event and must restart antithrombotic therapy.[98] Moreover, NOACs may be considered as a safe choice for AF or VTE patients after an AAICH.[75] The available data show an advantage in reinitiating anticoagulation therapy after 4–8 weeks, taking into consideration the fact that the causative factor of bleeding has been dealt with and the anticoagulant agent presents a low bleeding risk.[74]

Anticoagulation therapy still remains a matter of controversy concerning the most appropriate time point for restarting anticoagulants after an ICH event. Even though there is no consensus, most studies agree on restarting antithrombotic therapy 7–14 days after an ICH episode.[88,99–104]

The use of reversal agents must be taken into consideration because they can temporarily change the coagulation profile of the patient and increase the thromboembolic risk.[96,103] Heparin or oral anticoagulants are considered to be safe for resumption on day 3 or day 7, respectively after an ICH event without changing the rebleeding risk.[105]

ICH SURGICAL TREATMENT

Even though surgical evacuation for deep ICH does not improve patients' survival, it is recommended for posterior fossa ICH whose maximum diameter is greater than 3 cm, and /or with a rapid neurological deterioration or with a mass effect on brainstem.[89,106–109] The biggest trial conducted for ICH was the STICH trial.[110] It included 1,033 patients with primary deep ICH and concluded that surgery did not offer a statistically significant benefit in survival over conservative treatment. Other surgical techniques such as minimal invasive techniques did not offer a significant benefit as investigated in the MISTIE[107] clinical trial.

The 30-day mortality of ICH is above 40%[111] and near 50% at 1 year.[20,112] The ICH Score by Hemphill is a grading scale used to predict 30-day mortality in ICH patients, most of the times contributing to the surgical decision. This scoring system ranges from 0 to 6[113–118] and includes five criteria: (1) GCS score, (2) ICH volume, (3) co-existence or not of intraventricular hemorrhage (IVH), (4) the origin of the ICH, supra- or infratentorial and (5) age. Each parameter is scored with one relevant credit, and the total sum corresponds to 30-day mortality. Furthermore, according to other studies, the outcome in medium and large-sized ICH could be assessed on admission by using the Canadian Stroke Scale, ICH location, and fibrinogen levels.[119]

COMPLICATIONS

ICH is a condition accompanied by severe complications. A list of them is presented in Table 5.

TABLE 5. Most Common Complications of ICH

Deep venous thrombosis
Pulmonary embolism
Neurological deficits or death
Aspiration pneumonia
Seizures
Hydrocephalus
Spasticity
Urinary complications
Neuropathic pain
Cerebral herniation

HEMATOMA EXPANSION

ICH continues to expand for up to 6 h in patients not receiving anticoagulation therapy, and up to 24 h in coagulopathy-associated bleedings.[56,99,120] Moreover, the perihematomal edema starts to develop and reaches its maximum size at 72 h, usually persisting for 5 days, and in some cases lasting for up to 15 days.[121] The formation of the initial hematoma is followed by a second phase of shearing and bleeding from multiple ruptures in the surrounding vasculature.[5,6,122] It is widely accepted that the shape, speed, space distribution, and the ratio of the amount of blood in an ICH is multifactorial. Primary ICH can expand and produce a mass effect on the brain, and therefore stopping the hematoma expansion may improve the outcome in ICH patients. Nevertheless, it is still uncertain if an ICH recurrence is due to a nearby but separate site event or it is a continuation of the initial event.

DISCUSSION

The size of an ICH is one of the most important factors that can determine a patient's prognosis. The discontinuation and reversal of antithrombotics is of great importance in preventing hemorrhage enhancement during the first hours after an ICH event. Reversal agents for NOACs are under development. In October 2015, the FDA approved idarucizumab as a reversal agent for dabigatran[123] and in 2018 andexanet alfa as a reversal agent of FXa-inhibitors (apixaban, edoxaban, rivaroxaban).[124,125]

If urgent surgery (in < 48 h) is indicated, given that NOACs have half-lives of 14–17 h and normal coagulation improves after 12 h, surgery

should be delayed as long as possible. If waiting is not an option, a hematologist should be consulted to discuss the possibility for an antidote. If surgery is not necessary in the first 48 h, it can be performed 48 h after the last dose of NOACs.

High blood pressure is the leading cause of acute primary ICH.[126,127] It is reported that high systolic blood pressure is associated with ICH enlargement and thus mortality.[127–129] According to 2015 guidelines by AHA/ASA (American Heart Association/American Stroke Association), immediate lowering to 140 mmHg is recommended in ICH patients with systolic blood pressure between 150 and 220 mmHg and with no contraindication to acute blood pressure treatment. If systolic blood pressure is > 220 mmHg, acute reduction by a continuous intravenous infusion and blood pressure monitoring are recommended.

ICH recurrence annual rates in survivors are 2–3%, and antithrombotic therapy is linked to an increased risk of recurrence. Warfarin-associated ICH is usually more extensive and is associated with a worse prognosis, with a 3-month mortality rate of approximately 54%.

Resuming antithrombotic therapy is an equilibrium between the risk of an ICH recurrence and the risk of an embolic ictus in case of discontinuation of therapy permanently. Patients with AF on oral anticoagulants must be stratified for a major bleeding event by using a scoring system, either HASBLED Score or by the most recent one ORBIT. Consecutively, these patients are also stratified for an ischemic stroke event, using CHADS2 and CHA2DS2VASc scoring systems. One-year thromboembolic risk according to these scores fluctuates between 0 and 20%, whereas the same risk of an ICH recurrence after resuming anticoagulants is 2.5–8%. Kuramatsu et al.[95] and Nielsen et al.[130] in 2015 reported a difference in the ICH recurrence risk within the first year, between patients who resumed anticoagulant treatment and those who did not. Nevertheless, both studies reported that the risk for an embolic episode within 1 year was almost double in patients who did not resume their antithrombotic therapy.

In spite of the fact that there is no consensus for the optimal timing of resuming anticoagulant therapy after an ICH event, most of the studies support the resumption of the antithrombotic treatment after 7–14 days.[88,99–104] Restarting heparin or oral anticoagulants after an ICH event is reported to be safe on day 3 or day 7 respectively, without increasing the rebleeding risk.[105] The newer category of NOACs is included in therapeutic strategies as a safe treatment option for restarting in AF patients after a warfarin-associated ICH according to recent guidelines of the European Heart Rhythm Association in 2018.[75,131] According to guidelines of ESC in 2016 restarting oral anticoagulation is supported when the drug of choice has low bleeding risk after 4–8 weeks.[132]

In patients with prosthetic mechanical valves resuming anticoagulant therapy is of the utmost importance. The 3-month risk for an ischemic event in patients who have mitral or aortic valve bioprosthesis is approximately 17%. For a mechanical mitral valve, the annual risk of a stroke is 22%, whereas in aortic mechanical prosthesis the annual risk is over 12%. A retrospective study reported restarting warfarin in patients with mechanical valves after 14–20 days without any thromboembolic events in a 6-month follow-up.[133] However, there is no consensus on the optimal timing of resumption of anticoagulation therapy. A study carried out by worldwide experts concluded that after an ICH, anticoagulation therapy in patients with a prosthetic heart valve should be reinstated 2–14 days after the event.[99]

CONCLUSIONS

Patients who present with an ICH due to any cause must discontinue oral anticoagulation for a restricted period of time. Nevertheless, restarting antithrombotic therapy is still considered to be a matter of debate. In AF patients with ICH,

oral anticoagulation with an agent of low intracranial bleeding risk is recommended to be reinitiated in 4–8 weeks. In patients with prosthetic mechanical valves, anticoagulation is suggested to be reinstated 10 days after the onset of ICH. In cases of DVT and/or PE, therapeutic doses of enoxaparin are recommended after the fourth day of the onset of an ICH and after it has been confirmed that the hematoma is not expanding any further. Nevertheless, the optimal timing of restarting antithrombotic treatment is a matter of discussion between a multidisciplinary team consisting of a stroke specialist, a cardiologist, and a neurosurgeon, who will individualize the therapeutic strategy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

The authors received no funding.

DATA AVAILABILITY STATEMENT

No datasets were generated for this review.

COMPLIANCE WITH ETHICAL STANDARDS

No ethics approval needed for this review.

REFERENCES

1. Sutherland GR, Auer RN. Primary intracerebral hemorrhage. J Clin Neurosci. 2006;13(5):511–17. https://doi.org/10.1016/j.jocn.2004.12.012
2. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. New Eng J Med. 2001; 344(19):1450–60. https://doi.org/10.1056/NEJM200105103441907
3. Intiso D, Stampatore P, Zarrelli MM, et al. Incidence of first-ever ischemic and hemorrhagic stroke in a well-defined community of southern Italy, 1993–1995. Eur J Neurol. 2003;10(5):559–65. https://doi.org/10.1046/j.1468-1331.2003.00648.x
4. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: Mechanisms of injury and therapeutic targets. Lancet Neurol. 2012;11(8):720–31. https://doi.org/10.1016/S1474-4422(12)70104-7
5. Greenberg CH, Frosch MP, Goldstein JN, Rosand J, Greenberg SM. Modeling intracerebral hemorrhage growth and response to anticoagulation. PLoS One. 2012;7(10):e48458. https://doi.org/10.1371/journal.pone.0048458
6. Barras CD, Tress BM, Christensen S, et al. Density and shape as CT predictors of intracerebral hemorrhage growth. Stroke. 2009;40(4):1325–31. https://doi.org/10.1161/STROKEAHA.108.536888
7. Cebral JR, Vazquez M, Sforza DM, et al. Analysis of hemodynamics and wall mechanics at sites of cerebral aneurysm rupture. J Neurointerv Surg. 2015;7(7):530–6. https://doi.org/10.1136/neurintsurg-2014-011247
8. Lieu AS, Hwang SL, Howng SL, Chai CY. Brain tumors with hemorrhage. J Formos Med Assoc. 1999;98(5):365–7.
9. Little JR, Dial B, Belanger G, Carpenter S. Brain hemorrhage from intracranial tumor. Stroke. 1979;10(3):283–8. https://doi.org/10.1161/01.STR.10.3.283
10. Broderick JP, Brott T, Tomsick T, Miller R, Huster G. Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. J Neurosurg. 1993;78(2):188–91. https://doi.org/10.3171/jns.1993.78.2.0188
11. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. Lancet Neurol. 2009;8(4):355–69. https://doi.org/10.1016/S1474-4422(09)70025-0
12. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origIn: A systematic review and meta-analysis. Lancet Neurol. 2010;9(2):167–76. https://doi.org/10.1016/S1474-4422(09)70340-0
13. Flaherty ML, Woo D, Haverbusch M, et al. Racial variations in location and risk of intracerebral hemorrhage. Stroke. 2005;36(5):934–7.

https://doi.org/10.1161/01.STR.0000160756.72109.95
14. Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: Incidence, prevalence, mortality, and risk factors. Neurol Clin. 2008;26(4):871–95, vii. https://doi.org/10.1016/j.ncl.2008.07.003
15. Bakris G, Ali W, Parati G. ACC/AHA versus ESC/ESH on hypertension guidelines: JACC guideline comparison. J Am Coll Cardiol. 2019;73(23):3018–26. https://doi.org/10.1016/j.jacc.2019.03.507
16. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet. 2010;376(9735):112–23. https://doi.org/10.1016/S0140-6736(10)60834-3
17. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: A systematic review. Stroke. 2003;34(8):2060–5. https://doi.org/10.1161/01.STR.0000080678.09344.8D
18. Maas MB, Rosenberg NF, Kosteva AR, Prabhakaran S, Naidech AM. Coagulopathy disproportionately predisposes to lobar intracerebral hemorrhage. Neurocrit Care. 2013;18(2):166–9. https://doi.org/10.1007/s12028-012-9814-x
19. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: The Rotterdam scan study. Neurology. 2008;70(14):1208–14. https://doi.org/10.1212/01.wnl.0000307750.41970.d9
20. Vermeer SE, Algra A, Franke CL, Koudstaal PJ, Rinkel GJ. Long-term prognosis after recovery from primary intracerebral hemorrhage. Neurology. 2002;59(2):205–9. https://doi.org/10.1212/WNL.59.2.205
21. Bailey RD, Hart RG, Benavente O, Pearce LA. Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. Neurology. 2001;56(6):773–7. https://doi.org/10.1212/WNL.56.6.773
22. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med. 2004;141(10):745–52. https://doi.org/10.7326/0003-4819-141-10-200411160-00005
23. Wieberdink RG, Poels MM, Vernooij MW, et al. Serum lipid levels and the risk of intracerebral hemorrhage: The Rotterdam study. Arterioscler Thromb Vasc Biol. 2011;31(12):2982–9. https://doi.org/10.1161/ATVBAHA.111.234948
24. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215–22. https://doi.org/10.1016/S0140-6736(10)60484-9
25. Cicero AFG, Fogacci F, Giovannini M, et al. Interaction between low-density lipoprotein-cholesterolaemia, serum uric level and incident hypertension: Data from the Brisighella Heart Study. J Hypertens. 2019;37(4):728–31. https://doi.org/10.1097/HJH.0000000000001927
26. Juvela S, Hillbom M, Palomaki H. Risk factors for spontaneous intracerebral hemorrhage. Stroke. 1995;26(9):1558–64. https://doi.org/10.1161/01.STR.26.9.1558
27. McEvoy AW, Kitchen ND, Thomas DG. Intracerebral haemorrhage and drug abuse in young adults. Br J Neurosurg. 2000;14(5):449–54. https://doi.org/10.1080/02688690050175247
28. McEvoy AW, Kitchen ND, Thomas DG. Lesson of the week: Intracerebral haemorrhage in young adults: The emerging importance of drug misuse. Br Med J. 2000;320(7245):1322–4. https://doi.org/10.1136/bmj.320.7245.1322
29. Huhtakangas J, Tetri S, Juvela S, Saloheimo P, Bode MK, Hillbom M. Effect of increased warfarin use on warfarin-related cerebral hemorrhage: A longitudinal population-based study. Stroke. 2011;42(9):2431–5. https://doi.org/10.1161/STROKEAHA.111.615260
30. Flaherty ML, Kissela B, Woo D, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007;68(2):116–21. https://doi.org/10.1212/01.wnl.0000250340.05202.8b

31. Neau JP, Couderq C, Ingrand P, Blanchon P, Gil R. Intracranial hemorrhage and oral anticoagulant treatment. Cerebrovasc Dis. 2001;11(3):195–200. https://doi.org/10.1159/000047638
32. Elkind MS, Sacco RL. Direct thrombin inhibition: A novel approach to stroke prevention in patients with atrial fibrillation. Stroke. 2004;35(6):1519–22. https://doi.org/10.1161/01.STR.0000128883.89984.52
33. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: A meta-analysis of randomized controlled trials. JAMA. 1998;280(22):1930–5. https://doi.org/10.1001/jama.280.22.1930
34. Hart RG, Boop BS, Anderson DC. Oral anticoagulants and intracranial hemorrhage. Facts and hypotheses. Stroke. 1995;26(8):1471–7. https://doi.org/10.1161/01.STR.26.8.1471
35. Sjalander A, Engstrom G, Berntorp E, Svensson P. Risk of haemorrhagic stroke in patients with oral anticoagulation compared with the general population. J Intern Med. 2003;254(5):434–8. https://doi.org/10.1046/j.1365-2796.2003.01209.x
36. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: Recent data and ideas. Stroke. 2005;36(7):1588–93. https://doi.org/10.1161/01.STR.0000170642.39876.f2
37. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: Patterns and risk factors. Stroke Prevention In Reversible Ischemia Trial (SPIRIT). European Atrial Fibrillation Trial (EAFT) study groups. Neurology. 1999;53(6):1319–27. https://doi.org/10.1212/WNL.53.6.1319
38. Aboyans V, Ricco JB, Bartelink ML, et al. [2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS)]. Kardiol Pol. 2017;75(11):1065–160.
39. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92. https://doi.org/10.1056/NEJMoa1107039
40. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806–17. https://doi.org/10.1056/NEJMoa1007432
41. Flaker GC, Eikelboom JW, Shestakovska O, et al. Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarIn: The apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. Stroke. 2012;43(12):3291–7. https://doi.org/10.1161/STROKEAHA.112.664144
42. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51. https://doi.org/10.1056/NEJMoa0905561
43. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. N Engl J Med. 2010;363(19):1875–6. https://doi.org/10.1056/NEJMc1007378
44. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91. https://doi.org/10.1056/NEJMoa1009638
45. Claassen DO, Kazemi N, Zubkov AY, Wijdicks EF, Rabinstein AA. Restarting anticoagulation therapy after warfarin-associated intracerebral hemorrhage. Arch Neurol. 2008;65(10):1313–18. https://doi.org/10.1001/archneur.65.10.1313
46. Molina CA, Selim MH. The dilemma of resuming anticoagulation after intracranial hemorrhage: Little evidence facing big fears. Stroke. 2011;42(12):3665–6. https://doi.org/10.1161/STROKEAHA.111.631689
47. Steiner T. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: Yes. Stroke. 2011;42(12):3661–2. https://doi.org/10.1161/STROKEAHA.111.621797
48. Schulman S. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: No. Stroke. 2011;42(12):3663–4. https://doi.org/10.1161/STROKEAHA.111.621813
49. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for

ischemic stroke: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e601S–36S. https://doi.org/10.1378/chest.141.4.1129b

50. Zia E, Engstrom G, Svensson PJ, Norrving B, Pessah-Rasmussen H. Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage. Stroke. 2009;40(11):3567–73. https://doi.org/10.1161/STROKEAHA.109.556324
51. Saloheimo P, Juvela S, Hillbom M. Use of aspirin, epistaxis, and untreated hypertension as risk factors for primary intracerebral hemorrhage in middle-aged and elderly people. Stroke. 2001;32(2):399–404. https://doi.org/10.1161/01.STR.32.2.399
52. Bae H, Jeong D, Doh J, Lee K, Yun I, Byun B. Recurrence of bleeding in patients with hypertensive intracerebral hemorrhage. Cerebrovasc Dis. 1999;9(2):102–8. https://doi.org/10.1159/000015906
53. Passero S, Burgalassi L, D'Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. Stroke. 1995;26(7):1189–92. https://doi.org/10.1161/01.STR.26.7.1189
54. Meretoja A, Strbian D, Putaala J, et al. SMASH-U: A proposal for etiologic classification of intracerebral hemorrhage. Stroke. 2012;43(10):2592–7. https://doi.org/10.1161/STROKEAHA.112.661603
55. Huttner HB, Schellinger PD, Hartmann M, et al. Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: Comparison of acute treatment strategies using Vitamin K, fresh frozen plasma, and prothrombin complex concentrates. Stroke. 2006;37(6):1465–70. https://doi.org/10.1161/01.STR.0000221786.81354.d6
56. Yasaka M, Minematsu K, Naritomi H, Sakata T, Yamaguchi T. Predisposing factors for enlargement of intracerebral hemorrhage in patients treated with warfarin. Thromb Haemost. 2003;89(2):278–83. https://doi.org/10.1055/s-0037-1613443
57. Bjorck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy revisited: A population-based study. Stroke. 2013;44(11):3103–8. https://doi.org/10.1161/STROKEAHA.113.002329
58. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. J Am Heart Assoc. 2015;4(1):e001486. https://doi.org/10.1161/JAHA.114.001486
59. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864–70. https://doi.org/10.1001/jama.285.22.2864
60. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857–67. https://doi.org/10.7326/0003-4819-146-12-200706190-00007
61. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest. 2010;138(5):1093–100. https://doi.org/10.1378/chest.10-0134
62. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151(3):713–19. https://doi.org/10.1016/j.ahj.2005.04.017
63. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395–401. https://doi.org/10.1016/j.jacc.2011.03.031
64. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: A simple bedside score to assess bleeding risk in atrial fibrillation.

Eur Heart J. 2015;36(46):3258–64. https://doi.org/10.1093/eurheartj/ehv476

65. Poli D, Antonucci E, Dentali F, et al. Recurrence of ICH after resumption of anticoagulation with VK antagonists: CHIRONE study. Neurology. 2014;82(12):1020–6. https://doi.org/10.1212/WNL.0000000000000245
66. Eckman MH, Rosand J, Knudsen KA, Singer DE, Greenberg SM. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. Stroke. 2003;34(7):1710–16. https://doi.org/10.1161/01.STR.0000078311.18928.16
67. Gorelick PB, Weisman SM. Risk of hemorrhagic stroke with aspirin use: An update. Stroke. 2005;36(8):1801–7. https://doi.org/10.1161/01.STR.0000174189.81153.85
68. Hart RG, Halperin JL, McBride R, Benavente O, Man-Son-Hing M, Kronmal RA. Aspirin for the primary prevention of stroke and other major vascular events: Meta-analysis and hypotheses. Arch Neurol. 2000;57(3):326–32. https://doi.org/10.1001/archneur.57.3.326
69. Hart RG, Benavente O, Pearce LA. Increased risk of intracranial hemorrhage when aspirin is combined with warfarIn: A meta-analysis and hypothesis. Cerebrovasc Dis. 1999;9(4):215–17. https://doi.org/10.1159/000015958
70. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: An individual patient meta-analysis. JAMA. 2002;288(19):2441–8. https://doi.org/10.1001/jama.288.19.2441
71. Cappelleri JC, Fiore LD, Brophy MT, Deykin D, Lau J. Efficacy and safety of combined anticoagulant and antiplatelet therapy versus anticoagulant monotherapy after mechanical heart-valve replacement: A meta analysis. Am Heart J. 1995;130(3 Pt 1):547–52. https://doi.org/10.1016/0002-8703(95)90365-8
72. Pezzini A, Grassi M, Paciaroni M, et al. Antithrombotic medications and the etiology of intracerebral hemorrhage: MUCH-Italy. Neurology. 2014;82(6):529–35. https://doi.org/10.1212/WNL.0000000000000108
73. Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke. 2009;40(2):394–9. https://doi.org/10.1161/STROKEAHA.108.523209
74. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62. https://doi.org/10.1016/S0140-6736(13)62343-0
75. Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ. New oral anticoagulants and the risk of intracranial hemorrhage: Traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. JAMA Neurol. 2013;70(12):1486–90. https://doi.org/10.1001/jamaneurol.2013.4021
76. Ogata T, Yasaka M, Wakugawa Y, Inoue T, Ibayashi S, Okada Y. Deep venous thrombosis after acute intracerebral hemorrhage. J Neurol Sci. 2008;272(1–2):83–6. https://doi.org/10.1016/j.jns.2008.04.032
77. Skaf E, Stein PD, Beemath A, Sanchez J, Bustamante MA, Olson RE. Venous thromboembolism in patients with ischemic and hemorrhagic stroke. Am J Cardiol. 2005;96(12):1731–3. https://doi.org/10.1016/j.amjcard.2005.07.097
78. Christensen MC, Dawson J, Vincent C. Risk of thromboembolic complications after intracerebral hemorrhage according to ethnicity. Adv Ther. 2008;25(9):831–41. https://doi.org/10.1007/s12325-008-0092-0
79. Orken DN, Kenangil G, Ozkurt H, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. Neurologist. 2009;15(6):329–31. https://doi.org/10.1097/NRL.0b013e3181a93bac
80. Maramattom BV, Weigand S, Reinalda M, Wijdicks EF, Manno EM. Pulmonary complications after intracerebral hemorrhage. Neurocrit Care. 2006;5(2):115–19. https://doi.org/10.1385/NCC:5:2:115
81. Goldstein JN, Fazen LE, Wendell L, et al. Risk of thromboembolism following acute intracerebral hemorrhage. Neurocrit Care. 2009;10(1):28–34. https://doi.org/10.1007/s12028-008-9134-3

82. Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med. 1998;339(2):80–5. https://doi.org/10.1056/NEJM199807093390204
83. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: A meta-analysis. Arch Intern Med. 2000;160(15):2327–32. https://doi.org/10.1001/archinte.160.15.2327
84. Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. Neurosurgery. 1998;43(5):1074–81. https://doi.org/10.1097/00006123-199811000-00039
85. Fukamachi A, Koizumi H, Nagaseki Y, Nukui H. Postoperative extradural hematomas: Computed tomographic survey of 1105 intracranial operations. Neurosurgery. 1986;19(4):589–93. https://doi.org/10.1227/00006123-198610000-00013
86. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. Chest. 2001;119(1 Suppl):132S–75S. https://doi.org/10.1378/chest.119.1_suppl.132S
87. Norwood SH, McAuley CE, Berne JD, et al. Prospective evaluation of the safety of enoxaparin prophylaxis for venous thromboembolism in patients with intracranial hemorrhagic injuries. Arch Surg. 2002;137(6):696–701; discussion 701–2. https://doi.org/10.1001/archsurg.137.6.696
88. Morgenstern LB, Hemphill JC3rd, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2010;41(9):2108–29. https://doi.org/10.1161/STR.0b013e3181ec611b
89. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. Stroke. 2007;38(6):2001–23. https://doi.org/10.1161/STROKEAHA.107.183689
90. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89(2):635–41. https://doi.org/10.1161/01.CIR.89.2.635
91. Cannegieter SC, van der Meer FJ, Briet E, Rosendaal FR. Warfarin and aspirin after heart-valve replacement. N Engl J Med. 1994;330(7):507–8; author reply 8–9. https://doi.org/10.1056/NEJM199402173300717
92. De Vleeschouwer S, Van Calenbergh F, van Loon J, Nuttin B, Goffin J, Plets C. Risk analysis of thrombo-embolic and recurrent bleeding events in the management of intracranial haemorrhage due to oral anticoagulation. Acta Chir Belg. 2005;105(3):268–74. https://doi.org/10.1080/00015458.2005.11679715
93. Hawryluk GW, Austin JW, Furlan JC, Lee JB, O'Kelly C, Fehlings MG. Management of anticoagulation following central nervous system hemorrhage in patients with high thromboembolic risk. J Thromb Haemost. 2010;8(7):1500–8. https://doi.org/10.1111/j.1538-7836.2010.03882.x
94. Yung D, Kapral MK, Asllani E, Fang J, Lee DS. Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: The Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) study. Can J Cardiol. 2012;28(1):33–9. https://doi.org/10.1016/j.cjca.2011.10.002
95. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA. 2015;313(8):824–36. https://doi.org/10.1016/j.cjca.2011.10.002
96. Bertram M, Bonsanto M, Hacke W, Schwab S. Managing the therapeutic dilemma: Patients with spontaneous intracerebral hemorrhage and urgent need for anticoagulation. J Neurol. 2000;247(3):209–14. https://doi.org/10.1007/s004150050565

97. Gathier CS, Algra A, Rinkel GJ, van der Worp HB. Long-term outcome after anticoagulation-associated intracerebral haemorrhage with or without restarting antithrombotic therapy. Cerebrovasc Dis. 2013;36(1):33–7. https://doi.org/10.1159/000351151
98. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42(4):S1–44.
99. Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: Literature review and expert opinion. Mayo Clin Proc. 2007;82(1):82–92. https://doi.org/10.1016/S0025-6196(11)60970-1
100. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42(1):227–76. https://doi.org/10.1161/STR.0b013e3181f7d043
101. Punthakee X, Doobay J, Anand SS. Oral-anticoagulant-related intracerebral hemorrhage. Thromb Res. 2002;108(1):31–6. https://doi.org/10.1016/S0049-3848(02)00398-5
102. Phan TG, Koh M, Wijdicks EF. Safety of discontinuation of anticoagulation in patients with intracranial hemorrhage at high thromboembolic risk. Arch Neurol. 2000;57(12):1710–13. https://doi.org/10.1001/archneur.57.12.1710
103. Wijdicks EF, Schievink WI, Brown RD, Mullany CJ. The dilemma of discontinuation of anticoagulation therapy for patients with intracranial hemorrhage and mechanical heart valves. Neurosurgery. 1998;42(4):769–73. https://doi.org/10.1097/00006123-199804000-00053
104. Estol CJ, Kase CS. Need for continued use of anticoagulants after intracerebral hemorrhage. Curr Treat Options Cardiovasc Med. 2003;5(3):201–9. https://doi.org/10.1007/s11936-003-0004-1
105. Chandra D, Gupta A, Grover V, Kumar Gupta V. When should you restart anticoagulation in patients who suffer an intracranial bleed who also have a prosthetic valve? Interact Cardiovasc Thorac Surg. 2013;16(4):520–3. https://doi.org/10.1093/icvts/ivs545
106. Passero S, Rocchi R, Rossi S, Ulivelli M, Vatti G. Seizures after spontaneous supratentorial intracerebral hemorrhage. Epilepsia. 2002;43(10):1175–80. https://doi.org/10.1046/j.1528-1157.2002.00302.x
107. Morgan T, Zuccarello M, Narayan R, Keyl P, Lane K, Hanley D. Preliminary findings of the minimally-invasive surgery plus rtPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. Acta Neurochir Suppl. 2008;105:147–51. https://doi.org/10.1007/978-3-211-09469-3_30
108. Nishihara T, Nagata K, Tanaka S, et al. Newly developed endoscopic instruments for the removal of intracerebral hematoma. Neurocrit Care. 2005;2(1):67–74. https://doi.org/10.1385/NCC:2:1:067
109. Vespa P, McArthur D, Miller C, et al. Frameless stereotactic aspiration and thrombolysis of deep intracerebral hemorrhage is associated with reduction of hemorrhage volume and neurological improvement. Neurocrit Care. 2005;2(3):274–81. https://doi.org/10.1385/NCC:2:3:274
110. Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): A randomised trial. Lancet. 2005;365(9457):387–97. https://doi.org/10.1016/S0140-6736(05)70233-6
111. Broderick JP, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. N Engl J Med. 1992;326(11):733–6. https://doi.org/10.1056/NEJM199203123261103
112. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993;24(7):987–93. https://doi.org/10.1161/01.STR.24.7.987

113. Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: A simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32(4):891–7. https://doi.org/10.1161/01.STR.32.4.891
114. Hemphill JC, 3rd, Farrant M, Neill TA, Jr. Prospective validation of the ICH Score for 12-month functional outcome. Neurology. 2009;73(14):1088–94. https://doi.org/10.1212/WNL.0b013e3181b8b332
115. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: The FUNC score. Stroke. 2008;39(8):2304–9. https://doi.org/10.1161/STROKEAHA.107.512202
116. Clarke JL, Johnston SC, Farrant M, Bernstein R, Tong D, Hemphill JC 3rd, . External validation of the ICH score. Neurocrit Care. 2004;1(1):53–60. https://doi.org/10.1385/NCC:1:1:53
117. Garrett JS, Zarghouni M, Layton KF, Graybeal D, Daoud YA. Validation of clinical prediction scores in patients with primary intracerebral hemorrhage. Neurocrit Care. 2013;19(3):329–35. https://doi.org/10.1007/s12028-013-9926-y
118. Van Asch CJ, Velthuis BK, Greving JP, et al. External validation of the secondary intracerebral hemorrhage score in The Netherlands. Stroke. 2013;44(10):2904–6. https://doi.org/10.1161/STROKEAHA.113.002386
119. Castellanos M, Leira R, Tejada J, Gil-Peralta A, Davalos A, Castillo J. Predictors of good outcome in medium to large spontaneous supratentorial intracerebral haemorrhages. J Neurol Neurosurg Psychiatry. 2005;76(5):691–5. https://doi.org/10.1136/jnnp.2004.044347
120. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke. 1996;27(10):1783–7. https://doi.org/10.1161/01.STR.27.10.1783
121. Zazulia AR, Diringer MN, Derdeyn CP, Powers WJ. Progression of mass effect after intracerebral hemorrhage. Stroke. 1999;30(6):1167–73. https://doi.org/10.1161/01.STR.30.6.1167
122. Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. Stroke. 2003;34(1):224–9. https://doi.org/10.1161/01.STR.0000046458.67968.E4
123. Burness CB. Idarucizumab: First global approval. Drugs. 2015;75(18):2155–61. https://doi.org/10.1007/s40265-015-0508-5
124. Dalal J, Bhave A, Chaudhry G, Rana P. Reversal agents for NOACs: Connecting the dots. Indian Heart J. 2016;68(4):559–63. https://doi.org/10.1016/j.ihj.2015.11.023
125. Connolly SJ, Gibson CM, Crowther M. Andexanet alfa for factor Xa inhibitor reversal. N Engl J Med. 2016;375(25):2499–500. https://doi.org/10.1056/NEJMc1613270
126. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med. 2007;25(1):32–8. https://doi.org/10.1016/j.ajem.2006.07.008
127. Zhang Y, Reilly KH, Tong W, et al. Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China. J Hypertens. 2008;26(7):1446–52. https://doi.org/10.1097/HJH.0b013e328300a24a
128. Rodriguez-Luna D, Pineiro S, Rubiera M, et al. Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. Eur J Neurol. 2013;20(9):1277–83. https://doi.org/10.1111/ene.12180
129. Sakamoto Y, Koga M, Yamagami H, et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: The stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. Stroke. 2013;44(7):1846–51. https://doi.org/10.1161/STROKEAHA.113.001212
130. Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: A nationwide cohort study. Circulation. 2015;132(6):517–25. https://doi.org/10.1161/CIRCULATIONAHA.115.015735
131. Group ESD, Steffel J, Roldan-Schilling V, et al. The 2018 European Heart Rhythm Association

practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330–93. https://doi.org/10.1093/eurheartj/ehy136

132. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC endorsed by the European Stroke Organisation (ESO). Europace; 2016. https://doi.org/10.1093/eurheartj/ehw210

133. Ananthasubramaniam K, Beattie JN, Rosman HS, Jayam V, Borzak S. How safely and for how long can warfarin therapy be withheld in prosthetic heart valve patients hospitalized with a major hemorrhage? Chest. 2001;119(2):478–84. https://doi.org/10.1378/chest.119.2.478