Canadian Stroke Best Practices

CANADIAN STROKE BEST PRACTICE RECOMMENDATIONS

Management of Spontaneous Intracerebral Hemorrhage Evidence Tables

Ashkan Shoamanesh (Co-chair), M. Patrice Lindsay, Lana A Castellucci, Anne Cayley, Mark Crowther, Kerstin de Wit, Shane W English, Sharon Hoosein, Thien Huynh, Michael Kelly, Cian J O'Kelly, Jeanne Teitelbaum, Samuel Yip, Dar Dowlatshahi, Eric E Smith, Norine Foley, Aleksandra Pikula, Anita Mountain, Gord Gubitz and Laura C. Gioia(Co-chair), on behalf of the Canadian Stroke Best Practices Advisory Committee in collaboration with the Canadian Stroke Consortium and the Canadian Hemorrhagic Stroke Trials Initiative Network (CoHESIVE).

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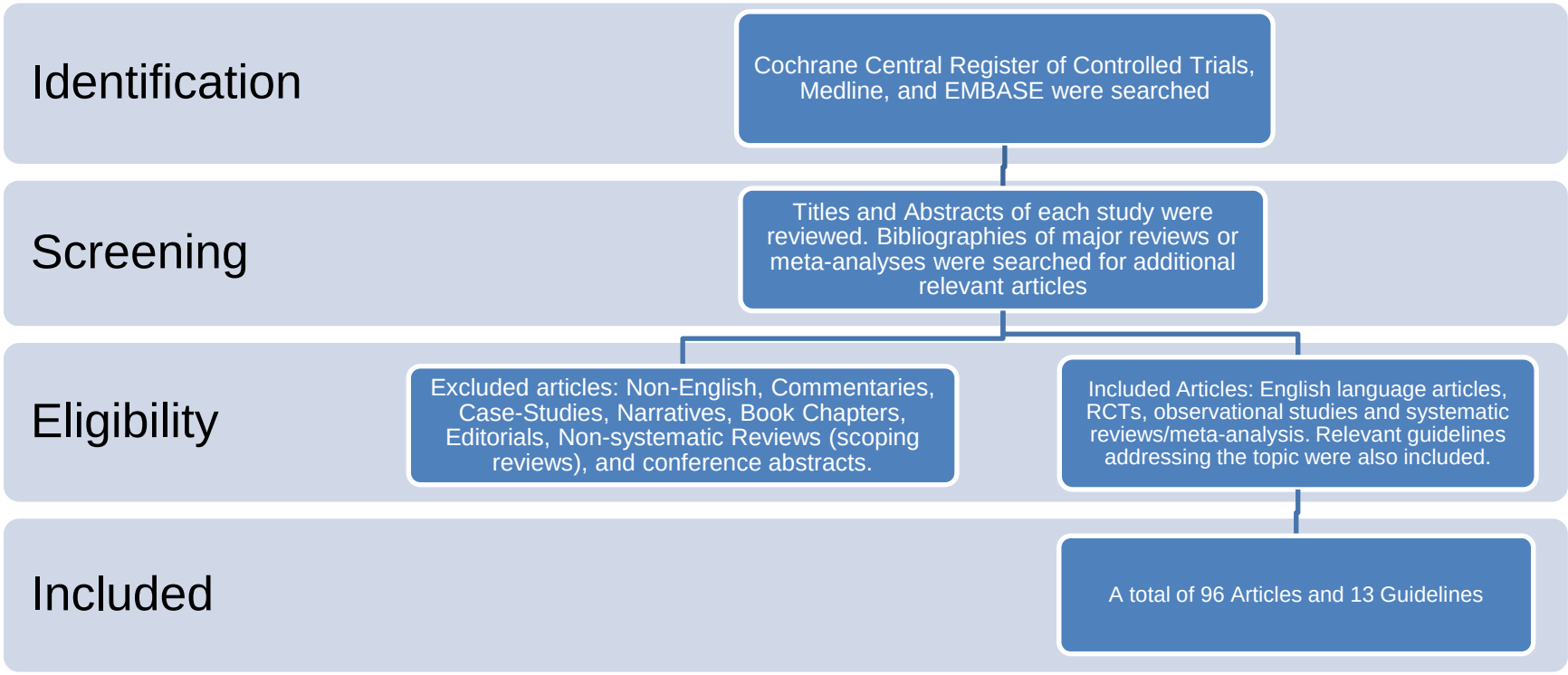
Search Strategy



Pubmed, EMBASE and the Cochrane Central Register of Controlled Trials databases were searched using the keywords: “Stroke OR “intracerebral hemorrhage” AND (risk factors OR therapy OR intervention OR rehabilitation OR Cognition OR Prevention). Titles and abstract of each article were reviewed for relevance. Bibliographies were reviewed to find additional relevant articles. Articles were excluded if they were: non-English, commentaries, case-studies, narrative, book chapters, editorials, non-systematic review, or conference abstracts. Additional searches for relevant best practice guidelines were completed and included in a separate section of the review. A total of 96 articles and 13 guidelines were included and were separated into categories designed to answer specific questions.

Published Guidelines

Guideline	Recommendations
Christensen H, Cordonnier C, Kõrv J, Lal A, Ovesen C, Purrucker JC, Toni D, Steiner T. **European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage.** ***European Stroke Journal*. 2019; 4(4) 294–306**	In adults with ICH occurring during use of VKA (with an INR above normal), we recommend using PCC to decrease mortality and normalise INR. Quality of evidence: Very low; Strength of recommendation: Strong In patients with VKA-induced ICH, we recommend PCC over FFP. Quality of evidence: Moderate; Strength of recommendation: Strong In adult patients with ICH occurring during use of VKA (with an INR 1.3), we recommend the initial use of vitamin K (10 mg intravenously (IV)) in addition to fast reversal strategies including PCC to prevent re-increase of INR, to decrease haematoma expansion and decrease mortality. Quality of evidence: Very low; Strength of recommendation: Strong In patients with ICH occurring during use of NOAC and when specific reversal agents are not available we recommend considering the use of four-factor PCC (37.5–50 IU/kg) to normalise coagulation tests. Quality of evidence: Very low; Strength of recommendation: Weak In patients with ICH occurring during use of NOAC and when specific reversal agents are not available we recommend considering the use of four-factor PCC (37.5–50 IU/kg) to normalise coagulation tests. Quality of evidence: Very low; Strength of recommendation: Weak In adult patients with ICH occurring during use of VKA and INR 1.3, we recommend against use of tranexamic acid. Quality of evidence: Very low; Strength of recommendation: Strong In patients with ICH occurring during use of NOAC, we recommend against using FFP to improve outcome, reduce mortality, decrease haematoma expansion or reverse the effects of NOAC. Quality of evidence: Very low; Strength of recommendation: Weak We recommend idarucizumab to reverse effects of dabigatran in adult patients with ICH occurring during use of dabigatran. Evidence for effects on clinical endpoints is limited. Quality of evidence: Low; Strength of recommendation: Strong We recommend using andexanet alfa if available – in adult patients with ICH occurring during use of rivaroxaban or apixaban. We also recommend randomising into trials as based on the low quality of evidence, there is significant uncertainty whether desirable outweigh undesirable effects. Quality of evidence: Low; Strength of recommendation: Weak
Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S, Sandset EC, Ntaios G, Charidimou A, Toni D, Pristipino C. **Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11–13**	**Diagnostic Tests and Timing** 1. ICH is a heterogeneous disease and clinicians should identify the underlying cause of the bleeding (Grade C). 2. At admission: CT angiography spot sign predicts haematoma growth but whether treatments tailored to this information may improve outcome remains uncertain (Grade C). 3. At admission: vessel imaging should be performed to detect an underlying cause: CTA/Computed tomography venography (CTV) or Magnetic resonance angiography (MRA)/Magnetic resonance venography (MRV) in patients in whom early intervention is considered (Grade C).

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November 2018. ***European Stroke Journal*. 2019;4(4): 307–317**	4. In patients without identified vascular malformations, brain parenchyma should be explored to see markers of the disease, ideally with MRI (Grade C). 5. In the absence of markers of deep perforating vasculopathy or cerebral amyloid angiopathy (CAA), even in CTA negative patients: conventional DSA should be performed if the benefit/risk ratio of the DSA is acceptable. Conventional DSA should be performed between two and six months after ICH (Grade C) **Tranexamic acid** 1. Inclusion window in acute ICH trials aiming at preventing haematoma expansion should be as short as possible and no longer than 4.5 h from ictus (Grade C). 2. As part of future trial protocols, BP should be controlled (≤140 mmHg systolic) (Grade C). 3. Future studies in ICH should include large number of patients, have no upper age limit and include proportional number of women (Grade C) **What is the optimal BP in acute ICH?** In patients with acute ICH we recommend to lower systolic BP below 140 mmHg but to keep it above 110 mmHg and to avoid Systolic blood pressure (SBP) reduction of more than 90 mmHg to prevent acute kidney injury (Grade B). In patient with acute ICH, we recommend to lower BP as soon and fast as possible: The optimal onset to treatment (OTT) time to impact on clinical outcome is probably as short as 2.5 h (Grade C). Still, after this period, BP should be kept **BP lowering in acute ICH: What is the influence of time, haematoma volume, choice of agent and previous hypertension?** Recommendation: In patients with acute ICH and previous hypertension recommend to lower BP as soon and fast as possible (Grade C). The optimal OTT to impact on clinical outcome may be 2.5 h, but BP should be kept <140 mmHg, because the risk of haematoma expansion exists even after this time (Grade C). We recommend the use of short-acting intravenous drugs to lower SBP in the acute phase of ICH (Grade C). In patients with acute ICH and small bleeding volumes we recommend to lower BP as soon and fast as possible to an SBP below 140 mmHg and above 110 mmHg but to avoid SBP reduction of more than 90 mmHg to prevent acute kidney injury (Grade C).
Klijn C, Paciaroni M, Berge E. Korompoki E, Kõrv J, Lal, A, Werring D. **Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke**	In patients with AF who have experienced an ICH, we cannot make recommendations regarding whether or not oral anticoagulation should be (re-)started or not. Quality of evidence: Low; Strength of recommendation: Weak Expert opinion (Delphi vote: 7/7 agree). In patients with AF who have experienced an ICH, restarting oral anticoagulation can be considered after careful weighing of risks and benefits.

Guideline	Recommendations
Organisation guideline. ***Eur Stroke J.* 2019; 4(3) 198–223**	
Halvorsen S, Storey RF, Rocca B, et al. **Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis.** ***Eur Heart J* 2017; 38: 1455–1462**	Consensus summary on oral anticoagulant after intracranial haemorrhage i. Whether and when to restart OAC after an ICH should be decided on an individual basis, depending on the patients thrombotic risk and the risk of recurrent bleeding. Close collaboration between neurologists and cardiologists is needed to make individualized decisions. ii. In the absence of mechanical valves, NOACs may be preferable to warfarin after ICH, given their lower incidence of ICH among nonvalvular AF patients in phase III trials, but their efficacy and safety have still to be established in this setting. If one of the NOACs is chosen, the lowest effective dose for stroke prevention in AF should be preferred. Renal function, body weight, age, and drug interactions should be carefully considered to avoid drug-overdosing
Holtkamp M, Beghi E, Benninger F, Kälviäinen R, Rocamora R, Christensen H, for the European Stroke Organisation. **European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy.** ***European Stroke Journal*. 2017 Jun;2(2):103-15.** **(selected)**	In the presence of only one underpowered RCT, there is no evidence if immediate primary prophylaxis with an antiepileptic drug compared to no treatment prevents occurrence of acute symptomatic seizure (ASS) in ischaemic stroke or intracranial (intracerebral or subarachnoidal) haemorrhage. Based on low incidence of ASS in observational studies, we make a weak recommendation against primary AED prophylaxis. QOE Very low, SOR Weak against strong intervention In the absence of RCTs, we cannot make strong recommendations when and in whom to treat ASS with immediate secondary AED prophylaxis compared to no treatment for prevention of further ASS. Low incidence of ASS recurrence suggests not implementing secondary prophylaxis. QOE Very low, SOR Weak against intervention In the absence of RCTs, we cannot make strong recommendations when to start immediate primary prophylaxis with an AED to prevent occurrence of post-stroke US. Low incidence of unprovoked seizure (US) occurrence suggests not implementing secondary prophylaxis Very low () Weak against intervention. QOE Very low, SOR Weak against intervention There is no consistent evidence from RCTs to support use against of AED to improve functional outcome after stroke. We suggest not administering AED treatment. QOE Very low, SOR weak against intervention There is insufficient evidence from RCTs to recommend temporary treatment with an antiepileptic drugs (AED) to reduce mortality. We suggest not administering AED treatment QOE Very low, SOR Weak against intervention
Clinical Guidelines for Stroke Management 2017. Melbourne (Australia): National Stroke Foundation.	Weak Recommendations For stroke patients with warfarin-related intracerebral haemorrhage, prothrombin complex concentrate should be urgently administered in preference to standard fresh frozen plasma to reverse coagulopathy. Intravenous vitamin K (5–10 mg) should be used in addition to prothrombin complex to reverse warfarin but is insufficient as a sole treatment. Stroke patients with intracerebral haemorrhage related to direct oral anticoagulants should urgently receive a specific reversal agent where available.

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	Strong Recommendation AGAINST For stroke patients with intracerebral haemorrhage previously receiving antiplatelet therapy, platelet transfusion should not be administered. Weak Recommendation AGAINST For stroke patients with supratentorial intracerebral haemorrhage (lobar, basal ganglia and/or thalamic locations), routine surgical evacuation is not recommended outside the context of research. Weak Recommendation AGAINST For stroke patients with intraventricular haemorrhage, the use of intraventricular thrombolysis via external ventricular drain catheter is not recommended outside the context of research. Weak Recommendation For stroke patients with intracerebral haemorrhage, blood pressure may be acutely reduced to a target systolic blood pressure of around 140 mmHg (but not substantially below)
Fried HI, Nathan BR, Rowe AS, Zabramski JM, Andaluz N, Bhimraj A, Guanci MM, Seder DB, Singh JM. **The insertion and management of external ventricular drains: an evidence-based consensus statement.** ***Neurocrit Care*. 2016 Feb 1;24(1):61-81.** **(selected)**	**Recommendations** We suggest that the location of EVD insertion (Operating Room or bedside) should be dictated by patient characteristics and clinical circumstances (Conditional recommendation; low-quality evidence). When ventricular anatomy is normal, we suggest using Kocher's point as entry, and a trajectory perpendicular to the skull or targeting the contralateral medial canthus to provide the highest likelihood of optimal EVD placement. The catheter should not be advanced more than 6.5 cm from the skull surface before CSF is encountered. In cases of distorted ventricular anatomy or unusually small ventricles, consider using image guidance if available (Conditional recommendation; low-quality evidence). In adult patients with an EVD: We recommend VTE prophylaxis for the duration of immobilization (Strong recommendation; low-quality evidence) We recommend against the routine use of inferior vena cava filters for primary prophylaxis of VTE (Strong recommendation; low-quality evidence) We suggest one dose of antimicrobials prior to EVD insertion (Conditional recommendation; low-quality evidence) We recommend against the use of antimicrobials for the duration of EVD placement; duration regimens may increase the risk of resistant organisms and Clostridium difficile colitis (Strong recommendation; low-quality evidence) We recommend using antimicrobial-impregnated catheters as part of a comprehensive management protocol to reduce the rate of VRI (Strong recommendation; moderate-quality evidence) We suggest avoiding routine CSF sampling and obtaining CSF for analysis only when clinically indicated (Conditional recommendation; low-quality evidence)
Frontera JA, Lewin JJ, 3rd, Rabinstein AA, et al. **Guideline for Reversal of Antithrombotics in Intracranial**	**Recommendations for VKA Reversal** (1) We recommend discontinuing vitamin K antagonists when intracranial hemorrhage is present or suspected. (Good Practice statement) (2) We recommend urgent reversal of vitamin K antagonists in patients with intracranial hemorrhage (Strong recommendation,

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Hemorrhage **A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine** ***Neurocritical care.* 2016;24(1):6-46.** **(selected)**	moderate quality evidence) with the following considerations: (a) We suggest against VKA reversal in patients where there is a high suspicion of intracranial hemorrhage due to cerebral venous thrombosis. (Conditional recommendation, very low-quality evidence) (b) We recommend assessing risks and benefits when considering VKA reversal in intracranial hemorrhage patients with concurrent symptomatic or life-threatening thrombosis, ischemia, heparin-induced thrombocytopenia, or DIC. (Good Practice statement). (3) We recommend administration of Vitamin K to ensure durable reversal of INR following VKA associated intracranial hemorrhage. Vitamin K should be dosed as soon as possible or concomitantly with other reversal agents. (Strong recommendation, moderate quality evidence) (a) We suggest one dose of Vitamin K 10 mg IV. Subsequent treatment should be guided by follow-up INR. (Good Practice statement) (b) If repeat INR is still elevated C1.4 within the first 24–48 h after reversal agent administration, we suggest redosing with vitamin K 10 mg IV. (Good Practice statement) (4) We recommend administering 3-factor or 4-factor PCC rather than FFP to patients with VKA-associated intracranial hemorrhage and INR C 1.4. (Strong recommendation, moderate quality evidence) (a) We suggest the use of 4-factor PCC over 3-factor PCC. (Conditional recommendation, low-quality evidence) (b) We suggest initial reversal with PCC alone (either 3- or 4-factor) rather than combined with FFP or rFVIIa. (Conditional recommendation, low-quality evidence) (c) We recommend that PCC dosing should be weight-based and vary according to admission INR and type of PCC used. (Strong recommendation, moderate quality evidence). (d) We recommend repeating INR testing soon after PCC administration (15–60 min), and serially every 6–8 h for the next 24–48 h. Subsequent treatment should be guided by follow-up INR, with consideration given to the fact that repeat PCC dosing may lead to increased thrombotic complications and risk of DIC. (Good Practice statement) (e) If the repeat INR is still elevated C1.4 within the first 24–48 h after initial PCC dosing, we suggest further correction with FFP. (Conditional recommendation, low-quality evidence) (5) We recommend against administration of rFVIIa for the reversal of VKA. (Strong recommendation, low-quality evidence) (6) If PCCs are not available or contraindicated, alternative treatment is recommended over no treatment. (Strong recommendation, moderate quality evidence) Treatment choice may be guided by available therapies and patient-specific factors. (Good Practice statement) (a) Treatment with FFP and Vitamin K is recommended over no treatment. (Strong recommendation, moderate quality evidence) (b) We suggest dosing FFP at 10–15 ml/kg IV along with one dose of vitamin K 10 mg IV. (Conditional recommendation, low-quality evidence). **Recommendations for Oral Direct Factor Xa Inhibitors Reversal** (1) We recommend discontinuing factor Xa inhibitors when intracranial hemorrhage is present or suspected. (Good Practice statement) (2) We recommend obtaining information on the time elapsed since the last dose of direct factor Xa inhibitor and possible medication interactions to assist in estimating the degree of anticoagulation exposure. (Good Practice statement) (3) We suggest that pharmacological reversal of oral factor Xa inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (Conditional recommendation, low-quality evidence) (4) We suggest administration of activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct factor Xa inhibitor. (Conditional recommendation, very low-quality evidence) (5) We suggest administering a 4-factor PCC (50 U/kg) or activated PCC (50 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure. (Conditional recommendation, low-quality evidence)

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	(6) We suggest administering 4-factor PCC or activated PCC over rFVIIa because of the lower risk of adverse thrombotic events. (Conditional recommendation, low-quality evidence). **Recommendations for Direct Thrombin Inhibitor Reversal** (1) We recommend discontinuing direct thrombin inhibitors when intracranial hemorrhage is present or suspected. (Good Practice statement) (2) We recommend assessing the time and amount of the last ingested dose, renal function, and possible medication interactions to assist in estimating the degree of anticoagulation exposure. (Good Practice statement) (3) We suggest that pharmacological reversal of direct thrombin inhibitors should be guided primarily by bleeding (major or intracranial) and not primarily by laboratory testing. (Conditional recommendation, low-quality evidence) (4) We suggest administering activated charcoal (50 g) to intubated intracranial hemorrhage patients with enteral access and/or those at low risk of aspiration who present within 2 h of ingestion of an oral direct thrombin inhibitor. (Conditional recommendation, very low-quality evidence) (5) We recommend administering idarucizumab (5 g IV in two divided doses) to patients with intracranial hemorrhage associated with dabigatran if: (a) the dabigatran was administered within a period of 3–5 half-lives and there is no evidence of renal failure (Strong recommendation, moderate quality of evidence) or (b) there is renal insufficiency leading to continued drug exposure beyond the normal 3–5 half-lives (Strong recommendation, moderate quality of evidence) (6) We suggest administering aPCC (50 units/kg) or 4-factor PCC (50 units/kg) to patients with intracranial hemorrhage associated with direct thrombin inhibitors if idarucizumab is not available or if the hemorrhage is associated with a DTI other than dabigatran if: (a) the direct thrombin inhibitor was administered within a period of 3–5 half-lives and there is no evidence of renal failure (Conditional recommendation, low-quality evidence) or (b) there is renal insufficiency leading to continued drug exposure beyond the normal 3–5 half-lives. (Conditional recommendation, low-quality evidence) (7) In patients with dabigatran-associated intracranial hemorrhage and renal insufficiency or dabigatran overdose, we suggest hemodialysis if idarucizumab is not available. (Conditional recommendation, lowquality data) (8) In patients with dabigatran-associated intracranial hemorrhage who have already been treated with idarucizumab, PCC, or aPCC, with ongoing evidence of clinically significant bleeding, we suggest consideration of redosing idarucizumab and/or hemodialysis. (Conditional recommendation, lowquality evidence) (9) We recommend against administration of rFVIIa or FFP in direct thrombin inhibitor-related intracranial hemorrhage. (Strong recommendation, low-quality evidence)
Intercollegiate Stroke Working Party. Royal College of Physicians. National Clinical guidelines for stroke. 5th Edition 2016, Edinburgh, Scotland	A-Patients with intracerebral haemorrhage in association with vitamin K antagonist treatment should have the anticoagulant urgently reversed with a combination of prothrombin complex concentrate and intravenous vitamin K. B- Patients with intracerebral haemorrhage in association with dabigatran treatment should have the anticoagulant urgently reversed with idarucizumab. C- Patients with intracerebral haemorrhage in association with factor Xa inhibitor treatment should receive urgent treatment with 4-factor prothrombin complex concentrate. D- Patients with primary intracerebral haemorrhage who present within 6 hours of onset with a systolic blood pressure above 150mmHg should be treated urgently using a locally agreed protocol for blood pressure lowering to a systolic blood pressure of

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	140 mmHg for at least 7 days, unless: – the Glasgow Coma Scale score is 5 or less; – the haematoma is very large and death is expected; – a structural cause for the haematoma is identified; – immediate surgery to evacuate the haematoma is planned. E- Patients with intracerebral haemorrhage should be admitted directly to a hyperacute stroke unit for monitoring of conscious level and referred immediately for repeat brain imaging if deterioration occurs. F- Patients with intracranial haemorrhage who develop hydrocephalus should be considered for surgical intervention such as insertion of an external ventricular drain.
Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, Scott PA, Selim MH, Woo D; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology. **Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.** ***Stroke* 2015;46:2032–2060.** **(selected)**	**Emergency Diagnosis and Assessment:** 1. A baseline severity score should be performed as part of the initial evaluation of patients with ICH (Class I; Level of Evidence B). (New recommendation) 2. Rapid neuroimaging with CT or MRI is recommended to distinguish ischemic stroke from ICH (Class I; Level of Evidence A). (Unchanged from the previous guideline) 3. CTA and contrast-enhanced CT may be considered to help identify patients at risk for hematoma expansion (Class IIb; Level of Evidence B), and CTA, CT venography, contrast-enhanced CT, contrastenhanced MRI, magnetic resonance angiography and magnetic resonance venography, and catheter angiography can be useful to evaluate for underlying structural lesions including vascular malformations and tumors when there is clinical or radiological suspicion (Class IIa; Level of Evidence B). (Unchanged from the previous guideline) **Hemostasis and Coagulopathy, Antiplatelet Agents, and DVT Prophylaxis:** 1. Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets, respectively (Class I; Level of Evidence C). (Unchanged from the previous guideline) 2. Patients with ICH whose INR is elevated because of VKA should have their VKA withheld, receive therapy to replace vitamin K–dependent factors and correct the INR, and receive intravenous vitamin K (Class I; Level of Evidence C). PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP (Class IIb; Level of Evidence B). rFVIIa does not replace all clotting factors, and although the INR may be lowered, clotting may not be restored in vivo; therefore, rFVIIa is not recommended for VKA reversal in ICH (Class III; Level of Evidence C). (Revised from the previous guideline). 3.For patients with ICH who are taking dabigatran, rivaroxaban, or apixaban, treatment with FEIBA, other PCCs, or rFVIIa might be considered on an individual basis. Activated charcoal might be used if the most recent dose of dabigatran, apixaban, or rivaroxaban was taken <2 hours earlier. Hemodialysis might be considered for dabigatran (Class IIb; Level of Evidence C). (New recommendation) 4. Protamine sulfate may be considered to reverse heparin in patients with acute ICH (Class IIb; Level of Evidence C). (New recommendation). 5. The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is uncertain (Class IIb; Level of Evidence C). (Revised from the previous guideline) 6. Although rFVIIa can limit the extent of hematoma expansion in noncoagulopathic ICH patients, there is an increase in thromboembolic risk with rFVIIa and no clear clinical benefit in unselected patients. Thus, rFVIIa is not recommended (Class III;

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	Level of Evidence A). (Unchanged from the previous guideline) 7. Patients with ICH should have intermittent pneumatic compression for prevention of venous thromboembolism beginning the day of hospital admission (Class I; Level of Evidence A). Graduated compression stockings are not beneficial to reduce DVT or improve outcome (Class III; Level of Evidence A). (Revised from the previous guideline). 8. After documentation of cessation of bleeding, lowdose subcutaneous low-molecular-weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in patients with lack of mobility after 1 to 4 days from onset (Class IIb; Level of Evidence B). (Unchanged from the previous guideline) 9. Systemic anticoagulation or IVC filter placement is probably indicated in ICH patients with symptomatic DVT or PE (Class IIa; Level of Evidence C). The decision between these 2 options should take into account several factors, including time from hemorrhage onset, hematoma stability, cause of hemorrhage, and overall patient condition (Class IIa; Level of Evidence C). (New recommendation) **Blood Pressure** 1. For ICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe (Class I; Level of Evidence A) and can be effective for improving functional outcome (Class IIa; Level of Evidence B). (Revised from the previous guideline) 2. For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (Class IIb; Level of Evidence C). (New recommendation) **General Monitoring and Nursing Care** 1. Initial monitoring and management of ICH patients should take place in an intensive care unit or dedicated stroke unit with physician and nursing neuroscience acute care expertise (Class I; Level of Evidence B). (Revised from the previous guideline) **Temperature Management:** 1. Treatment of fever after ICH may be reasonable (Class IIb; Level of Evidence C). (New recommendation) **Seizures and Antiseizure Drugs:** 1. Clinical seizures should be treated with antiseizure drugs (Class I; Level of Evidence A). (Unchanged from the previous guideline) 2. Patients with a change in mental status who are found to have electrographic seizures on EEG should be treated with antiseizure drugs (Class I; Level of Evidence C). (Unchanged from the previous guideline) 3. Continuous EEG monitoring is probably indicated in ICH patients with depressed mental status that is out of proportion to the degree of brain injury (Class IIa; Level of Evidence C). (Revised from the previous guideline) 4. Prophylactic antiseizure medication is not recommended (Class III; Level of Evidence B). (Unchanged from the previous guideline) **Management of Medical Complications:** 1. A formal screening procedure for dysphagia should be performed in all patients before the initiation of oral intake to reduce the risk of pneumonia (Class I; Level of Evidence B). (New recommendation)

Guideline	Recommendations
	2. Systematic screening for myocardial ischemia or infarction with electrocardiogram and cardiac enzyme testing after ICH is reasonable (Class IIa; Level of Evidence C). (New recommendation) **ICP Monitoring and Treatment:** 1. Ventricular drainage as treatment for hydrocephalus is reasonable, especially in patients with decreased level of consciousness (Class IIa; Level of Evidence B). (Revised from the previous guideline) 2. Patients with a GCS score of ≤8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A CPP of 50 to 70 mmHg may be reasonable to maintain depending on the status of cerebral autoregulation (Class IIb; Level of Evidence C). (Unchanged from the previous guideline) 3. Corticosteroids should not be administered for treatment of elevated ICP in ICH (Class III; Level of Evidence B). (New recommendation) **Intraventricular Hemorrhage:** 1. Although intraventricular administration of rtPA in IVH appears to have a fairly low complication rate, the efficacy and safety of this treatment are uncertain (Class IIb; Level of Evidence B). (Revised from the previous recommendation) 2. The efficacy of endoscopic treatment of IVH is uncertain (Class IIb; Level of Evidence B). (New recommendation) **Surgical Treatment of ICH:** 1. Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible (Class I; Level of Evidence B). Initial treatment of these patients with ventricular drainage rather than surgical evacuation is not recommended (Class III; Level of Evidence C). (Unchanged from the previous guideline) 2. For most patients with supratentorial ICH, the usefulness of surgery is not well established (Class IIb; Level of Evidence A). (Revised from the previous guideline) Specific exceptions and potential subgroup considerations are outlined below in recommendations 3 through 6. 3. A policy of early hematoma evacuation is not clearly beneficial compared with hematoma evacuation when patients deteriorate (Class IIb; Level of Evidence A). (New recommendation) 4. Supratentorial hematoma evacuation in deteriorating patients might be considered as a life-saving measure (Class IIb; Level of Evidence C). (New recommendation). 5. DC with or without hematoma evacuation might reduce mortality for patients with supratentorial ICH who are in a coma, have large hematomas with significant midline shift, or have elevated ICP refractory to medical management (Class IIb; Level of Evidence C). (New recommendation) 6. The effectiveness of minimally invasive clot evacuation with stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain (Class IIb; Level of Evidence B). (Revised from the previous guideline) **Prevention of Recurrent ICH**

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	1. When stratifying a patient's risk for recurrent ICH may affect management decisions, it is reasonable to consider the following risk factors for ICH recurrence: (1) lobar location of the initial ICH; (2) older age; (3) presence and number of microbleeds on gradient echo MRI; (4) ongoing anticoagulation; and (5) presence of apolipoprotein E ε2 or ε4 alleles (Class IIa; Level of Evidence B). (Revised from the previous guideline) 2. BP should be controlled in all ICH patients (Class I; Level of Evidence A). (Revised from the previous guideline) Measures to control BP should begin immediately after ICH onset (Class I; Level of Evidence A). (New recommendation) A long-term goal of BP <130 mmHg systolic and 80 mmHg diastolic is reasonable (Class IIa; Level of Evidence B). (New recommendation) 3. Lifestyle modifications, including avoidance of alcohol use greater than 2 drinks per day, tobacco use, and illicit drug use, as well as treatment of obstructive sleep apnea, are probably beneficial (Class IIa; Level of Evidence B). (Revised from previous guideline) 4. Avoidance of long-term anticoagulation with warfarin as a treatment for nonvalvular atrial fibrillation is probably recommended after warfarin-associated spontaneous lobar ICH because of the relatively high risk of recurrence (Class IIa; Level of Evidence B). (Unchanged from the previous guideline) 5. Anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents (Class IIb; Level of Evidence B). (Revised from the previous guideline). 6. The optimal timing to resume oral anticoagulation after anticoagulant-related ICH is uncertain. Avoidance of oral anticoagulation for at least 4 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence (Class IIb; Level of Evidence B). (New recommendation) If indicated, aspirin monotherapy can probably be restarted in the days after ICH, although the optimal timing is uncertain (Class IIa; Level of Evidence B). (New recommendation) 7. The usefulness of dabigatran, rivaroxaban, or apixaban in patients with atrial fibrillation and past ICH to decrease the risk of recurrence is uncertain (Class IIb; Level of Evidence C). (New recommendation) 8. There are insufficient data to recommend restrictions on the use of statins in ICH patients (Class IIb; Level of Evidence C). (Unchanged from the previous guideline)
Steiner T, Al-Shahi Salman R, Beer R, et al. **European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral haemorrhage.** ***Int J Stroke 2014*;9:840–855.** **(selected)**	Acute stroke unit care reduces both death and dependency for patients with ICH in comparison with care on a general ward. Quality of evidence: High Strength of recommendation: Strong In acute ICH within 6 h of onset, intensive blood pressure reduction (systolic target <140 mmHg in <1 h) is safe and may be superior to a systolic target <180 mmHg. No specific agent can be recommended. Quality of evidence: Moderate Strength of recommendation: Weak We do not recommend the use of rFVIIa for adults with acute spontaneous ICH not associated with antithrombotic drug use outside ongoing trials. Quality of evidence: High Strength of recommendation: Strong In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to normalize coagulation for patients with acute spontaneous ICH who had been on anticoagulant drugs.

Guideline	Recommendations
	Quality of evidence: Very low Strength of recommendation: None In the absence of RCTs, we cannot make strong recommendations about how, when, and for whom to normalize clotting for patients with acute spontaneous ICH who had been on antiplatelet drugs. Quality of evidence: Very low Strength of recommendation: None There is no evidence to support surgical intervention on a routine basis to improve outcome after supratentorial ICH in comparison with conservative management, but early surgery may be of value for patients with a GCS score 9–12. Quality of evidence: Moderate Strength of recommendation: Weak There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom surgical evacuation should be performed in adults with infratentorial ICH. Quality of evidence: Low Strength of recommendation: Weak We recommend lowering blood pressure for secondary prevention after ICH. Quality of evidence: Moderate Strength of recommendation: Strong There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom antiepileptic drugs (AEDs) should be given to reduce the risk of epilepsy after ICH. Quality of evidence: Low Strength of recommendation: Weak In the absence of RCTs we cannot not make strong recommendations about how, when, and for whom invasive monitoring of intracranial pressure should be performed for patients with acute ICH. Quality of evidence: Very low Strength of recommendation: None
Lansberg, M. G., O'Donnell, M. J., Khatri, P., Lang, E. S., Nguyen-Huynh, M. N., Schwartz, N. E. & Alonso-Coello, P. **Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines.**	**Use of Anticoagulation for Secondary Stroke Prevention** 4.3. In patients with a history of a symptomatic primary intracerebral hemorrhage (ICH), we suggest against the long-term use of antithrombotic therapy for the prevention of ischemic stroke (Grade 2C).

Guideline	Recommendations
***CHEST* 2012; 141 (2 Suppl)**: **e601S-e636S.**	
American Association of Neuroscience Nurses. Care of the patient undergoing intracranial pressure monitoring/external ventricular drainage or lumbar drainage. Glenview (IL): American Association of Neuroscience Nurses. 2011:1-38. **(selected)**	Manipulation and accessing of the EVD drainage tubing have been shown to be sources for bacterial contamination (Level 2). The risk of CSF infection increases with the duration of the EVD (Level 2). The drainage tubing should not be routinely changed; it should remain for the duration of the EVD (Level 3). For EVD-associated infection rates greater than 10%, it is recommended the institution should investigate its practices and EVD protocols (Level 3). Daily CSF surveillance may expose the EVD to contamination and should be avoided (Level 2).

Evidence Table

Risk Factors & Prognosis

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Casolla et al. 2019 **France** **Prospective study**	NA	313 patients ≥18 years, admitted to a single institution from November 3, 2004, to March 29, 2009 with ICH who were alive 30 days later. Median age was 70 years, 55% were men.	The cumulative incidence of major vascular events and their independent predictors were estimated.	**Primary outcome:** Vascular events at 1 and 5 years follow- up	Median duration of follow-up was 6 years. ICH location was deep in 195 patients and lobar in 115 patients. 82 patients had a major vascular event within 5 years (cumulative incidence of 20.0%, (95% CI, 15.7–24.7%). There were 61 strokes (cumulative incidence of 7.1% at 1 year after ICH and 14.2% at 5 years. The incidence of ischemic stroke was 3.2% at 1 year and 9.0% at 5 years. The corresponding percentages for recurrent ICH were 3.9% and 4.9%, respectively. Independent predictors of major ischemic events during follow-up were ICH in deep location (HR=1.85; 95% CI, 1.01–3.40), previous history of stroke/TIA, impaired renal function, diabetes mellitus, anticoagulant use at admission, and younger age. The only independent predictor of a major hemorrhagic event was ICH location. Patients with deep ICH had a lower risk of major hemorrhagic event during follow-up (subhazard ratio, 0.40; 95% CI, 0.20–0.82, compared with lobar location)
Carlsson et al. 2019 **Norway** **Retrospective study**	N/A	28,167 inhabitants of Tromsø aged ≥30 years, without a history of previous ICH and who attended one or more of the three surveys conducted in 1994–1995, 2001, and 2007–2008.	The association between incident ICH and risk factors (age, sex, SBP, DBP, HTN, total chol, HDL chol, triglycerides, BMI, diabetes, daily smoking, activity, alcohol intake and the use of blood-and lipid-lowering medications) was examined using questionnaires and non-	**Primary outcomes:** Independent predictors of ICH and temporal trends	There were 219 incident cases of ICHs during 396,976 person-years follow-up, of which 40% were lobar, 51% were non-lobar, and 9% involved holohemispheric/other location. In the fully adjusted model, independent predictors of ICH were: Increasing age: HR=2.84 (95% CI 2.38–3.40) Male sex: HR= 1.86 (95% CI 1.38–2.52) Increasing SBP: HR=1.46 (95% CI 1.29–1.66) Increasing DBP: HR=1.55 (95% CI 1.39–1.74) HTN (SBP≥140; and/or DBP≥90 mm Hg): HR=

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			fasting blood samples		3.26 (95% CI 2.20–4.85) 84% of ICH cases had HTN Male sex was a significant predictor of non-lobar (but not lobar) ICH (HR= 2.42, 95% CI 1.57-3.73 vs. HR=1.37, 95% CI 0.86-2.18). Hypertension was more strongly associated with nonlobar (HR= 5.08, 95% CI 2.86–9.01) than with lobar ICH (HR= 1.91, 95% CI 1.12–3.25). The incidence rates of ICH did not change significantly over time (IRR 2013 vs. 1995 = 0.81, 95% CI 0.52–1.27). Analyses stratified by sex showed a significant decrease in the incidence of ICH in women (IRR= 0.46, 95% CI 0.23–0.90), while the incidence in men remained stable (IRR= 1.27, 95% CI 0.69–2.31, p value for interaction 0.02). The difference may be attributable to lower BPs in women, with steeper declines over time.
Sturgeon et al. 2007 **USA** **Prospective study**	NA	21,680 men and women, included in 2 prospective studies, Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS). The ARIC cohort was recruited in 1987-1989 and included 15,792 men and women, aged 45-64 years at baseline, sampled from 4 US communities. The CHS cohort was recruited from 1989 -1993 and involved 5,888 men and women, aged ≥65 years at baseline, sampled from 4 US communities.	Participants with a history of stroke, and those who were not White, of African American, were excluded. The association between incident ICH and risk factors (age, sex, ethnicity, education, history of CHD, blood pressure, alcohol intake, smoking, total chol, HDL, LDL, triglycerides, BMI, waist:hip, and diabetes) was examined. Outcomes were assessed by phone call (every 6 months or yearly)	**Primary outcome:** Definite or probable incident ICH.	There were 135 incident ICHs over 263,489 person-years of follow-up. The median follow-up time was 13.5 years for participants free of ICH. The median time to event was 8.0 years for participants experiencing an ICH. Independent predictors of ICH included: Age: RR per 10-year increase=2.00, 95% CI 1.69-2.38 Stages 2 and 3 HTN: RR=2.71, 95% CI 1.58-4.67 and RR=5.55, 95% CI 3.07-10.03 African American ancestry (vs. White): RR=1.89, 95% CI 1.28-2.80 Elevated triglycerides and increased LDL were both associated with a lower risk of ICH

Predicton of Hematoma Expansion

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Xu et al. 2018 **China** **Systematic review & meta-analysis**	Assessed using the QUADAS-2 tool. Only blinding of outcome assessor was reported. In 17 studies assessors were blinded. The attribute was not reported in the remaining studies.	29 studies including persons with sICH. Sample sizes ranged from 21 to 817.	The sensitivity and specificity of the presence of the spot sign detected on CTA to predict hematoma expansion, defined as an increase in hematoma volume of >6mL or >30% from the baseline volume, was assessed.	**Primary outcome:** Hematoma expansion (HE) **Secondary outcomes:** Death and poor clinical outcome (mRS≥3)	The spot sign was present in 23.4% patients. Using the results from 25 studies (n=5,514), the sensitivity of the spot sign to predict HE was 62% (95% CI 54–69%), with a specificity of 88% (95% CI 85–91). The pooled incidence of HE was 57.5% among patients with spot sign versus 10.6% in patients without. (OR= 8.49, 95% CI 7.28–9.90). The receiver operator AUC (ability of the spot sign to predict HE) was 0.86. The risk of in-hospital and 30-day mortality was significantly higher in patients with spot sign (OR= 5.08, 95% CI 3.16–8.18, n=10 studies, and OR=3.80, 95% CI 2.62–5.52, n=6 studies, respectively). The risk of poor outcome at hospital discharge and 3 months was significantly higher in patients with spot sign (OR=6.40, 95% CI 3.41–12.03, n=3 studies and OR=4.44, 95% CI 2.33–8.46, n=4 studies, respectively).
Al-Shahi Salman et al. 2018 **UK** **Systematic review & patient-level meta-analysis**	NA	77 studies (36 cohorts, n=5,435) including patients ≥ 18 years with data available from brain imaging initially done 0·5–24 h and repeated fewer than 6 days after symptom onset, who had baseline intracerebral haemorrhage volume of < 150 mL, who did not undergo acute treatment that could reduce intracerebral haemorrhage volume.	The absolute risk and predictors of the primary outcome of intracerebral haemorrhage growth (defined as >6 mL increase in ICH volume on repeat imaging), were estimated using multivariable logistic regression models, in 4 sub cohorts (patients not taking anticoagulant therapy at ICH onset, n=5,076), patients taking anticoagulant therapy at ICH onset (n=351), patients from cohorts that	**Primary outcome:** Predictors of hematoma growth	Of the patients who were not taking antiplatelets or anticoagulants at the time of ICH, 1,009 (20%) had ICH growth (i.e., CT angiogram spot sign present). Median age was 67 years, 60% were men. Median ICH volume at baseline was 13.2 mL. Independent predictors of ICH growth in this group were decreased time from symptom onset to baseline imagine (3·4 vs. 1·2 hours, OR=0·65, 95% CI 0·51–0·82, p=0·0003), increasing ICH volume at baseline (28 vs 7 mL; OR=4·73, 95% CI 3·81–5·87, p<0·0001) and the use of antiplatelet therapy at symptom onset (yes vs no: OR= 1·38, 95% CI 1·06–1·79, p=0·016). Of the cohort that included some patients that were taking anticoagulants therapy at symptom onset, median age was 69 years, 59% were men.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			included at least some patients taking anticoagulant therapy at ICH onset (n=3,550), and patients for whom both information about anticoagulant therapy at ICH onset and spot sign on acute CT angiography were known (n=868).		Median ICH volume at baseline was 13.4 mL. Independent predictors of ICH growth in this group were decreased time from symptom onset to baseline imagine (3·5 vs. 1·2 hours, OR= 0·59, 95% CI 0·42–0·82, p=0·0021), increasing ICH volume at baseline (29 vs 7 mL; OR=4·81, 95% CI 3·82–6.05, p<0·0001), the use of antiplatelet therapy at symptom onset (yes vs no: OR= 1·36, 95% CI 1·04–1·78, p<0.0001), and the use of anticoagulants at symptom onset (yes vs no; OR= 2·91, 95% CI 1·97–4·26, p <0·0001). In the cohort of patients with spot sign on angiography (median age 70 years, 56% were men, median baseline ICH volume was 15.0 mL), independent predictors of hematoma expansion included decreased time from symptom onset to baseline imaging (5·1 vs 1·5 hours; OR=0·50, 95% CI 0·36–0·70, <0·0001), increasing ICH volume at baseline (33 vs 6 mL; OR=7.18, 95% CI 4.46–11.56, p<0·0001), the use of antiplatelet therapy at symptom onset (yes vs no: OR= 1·68, 95% CI 1·06–2·66, p=0.026), and the use of anticoagulants at symptom onset (yes vs no; OR= 3·48, 95% CI 1·96–6·16, p <0·0001). The presence of the spot sign was an independent predictor of hematoma expansion and improved the C-index of the prediction model from 0·78, 95% CI 0·75–0·82, to 0·83, 95% CI 0·80–0·86).
Di Napoli et al. 2014 **Italy/International** **Observational study**	NA	399 patients aged ≥18 years admitted to hospital with ICH within 6 hours of symptom onset. Mean age was 72 years, 54% male. Median hematoma volume was 15.5 mL	Predictive value of C-reactive protein (CRP) on hematoma expansion at levels ≤10 and > 10 mg/L, measured within 6 hours of symptom onset, was explored	**Primary outcome:** Early hematoma growth (EHG) (absolute growth>12.5 mL or increase of >33% from baseline). **Secondary outcomes:** Early neurological worsening, 30-day mortality	213 patients had CRP values ≤10 mg/L and 186 had values > 10 mg/L. EHG occurred in 103 patients (25.8%). CRP >10 mg/L was an independent predictor of EHG (adj OR=4.71, 95% CI 2.75-8.06, p<0.0001). Early neurological worsening occurred in 77 patients (19.3%). CRP >10 mg/L was an independent predictor of ENW (adj OR=2.70, 95% CI 1.50-4.84, p<0.0009). At 30 day, 127 patients (31.8%) had died. A higher percentage of patients who died had CRP values

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					>10 mg/L (50.5% vs. 25.3%, HR=2.13, 95% CI 1.42-3.18, p<0.0001).
Brouwers et al. 2014 **USA** **Observational study**	NA	Development cohort: 817 patients admitted with ICH. Mean age was 72 years, 56% male. Median ICH volume was 16 mL Validation cohort: 195 patients with ICH	Potential predictors of hematoma expansion were explored by comparing clinical variables between groups with/without hematoma expansion, defined as >33% increase from baseline of absolute increase of ≥6mL.	**Primary outcome:** Independent predictors were used to develop a 10-point prediction scale (0-9) for hematoma expansion and mortality	156 patients in the development cohort developed hematoma expansion In both univariate and multivariable analyses, warfarin use, CTA spot sign, larger baseline ICH volume, and shorter time to CT were all significant, independent predictors of hematoma expansion Warfarin use: adj OR=2.61, 95% CI 1.73-3.95, p<0.001 Time to CT (≤6 vs. > 6 hrs); adj OR=2.55, 95% CI 1.53-4.27, p<0.001. Baseline ICH volume (30-60 mL): adj OR=1.64, 95% CI 1.04-2.59, p=0.03), >60 mL: adj OR=2.10, 95% CI 1.25-3.55, p=0.005. Spot sign: adj OR=3.81, 95% CI 2.08-6.98, p<0.001. Prediction Scale: warfarin use (no [0 points] or yes [2 points]), shorter time to CT (>6 [0 points] or ≤6 [2 points] hours), CTA spot sign (absent [0 points], present [3 points], or unavailable [1 point]), and baseline ICH volume (<30 [0 points], 30-60 [1 point], or >60 [2 points] mL). 5.7% of patients with a prediction score of 0 developed hematoma expansion compared with 80% of patients with a score of 9. Higher prediction scores tended to correlate with increased hematoma development. In-hospital mortality occurred in 193 patients (23.6%). Three-moth mortality was 244 (29.9%). Higher prediction scores were generally associated with increased mortality (in-hospital and 3-month). In the validation study, hematoma expansion occurred in 15.9% of patients. 5.9% of patients with a score of 0 had hematoma expansion, compared with 32.0% with a score of 4-9. A higher score (4-9 vs 0-3) was associated with increased of expansion (OR =4.59, 95% CI, 2.06-10.2, p <

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					.001).
Demchuk et al. 2012 **Canada (PREDICT)** **Observational study**	NA	268 patients ≥18 years, who presented within 6 hours of onset with a primary or anticoagulant-associated ICH of less than 100 mL. Exclusion criteria included known renal impairment, premorbid dependence, secondary cause of ICH, deep coma, or major comorbid or terminal illness.	All patients received a non-contrast CT and CT angiography (CTA) and the results were reviewed separately and independently. CT hematoma volumes were estimated using computerized planimetry. CTA images were used to determine presence/absence of the spot sign using standardized, accepted criteria. A model to predict hematoma expansion was developed.	**Primary outcome:** Hematoma expansion (+/-), defined as an increase in 6 mL from baseline at follow-up CT or increase in growth of 33%. **Secondary outcomes:** Neurological worsening (NIHSS≥4 points at 24 hours, mRS score and mortality at 3 months.	Data from 228 patients were included in the analysis. 61 patients (26.8%) were spot-sign positive. These patients had lower median GCS scores (13.5 vs. 15, p=0.016), higher median NIHSS scores (17 vs. 11, p<0.0001), and greater median ICH volumes (19.9 vs. 10.0, p<0.001), compared with spot-sign negative patients. Hematoma expansion occurred more frequently in the spot-sign positive patients (60.7% vs. 21.6%, p<0.001). Absolute ICH growth was greater in the spot-sign positive patients (median 8.6 vs. 0.4 mL, p<0.001). Spot-sign positive patients had worse outcomes Percentage of patients with: Neurological worsening: 32.1% vs. 13.7%, p=0.006. Median mRS scores: 5 vs. 3, p<0.001. Mortality: 43.3% vs. 19.6%, p=0.001. After adjusting for baseline factors, positive spot sign on CTA was an independent predictor of hematoma expansion (RR=2.3, 95% CI 1.6 to 3.1)
Delgado Almandoz et al. 2009 **USA** **Retrospective study**	NA	367 patients admitted to a single institution from 2000-2008, with nontraumatic ICH who received a CTA within 24 hours of admission and a non-contrast CT within 48 hours of the CTA.	CTAs were independently reviewed by 3 neuroradiologists to determine the presence and characteristics of the spot sign using standardized 4-point criteria. ICH and IVH volumes were estimated from the initial and follow-up CTs. Significant hematoma expansion was defined as an increase in ICH volume of	Accuracy of spot signs to predict expansion of hematoma (>30% or >6mL).	Spot signs were identified in 71 patients (19%). The spot sign (+/-) was the only independent predictor of hematoma expansion to remain in a multivariable model. Sensitivity: 88%, (75% to 94%) Specificity: 96% (89% to 95%) Positive Predictive Value: 69% (57% to 79%) Negative Predictive Value: 98% (95% to 99%) Accuracy: 92%

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			>6 mL or >30% from the baseline ICH volume.		
Cucchiara et al. 2008 **USA** **Observational study**	NA	303 patients enrolled within 6 hours of symptom onset, and the presence of limb weakness as part of the neurological deficit. Participants were included in the placebo arm of the CHANT study.	Brain imaging scans taken at baseline and 72 hours were used to determine ICH volume. Scans were read by a neuroradiologist unaware of the patient's clinical information. A model was developed to predict hematoma expansion at 72 hours and mortality at 3 months. Oral anticoagulant use was examined as a possible predictor. ICHs were classified as oral anticoagulant (OAT) ICHs based on a history of prior use and usage at the time of enrolment.	**Primary outcome:** Hemaotoma expansion (>33% increase in ICH volume from baseline). **Secondary outcomes:** Mortality and poor clinical outcome (mRS 4-6) at 90 days.	OAT ICH was identified in 21 patients (6.9%). Median ICH volume was greater in patients with OAT ICH (30.6 vs. 14.4 mL, p=0.03). Hemorrhage expansion occurred more frequently in OAT ICH (56% vs. 26%, p=0.006). Mortality was significantly increased in OAT ICH (62% vs. 17%, p<0.001). Baseline ICH volume, time to neuroimaging and oral anticoagulant use were independent predictors of absolute change in ICH volume. Increased age, male gender and use of oral anticoagulants were independent predictors of mortality.
Goldstein et al. 2007 **USA** **Retrospective study**	NA	104 patients ≥18 years admitted from 2002-2006 with ICH who had received a CTA (performed at the discretion of the treating physicians) and received at least one more CT scan within 48 hours after their CTA. Patients were excluded if ICH was secondary to head trauma, ischemic stroke with hemorrhagic transformation, tumor, vascular malformation, or vasculitis.	The CT scans and CTAs were reviewed. ICH volumes were determined from baseline CT scans based on independent assessment of two reviewers blinded to all clinical data. The presence of contrast extravasation was operationally defined as the presence of high-density material within the hematoma. A regression model was developed to predict variables associated with hematoma expansion.	**Primary outcome:** Hematoma expansion within 24 hours, defined by an increase in volume of >33% from baseline. **Secondary outcome:** In-hospital mortality	14 patients (13.5%) developed hematoma expansion. The median increase was 12 mL. On univariate analysis, contrast extravasation was the most powerful predictor of hematoma expansion presenting in 92% of patients who developed hematoma expansion, compared with 51% of those who did not (p = 0.006). Contrast extravasation was the only significant predictor of hematoma expansion (OR=18, 95% CI 2.1-162, p=0.009) in the multivariable model that included age, time to CTA (<3 hours), admission systolic blood pressure and initial hematoma volume. In-hospital mortality was more common in patients with contrast extravasation (33% vs. 15%, p=0.04.

Acute Intracerebral Hemorrhage Management

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Initial Assessment					
Finocchi et al. 2018 **Italy** **Prospective study**	NA	156 patients admitted to a single facility with an acute ICH, confirmed by cerebral CT scan. Mean age was 76 years, 56% were men. Mean and median baseline NIHSS scores were 10.9 and 7, respectively. 94 patients had hypertensive primary ICH, 45 had lobar primary ICH	The association between baseline NIHSS scores and 30-day and 3-month outcomes (mRS scores) was evaluated	Sensitivity, specificity and area under ROC, using a cut point of NIHSS scores of ≤7 and >7 and mRS scores of ≥4 and 0-3.	32 patients (20.5%) died within 30 days and other 22 (14.1%) within 3 months. 79 patients had a baseline NIHSS score of ≤7, and 77 had a score >77. The median and mean mRS scores at 3 months were 4 and 3.38. Spearman's rank correlation between NIHSS and mRS scores at 30 and 90 days were 0.74 and 0.66, respectively. Sensitivity and specificity for 30-day outcomes were 93.5% and 82.3%, respectively. AUC ROC was 0.914. Sensitivity and specificity for 90-day outcomes were 92.2% and 69.6%, respectively. AUC ROC was 0.833.
Fiebach et al. 2004 **Germany** **Prospective study**	NA	62 ICH patients admitted to 6 hospitals within the first 6 hours after ictus and 62 control patients without ICH. All participants fulfilled the following inclusion criteria: (1) known onset of symptoms, (2) focal neurological deficit with stroke severity of >3 on the NIHSS, and (3) stable vital signs. Mean age of patients in both groups was 65.5 years.	Three readers experienced in stroke imaging and 3 medical students, unaware of clinical details, separately evaluated sets of diffusion-, T2-, and T2*-weighted images, which were presented in random order. The reference standard was CT imaging. The sensitivity, specificity and accuracy of MRI to identify ICH was evaluated	Sensitivity, specificity, accuracy	The experienced readers identified all ICH on MRIs (100% sensitivity, 95% CI 97.1% to 100%). Specificity and accuracy were also 100%. The mean sensitivity of the medical students was 95.2% (95% CI, 89.8% to 99.8%). Mean specificity was 95.5% with a positive predictive value of 100% and a negative predictive value of 95.5%. Accuracy was 97.6%.
Blood Pressure Variability					
Meeks et al. 2019	NA	566 adult patients admitted to 4 certified	During hospitalization, patients were treated when SBP≥150	**Primary outcome** 30 and 90-day mRS score	The mean SBP on admission was 173.5 mm Hg, 151.9 mm Hg during hospitalization, and

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
USA **Prospective study** ***Efficient Resource Utilization for Patients with Intracerebral Hemorrhage (EnRICH)***		stroke centers with radiologically confirmed primary ICH. Mean age was 63.5 years, 36.6% were women. 25.4% had a previous stroke.	mm Hg. SBP of 130-150 mm Hg was maintained within the first 24 hours. After the first 24 hours, SBP was controlled in the range of 100–150 mmHg, with DBP in the range of 60–90 mmHg. The association between variability in serial in-hospital blood pressure measurements and the primary outcome was examined. A standard deviation (SD) of 13.0 was used as a cut-off point to categorize persons with high systolic blood pressure variability (HSBPV).	post discharge Patients with an mRS score of 4–6 were classified as those who experienced severe disability or death (SDD).	129.1 mm Hg upon discharge (within the previous 12 hours). Median LOS was 6 days. There were 288 patients with HSBPV and 278 with no HSBPV. Patients with HSBPV had a significantly higher risk of SDD at day 90 (RR=95% CI: 1.20, 1.04–1.39), after controlling for age, hemorrhage volume, GCS, NIHSS, and high pre-morbid mRS. Pre-hospital predictors of HSBPV included female sex, increasing age, higher baseline SBP, higher Glasgow Coma Scale score, and higher baseline blood glucose.
Chung et al. 2018 **USA** **RCT (secondary analysis)**		386 patients with ICH included in the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) Trial	BP was recorded at 11 timepoints in the first 24 hours post stroke. BP was analyzed in the hyperacute period, from 0 to 4–6 hours, and in the acute period, from 0 to 24–26 hours after onset. BPV was analyzed by standard deviation, coefficient of variation, and successive variation. The association between BP variation and the primary outcome was analyzed.	**Primary outcome:** Favourable outcome (mRS 0-2) at 3 months	116 patients had a favourable outcome, 270 had an unfavorable outcome. Median SBP measurements were 176 mm Hg, at 23 minutes (median) after last known well, 178 mm Hg at ED arrival, (median of 57 minutes), and 138 mm Hg at 24 hours. BP variability was associated with significantly increased odds of a poor outcome in both the hyperacute period (0-6 hours) and the acute period (6-26 hours) using any of the 3 measures of variability, comparing the highest with the lowest quintiles of variability. In the hyperacute stage, the odds of a poor outcome were increased 3-5-fold, and 5-6 fold in the acute stage.
Management of Hypertension					
Moullaali et al. 2019 **UK/International** **Systematic**	See assessment for both trials below	3,829 patients included in the INTERACT-2 and ATTACH-2 trials. Mean age was 63.1 years, 37% were women. Median NIHSS score of	Patient-level meta-analysis. Baseline variables included age (<65 vs. ≥ 65 years), race (Asian versus nonAsian), time from the onset of symptoms to randomisation (<4 h vs ≥4 h),	**Primary outcome:** Distribution of mRS scores at 90 days **Secondary outcomes:** Good outcome (mRS 0-3)	Overall, the mean drop in SBP over the first hour was 29 mm Hg. Mean level of achieved SBP in 24 hours was 147 mm Hg. The mean variability in SBP over 24 hours was 14 mm Hg.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
review & meta-analysis		11.	degree of neurological impairment (NIHSS <10 vs ≥10), medical history (presence of diabetes, hypertension, or cardiac disease), presence of intraventricular haemorrhage, and haematoma volume (<15 mL vs ≥15 mL)	at 90 days, functional independence at 90 days (mRS 0-2), hematoma expansion from baseline to 24 hours (>6 mL or <33%), death within 90 days **Safety outcomes:** Neurological deterioration, symptomatic hypotension, fatal or non-fatal, cardiac, or renal serious adverse events, within 90 days Outcomes were analyzed according to the level of SBP achieved within 24 hours, variability in SBP over 24 hours and the magnitude in change from baseline to minimum ≤1 h post-randomization	Achieved target SBP was associated with functional status. Each 10 mm Hg increase in SBP resulted in significantly reduced odds of a favourable shift in mRS scores (OR=0·90, 95% CI 0·87–0·94, p<0·0001), reduced odds of a good outcome (OR=0·90, 95% CI 0·85–0·95, p=0·0002) and increased odds of hematoma expansion, neurological deterioration, death at 90 days and serious adverse events. The same pattern of results was evident for all outcomes when assessed as a function of variability in SBP over 24 hours. There were no associations between the magnitude of SBP reductions and any of the outcomes.
Qureshi et al. 2016, Leasure et al. 2019, Toyoda et al. 2019 **USA** **RCT** ***Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,000 patients aged 18-89 years, admitted to hospital with ICH (sudden onset of focal neurological deficit presumed due to intracerebral hematoma demonstrated on CT scan), with an initial NIHSS score of ≥4 and Glasgow Coma Scale score of ≥5. Admission SBP > 180 mmHg on two repeat measurements at least 5 min apart. Possible to treat with IV nicardipine within 4.5 hours of symptom onset. Main exclusions were	Standard SBP reduction (Nicardipine hydrochloride used PRN as the primary agent in lowering SBP, with a goal to reduce and maintain SBP < 180 mm Hg for 24 hours from randomization with a target of 140-179 mmHg, n=500) vs. Intensive SBP reduction (Nicardipine hydrochloride used PRN as primary agent in lowering SBP, with a goal for to reduce and maintain SBP < 140 mmHg for 24 h from randomization and target of 110-139 mmHg, n=500). In both groups the maximum dose of Nicardipine was 15 mg/hr, with the addition of a	**Primary outcome:** Death or disability, (mRS of 4-6) at 3 months following treatment **Secondary outcomes:** EQ-5D, hematoma expansion (defined as an increase in the volume of intraparenchymal hemorrhage of >33% at 24 hours compared with the baseline CT scan), serious adverse events at 72 hours post treatment. **Primary treatment failure:** failure to reach the target SBP (< 140 mm Hg in the intensive-treatment group and < 180 mm Hg in the	Trial was stopped prematurely due to futility. The mean interval between symptom onset and randomization was 182.2±57.2 minutes (intensive-treatment group) and 184.7±56.7 minutes (standard-treatment group). The mean minimum SBP during the first 2 hours was 128.9±16 mm Hg (intensive-treatment group) and 141.1±14.8 mm Hg (standard-treatment group). Primary and secondary treatment failures were significantly higher in the intensive treatment group (12.2% vs. 0.8%, p<0.001 and 15.6% and 1.4%, p<0.001, respectively). The risk of death or disability was not reduced significantly with intensive treatment (38.7% vs. 37.7%, adjusted OR=1.04, 95% CI 0.85-1.27, p=0.72). In subgroup analysis, there were no

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		admission SBP > 240 mmHg, trauma-related ICH, lesion location is infratentorial regions such as pons or cerebellum or the patient is a candidate for immediate surgical intervention. Mean age was 61.9 years, 62% were male. Mean SBP at baseline was 200 mm Hg. Median NIHSS score was 11. 16.4% of patients had suffered a previous stroke/TIA	second agent, if required (labetalol 5-20 mg IV bolus every 15 min)	standard treatment group) within 2 hours after randomization. **Secondary treatment failure:** the hourly minimum SBP remaining higher than the upper limit of the target range for 2 consecutive hours 2 to 24 hours after randomization. Analysis was adjusted for age, initial GCS score, and +/- intraventricular hemorrhage.	significant differences between groups on the primary outcome (GCS, +/- intraventricular hemorrhage, baseline hematoma volume, hematoma location, diabetes, sex, race or achieving target SBP within 2 hours). There was no significant difference between groups in the ordinal distribution of mRS scores at 3 months. The number of patients with hematoma expansion was non-significantly lower in the intensive treatment group (18.9% vs. 24.4%, adj OR=0.78, 95% CI 0.58-1.03, p=0.08). The risk of neurological deterioration within 24 hours was not reduced significantly for patients in the intensive-treatment group (11.0% vs. 8.0%, adj OR=1.39, 95% CI 0.92-2.09, p=0.11). While there was no significant difference between groups in the number of total number of adverse events occurring within 72 hours (1.6% vs. 1.2%, p=0.56), the risk of serious renal adverse events was significantly higher in the intensive-treatment group (9.0% vs. 4.0%, adj OR=2.32, 95% CI 1.37- 3.94, p=0.002). The occurrence of any serious adverse event within 3 months was significantly higher in the intensive-treatment group (25.6% vs. 20.0%, adj OR=1.30, 95% CI 1.00-1.69, p=0.05). There were no significant differences between groups in the number of deaths (6.6% vs. 6.8%, p=0.97) or median EQ-5D scores. **Subgroup analysis (Leasure et al. 2019)** Analysis of 780 with deep intracranial hemorrhage and complete neuroimaging data. Analysis was adjusted for age, sex, history of hypertension, history of smoking, baseline international normalized ratio, baseline ICH

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					volume, and minutes to baseline scan. The risk of hematoma expansion (≥33%) was significantly lower for patients in the intensive group (17.3% vs. 25.3%, adj OR=0.61, 95% CI 0.42-0.88, p=0 .009), as was the risk of hematoma expansion, defined as >6 mL (10.9% vs. 18.7%, adj OR=0.55, 95% C 0.35-0.87, p= 0.01). The risk was modified by deep ICH location (p for interaction=0.02), whereby the patients with a basal ganglia hemorrhage benefited from intensive BP reduction and those with thalamic hemorrhages did not. There was no difference in the proportion of patients who had a poor outcome at 3 months (36.5% vs. 35.6%, p=0.93). **Subgroup analysis (Toyoda et al. 2019)** Analysis of blood pressure strata and clinical outcomes. Patients were divided into 5 groups by 10-mmHg strata of average hourly minimum SBP (<120, 120–130, 130–140, 140–150, and ≥ 150 mmHg) during 2 to 24 hours after randomization. Analysis was adjusted for sex, race, age, onset-to-randomization time, baseline NIHSS score, hematoma volume, and hematoma location Using 120-130 mm Hg as a reference, the odds of mRS score of 4-6 at 90 days were significantly increased in patients in the 140-150 mmHg strata (adj OR=1.62, 95% CI 1.02-2.58). The odds of hematoma expansion were significantly increased in the 140-150 and ≥150 mmHg strata (adj OR=1.80, 95% CI 1.05- 3.09 and adj OR= 1.98, 95% CI 1.12-3.51, respectively). There was no significant increase in the odds of death at 90 days in any of the stratum (using 120-130 mmHg as a reference).

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					The odds of cardiorenal adverse events were significantly lower in the 140-150 and ≥150 mmHg strata, compared with the reference group (120-130 mmHg) adj OR=0.43, 95% CI 0.19- 0.88 and adj OR=0.44, 95% CI 0.18-0.96, respectively).
Butcher et al. 2013 **Canada** **RCT** ***The Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH ADAPT)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	75 patients ≥18 years with spontaneous ICH <24 hours after symptom onset and systolic BP≥150 mmHg	Patients were randomized to one of two target systolic BP groups < 150 mmHg (n=39) or < 180 mmHg (n=36) within one hour of admission, and both treated with intravenous labetalol (10 mg starting dose)/hydralazine (5 mg starting dose)/enalapril (1.25 mg starting dose).	**Primary outcome:** Cerebral blood flow (CBF) in the perihematoma region, measured with CT perfusion, 2 hours after randomization. **Secondary outcomes:** Hematoma expansion rates at 24 hours, NIHSS scores at 2 hrs, 1, 30 and 90 days, Barthel Index (BI) and mRS scores at 1, 30 and 90 days, 30-day mortality.	Mean ±sd perihematoma rCFB were not significantly different between groups: 0.98±0.14 (<150 mmHg) vs. 0.89±0.09 (<180 mm Hg), p=0.18 There was no difference in the median ICH volume change at 2 hours: 0.67 (<150 mmHg) vs. 0.71(<180 mm Hg), p=0.53 There were no significant differences in clinical outcomes between groups (<150 vs. <180 mmHg): Median (IQR) 24-hour NIHSS scores: 10 (5-19) vs. 15 (6-20), p=0.85 Median (IQR) 90-day mRS scores: 2.5 (1-5.75) vs. 4 (2-50), p=0.65 Median (IQR) 90-day BI scores: 95 (75-100) vs. 95 (40-100), p=0.51 30-day mortality: 7 (18%) vs. 4 (11%), p=0.40 Losses to follow-up: none (36 patients in <150 mmHg group included in primary analysis)
Anderson et al. 2008 **Australia** **RCT** ***Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 1)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☒	404 patients ≥18 years with spontaneous ICH diagnosed within 6 hours of symptom onset with elevated systolic BP (150-220 mmHg)	Patients were randomized to early intensive lowering of BP (target systolic BP 140 mm Hg; n=203) or standard guideline-based management of BP (target systolic BP 180 mm Hg; n=201 control group), using medications and protocols according available in each participating country. The goal was to achieve target BP within 1 hour and to maintain for the next 7 days or until discharge	**Primary outcome:** Proportional change or growth in hematoma volume after 24 hours, death or dependency (mRS score of 3-5 days) at 90 days **Secondary outcomes:** Absolute and substantial growth (increase in volume of ≥ 33%) of the hematoma + any intraventricular hemorrhage (IVH) at 24	Adjusted for baseline volume of hematoma and time from onset of ICH to CT scan, the median percentage increase in hematoma volume was greater for patients in the control group: 16.2% vs. 6.2%, diff of 10%, 95% CI 0.0 to 20.5%, p=0.06. Proportion increase in hematoma +IVH was greater for patients in the control group: 17.6% vs. 7.6%, diff of 10%, 95% CI 0.0 to 20.8%, p=0.06. More patients in the control group experienced substantial hematoma growth: 40 (23%) vs. 26

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				hours, mRS, NIHSS, BI, EQ-5D scores at day 90.	(15%), p=0.05. There were no differences between groups on any of the clinical secondary outcomes at 90 days (control group vs. <140 mmHg) Death or dependency: 95 (49%) vs. 95 (48%), p=0.81 Median (IQR) mRS scores: 2 (1-4) vs. 2 (1-4), p=0.66 Median (IQR) NIHSS scores: 2 (1-5) vs. 2 (1-5), p=0.97 Median (IQR) BI scores: 95 (65-100) vs. 95 (65-100), p=0.77 Median (IQR) EQ-5D scores: 0.78 (0.59-1.00) vs. 0.75 (0.52-1.00), p=0.97. There was no difference in the # of patients who experienced serious adverse events between groups: 42(21%) vs. 42 (21%), p=0.96. Losses to follow-up: n=29 intensive group, n=29 control group
Anderson et al. 2013 **Australia** **RCT** ***Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 2)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☒	2,839 patients ≥18 years who had experienced an ICH within the previous 6 hours and were hypertensive (SBP 150-220 mm Hg). Mean age was 64 years, 63% male, mean baseline NIHSS score 10.	Patients were randomized to receive intensive BP lower with oral agents to obtain a target SBP of <140 mm Hg within 1 hour of randomization, which was to be maintained for 7 days (n=1399) or standard treatment using guideline recommendations in which elevated BP was to be treated when SBP > 180 mm Hg for 7 days (n=1430)	**Primary outcome:** Death or disability at 90 days (mRS score of 3-5) **Secondary outcomes:** Ordinal analysis of mRS scores, all-cause and cause-specific mortality, EQ-5D, hospital LOS, poor outcomes at days 7 and 28, safety outcomes (early neurological deterioration, severe hypotension	More patients in the intensive group were treated with 2+ agents to reduce BP (26.6% vs. 8.1%, p<0.001). At one hour after randomization, the mean SBP was significantly lower in the intensive group (150 mm Hg vs. 164 mm Hg, p<0.001). There was no difference between groups in the volume of hematoma expansion at 24 hours (18.2 vs. 20.6 ml). At 90 days, 52% of patients in the intensive group experienced death or disability vs. 55.6% in standard care group (OR=0.87, 95% CI 0.75-1.01, p=0.06). There were no significant interactions identified in subgroup analyses of the primary outcome: age (<65 vs. ≥65 yrs), region (China vs. other), time to randomization (< 4 hrs vs. ≥4 hrs), baseline SBP (<180 mm Hg vs. ≥180 mm Hg), history of hypertension

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					(yes vs. no), baseline NIHSS score (<15 vs. ≥15), baseline hematoma volume (15 mL vs. ≥15 mL), and hematoma location (deep vs. other) In the ordinal analysis, there was a favourable shift in mRS scores among patients in the intensive group, whereby a greater proportion of patients had lower scores compared with the standard group (OR for greater disability=0.87, 95% CI 0.77-1.00, p=0.04). There was no difference in 90-day mortality between groups (11.9% vs. 12%, OR=0.99, 95% CI 0.79-1.25, p=0.99). Patients in the intensive group had significantly better scores in 4/5 domains of the EQ-5D. There were no differences in early neurological worsening between the group (14.5% vs. 15.1%, OR=0.95, 95% CI 0.77-1.17, p=0.62). There were no differences between groups in nonfatal serious adverse events (recurrent ICH, ischemic stroke, acute coronary event, noncardiovascular disease, severe hypotension). Losses to follow-up: intensive group n=17, standard group n=18.
Sakamoto et al. 2013 **Japan** ***Stroke Acute Management with Urgent risk factor Assessment and Improvement (SAMURI)-ICH***	NA	211 patients aged ≥20 years with Glasgow Coma Scale scores of ≥5, admitted within 3 hours of ICH with elevated SBP (>180 mm Hg). Median age was 65 years, 62% male, median baseline NIHSS score of 13. Median SBP on admission was 200 mm	All patients were initially treated with i.v. nicardipine using a standardized protocol to maintain SBP of 120-160 mm Hg for the first 24 hours. Oral antihypertensive agents were then initiated and continued at the discretion of the treating physician. Two groups were created- those with a favourable	**Primary outcome:** Neurological deterioration (decrease of 2 or more points on GCS), or an increase of 4 or more points on NIHSS at 72 hours, hematoma expansion (<33% from baseline)	17 patients (8%) experienced early neurological. Their distribution among SBP groups was: <130 mm Hg: 0 130-135: 2 (4.5%) 135-140: 2 (3.4%) 140-145: 5 (10%) 145+: 8 (30%) In adjusted analysis, the odds of early neurological worsening were significantly lower in all SBP groups compared with the highest group.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Observational study		Hg.	outcome (mRS 0-3) and those with an unfavourable outcome (4-6) at 3 months. The independent contribution of elevated SBP on outcome was explored.		36 patients (17%) experienced hematoma expansion. Their distribution among SBP groups was: <130 mm Hg: 2 (6.1%) 130-135: 4 (9.1%) 135-140: 13 (22%) 140-145: 10 (21%) 145+: 7 (26%) In adjusted analysis, there was a trend towards decreased odds of hematoma expansion with lower SBP compared with the highest group. 87 patients (41%) experienced a poor outcome. Their distribution among SBP groups was: <130 mm Hg: 7 (21%) 130-135: 20 (46%) 135-140: 22 (37%) 140-145: 24 (50%) 145+: 14 (52%) In adjusted analysis, the odds of a poor outcome were significantly lower in the lowest SBP compared with the highest
Qureshi et al. 2010 **USA** ***Open-label, non-randomized trial Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH I)***	NA	60 patients > 18 years, with new neurological signs of a stroke within 6 hours of the time to evaluation and initiation of treatment with intravenous nicardipine, total baseline GCS score >8, hematoma volume <60 cc, admission systolic blood pressure >170 mm Hg and evidence of chronic hypertension.	Pilot trial to determine safety and tolerability of BP reduction Patients were allocated to one of 3 treatment tiers with escalating targets for PB control: 1) 170-200 mmHg (n=18), 2) 140-170 mmHg (n=20), 3) 110-140 mmHg (n=22), which were maintained for 24 hours.	**Primary outcome:** Treatment success (i.e., target BP was achieved and maintained), neurological deterioration (NIHSS ≥4 points or decline in GCS score by 2 or more points within 24 hours), serious adverse events within 24 hours. **Secondary outcomes:** Hematoma expansion (>33% volume increase within 24 hours), favourable outcome (mRS 0-2) and mortality at 90 days	There was a total of 9 treatment failures (all in tier 3). The number (%) of patients with neurological deterioration within 24 hours in tiers, 1, 2 and 3 were 1(6%), 2 (10%) and 4 (18%), respectively. Symptomatic hematoma expansion: 0, 1 (5%) and 4 (18%), in tiers 1, 2, 3. 90-day mortality: 3 (17%), 2 (10%), 5 (23%) in tiers 1, 2, 3, p>0.05. Good outcome: 8 (44%), 9 (45%), 7 (18%) in tiers 1, 2, 3. Serious adverse events: 0, 1 (5%), 3 (14%) in tiers 1, 2, 3. Losses to follow-up: n= 9

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Qureshi et al. 2012 **USA** **Post-hoc analysis of ATACH 1**	NA	See above. Additional exclusions not reported above were patients with renal insufficiency (serum creatinine >2.0 mg/dL) or on renal dialysis.	Patients who experienced acute renal failure (defined by increases in creatinine, using the Acute Kidney Injury Network Classification system) following initiation of treatment were identified.	**Primary outcome:** Associations between renal failure and maximum dose of nicardipine and SBP reduction at 72 hours	5 patients developed stage 1 renal injury (increase of ≥0.3 mg/dL). No patients developed 2, 3 or 4 stage injury. The peak creatinine levels were observed at 18, 30, 57-58 and 71 hours from baseline. The only significant baseline difference reported between the groups (renal injury vs. no injury) was a higher mean baseline hematoma volume in patients with renal injury (25.2 vs. 12.5 mL, p=0.179). The mean nicardipine maximum dose was non-significantly higher in patients with renal injury (8.5 vs. 4.4 mg/hr, p=0.156). A significantly higher proportion of patients with renal injury experienced neurological deterioration with 24 hrs (60% vs. 15%, p=0.039), but there were no differences between groups in symptomatic hematoma expansion (40% vs. 6%, p=0.51), asymptomatic hematoma expansion (0% vs. 7%, p=0.57) or in-hospital mortality (0% vs. 7%, p=1.00). In adjusted analysis, mean maximum dose of nicardipine was associated with an increased risk of renal injury (OR for every 1 unit increase in nicardipine dose=1.30, 95% CI 1.02-1.65, p=0.036). In adjusted analysis, the risk of developing renal injury was not significantly associated with increases in SBP at 2 hours (OR for every 10-unit increase in SBP=1.35, 95% CI 0.94-1.95, p=0.105).
Reversal of Anticoagulants					
Connolly et al. 2016, 2019 **Canada/ International**	NA	352 patients ≥18 years, recruited from 63 centres, who had received a factor Xa inhibitor within the	Patients received an andexanet bolus during a period of 15 to 30 minutes, followed by a 2-hour infusion of the drug. Bolus and infusion	**Efficacy outcome:** The rate of excellent or good hemostatic efficacy 12 hours after the andexanet infusion. (For intracerebral	In the efficacy subgroup of patients (n=254) who had confirmed major bleeding and baseline anti–factor Xa activity of at least 75 ng per milliliter:

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Prospective study ***Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors (ANNEXA-4)***		previous 18 hours and had experienced a major bleeding event. Mean age was 77 years, 53% were men. 227 patients (64%) had ICH.	doses were 400 and 800 mg, and 480 and 960 mg, respectively, depending on the agent used and the timing of their administration. Patients were evaluated for changes in measures of anti–factor Xa activity and were assessed during a 12-hour period and followed for 30 days.	hemorrhage, an increase in volume ≤ 20% from baseline at both 1 hour and 12 hours after infusion was considered to be excellent hemostasis, whereas an increase in volume of ≤35% was considered to be good). **Safety outcome:** Thromboembolic events during 30-day follow-up	The median anti–factor Xa activity among the 53% of patients who received apixaban decreased from 149.7 ng per milliliter at baseline to 11.1 ng per milliliter after the andexanet bolus (92% reduction). The median reduction among the 39% who received rivaroxaban, fell from 211.8 ng per milliliter to 14.2 ng per milliliter (92% reduction). Among the 6% of patients who were receiving enoxaparin, the median value for anti–factor Xa activity decreased from 0.48 IU per milliliter at baseline to 0.15 IU per milliliter at the end of the bolus administration, a 75% reduction. 204 patients (82%) had excellent or good hemostasis at 12 hours. In the safety population (n=352), thrombotic events occurred in 34 patients (10%). There were 10 deaths (15%). There were 14 ischemic strokes. There were 49 deaths.
Baharoglu et al. 2016 **Netherlands** **RCT** ***Platelet Transfusion in Cerebral Haemorrhage (PATCH) trial***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	190 patients, recruited from 60 hospitals in the Netherlands, United Kingdom, and France, within 6 hours of supratentorial ICH symptom onset with GCS score ≥8, who had used antiplatelet therapy for at least 7 days previously. Mean age was 74 years, 42% female. Majority of patients (~80%) had been taking aspirin (only) prior to ICH.	Patients were randomized to receive standard care (per national best practice guidelines) or standard care with platelet transfusion within 90 minutes of diagnostic brain imaging	**Primary endpoint:** Shift in mRS scores at 3 months **Secondary clinical outcomes:** Hematoma growth at 24 hours, survival and poor outcome at 3 months **Safety outcomes:** Complications of platelet transfusion	The odds of a shift towards death or dependence at 3 months were higher in the platelet transfusion group, after adjusting for type of antiplatelet and Intracerebral Haemorrhage Score (common OR=2.05, 95% CI 1.18-3.56, p=0.0114). In sub group analysis, there were no significant interactions for the primary outcome, based on type of antiplatelet therapy regimen pre-ICH (single vs. dual); country of randomization (Netherlands vs. France vs UK); or baseline ICH volume (≤7 mL vs. >7 to 30 mL vs. >30 mL) There was no significant difference between groups in the odds of 3-month survival (68% vs.78%, OR=0.62, 95% CI 0.33-1.19, p=0.15).

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					The odds of a poor outcome (mRS score 4–6) at 3 months were significantly higher in the platelet transfusion group (72% vs. 56%), OR= 2.04, 95% CI 1.12–3.74, p= 0.0195. The odds of a poor outcome, defined as mRS score 3–6 at 3 months were not increased significantly in the platelet transfusion group (89% vs. 82%, OR=1.75, 95% CI 0.77-3.97, p=0.18). There was no significant difference between groups in the median ICH growth at 24 hrs. 2.01 vs. 1.16 mL, p=0.81. The odds of any serious adverse event as not increased significantly in the platelet transfusion group (42% vs. 29%, 1.79, 95% CI 0.98–3.27).
Steiner et al. 2016 **Germany** **RCT** ***Normalized Ratio (INR) Normalization in Coumadin Associated Intracerebral Haemorrhage (INCH)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	54 patients ≥18 years, who had sustained an ICH within the previous 12 hours who were receiving VKA therapy with INR ≥2.0. Patients with secondary ICH related to infarction, hemophilia or other coagulopathy, were excluded. Mean age was 75.6 years, 62% were male,	Patients were randomized 1:1 to receive 20 mL/kg body weight of intravenous fresh frozen plasma (FFP) or 30 IU/kg 4-factor prothrombin complex concentrate (PCC) within 1 hour of CT. All patients received 10 mg of iv vitamin K	**Primary endpoint:** Proportion of patients with anticoagulation reversal (INR ≤1.2) 3 hours after treatment **Secondary clinical outcomes:** Death or hematoma expansion by day 90, proportion of patients with Good functional outcome at 15 and 90 days (mRS 0-3), Barthel Index scores at 90 days, NIHSS score at day 15 or discharge **Secondary imaging outcomes:** Time until INR normalized, hematoma expansion at 3 and 24 hours **Safety outcomes:**	The trial was halted early due to safety concerns. Significantly more patients in the PCC group achieved the primary outcome (67% vs. 9%, OR=30.6, 95% CI 4.7-197.9, p=0.0003). 35% of patients in FFP died by 90 days vs. 19% in the PCC group (p=0.14). There were no significantly differences between groups in the remainder of the secondary clinical outcomes Mean Time to INR normalization was significantly shorter in the PCC group (40 vs. 1,482 minutes (p=0.050). Mean volume hematoma expansion was significantly greater in the FFP group at both 3 and 24 hours (23.7 vs 9.7 mL, p=0.023 and 22.1 vs. 8.3 mL, p=0.018, respectively). There was no significant difference between

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
				Serious adverse events (SAE) at day 90	groups in the total number of SAE (20 vs. 23) in 26 patients.
Pollack et al. 2015 **International** **Prospective study** ***Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD)***	NA	90 participants ≥18 years who were taking dabigatran. Group A (n=51) were those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent. Group B (n=39) were those who required surgery or other invasive procedures that could not be delayed for at least 8 hours. Mean age was 76.5 years, 56% were male.	Patients received 5 g of intravenous idarucizumab, administered as two 50-ml bolus infusions, (2.5 g each), no more than 15 minutes apart.	**Primary endpoint:** Maximum percentage reversal of the anticoagulant effect of dabigatran achieved within 4 hours **Secondary outcome:** Restoration of homeostasis	At study entry the results of 22 patients were excluded as their dilute thrombin time were within normal limits. The median maximum reversal in patients in both groups A and B was 100%, assessed by dilute thrombin time and ecarin clotting time. Among those whose data could be analyzed, the dilute thrombin time was normalized in 98% of the patients in group A and in 93% of those in group B. The ecarin clotting time was normalized in 89% of Group A patients and in 88% of the Group B patients. At 12 hours and 24 hours, the dilute thrombin time was below the upper limit of the normal range in 90% of the patients in group A and in 81% of those in group B. The ecarin clotting time was below the upper limit of the normal range in 72% and 54% of the patients who could be evaluated, respectively. The concentration of unbound dabigatran was < 20 ng per milliliter in 93%and 79% of patients at 12 and 24 hours, respectively. There were 18 deaths (9 in each group) and 5 thrombotic events. 21 patients (13 patients in group A and 8 in group B) had serious adverse events. Among patients in group A who could be assessed, homeostasis was restored within a median of 11.4 hours.
Kuramatsu et al. 2015	NA	Data from 1,176 patients from 19 centres (2006-2010) with	Review of medical records pertaining to use of oral anticoagulants (OAC) and	**Primary outcome:** Mortality, hematoma enlargement, and	Of the entire cohort, mortality was 31% at hospital discharge, 43.1% at 3 months and 56.1% at one year.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany **Retrospective study (included all types of OAC)**		spontaneous ICH related to anticoagulation (INR>1.5 on admission). Mean age was 74.1 years. Median INR was 2.77 upon admission to hospital.	reversal agents and dose with one-year follow-up by mailed questionnaires or telephone interviews. Models were developed to identify factors associated with the lowest risk of hematoma expansion	resumption of OAC	853 had follow-up imaging. Of these, 707 (36.0%) had a hematoma enlargement, with a median increase in volume of 14.0 mL. When comparing patients with and without hematoma enlargement, there were no significant differences between groups with respect to initial INR (2.8 with enlargement vs. 2.68 no enlargement, p=0.13) or agents (PCC, FFP, vitamin K or combinations of agents) used for its reversal. PCCs reversed elevated INR levels to a greater extent compared with FFP (absolute median INR reversal 1.45 [IQR, 0.97-2.10] vs. 0.36 [IQR, 0.04-0.86], p < .001). Independent predictors of no hematoma expansion included: INR <1.3 (26.9% vs. 45.4%, OR=0.37, 95% CI 0.26-0.59, p<0.001) INR <1.3, achieved within 4 hours of admission (19.8% vs. 41.5%, OR=0.27, 95% CI 0.15-0.43, p<0.001) INR <1.3, achieved within 4 hours of admission + systolic blood pressure <160 mm Hg (18.1% vs. 44.2%, OR=0.28, 95% CI0.19-0.42, p<0.001) The risk of in-hospital mortality was also reduced significantly for the combination of these 3 factors (13.5% vs. 20.7%, OR=0.60, 95% CI 0.37-0.95, p=0.03). **Long-term follow-up** Data for 719 patients were available at 1 year. Of these, 172 (23.9%) resumed oral anticoagulant therapy. Median time to restart was 31 days. In propensity-match analysis of surviving

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					patients with atrial fibrillation, the risk of ischemic stroke was reduced significantly among those who restarted OACs (3.9 vs. 12.7/100 patient years, 95% CI 6.5-19.1, p=0.02)
Tranexamic Acid					
Sprigg et al. 2018 **UK/International** **RCT** ***Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	2,325 patients, recruited from 124 centres in 12 countries with acute intracerebral haemorrhage, with symptom onset within 8 hours or time last seen well. Patients with ICH secondary to anticoagulation, thrombolysis, trauma, or a known underlying structural abnormality, were excluded. Mean age was 68.9 years, 56% were men. Mean NIHSS score was 13.	Patients were randomized 1:1 to receive tranexamic acid, given intravenously as a 1 g loading dose in 100 mL normal saline 0·9% infused over 10 min, followed by another 1 g in 250 mL normal saline 0·9%, which was infused over 8 hours, or matching placebo	**Primary outcome:** mRS at 90 days **Secondary outcomes:** NIHSS at 7 days or D/C, mortality at 7 and 90 days, EQ-5D, Barthel Index (BI), Telephone Interview for Cognitive Status modified (TICS-M), Zung Depression Scale, at 90 days, LOS, discharge destination and change in hematoma size 24 hours after treatment. **Safety outcomes:** Death, DVT, ischemic events and seizures within 90 days	Mean time from randomization to initiation of treatment was 3.65 hours. There was no difference in the distribution (shift) in the mRS at day 90 after adjustment for stratification and minimization criteria (adj OR=0·88, 95% CI 0·76–1·03, p=0·11). At 24 hours, the mean change in hematoma volume was significantly lower in the tranexamic acid group (3·72 vs. 4·90 mL, MD –1·37, 95% CI -2·71 to –0·04, p=0·0432). The odds of hematoma expansion were significantly lower in the tranexamic acid group (25% vs. 29%, OR=0·80, 95% CI 0·66 to 0·98, p=0·0300). At 7 days, the odds of death were significantly lower in the tranexamic acid group (9% vs. 11%, OR= 0·73, 95% CI 0·53 to 0·99, p=0·0406), but not at day 90. The mean NIHSS score did not differ between groups (10.1 vs. 10.3, p=0.10). There were no significant differences between groups for any of the secondary outcomes. There were significantly fewer serious adverse events and a lower risk of the safety outcomes among patients in the tranexamic acid group at days 2, 7 and 90.
Recombinant Activated Factor VII					
Gladstone et al. 2019 **Canada**	NA	69 patients with primary spontaneous acute ICH who were SPOT-sign positive included in the	Patients were randomly assigned 80 µg/kg of intravenous rFVIIa or placebo as soon as possible within 6.5	**Primary outcome:** Parenchymal ICH volume expansion from baseline to 24 hours	Time from stroke onset to treatment was 178 minutes. The median baseline ICH volume was 16.3

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Patient-level meta-analysis ***Effect of Recombinant Activated Coagulation Factor VII on Hemorrhage Expansion Among Patients with Spot Sign–Positive Acute Intracerebral Hemorrhage-The SPOTLIGHT and STOP-IT Randomized Clinical Trials***		SPOTLIGHT and STOP-IT RCTs. Median age was 70 years, 51% were men.	hours of stroke onset	**Secondary outcome:** Total hemorrhage volume expansion (parenchymal plus intraventricular)	mL in the rFVIIa group and 20.4 mL in the placebo group. Median baseline total (ie, IVH plus ICH) hemorrhage volume was 23.8 mL in the rFVIIa group and 24.5 mL in the placebo group. There were no significant differences between groups in the change (increase) in median parenchymal ICH volume from baseline to 24 hours (2.5 mL in the rFVIIa group and 2.6 mL in the placebo group, p=0.89), or in median total hemorrhagic volume (3.2 mL in the rFVIIa group and 4.8 mL in the placebo group, p=0.91).
Yuan et al. 2010 **China** **Meta-analysis**	NA	5 RCTs (1,402 participants) including patients ≥18 years, with spontaneous ICH (sICH) or traumatic ICH. Studies of patients with hemophilia, acquired inhibitors, other congenital coagulation factor deficiencies, and inherited platelet disorders were excluded. Average ages of included patients ranged from 52 to 65 years.	Comparisons of rFVIIa (doses included 10, 20, 40, 80, 120, 160 and 180 µg/kg) vs. placebo. 4/5 trials were dose-escalation studies.	**Primary outcomes:** All-cause mortality or dependency (mRS≥3 or Glasgow Outcome Scale 1-4) at the end of follow-up, which was 90 days in 4/5 studies and 15 days in the 5th. **Secondary outcomes:** Thromboembolic adverse events (TAE)	There was no significant overall reduction in mortality associated with treatment Overall: OR=0.86, 95% CI 0.65 to 1.15, p=0.31. Results from 4 trials included). Subset of patients with sICH: OR=0.85, 95% CI 0.64 to 1.15, p=0.29. Results from 4 trials included. There was no reduction in the odds of a poor outcome at day 90 using mRS criteria (OR=0.81, 95% CI 0.48 to 1.39) or GOS criteria (OR=0.70, 95% CI 0.44 to 1.11, p=0.13). There was trend towards an increase in the number of overall TAEs in the treatment group (OR=1.56, 95% CI 0.98 to 2.48, p=0.06). There was a significant increase in the odds of arterial TAEs in the treatment group (OR=2.18, 95% CI 1.13 to 4.19, p=0.02) but not venous TAEs (OR=0.73, 95% CI 0.36 to 1.47, p=0.38).

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Mayer et al. 2008 USA **Diringer et al. 2010 (additional reporting)** **RCT** ***Factor Seven for Acute Hemorrhagic Stroke (FAST)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	841 patients >18 years with spontaneous ICH documented on CT scan within 3 hours of symptom onset. Exclusion criteria: Glasgow Coma Scale score ≤ 5, planned surgical evacuation of hematoma within 24 hours secondary ICH resulting from any cause, known use of oral anticoagulant therapy, thrombocytopenia, or coagulopathy, pregnancy, previous pre-stroke disability (mRS score >2).	Patients were randomized to receive a single intravenous dose of placebo (n=268) or rFVIIa at a dose of 20 µg (n=276) or 80 µg (n=297) per kg, based on estimated weight. Treatment was administered within 1 hour after the baseline CT scan and no later than 4 hours after the onset of symptoms. Follow-up CT scans were performed at 24 and 72 hours.	**Primary outcomes:** Poor outcome (mRS score 5-6) at 90 days, Barthel Index (BI) score, NIHSS score, and mortality at 90 days **Secondary outcomes:** Estimated percentage increase from baseline-24 hours in intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH), and estimated percentage increase from baseline-72 hours in ICH+IVH+edema Frequency of thromboembolic events (TEs), assessed up to 90 days following treatment.	Initial median NIHSS score was 13 in all study groups. At 90 days there were no significant differences between groups (20µg vs. 80µg vs. placebo) on any of the outcomes. Death: 18% vs. 21% vs. 19% Poor outcome: 26% vs. 30% vs. 24% Median BI score: 72.5 vs. 70.0 vs. 70.0 Median NIHSS score: 5.0 vs. 4.0 vs. 5.0 Compared with placebo there was a smaller mean increase in volume of ICH at 24 hours in patients in the 80µg group: 11% vs. 26%, p<0.001. Compared with placebo there was no significant difference in the mean increase in volume of ICH at 24 hours in patients in the 20 µg group: 18% vs. 26%, p=0.08. There were no differences in the mean increases in volume of IVH at 24 hours between treatment groups: 20µg vs. placebo= 2.0 vs. 1.6 mL, p=0.74 and 8 µg vs. placebo=1.0 vs. 1.6 mL, p=0.51 There were no differences in the mean increases in volume of ICH+IVH+edema at 72 hours between treatment groups: 20µg vs. placebo= 26 vs. 29mL, p=0.53 and 80µg vs. placebo=22.0 vs. 29 mL, p=0.06 Adverse events: There were no significant differences between groups in the total number of thromboembolic events (arterial + venous): 9% (20 µg) vs. 10% (80µg) vs. 8% (placebo), but compared with placebo, arterial events occurred more frequently in patients in the 80µg group (8% vs. 4%, p=0.04). Losses to follow-up or drop-outs: n=22 (11 from 20 µg group and 11 from 80µg group. The percentages of the total number of 225

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					TEs did not differ among study groups: 22% (20 µg) vs. 32% (80 µg) vs. 25% (placebo). The percentages of the total number of 47 venous events did not differ among study groups: 5% (20 µg) vs. 5% (80 µg) vs. 6% (placebo). Of the 178 of arterial events, 141 were myocardial events and 37 were cerebral infarctions. The percentages of patients who experienced a myocardial event was higher among patients in the 80 µg group: 22% vs. 13% (20 µg) vs. 15% (placebo group), p=0.04. There was no difference in the percentages of patients among the groups who experienced a cerebral infarction: 4% (20 µg) vs. 6% (80 µg) vs. 3% (placebo). Independent risk factors for arterial TEs were: receiving 80 µg/kg rFVIIa (OR=2.14; p=0.031), signs of cardiac or cerebral ischemia at presentation (OR=4.19; p=0.010), age (OR=1.14/5 years, p=0.0123), and prior use of antiplatelet agents (OR=1.83; p=0.035).
Mayer et al. 2005 **USA** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	399 patients ≥ 18 years, with spontaneous ICH occurring within three hours of the onset of symptoms. Mean age of patients was 66 years. Exclusion criteria included a GCS score of 3 to 5, planned surgical evacuation of hematoma within 24 hours, secondary ICH related to aneurysm, arteriovenous malformation, trauma, or other causes, known use of oral	Patients were randomly assigned to receive a single intravenous dose of 40 µg (n=108), 80 µg (n=92), or 160 µg (n=103) per kilogram of rFVIIa or placebo (n=96). Follow-up CT scanning was performed at 24 and 72 hours after study treatment	**Primary outcome:** Estimated increase in ICH volume from baseline at 24 hours and increase in intraventricular hemorrhage (IVH) from baseline to 72 hours. **Secondary outcomes:** Poor outcome defined as mRS score of 4-6 and Extended Glasgow Outcome Scale (GOS) score of 1-4, NIHSS and Barthel Index scores (BI) scores and death at 90 days, adverse events	When results from all treatment groups were combined, there was significantly less mean relative increase in ICH volume compared with placebo (14% vs. 29%, p=0.01). When results from all treatment groups were combined, there was significantly less mean relative increase in ICH + IVH volume compared with placebo (14% vs. 31%, p=0.006). When results from all treatment groups were combined, the percentage of patients who were dead was lower compared with patients in the placebo group (18% vs. 29%, p=0.02), there were fewer patients with a poor outcome in the treatment group using the mRS criteria (53% vs. 69%, p=0.004).

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		anticoagulant agents; known thrombocytopenia; history of coagulopathy, preexisting disability and symptomatic thrombotic or vaso-occlusive disease within 30 days.			The median BI and NIHSS scores were better for patients in the treatment group (60 vs. 25, p=0.006 and 6.0 vs. 12.5, p=0.008, respectively). There was a total of 21 serious thromboembolic events in the combined treatment groups and 2 in the placebo group, p=0.12. There were more serious arterial thromboembolic events among patient in the treatment groups (16 vs. 0, p=0.01. There were 5 serious venous thromboembolic events in the treatment groups and 2 in the placebo group.
Additional Neuroimaging					
Van Asch et al. 2015, Hilkens et al. 2017 **The Netherlands** **Prospective study** ***DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) study***	NA	298 patients with non-traumatic ICH, aged 18-70 years, treated in 22 participating hospitals. Mean age was 53 years,	CT angiography (CTA) was performed within seven days of hemorrhage, to identify an underlying vascular abnormality, responsible for the hemorrhage. If the result was negative, MRI/MRA was performed 4-8 weeks later. Digital subtraction angiography (DSA) was performed when the CTA or MRI/MRA results were inconclusive or negative. In the 2017 publication, independent predictors of a macrovascular cause were identified using multivariable analysis	**Primary outcome:** Presence of a macrovascular cause	According to the reference standard (best available evidence from all diagnostic procedures), 69 patients (23%) had an underlying macrovascular cause. In 51 of 298 patients a macrovascular cause was diagnosed with CT angiography, resulting in a yield of 17% (95% CI 13% to 22%), Additional MRI/MRA was performed in 214 of 232 patients with a negative or inconclusive CTA. CTA + MRI/MRA identified 2 additional macrovascular causes, resulting in a yield of 18% (95% CI 14% to 23%). DSA was assessed in 103 of 232 patients with negative or inconclusive CT angiography test results. CTA+MRI/MRA+DSA identified 15 additional macrovascular causes, resulting in a yield of 23% (95% CI 18% to 28%). The positive predictive value (PPV) of CTA was 72% (95% CI 60% to 82%), of MRI/MRA, 35% (95% CI 14% to 62%), and of DSA 100% (95%

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					CI 80% to 100%). The associated negative predictive values (NPV) were 92%, 93% and 100%. A single cavernoma was not identified using any of the imaging techniques. The addition of MRI/MRA to CTA increased the PPV to 77%, (95% CI 65% to 86%) with the additional of DSA increasing PPV to 100% (95% CI 80%-100%). **Hilkens et al. 2017** Independent predictors of a macrovascular cause were younger age, lobar or posterior fossa (vs deep) location of ICH, and absence of small vessel disease. The model was validated in an external cohort of 173 patients with ICH (45% with a macrovascular cause). The C-statistic showed moderate performance (0.66; 95% CI 0.58 to 0.74), which was improved when the CTA results were added (0.88; 95% CI 0.83 to 0.94).
Josephson et al. 2014 **Canada** **Cochrane review**	Using a modified QUADAS criteria (possible scores 0-12), scores ranged from -10. Median score was 7	11 studies (n = 927), including participants with radiographically verified ICH. Minimum sample size was 20.	The diagnostic test accuracy of CTA and MRA versus intra-arterial digital subtraction angiography (IADSA) for the detection of intracranial vascular malformations as a cause of ICH, was examined. IADSA was used as the reference standard.	**Primary outcome:** Sensitivity and specificity of CTA and MRA	8 studies compared CTA with IADSA (n = 526) and 3 studies compared MRA with IADSA (n = 401). The sensitivity and specificity of CTA was 0.95 (95% CI 0.90 to 0.97) and 0.99 (95% CI 0.95 to 1.00), respectively. The sensitivity and specificity of MRA was 0.98 (95% CI 0.80 to 1.00) and 0.99 (95% CI 0.97 to 1.00), respectively.
Wong et al. 2011 **China** **Prospective study**	NA	109 patients aged 18-45 years admitted to a single institution following spontaneous ICH, which had occurred ≤96 hours previously. Mean age	A comparison of the accuracy of computed tomography angiography and venography (CTAV) completed within 24 hours of admission with digital subtraction angiography (DSA) completed within 48 hours of	**Primary outcome:** Test characteristics of CTVA	DSA-positive pathologies causing hemorrhage were identified among 37 (33%) patients. All lesions were also identified by CTVA, with one false positive. Sensitivity: 100% (95% CI 92.4%–100%) Specificity: 98.6% (95% CI, 93.6%–99.9%)

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		was 47.6 years, 67% were men. Patients > 45 years with preexisting hypertension and thalamic, putaminal, or posterior fossa hemorrhage, were excluded.	admission, to identify vascular abnormalities.		Accuracy: 99.1% (95% CI, 95.7%–100%) Positive predictive value: 97.3% (95% CI, 88.3%–99.9%) Negative predictive value: 100% (95% CI, 95.9%–100%)
Chalela et al. 2007 **USA** **Retrospective study**	NA	356 patients consecutively seen for emergency assessment of suspected stroke at a single institution from 2000 to 2002. Patients suspected of having SAH were excluded.	Diffusion-weighted MRI and CT scans were performed on each patient within 120 minutes of each other and the pairs of scans corresponding to each patient were reviewed by 4 blinded assessors.	Sensitivity, specificity of CT and MRI scans compared to clinical diagnosis, and accuracy of findings.	217 patients had a final diagnosis of stroke. The median onset time to MRI and CT imaging was 367 and 390 minutes, respectively. Median NIHSS scores for patients with ICH was 3. Based on clinical diagnosis, 190 (53%) had ischemic stroke and 27 (8%) had an ICH. In these cases, detection was more frequent with MRI than CT (p<0.001). ICH was identified in 23 cases (6%) with MRI and in 25 (7%) of cases with CT. Compared with the final clinical diagnosis of ICH, the sensitivity of MRI was 81% (95% CI 61% to 93% and a specificity of 100% (95% CI 98% to 100%). The corresponding values for comparison with CT were sensitivity 89% (95% CI 70% to 97%) and specificity of 81% (95% CI 98% to 100%). MRI had an accuracy of 89% (85% to 92%) and CT, 54% (95% CI49% to 59%)
Surgery for Hematoma Evacuation (Systematic reviews)					
Sondag et al. 2020 **The Netherlands**	4 trials were of high methodological quality, 8 were of moderate quality and 9 were of low quality	21 RCTs including n=4,145 patients with supratentorial spontaneous ICH	Comparisons of various surgical treatments aimed at clot removal were compared with standard medical management, with duration of follow-up of ≥3 months. 13 studies assessed minimally invasive surgical approaches,	**Primary outcome:** Good functional outcome at follow-up, defined as mRS score of 0 to 3, a Glasgow Outcome Scale score of 4 to 5, an extended Glasgow Outcome Scale score of 5 to 8, or a Barthel Index of ≥60.	Collectively, surgery significantly improved the chances of a good outcome (RR=1.40, 95% CI 1.22-1.60). Minimally invasive surgery (MIS) improved the chances of a good outcome (RR=1.47, 95% CI 1.26-1.72).

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			6 in combination with thrombolysis, 9 assessed craniotomy	**Secondary outcomes:** Death and serious adverse events	Surgical treatment significantly reduced the risk of death at the end of follow-up (RR= 0.77, 95% CI 0.68–0.85), and at the end of 30 days (RR=0.68, 95% CI 0.51–0.92). MIS significantly reduced the risk of death at the end of follow-up, but not at 30 days (RR=0.68, 95% CI 0.56–0.83 and RR=0.65, 95% CI = 0.41–1.02). Craniotomy significantly increased the chance of good functional outcome (RR=1.44, 95% CI 0.69–2.93, I 2), while reducing the risk of death a follow-up (RR=0.79, 95% CI 0.66–0.94). Age, Glasgow Coma Scale, and hematoma volume did not modify the effect of surgery.
Kuramatsu et al. 2019 **Germany** **Systematic review & patient-level meta-analysis**	Outcomes were at moderate risk of bias using the ROBINS-I tool	4 observational studies ICH studies (RETRACE, RETRACE II, UKER and ERICH), including 578 adult patients with **cerebellar** ICH (+/- related to OAC) treated at 64 hospitals across the United States and Germany from 2006-2015.	The outcomes of patients who underwent surgical hematoma evacuation (craniectomy, open craniotomy, or minimal invasive surgery, excluding external ventricular drainage, n=152) were compared with those that received conservative treatment (n=152). (In the unmatched cohort, 174 patients underwent surgery and 404 received conventional treatment)	**Primary outcomes:** mRS scores at 3 months, favourable outcome (mRS 0-3) at 3 months **Secondary outcomes:** Survival at 3 and 12 months	In the propensity-matched cohort, the mean ages of patients were 68.9 years (surgery) and 69.2 years (conventional). The corresponding percentages of men were 55.9% and 51.3%. 21.5% of patients had a previous ischemic stroke. In propensity-matched analysis, the percentage of patients with a favourable outcome at 3 months was not significantly different between groups (30.9% vs. 35.5%; adj OR=0.94, 95% CI, 0.81 to 1.09, adjusted risk difference [ARD]= −3.7% [95% CI, −8.7% to 1.2%]). Hematoma evacuation was associated with better odds of survival at 3 months (78.3% vs. 61.2%; adj OR=1.25, 95% CI 1.07 to 1.45, ARD=18.5%, 95% CI, 13.8% to 23.2%) and at 12 months (71.7% vs. 57.2%; adj OR=1.21, 95% CI, 1.03 to 1.42; ARD=17.0%, 95% CI 11.5% to 22.6%). In subgroup analysis, the odds of favourable outcome at 3 months were significantly higher

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					for patients with smaller ICH volumes (0-14 mL) receiving conservative treatment. The odds of 3-month survival were significantly higher for patients with larger ICH volumes (11-14 mL and ≥15 mL) who received surgical evacuation.
Gregson et al. 2012 **USA** **Patient-level meta-analysis**	NA	8 RCTs (n=2,186) including patients who had received surgery for ICH	Comparisons of patients treated with surgery vs. conservative treatment. Subgroup analyses were performed stratifying for age and sex, Glasgow Coma Score (GCS) at presentation, volume and site of hematoma and presence of intraventricular hemorrhage (IVH), method of evacuation of hematoma, time to randomization, and outcome at 3 to 6 months.	**Primary outcome:** Unfavorable outcome (death plus the vegetative state or severe disability on the 5-point Glasgow Outcome Scale).	Location: Surgery did not decrease the odds of unfavorable outcome for any lesion location Time from event: Surgery was associated with significantly reduced odds of unfavorable outcome when performed within 8 hours (OR= 0.59, 95% CI 0.42 to 0.84), while surgery performed within 8-24 hours and between 24 and 72 hours did not reduce the odds of unfavorable outcome. Age: Surgery was associated with significantly reduced odds of unfavorable outcome in patients aged 50-69 years (OR=0.71, 95% CI 0.54-0.94). The odds were not reduced significantly among patients who received surgery aged <50 years, or for those aged ≥70 years. Initial GCS score: Surgery was associated with significantly reduced odds of unfavorable outcome in patients with initial GCS of 9-12 (OR=0.54, 95% CI 0.37-0.77) and in those with scores of 13-15 (OR=0.74, 95% CI 0.55-0.99), but not in those with scores of 3-8. Volume of hematoma: Surgery was associated with significantly reduced odds of unfavorable outcome in patients with ICH volumes of 20-50 mL (OR=0.69, 95% CI 0.54-0.89), but not with smaller volumes (<20 mL) and larger (50-80 mL and ≥80 mL).
Prasad et al. 2008 **India**	NA	10 RCTs (2,059 patients) with primary supratentorial intracerebral	Comparisons of patients treated with surgery (craniotomy, stereotactic endoscopic evacuation or	**Primary outcome:** Death or dependence at the end of follow-up (mRS>2, or Barthel Index score ≥60, or	Death or dependency at 6-12 months: OR=0.71, 95% CI 0.58-0.88, p<0.001, favouring surgery group. Results from 9 trials (1,994 patients) included.

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Cochrane Review		hematoma, confirmed by CT scanning. Average age was 57 to 69 years. Most patients arrived and had their surgeries within 24 hours of symptom onset. The average hematoma volume varied from 37 ml to 66 mL (most were between 40 ml to 50 mL). The average Glasgow Coma Scale score varied from 4 to 15 (eye motor score 2 to 10).	stereotactic aspiration) + medical management vs. medical management.	Glasgow Outcome Scale score of 4 or 5. **Secondary outcomes:** Death at end of follow-up	Death at the end of follow-up: OR=0.74, 95% CI 0.61-0.90, p=0.0026), favouring surgery group. Results from 10 trials (2,059 patients) included.
Craniotomy vs. Best Medical Management					
Mendelow et al. 2013 **UK** **RCT** ***Surgical Trial in in IntraCerebral Hemorrhage (STICH II)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	601 patients admitted to one of 78 neurosurgical units in 27 countries with CT evidence of a spontaneous lobar ICH (≤1 cm from the cortical surface of the brain) with a volume of 10-100 mL that had occurred within 48 h, with a best GCS score of 5-6 and were conscious at study entry. Patients were excluded if the likely etiology of the hemorrhage was an aneurysm, or was secondary to a tumour or trauma, patients had a cerebellar hemorrhage or extension into the brainstem, patients had severe pre-existing	Patients were randomized to early (within 12 hours) surgery for evacuation of the hematoma combined with appropriate and best medical treatment (n=307) or to initial conservative treatment (n=294) with later evacuation permissible if necessary due to neurological deterioration	**Primary outcome:** Favorable vs. unfavorable outcome at 6 months, based on a dichotomized Extended Glasgow Outcome Scale score, which was calculated based on responses to a postal questionnaire. Outcome was also reported separately for patients with poor and good prognosis. **Secondary outcomes:** Mortality, Barthel Index (BI), dichotomized modified Rankin score and EuroQol, at 6 months	The mean time to surgery was 26.7 hours. 17% of patients in the early surgery group had their surgery within 12 hours of stroke. There was no difference between groups in the proportion of patients who experienced a good outcome (41% surgical group vs. 38% medical management group; OR=0.86, 95% CI 0.62-1.20, p=0.367). Absolute difference=3.7%, 95% CI -4.6 to 11.6%). There was no difference between groups in mortality at 6 months (18%. Surgical vs. 24% medical management, OR=0.71, 95% CI 0.48-1.06, p=0.095). Absolute difference=5.6%, 95% CI -1.0 to 12.2%). There was no difference between groups in favourable outcome, based on mRS scores at 6 months (47%. Surgical vs. 44% medical management). Absolute difference=3.1%, 95% CI -5.0 to 11.2%). Patients with poor prognosis were more likely to have a favourable outcome (OR=0.49, 95%

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		physical or mental disability or severe comorbidity.			CI 0.26-0.92, p=0.04), while patients with a good prognosis were no more likely to benefit (OR=1.12, 95% 0.75-1.68, p=0.57). There was no difference between groups in median EuroQol Index scores (0.64 vs. 0.69, p=0.751) In sub group analysis, age (<65 vs. ≥65 years), hematoma volume (≤35 vs. >35 mL), GCS score at randomization (8-12 vs. 13-15), time to randomization (<21 vs. ≥21 hrs) limb deficit, country or previous use of anticlotting agents the treatment effect associated with the odds of a favourable outcome were similar between groups. There were 139 serious adverse events, although no significant difference in their frequency between groups.
Mendelow et al. 2005 **UK** **RCT** ***Surgical Trial in in IntraCerebral Hemorrhage (STICH)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	1,033 patients with CT evidence of a spontaneous ICH that had occurred within 72 hours and if the treating neurosurgeon was uncertain about the benefits of either treatment. Study guidelines recommended that eligible patients should have a minimum hematoma diameter of 2 cm and a Glasgow coma score ≥5. Patients were excluded if the likely etiology of the hemorrhage was an aneurysm, or was secondary to a tumour or trauma,	Patients were randomized to early (within 24 hours) surgery for evacuation of the hematoma combined with appropriate and best medical treatment (n=503) or to initial conservative treatment (n=530). Later evacuation was allowed if necessary due to neurological deterioration	**Primary outcome:** Favorable outcome at 6 months. For patients with a poor prognosis, a favourable outcome was defined as good recovery or moderate disability on the extended Glasgow Outcome scale. For the poor prognosis group, a favourable outcome also included the upper level of severe disability. **Secondary outcomes:** Mortality, Barthel Index (BI), and mRS at 6 months	There was no difference in the percentage of patients with a favourable outcome. 26% of patient in the early surgical group vs. 24% of patients in the medical management group, OR=0.89, 95% CI 0.66-1.19, p=0.414, absolute benefit=2.3, 95% CI -3.2-7.7. There was no difference in the percentage of patients who were dead at 6 months: 64% vs. 63%. The percentage of patients with a favourable outcome at 6 months, based on BI ≥95 for patients with good prognosis and ≥65 for those with a poor prognosis did not differ between groups: 33% vs. 28%, absolute benefit: 4.7, 95% CI -1.2-10.5. The percentage of patients with a favourable outcome at 6 months, based on mRS≤2 for patients with good prognosis and ≤3 for those with a poor prognosis did not differ between groups: 27% vs. 23%, absolute benefit: 4.1,

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		patients had a cerebellar hemorrhage or extension into the brainstem, patients had severe pre-existing physical or mental disability or severe comorbidity.			95% CI -1.4-9.5. In subgroup analysis (age, initial GCS, side of hematoma, site of hematoma, depth from cortical surface, method of evacuation, deficits of affected arm/leg/speech), the odds of a good outcome were not increased by early surgery. Losses to follow-up: n=68, 35 in early surgery group, 33 in medical management group.
Endoscopic Surgery vs. Best Medical Management					
Vespa et al. 2016 **USA** **RCT** ***Intraoperative Stereotactic Computed Tomography Guided Endoscopic Surgery (ICES)*** **Interim analysis**	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	20 patients aged 18-80 years with primary ICH and stable volume of >20 mL, with pre-morbid mRS score of 0-1recruited within 48 hours of ICH onset. Study was part of MISTIE (see below).	Patients were randomized 3:1 to endoscopic surgery within 48 hours of CT scan using a CT image–guided endoscopic technique (n=14) vs. standard medical management (n=6)	**Primary safety outcomes:** 30-day mortality, 7-day procedure-related mortality, 30-day rate of bacterial brain infection, and symptomatic bleeding within the 72 hours post last dose timeframe. **Primary efficacy outcomes:** mRS score at 180 days (0-3 vs. 4-6), 180 and 365-day ordinal mRS scores, clot size reduction	No patients in either group died within 7 days of the procedure, while one patient died within 30 days. No patients in either group developed a bacterial brain infection or experienced symptomatic bleeding, while one patient in the medical group and 3 patients in the surgical group developed asymptomatic bleeding. At 180 days, 6 (42.9%) patients in the surgical group had a mRS score of 0-3 vs 9. (23.7%) in the medical management group (OR=2.4, 95% CI 0.53-10.51, p= 0.19). Surgery resulted in a 71.2% reduction in ICH volume.
Minimally Invasive Surgery vs. Best Medical Management					
Hanley et al. 2019 **USA** **RCT** ***Minimally Invasive Surgery and rtPA for Intracerebral Hemorrhage Evacuation***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	506 patients, ≥18 years with a spontaneous, non-traumatic ICH ≥30 mL due to cerebral small-vessel disease, with a GCS score of ≤14 or NIHSS score of ≥6, with an mRS score of 0-1 before the bleed, and an intracerebral haemorrhage that remained the same size	Patients were randomized 1:1 to receive image guided MISTIE treatment (1·0 mg alteplase every 8 h for up to 9 doses) or standard medical care	**Primary outcome:** Good functional outcome (mRS 0-3) at 1 year. **Secondary outcomes:** eGOS score, good (4–8) vs poor (1–3) at 1-year, all-cause mortality at 1 year,	The mean reduction in hematoma size was 69% in the MISTIE group vs. 3% in the standard medical care group. The corresponding mean end-of-treatment volumes were 16 mL vs. 47 mL, respectively (mean difference= 32 mL, 95% CI 30–34; p<0.0001). Using a modified ITT analysis set, adjusting for baseline variables, primary adjusted efficacy analysis estimated that 45% of patients in the MISTIE group and 41% patients

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(MISTIE III)		(growth <5 mL) for at least 6 h after diagnostic CT. Ability to randomize 12-72 h after the event. Median age was 62 years, 39% were women. Median ICH volume at baseline was ~45.5 mL			in the standard medical care group had achieved an mRS score of 0–3 (absolute risk difference 4% [95% CI –4 to 12]; p=0·33). 39% of patients in the MISTIE group and 36% of patients in the standard care group had a poor outcome at 1 years using eGOS criteria (adjusted risk difference 4·2%, 95% CI –3·3 to 11·8%, p=0·28). Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location, diabetes, CVD, race, mortality was lower in the MISTIE group at 1 year (HR = 0.67 (95% CI 0.45-0.98), p=0.037). Significantly fewer patients in the MISTIE group had died at 30 days and within 180 days (1% vs. 4%, p=0.018 and 15% vs. 23%, p=0.03, respectively), but not within 30 days (9% vs. 15%, p=0.06). There was no significant difference between groups in the number of asymptomatic brain bleeds within 72 h after last dose (2% vs.1%, p=0.33), while there w significantly higher number of asymptomatic brain bleeds in the MISTIE group (32% vs. 8%, p<0.001). The number of serious adverse events within 30 days was significantly lower in the MISTIE group (30% vs. 33%, p=0.012).
Hanley et al. 2016 **USA** **RCT** ***Minimally Invasive Surgery and rtPA for Intracerebral Hemorrhage Evacuation (MISTIE II)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	96 patients, aged 18-80 years with a non-traumatic (spontaneous) intracerebral hemorrhage of ≥20 mL, resulting from cerebral small-vessel disease but not a macrovascular cause, with a GCS score of ≤14, a NIHSS score of ≥6 and a history of a mRS score	Patients were randomized to receive standard medical care (n=42) vs. image-guided minimally-invasive surgery (MIS) plus alteplase (0·3 mg or 1·0 mg every 8 h for up to nine doses, n=54) to remove clots using surgical aspiration followed by alteplase clot irrigation.	**Primary (safety) outcomes:** 30-day mortality, 7- day procedure-related mortality, 72 hrs symptomatic bleeding, and 30-day brain infections	30-day mortality did not differ significantly between groups (0% vs. 1.9%, p=0.562). 7-day procedure-related mortality did not differ significantly between groups (9.5% vs.14.8%, p=0.542). The number of bacterial brain infections within 30 days did not differ between groups (2.4% vs. 0%, p=0.468). The number of patients with a symptomatic ICH at 72 hours was 2.4% in the medical

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		of 0-1. Mean age was 61 years, 66% were men. Mean NIHSS score was 21.			management group and 9.3% in the MIS group (p=0.226). The number of patients with an asymptomatic ICH at 72 hours was 7.1% in the medical management group and 22.2% in the MIS group (p=0.051). The numbers of symptomatic or asymptomatic bleeds occurring 72 h after last dose of alteplase was significantly higher in the MIS group (9.5% vs. 27.8%, p=0.038).
Thrombolysis via Extraventricular Drain					
Hanley et al. 2017 **USA/Canada** **RCT** ***Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III)***	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	500 patients, recruited from 78 hospitals, aged 18-80 years with spontaneous ICH ≤30 cc and intraventricular hemorrhage (IVH) obstructing third and/or fourth ventricles, symptom onset <24 hours, with extraventricular drainage in place, SBP < 200 mm Hg, pre-morbid mRS 0-1. Median age was 59 years, 42.5% women, Median NIHSS scores were 19 (alteplase) and 20 (saline).	Patients were randomized 1:1 to receive up to 12 (1.0 mg) doses every 8 hours of rt-PA or saline placebo via an intraventricular catheter	**Primary Outcome:** Modified Rankin Scale (0–3 vs. 4–6) at 6 months **Secondary Outcomes:** mRS (0–4 vs. 5–6), ordinal modified Rankin Scale (0–6) and mortality at 3 months, safety events at 30 days, residual blood clot remaining at 72 hours, intensity of critical care management within 30 days (measured by hospital and ICU LOS), frequency of ICP >20 mmHg events, use of mechanical ventilation, pressors, and ventriculoperitoneal shunts, frequency of systemic infections.	Mean time from ictus to randomization was 52 hours. The risk of achieving mRS of ≤3 at 6 months was non-significantly higher in the t-PA group (48% vs. 45%, RR=1.06, 95% CI 0.88-1.28, p=0.554). The risk was slightly increased after adjustment for intraventricular size and thalamic ICH (RR=1.08, 95% CI 0.90-1.29, p=0.42). The odds of being dead at 6 months were significantly reduced for patients in the t-PA group (OR=0.50, 95% CI 0.31-0.80, p=0.004). Probability of survival was greater over the 6 months in the t-PA group (cumulative case fatality 18% vs. 29%, p=0.006). The risk of serious adverse events was significantly lower in the t-PA group (46% vs. 60%, RR=0.76, 95% CI 0.64-0.90, p=0.002). The risk of symptomatic bleeding was not significantly increased in the t-PA group (2% vs. 2%, RR=1.21, 95% CI 0.37-3.91, p=0.77). Post Hoc analyses At 6 months, the risk of mRS 5 was

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					significantly higher in the t-PA group (17% vs. 9%, RR=1.99, 95% CI 1.22-3.26, p=0.007). There was a significant association between the amount of clot removed and mRS ≤3 (OR=0.96, 95% CI 0.94-0.97, p<0.0001) and case fatality (OR=1.03, 95% CI 1.02-1.04, p<0.0001), respectively.
Gaberel et al. 2011 **France** **Systematic review & meta-analysis**	NA	4 RCTs and 8 observational studies including 316 patients ≥18 years with an intraventricular hemorrhage (IVH) that was secondary to a spontaneous supratentorial ICH, and was associated with obstructive hydrocephalus that required external ventricular drainage (EVD)	Comparisons of treatment with intraventricular fibrinolysis (IVF)+ EVD vs. EVD alone. Fibrinolytic agents included urokinase (n=8) and t-PA (n=4).	**Primary outcome:** All-cause mortality at the end of follow-up **Secondary outcomes:** Good functional outcome (independence in ADL), chronic hydrocephalus requiring shunting, occurrence of rebleeding and occurrence of ventriculitis.	Mortality was significantly lower among patients in the IVF + EVD group (22.7% vs. 46.7%, OR=0.32, 95% CI 0.19 to 0.52, p<0.0001. Results from 12 studies included). The odds of good functional outcome were significantly higher for patients in the IVF + EVD group at one month or at hospital discharge (31.4% vs. 7.1%; OR=5.02, 95% CI 2.07 to 12.20, p=0.0004, results from 6 studies included), but not ≥3 months (54.5% vs. 34%, OR=2.35, 95% CI 0.97 to 5.69, p=0.06. Results from 6 studies included). The odds of chronic hydrocephalus were not significantly lower in the IVF+EVT group (OR=0.68, 95% CI 0.35 to 1.30, p=0.24. Results from 11 studies included). There were no significant differences between groups in the odds of the rebleeding or the occurrence of ventriculitis.
Naff et al. 2011 **USA** **RCT** ***Intraventricular Hemorrhage Thrombolysis Trial***	Concealed Allocation: ☒ Blinding: Patient ☑ Assessor ☒ ITT: ☒	48 patients aged 18-75 years, recruited from 14 centres with a small supratentorial ICH (≤30 mL) with massive IVH with an external ventricular drain EVD in place, and who could be randomized within 24 hours of diagnostic CT. Mean age was 55	Patients were randomized to re receive 3 mg of t-PA (n=26) or 3 mL of normal saline (n=22) injected into the ventricular spaces, every 12 hours until evidence of resolution of the clot, or until a safety end point (symptomatic bleeding, infection, or death) occurred, whichever came first.	**Primary outcomes (safety):** 30-day mortality, ventriculitis, symptomatic bleeding **Secondary outcomes:** Good clinical outcome at 30 days, assessed using Glasgow Outcome Scale (GOS) ≤2, mRS ≤4, NIHSS ≤10 and Barthel Index (BI)	The mean duration of treatment was 10.2 days (t-PA) and 12.7 days (placebo). There were no significant differences between groups for any of the safety outcomes. 30-day mortality was 19% (t-PA) vs. 23% placebo), symptomatic bleeding: 23% (t-PA) vs. 5% (placebo), and ventriculitis 8% (t-PA) vs. 9% (placebo). There was no significant difference between groups in the proportion of patients who

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		years. There were significantly more males in the t-PA group (73.1% vs. 31.8%, p=0.008). median admission NIHSS score was 24.5. Median IVH volume was 52.7 mL		≥80.	achieved a good clinical outcome (GOS ≤2, 57% t-PA vs. 64% placebo; mRS ≤4, 52% t-PA vs. 27% placebo; NIHSS ≤10, 54% t-PA vs. 29% placebo; and BI≥ 80 19% t-PA vs.18% placebo). The rate of blood clot resolution was significantly greater in the t-PA patients (18% per day vs. 8% per day, p<0.001).

Acute Inpatient Care

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Specialized Care Units					
Ungerer et al. 2020 **Germany** **Retrospective study**	NA	10,811 noncomatose ICH patients consecutively admitted to hospitals over a large geographical region over a 7-year period. Mean age was 73.8 years, 48.2% were women. Mean NIHSS score was 8.76.	The outcomes of patients treated in stroke units (SU 64.3%), ICUs (20.2%) and non-specialized wards (NW,15.5%), were compared. Outcomes were also compared between patients with NIHSS10-25 treated on a SU (n=631) vs. those treated on a neurointensive ICU (NICU, n=173)	**Primary outcomes:** Unfavourable outcome (mRS >2 at discharge and intrahospital mortality	Mean length of hospital stay was 12 days. Compared with an SU, treatment in an ICU and NW were associated with significantly higher odds of an unfavourable outcome (OR=1.27, 95% CI 1.09-1.46 and OR=1.28, 95% CI 1.08–1.52, respectively). Patients treated in ICUs and in NWs had a higher risk of intrahospital mortality than those treated in SU (OR= 2.11, 95% CI 1.75-2.55 and OR=1.52 95% CI 1.23-1.89, respectively). The odds of a poor outcome were not significantly lower for patients treated on a NICU, compared with those treated on a SU, nor were the odds of mortality higher. The odds of a poor outcome (mRS>3) were significantly lower for patients treated on a NICU (OR=0.45, 95% CI 0.26-0.79).
Langhorne et al. 2013 **UK** **Systematic review**	NA	8 trials (n=2657) published from 1990 onward that included patients with ICH and acute ischemic stroke who had been	Subset analysis of patients with ICH and ischemic stroke	**Primary outcomes:** Death or dependence at the end of follow-up **Secondary outcomes:** Death, death or institutional	Stroke unit care was associated with a significant reduction in the risk of death or dependency for both ICH and ischemic stroke patients (overall RR=0.81, 95% CI 0.71-0.92, p<0.0001, p for interaction=0.77).

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& meta-analysis		randomized to receive care in stroke units or in an alternative setting, usually general medical wards.		care, LOS	Stroke unit care was also associated with a significant reduction in the risk of death at the end of scheduled follow-up (up to 12 months) (overall RR=0.79, 95% CI 0.64-0.97, p=0.02, p for interaction=0.58). Stroke unit care was also associated with a significant reduction in the risk of death or institutional care (overall RR=0.81, 95% CI 0.72-0.93, p=0.002, p for interaction=0.71).
Terent et al. 2009 **Sweden** **Retrospective study**	NA	105,043 patients who met the WHO definition of an acute stroke who were included in the Swedish Stroke Register from 2001 through 2005, and followed until January 2007	The effect size for care at a non-intensive stroke unit was compared with stroke care at other types of wards. Data were obtained by cross-linking to the Swedish Hospital Discharge and Cause of Death registers, which provided additional information regarding previous hospitalization and date of death, respectively. Previous hospitalization was traced back to January 1, 1987. The effect size of stroke care in the following subgroups of patients were of: age: 18-64, 65-74, 75-84, 85+ years and above; sex; stroke type: ICH, cerebral infarction and unspecified stroke; and level of consciousness (LOC-conscious, reduced, unconscious). Cox proportional hazards and logistic regression analyses were used to estimate the risk for man	**Primary outcome:** Death or institutional living (alternatively death or dependency) after 3 months and death during follow-up	Mean duration of follow-up was 2.4 years (254,824 patient years). There were 12,497 patients (11.9%) with ICH **Location of treatment:** 79 689 (76%) were treated in stroke units 25,354 (24%) were treated in other types of wards **Time spent in-hospital, including in-hospital rehabilitation:** Stroke unit: 18.4 (19.1) days Other types of wards: 14.7 (17.4) days Stroke care was associated with better long-term survival across all patient subgroups, with the best largest reduction of death hazard seen among those: Aged 18-64 years for death: HR=0.53; 95% CI 0.49-0.58 **With ICH stroke: HR=0.61, 95% CI 0.58-0.65** Who were unconscious: HR= 0.70, 95% CI 0.66-0.75. Stroke unit care was associated with reduced risk for death or institutional living after 3 months, with the largest reduction seen among those: Who were unconscious: OR= 0.47, 95% CI 0.39-0.57. **With ICH stroke subtype: OR=:0.56, 95% CI 0.50-0.61** Aged 18-64 years: OR=0.60, 95% CI 0.54-0.68

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			outcomes.		
Diringer & Edwards 2001 **USA** **Retrospective study**	NA	1,038 patients admitted to a general (n=772) or neuro (n=772) ICU within the same 3-year time frame with a diagnosis of ICH, were included.	Comparisons of patient outcomes between care environments.	**Primary outcome:** Independent predictors of hospital mortality	Of the 42 units evaluated, 2 were neuro ICUs and 40 were medical/surgical (n=21), surgical (n=10) and medical (n=9). Average admission GCS scores were higher for patients admitted to a neuro ICU (9.5 vs. 8.7, p<0.05). The average age of patients was lower for those admitted to a neuro ICU (56 vs. 62.6 years). The average number of beds/unit was higher for neuro ICUs (17.3 vs. 14.8) and the number of ICH patients treated/year was higher in the neuro units (49 vs. 29.3) After adjusting for demographics, severity of ICH, and ICU and institutional characteristics, admission to a general ICU was associated with an increase in hospital mortality: OR=3.4; 95% CI 1.65–7.6. Additional independent predictors of higher mortality were advancing age (OR=1.03/year, 95% CI, 1.01–1.04), lower GCS (OR=0.6/point, 95% CI 0.58–0.65), fewer ICH patients (OR=1.01/patient; 95% CI, 1.00–1.01), and smaller ICU (OR= 1.1/bed; 95% CI, 1.02–1.13). Having a full-time intensivist was associated with lower mortality rate (OR= 0.388; 95% CI, 0.22–0.67)
Ronning et al. 2001 **Norway** **Controlled trial**	NA	121 patients, 60 to 85 years admitted with acute primary ICH from 1995 to 1997. Exclusion criteria included symptoms of stroke>24 hours before admission to hospital, SAH or subdural hemorrhage.	Patients were allocated to treatment either in an acute stroke unit (n=56), characterized by intensive fluid management, blood pressure control, early mobilization and prompt treatment of medical complications or in general medical wards (n=65) by a quasi-randomized process, based on birth date. Patients treated on the	**Primary outcomes:** 30 day and one-year mortality **Secondary outcomes:** LOS and proportion of the patients alive and discharged to their homes	The survival curves for during the first 30 days and during one-year favoured patients in the stroke unit group (p=0.007 and 0.013, respectively), and remained significant after adjusting for differences in stroke severity, history of prior stroke and diabetes. There was no difference between groups for survival from 30 days and 1 year. At 30 days, fewer patients in the stroke unit group were dead (39% vs. 63%, adjusted OR=0.40, 95% CI 0.17-0.94). There was no difference in one-year mortality between groups (52% vs. 69%, adjusted OR=0.58, 95% CI 0.24-1.38).

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			general ward were immobilized for up to one week, and care was not organized into multidisciplinary teams.		There was no difference in the number of patients discharged home between groups (27% vs. 52%, adjusted OR=1.60, 95% 0.62-4.00). Patients in both groups remained in hospital for a median of 7 days.
Prevention of seizures					
Angriman et al. 2019 **Canada** **Systematic review & meta-analysis**	Risk of bias was unclear in all studies	1 RCT and 6 observational studies (n=3,241) including adult patients with spontaneous ICH.	The use of prophylactic antiepileptic drugs (AEDs) vs. no preventive treatment	**Primary outcome:** Poor clinical outcome at the longest recorded follow-up (mRS >3 or all-cause mortality during follow-up if mRS not recorded). **Secondary outcomes:** Good neurological outcome based on mRS at hospital discharge, 30 and 90 days and the occurrence of early (<7 days) and late seizures (≥7 days)	AEDs included phenytoin (n=4), levetiracetam (n=2), and valproic acid (n=1). Treatment with AEDs did not increase the odds of poor clinical outcome (OR=0.99, 95% CI, 0.66–1.49; p=0.96). Follow-up duration varied from hospital discharge, 30 days, 90 days, to 1 year). The use of AEDs did not reduce the odds of seizures during follow-up (OR=0.89, 95% CI, 0.52–1.51; p=0.66, n=4 studies). There were insufficient studies to examine early or late seizure activity.
Gilad et al. 2011 **Israel** **RCT**	Concealed Allocation: ☒ Blinding: Patient ☑ Assessor ☑ ITT: ☒	84 patients consecutively admitted to a single institution from 2003-2008 with spontaneous ICH. Patients with early-onset seizures (i.e., within 24 hours of onset) were excluded. Mean age was 70 years, 66% were men. A plurality of patients had ICH in the basal ganglion (40%).	Patients were randomized 1:1 to receive oral valproic acid (400 mg bid) vs. placebo for one month.	**Primary outcome:** Seizure occurrence at 1 year of follow-up. **Secondary outcome:** NIHSS score at 1 year.	5 patients suffered immediate seizures and 7 were lost to follow-up. The results from 72 patients are included. 7 patients in the valproic acid group had a seizure during the study period (1 early after ICH, 6, late) compared with 8 episodes in the control group (4 early, 4 late). The difference between groups was non-significant (19.5% vs. 22.2%, p=0.8). 6 patients in the valproic acid group died during the study period compared with 5 in the control group (4 early, 4 late). The difference between groups was non-significant (16.6% vs. 14%, p=0.7). The mean NIHSS score of patients in the valproic acid group was significantly lower (4.4 vs. 8.6, p=0.002).
Prevention of Venous Thromboembolism					
Sprügel et al. 2019	NA	1,536 patients with VKA-	The outcomes of patients	**Primary outcome:**	There were 28 IHC in patients with VKA (n=27) or

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Germany **Retrospective study**		associated or NOAC-associated ICH and 880 patients with non OAC-ICH with heparin prophylaxis admitted between 2006 and 2015. Patients with VKA-ICH and NOAC-ICH were significantly older than patients with non-OAC-ICH (76 and 78 years vs. 71 years). There were many other differences in baseline characteristics between groups.	who experienced an intracranial hemorrhagic complication (IHC) during hospital stay among patients with non-OAC-ICH, VKA-ICH and NOAC-IC, were compared.	ICH (any new intracranial haemorrhage, any hematoma enlargement and new subarachnoid or subepidural/epidural haemorrhage **Secondary outcomes:** Mortality and functional outcome at 3 months (favourable outcome mRS 0-3).	NOAC-associated ICH (n=1) and 14 patients with non-OAC ICH. There were no significant differences (p=0.577) in the crude incidence rates of IHC comparing patients with VKA-ICH, NOAC-ICH and non-OAC-ICH (crude incidence rates per 1,000 patient days were 1.49, 0.63 and 1.45, respectively). Significantly more patients who experienced an IHC were more likely to experience a poor outcome or death (78.4% vs. 59.2%, p=0.019) and 37.8% vs. 23.7%, p=0.045)
Arabi et al. 2019 **Saudi Arabia** **RCT** ***The Pneumatic Compression for Preventing Venous Thromboembolism (PREVENT)* trial**	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT (modified): ☑	2,003 adults admitted to an intensive care unit at 20 sites with medical, surgical, or traumatic conditions. Mean age was 58 years, 57% were men. 78% of admissions were for medical conditions. (number of patients with stroke not stated)	Participants were randomized 1:1 within 48 hours of admission to receive intermittent pneumatic compression (IPC) with knee or thigh-length devices for ≥ 18 hours each day + pharmacologic thromboprophylaxis with unfractionated or low-molecular-weight heparin (pneumatic compression group) or pharmacologic thromboprophylaxis alone (control group)	**Primary outcomes:** Incident proximal lower-limb deep-vein thrombosis (DVT), until ICU discharge, death, attainment of full mobility, or trial day 28, whichever occurred first. **Secondary outcomes:** Incident proximal or distal DVT, proximal, distal, incident, or prevalent lower-limb DVT, pulmonary embolus, venous thromboembolism: lower-limb DVT or pulmonary embolism, all-cause mortality	IPC was applied for a median of 22 hours/day for 7 days. The risk of incident proximal DVT was not significantly lower in the IPC group (3.9% vs. 4.2%; RR= 0.93; 95% CI 0.60 to 1.44; p=0.74). The risks of the secondary outcomes were not reduced significantly in the IPC group. There were no serious adverse events.
Cherian et al. 2018 **USA** **Retrospective study**	NA	74,283 patients with ICH from 1,358 hospitals, included in the Get with the Guidelines Stroke Registry from 2009-2013.	The characteristics and outcomes of patients who received early chemoprophylaxis (CP, n=5,929,7.9%), or early mechanical/non-CP (n= 66,444 (89.4%) were compared with those who had no prophylaxis,	**Primary outcome:** VTE, (DVT or PE), during hospital stay and in-hospital mortality	There was no change in the use of early CP over time. There were 2,721 VTE events 18,463 deaths. The odds of VTE were not reduced significantly among patients who received early VTE prophylaxis compared with those who received none. (OR=95% CI 0.70-1.24, p=0 .63).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			mechanical or CP, within the first 2 days (n=1,910, 2.6%). Models were adjusted for age, gender, race, medical history, admission information, hospital characteristics, and date of prophylaxis.		Early CP significantly reduced the odds of in-hospital mortality (OR= 0.74, 95% CI 0.67-0.81, p< 0.0001) compared to all other groups. The adjusted OR for VTE occurrence comparing early CP with all other categories was 1.18 (95% CI 1.01-1.39, P = .038). Comparing mortality rates between groups, early CP was associated with lower mortality (adjusted OR 0.74, 95% CI 0.67-0.81, P < .0001) compared to all other groups Independent predictors of early CP use compared with no CP were female, atrial fibrillation, diabetes, coronary, carotid, and peripheral artery disease, prior ischemic stroke or TIA, hospital size >500 beds, and geographic region.
Dennis et al. 2013 **UK** **RCT** ***Clots in Legs Or sTockings after Stroke (CLOTS)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑ (Primary outcome)	2,876 patients admitted to 105 hospitals in the UK within 3 days of acute stroke, who were immobile. Mean age was 74.5 years. 13% of patients had ICH. 68% of patients had been taking an antiplatelet agent within the previous 24 hours.	Patients were randomized to wear thigh length intermittent pneumatic compression (IPC) device (n=1,438) or to no IPC (n=1,438) at all times except for washing and therapy, for a minimum of 30 days, or until the patient became mobile, was discharged from hospital, or declined to continue to IPC.	As per CLOTS 1 & 2+ additional 6-months outcomes **Primary outcome:** Symptomatic or asymptomatic DVT detected by Doppler u/s in the popliteal or femoral veins within 30 days of randomization. **Secondary outcomes:** Death, any DVT, PE, complications and compliance with treatment within 30 days (2 scans were performed between days 7-10 and 25-30, when possible) 6-month outcomes: Death from any cause, any symptomatic or asymptomatic DVT or PE.	Mean duration of IPC use was 12.5 days. Complete adherence to treatment was 31% in IPC group. The incidence of proximal DVT within 30 days was significantly lower for IPC group (8.5% vs. 12.1%, OR=0.65, 95% CI 0.51-0.84, p=0.001, ARR=3.6%, 95% CI 1.4%-5.8%). There were no significant differences between groups for the outcomes of: death at 30 days (10.8% vs. 13.1%, p=0.057), symptomatic proximal DVT (2.7% vs. 3.4%, p=0.269), or PE (2.0% vs. 2.4%, p=0.453). The incidence of any DVT (symptomatic, asymptomatic, proximal or calf) was significantly lower for IPC group (16.2% vs. 21.1%, OR=0.72, 95% CI 0.60-0.87, p=0.001). The incidence of any DVT, death or PE was significantly lower for IPC group (27.2% vs. 34.1%, OR=0.72, 95% CI 0.61-0.84, p<0.0001). Skin breakdown was more common in IPC group (3.1% vs. 1.4%, OR=2.23, 95% CI 1.31-3.81,

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					p=0.002). At 6 months, the incidence of any DVT remained significantly lower in the IPC group (16.7% vs. 21.7%, OR=0.72, 95% CI 0.60-0.87, p=0.001). The incidence of any DVT, death or PE also remained significantly lower for IPC group (36.6% vs. 43.5%, OR=0.74, 95% CI 0.63-0.86, p<0.0001). Although the interaction term of stroke type was not significant, the incidence of the primary outcome was significantly lower among patients with ICH (6.7% vs. 17.0%, OR=0.36; 95% CI 0.17–0.75). There were no significant interactions found in sub-group analyses including: time to initiation of treatment (days), concurrent use of anticoagulants, or antithrombotics, baseline prognosis, baseline risk for DVT, stroke type (ischemic vs. hemorrhagic) or type of sleeve used.
Paciaroni et al. 2011 **Italy** **Meta-analysis**	NA	4 studies (2 RCTs, 2 non RCTs) in which prophylactic treatment for venous thromboembolism, following hemorrhagic stroke was initiated within 4 days of the event	Studies compared anticoagulants (UFH, n=2 or LMWH, n=2) with alternative treatment (placebo n=1, or compression stockings n=3). Mean follow-up periods were 10 days, 21 days, 3 months and were not recorded. Mean treatment durations were 10 days and 7-14 days and were not recorded in 2 studies	**Primary outcomes:** Symptomatic and asymptomatic DVT, PE, hematoma enlargement or death	Treatment with heparin was associated with a non-significant reduction in the risk of DVT (RR=0.77, 95% CI 0.44-1.34) and death (RR=0.76, 95% CI 0.57-1.03) Treatment with heparin was associated with a significant reduction in the risk of PE (RR=0.37, 95% CI 0.17-0.80) Treatment with heparin was associated with a non-significant increase in the risk of hematoma expansion (RR=1.42, 95% CI 0.15-90.7)
Lacut et al. 2005 **France** **RCT** ***Venous Intermittent***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑	151 patients ≥18 years, with traumatic or spontaneous ICH with or without SAH. Patients with extra- or subdural hematomas, traumatic ICH due to polytrauma,	Patients were randomized to wear intermittent pneumatic compression devices (IPC) + graded compression stocking (GCS) or GCS alone for	**Primary outcomes:** Symptomatic and non-symptomatic DVT at 10 days, nonfatal and fatal pulmonary embolus (PE) at 10 days	Patients in the GCS group were significantly older (65.5 vs. 59.9 years, p<0.01). There was no symptomatic DVTs in either group. 14 patients died before evaluation, but no death was definitely related to PE.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Compression and Thrombosis Occurrence Related to Intra-cerebral Acute hemorrhage (VICTORIAh)	ITT: ☒	hemorrhagic transformation of ischemic infarct or vasculitis, were excluded.	10 days or until hospital discharge.	**Secondary outcomes:** DVT at 30 and 90 days	There were significantly fewer DVTs in the IPC + GCS group (4.7% vs. 15.9%; RR=0.29; 95% CI 0.08 to 1.00; p =0.03). During the 3-month follow-up, one patient in each group experienced a clinically overt and well-documented DVT. 14 patients allocated to IPC did not tolerate the device and stopped wearing it within 5 days after randomization. There were 18 losses to follow-up.
Boeer et al. 1991 **Germany** **RCT**	Concealed Allocation: ☒ Blinding: Patient ☒ Assessor ☒ ITT: ☒	68 patients with acute ICH (within previous 24 hours) admitted to a single institution. Mean age was 61 years, 50% were men.	Patients were randomized 1:1:1 to treatment with low dose heparin (5,000 units x3/day), initiated on days 2 (group 3), 4 (group 2) or 10 (group 1).	**Primary outcomes:** DVT, rebleeding, pulmonary embolus (PE), death	Compared with the patients in groups 1 and 2, group 3 patients had significantly reduced odds of PE (OR=9.2, 95% CI 1.-1-75). There were no cases of rebleeding in group 3, 1 case in group 2 and 3 cases in group 1. There were 2 deaths in group 3, 5 in group 2 and 4 in group 1. At day 2, there were 5 DVTs in group 3, 7 in group 2 and 8 in group 1.
Increased Intracerebral Pressure (ICP)					
Anderson et al. 2017 **China/International** **RCT (cluster)** ***Head Po- sitioning in Acute Stroke Trial (Head- PoST)***	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	11,093 adult patients from 114 institutions, with acute stroke. Mean age was 68 years, 40% were women. 85% of strokes were ischemic. Median NIHSS score was 4. There were 931 ICHs. Median NIHSS score was 6.0.	Patients were randomized to receive care in either a lying-flat position or a sitting-up position with the head elevated to at least 30 degrees, initiated as soon as possible and maintained for 24 hours.	**Primary outcome:** mRS score at 90 days **Secondary outcomes:** death or major disability (mRS score of 3 to 6) at 90 days, death within 90 days after stroke, mRS scores at 7 days, NIHSS scores at 7 days, serious adverse events, pneumonia	Median time from stroke onset to intervention was 14.0 hrs. In ordinal analysis, there was no significant difference between groups in the shift in the distribution of mRS scores at 90 days (OR=1.01, 95% CI 0.92–1.10, p= 0.84). There were no significant differences between groups on any of the secondary outcomes. In subgroup analysis of ICH patients, there were no significant differences between groups on the primary outcome or any of the secondary outcomes.
Rehabilitation					

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Mortensen et al. 2016 **Denmark** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	16 patients, aged 19-80 years who sustained a spontaneous ICH >6months to <5 years previously.	Patients were randomized to receive 5 consecutive days of occupational therapy for 30 minutes combined with either 1.5 mA anodal or sham transcranial direct current stimulation (tDCS), applied for 20 minutes.	**Primary outcome:** Jebsen–Taylor test (JTT) + grip strength	From baseline to the end of treatment, there was a mean improvement of 29.3% in JTT scores for patient in the active tDCS group and 23.4% for patients in the sham group (p=0.179) The mean improvement from baseline to one-week follow-up was 30.5% in the active tDCS group and 24.2% in the shame group (p=0.259). The improvement in grip strength from baseline to end of treatment period was significantly greater for patients in the active tDCS group (12% vs. -1.3%, p=0.025). By the end of one-week follow-up, there was no longer a significant difference between groups in level of improvement (23% vs. 12.2%, p=0.369).
Liu et al. 2014 **China** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☒ Assessor ☑ ITT: ☑	234 patients, presenting with first-ever ICH, with no contraindications to being mobilized within 48 hours of stroke onset and with moderate disability. Mean age was 59 years, 56% were men. Mean NIHSS score was 10.	Patients were randomized 1:1 to receive standard rehabilitation (delivered by relatives) + very early rehabilitation (VER) vs. standard rehabilitation. Standard rehabilitation usually commenced within 7 days, while patients in VER group started rehabilitation within 48 hours of stroke onset.	**Primary outcome:** Death at 6 months **Secondary outcomes:** SF-36, modified Barthel Index (BI), Zung Self-Rated Anxiety Scale, recurrent stroke. Assessments were conducted at 3 and 6 months	Average length of hospital stay was significantly shorter for patients in the VER group (24 vs. 34 days, p<0.001). The risk of death at 6 months was significantly higher for patients in the standard rehabilitation group (97% vs. 89%, HR (adjusted for age and heart valve disease) =4.44, 95% CI 1.24–15.87. At 3 months, there were no significant differences in mean scores between groups for any of the secondary outcomes except for the General Heath subscale of the SF-36. The mean score for the VER group was significantly higher (53.7 vs. 47.9, mean difference=5.8 (95% CI 2.1-9.4). At 6 months, the mean differences in scores between groups for all secondary outcomes were significantly different; all favouring the VER group. The mean differences for the sub scales of the SF-36 components ranged from 9.8 (physical) to 25.5 (general health). The mean BI score was significantly higher in the VER group (73.8 vs. 61.3, mean difference=12.5, 95% CI 6.8-18.3. The mean Zung anxiety score was significantly

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					lower in the VER group (48.9 vs. 55.2, mean difference=-6.4, 95% CI -8.3 to -4.4.

Secondary Prevention

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Hypertension & Risk of Recurrent Hemorrhagic Stroke					
Schmidt et al. 2016 **Denmark** **Retrospective study**	NA	15,270 persons aged ≥20 years, diagnosed with a first-ever primary ICH in Denmark from 1996-2011.	Patients were followed from 7 days after the event until recurrent ICH, death or until the study's end (2011). Associations between typical comorbid diseases, surgical treatment, and the use of with medications including antithrombotics, SSRI's and NSAID's and recurrent ICH, were examined.	**Primary outcome:** Recurrent ICH	The were 2,053 cases of recurrent ICH. The one and 5-year cumulative recurrence risks were 8.86% (95% CI: 8.41–9.31%) and 13.72% (95% CI: 13.15–14.29%), respectively. Antihypertensive treatment was associated with a significantly reduced recurrence risk (RR 0.82, 95% CI: 0.74–0.91). The 1-year cumulative recurrence risk for patients treated for hypertension was 7.5% vs. 9.7% for others. There were no associations between antithrombotic, SSRI or NSAID use and recurrent ICH
Biffi et al. 2015 **USA** **Retrospective study**	NA	Follow-up of 1,145 patients, aged ≥18 years, admitted to a single facility from 1994-2013 with ICH who had survived for at least 90 days following event. Mean age was 73.4 years, 52% were male. 67.1% had a history of hypertension.	Blood pressure measurements were obtained every 6 months (every 3 months during year one post event) and its risk of recurrent ICH, examined	**Primary outcome:** Recurrent ICH	Median duration of follow-up was 36.8 months. Among 505 survivors of lobar ICH, there were 102 recurrent cases of lobar ICH and no cases of nonlobar ICH. Among 640 survivors of nonlobar ICH, there were 2 recurrent cases of lobar and 42 cases of nonlobar ICH. Inadequate BP control was an independent risk factor for recurrent lobar ICH (HR=3.53,95% CI 1.65-7.54, p=0.001) and nonlobar ICH (HR=4.23, 95% CI 1.02-17.52, p=0.048) Each 10 mm Hg increase in SBP was associated with an increased risk of lobar ICH (HR=1.33, 95% CI 1.02-1.76, p=0.04).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Each 10 mm Hg increase in SBP and DBP was associated with an increased risk of nonlobar ICH (HR=1.54, 95% CI 1.03-2.30, p=0.04 and HR=1.21, 95% CI 1.01-1.47, p=0.05, respectively).)
Treatment of Hypertension to Reduce the Risk of Hemorrhagic Stroke					
Arima et al 2010 **Additional reporting from *Perindopril Protection Against Recurrent Stroke Study (PROGRESS)* Collaborative Group** **Australia** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑ ITT: ☑	6,105 patients with a history of stroke (ischemic or hemorrhagic) or TIA within the previous 5 years. No blood pressure entry criteria. Mean age was 64 years, 70% of patients were men. Mean BP at baseline was 147/86 mm Hg. 11% of patients had experienced a previous ICH.	Patients who adhered to, and tolerated, the run-in treatment were randomly assigned to continued active therapy (n=3,051) or matching placebo (n=3,054). Patients in the active treatment group received a flexible regimen based on perindopril (4 mg daily) with the addition of indapamide (2.5 mg daily) in patients for whom the responsible physician judged there to be no specific indication for or contraindication to treatment with a diuretic.	**Secondary outcomes:** Probable cerebral amyloid angiopathy (CAA)-related ICH and probable hypertension-related ICH	Mean duration of follow-up was 3.9 years. There were 16 probable CAA-related ICHs, 51 probably HTN-related ICHs and 44 unclassified ICHs. The associated risk reductions associated with active treatment for each stroke types were: CAA ICH 77%, 95% CI 19%-93% HTN ICH 46%, 95% CI 4%-69% Unclassified ICH 43%, 95% CI -5-69% Overall risk reduction 50%, 95% CI 26%-67%
Resumption of Antithrombotics					
Murthy et al. 2019 **USA** **Meta-analysis *VISTA-ICH***	NA	Data from 2,801 ICH adult patients with no previous history of ICH collected from 3 databases/registries. Mean ages in the 3 cohorts ranged from 65.4-71.3 years, 50.3%-63.1% were men. 18.1% had a previous stroke.	The outcomes of 228 patients who were started on an antiplatelet, were compared with those of patients not on antiplatelet therapy.	**Primary outcomes:** All-cause mortality and a composite of major disability or death (mRS score 4–6) at 90 days	Median time to antiplatelet therapy ranged from 7 to 39 days. Antiplatelet therapy was not associated with mortality (HR=0.85; 95% CI, 0.66–1.09), or death or major disability (HR=0.83; 95% CI, 0.59–1.16).
The RESTART Collaboration 2019 **UK** **RCT**	Concealed Allocation: ☑ Blinding: Patient ☑ Assessor ☑	537 patients ≥18 years, who were taking antithrombotic (antiplatelet or anticoagulant) therapy for the prevention of occlusive vascular disease when they developed an ICH, discontinued	Patients were randomized (1:1) to start or avoid antiplatelet therapy	**Primary outcome:** Symptomatic ICH **Secondary outcomes:** A composite of all major haemorrhagic events and a composite of all major occlusive vascular events.	Planned recruitment was 720 patients. Median duration of follow-up was 2.0 years. Patients taking antiplatelets had a non-significantly lower recurrence of ICH (4% vs. 9%; adj HR= 0·51, 95% CI 0·25–1·03, p=0.06).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
REstart or STop Antithrombotics Randomised Trial (RESTART)	ITT: ☑	antithrombotic therapy, and survived for 24 hours. Patients were recruited a median of 76 days after ICH. Median age was 77 years, 68% were men. Antithrombotic treatment included aspirin (~50%), clopidogrel (~25%) and oral anticoagulation (~1/5)		Analyses were adjusted ICH location (lobar vs non-lobar); time since symptom onset (1–6 days, 7–30 days, >30 days); antiplatelet therapy preferred by the patient's physician if allocated to start (aspirin alone vs other antiplatelet therapy); participant age at (<70 vs. ≥70 years); and predicted probability of being alive and independent at 6 months (<0·15 vs. ≥0·15)	The occurrence of patients who experienced major haemorrhagic events was similar between groups (7% taking antiplatelet vs. 9% avoiding; HR=0·71, 95% CI 0·39–1·30, p=0·27), as was the occurrence of patients who experienced major occlusive vascular events (15% taking antiplatelet vs. 14% avoiding; HR=1.02, 95% CI 0·65–1·60, p=0·92).
Nielsen et al. 2019 **Denmark** **Retrospective study**	NA	622 persons with a discharge diagnosis of spontaneous ICH included in the Danish Stroke Registry with a known history of AF who claimed a prescription for warfarin or a NOAC agent (dabigatran, rivaroxaban, or apixaban) after discharge. Mean age was 76.1 years, 39.1% were women. Mean Scandinavian Stroke Score was 42.2.	The risk of study outcomes between patients taking warfarin (n=274) and NOACs (n=348), was examined. Models were adjusted for sex, age stroke severity, days since hospital discharge, length of hospital stay, reduced renal function, alcohol consumption, smoking status, CHA_2 DS_2 -VASc score, and aspirin treatment.	**Primary outcomes:** Ischemic stroke, recurrent ICH	The absolute risks of stroke during the first year of follow up were 7.85% (warfarin) and 4.01% (NOAC). The weighted risk difference was 3.78% (95% CI −0.15% to 7.71%). The absolute risks of recurrent ICH during the first year of follow up were 7.0% (warfarin) and 5.07% (NOAC). The weighted risk difference was 1.93% (95% CI −2.02% to 5.87%). The absolute risks of stroke during the first 3 years of follow up were 11.6% (warfarin) and 8.8% (NOAC). The weighted risk difference was 3.28% (95% CI −1.60% to 8.20%). The absolute risks of recurrent ICH during the first 3 years of follow up were 7.85% (warfarin) and 7.35% (NOAC). The weighted risk difference was 0.51% (95% CI −3.77% to 4.78%).
Kuramatsu et al. 2018 **Germany** **Retrospective study**	NA	137 patients with OAC-ICH included in the RETRACE cohorts 1 & 2 with mechanical heart valves.	The outcomes of patients who received/did not receive therapeutic anticoagulation (TA), were compared.	**Primary outcomes:** Any intracranial or extracranial hemorrhage **Secondary outcomes:** Thromboembolic complications, the composite of haemorrhagic	71 patients did not receive TA, 66 patients did. Patients who did not receive TA had a significantly lower median Glasgow coma scale (12 vs. 14, p<0.01) and had a significantly higher median ICH score (2 vs. 1, p<0.01). Patients who received TA had significantly more hemorrhagic complications (17 vs. 4; Incidence rate

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				and thromboembolic complications, timing of TA, and mortality and functional outcome at discharge and day 90	per 100 patient days: 3.53, 95% CI 2.05–5.6 vs. 0.34, 95% CI 0.09–0.88, p<0.01). The rate of thromboembolic complications was not significantly higher in patients who did not receive TA (7 vs. 1: Incidence rate per 100 patient days: 0.60, 95% CI 0.24-1.23 vs. 0.21, 95% CI 0.01–1.15, p=0.34). The composite outcome occurred more frequently in patients who received TA (18 vs. 11; Incidence rate per 100 patient days: 3.73, 95% CI 2.21–5.90 vs. 0.94, 95% CI 0.47–1.68, p<0.01). Re-initiation of TA was associated with a significantly increased risk of hemorrhagic complications until 13 days after ICH (HR=7.06, 95% CI 2.33–21.37; P < 0.01), whereas TA initiated ≥14 days after ICH until hospital discharge was no longer significantly related to haemorrhagic complications (HR 1.50, 95% CI 0.17– 13.32; P = 0.71).
Murthy et al. 2017 **USA** **Systematic review & meta-analysis**	NA	8 retrospective studies including 5,306 patients ≥18 years with non-traumatic ICH and in which documentation of resumption of oral anticoagulants had been reported. Mean age of patients ranged from 69-78 years. The majority of patients were men.	The associations between anticoagulation resumption and thromboembolic complications and recurrent ICH, were examined.	**Primary outcome:** Recurrent ICH and composite of ischemic stroke or MI	Mean or median duration of follow-up ranged from 12 to 43 months. Oral anticoagulants were initiated at 10, 11, 31 and 39 days in 4 studies, within 2 and 6 months in 2 studies and timing was not reported in 2 studies. Anticoagulation therapy was reinitiated in 786 patients (38.4%) in 6 studies examining the relationship between thromboembolic complications and anticoagulants. The risk of stroke or MI was significantly lower in patients who restarted anticoagulants (6.7% vs. 17.6%, RR=0.34, 95% CI 0.25-0.45). Anticoagulation therapy was reinitiated in 1,899 patients (35.8%) in 8 studies examining the relationship between recurrent ICH and anticoagulants. The risk of recurrent ICH was not significantly higher in patients who restarted anticoagulants (8.7% vs. 7.8%, RR=1.01, 95% CI0.58-1.77).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Pennlert et al. 2017 **Sweden** **Retrospective study**	NA	2,619 first-ever ICH survivors with atrial fibrillation included in the Swedish Stroke Registry between July 1, 2005, and December 31, 2012. Mean age was 78 years, 40.7% were women.	The optimal timing of treatment in patients with low and high thromboembolic risk was examined. Low risk individuals were classified as 69 years of age, who had spent 14 days in hospital after the index ICH, had no previous risk factors other than AF, and had no previous antithrombotic treatment. High-risk individuals were 80 years of age, had spent 28 days in hospital, had a previous ischemic stroke, hypertension, and diabetes mellitus and was on previous anticoagulant treatment at the time of ICH	**Primary outcome:** Vascular death or non fatal stroke	Total follow-up time from treatment initiation was 581 person-years for anticoagulants, and 3,001 person-years for antiplatelets (starting from 28 days following ICH). Of the 232 patients initiating anticoagulant treatment, 59.5% had a dispensed prescription within the first 3 months after ICH onset. Among the 1136 patients who received antiplatelet therapy, 58.9% claimed a prescription within 3 months. During follow-up, there were 379 severe thrombotic events of which 302 (79.7%) were ischemic strokes. Of 115 severe hemorrhagic events, 96 (83.5%) were recurrent ICH events. In the low-risk group, the lowest estimated cumulative incidences of vascular death or nonfatal stroke were found when anticoagulant treatment was started in the 7- to 8-week interval after ICH. For high-risk women, the total risk of the primary outcome within 3 years was 17.0% when anticoagulant treatment was initiated 8 weeks after ICH compared with 28.6% in those without any antithrombotic treatment. For high-risk men, the corresponding risks were 14.3% vs. 23.6%. The authors concluded the optimal timing of starting anticoagulant treatment in patients with AF who have survived an ICH appears to be around 7 to 8 weeks after ICH.
Ottosen et al. 2016 **Denmark** **Retrospective study**	NA	6,369 patients ≥18 years admitted to hospital from 2005-2013 with first-ever spontaneous, non-traumatic ICH, who survived for the first 30 days. Patients were included in the Danish Stroke Registry	Patients with an indication for antithrombotic therapy (AT) were identified. Indications included MI, ischemic stroke, peripheral arterial disease, venous thromboembolism, atrial	**Primary outcome:** All-cause mortality **Secondary outcomes:** Thromboembolic events, major bleeding, recurrent ICH Analyses were adjusted for	Less than 34% of survivors had filled their AT prescription. For those who did, post ICH use of AT was initiated during first 3-6 months. Median duration of follow-up was 2.3 years. 1,281 patients (43%) with an indication for AT died, 497 (17%) developed a thromboembolic event and 536 (18%) had a major bleeding event.

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			fibrillation, or artificial heart valve. Post-admission use of AT was determined by the number of prescriptions filled. The outcomes of patients who received/did not receive antithrombotic therapy post ICH were compared.	age, sex, comorbidities, BMI, alcohol use, smoking stroke severity, year of admission and indications for AT	Among patients who received AT after ICH 6.1% experienced a recurrent ICH compared with 7.6% who did not receive AT. Among patients with an indication for oral anticoagulant therapy, post-discharge use of oral anticoagulants was associated with a significantly reduced risk of death (HR=0.59, 95% CI 0.43-0.82) and thromboembolic events (HR=0.58, 95% CI 0.35-0.97), with no increased risk of major bleeding (HR=0.65, 95% CI 0.41-1.02) or recurrent ICH (HR=0.90, 95% CI 0.44-1.82) Among patients with an indication for oral anticoagulant therapy, post-discharge use of antiplatelets was associated with a significantly reduced risk of death (HR=0.81, 95% CI 0.67-0.98), but not thromboembolic events (HR=1.03, 95% CI 0.75-1.41), with no increased risk of major bleeding (HR=0.96, 95% CI 0.70-1.31) or recurrent ICH (HR=1.24, 95% CI 0.75-2.05). Among patients with an indication for antiplatelets, post-discharge use of antiplatelets was associated with a significantly reduced risk of death, but not thromboembolic events, with no increased risk of major bleeding or recurrent ICH.
Nielsen et al. 2015 **Denmark** **Retrospective study**	NA	1,752 patients with nonvalvular atrial fibrillation subsequently admitted to hospital from 1997-2013 with an intracranial hemorrhage (ICH) who survived for the first 6 weeks who had been receiving anticoagulation therapy with warfarin or a novel anticoagulant, at least 6 months prior to the event. Median age was 78 years, 62% were male, 812 patients had an ICH, 755,	Patients were classified by antithrombotic regimens and their outcomes compared: antiplatelet therapy (AT), oral anticoagulants (OAC) and no antithrombotic treatment	**Primary outcome:** Combined end point of ischemic stroke/systemic embolism (SE), and all-cause mortality, and recurrent ICH **Secondary outcomes:** Individual components of primary study outcome and major extracranial bleeding Analyses were adjusted for age, sex, year of inclusion, time since last claimed	At the time of stroke, 65% of patients were treated with warfarin, 2% with a novel anticoagulant, 33% with dual therapy (warfarin + antiplatelet) and <1% dual therapy with a novel anticoagulant+ antiplatelet. 621 patients resumed anticoagulation therapy following stroke. The median time to claim first prescription was 34 days. 759 patients received antiplatelet therapy following stroke. The median time to claim first prescription was 24 days. Event rates (per 100-person years) using 1-year follow-up

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
		subdural bleeding and 185, subarachnoid bleeding		OAC prescription prior to ICH and CHA_2DS_2 and HAS-BLED scores	*Stroke/SE and all-cause mortality* No treatment 27.3, 95% CI 23.6-31.6 OAC: 13.6, 95% CI 10.1-18.3 AT: 25.7, 95% CI 20.7-31.9 OAC vs. no treatment: HR=0.55, 95% CI 0.39-0.78 OAC vs. AT: HR=0.87, 95% CI 0.67-1.14 *Recurrent ICH* No treatment 8.6, 95% CI 6.6-11.2 OAC: 8.0, 95% CI 5.4-11.8 AT: 5.3, 95% CI 3.3-8.4 OAC vs. no treatment: HR=0.91, 95% CI 0.56-1.49) OAC vs. AT: HR=0.60, 95% CI 0.37-1.03 *Major Extracranial Bleeding* No treatment 1.5, 95% CI 0.8-2.7 OAC: 1.5, 95% CI 0.6-3.7 AT: 2.6, 95% CI 1.3-5.0 OAC vs. no treatment: HR=0.92, 95% CI 0.30-2.76 OAC vs. AT: HR=1.57, 95% CI 0.62-3.92
Kuramatsu et al. 2015 **Germany** **Retrospective study**	NA	719 patients admitted to one of 19 tertiary care centres in Germany from 2006-2010, with OAC-ICH, an INR>1.5, and for whom 1-year follow-up data were available. This group of patients represented 1 tier of 3 in the RETRACE study. Mean age was 74 years	ICH recurrence of patients who restarted oral anticoagulation therapy with VKA was compared with patients who did not restart OACs.	**Primary outcome:** ICH recurrence	OAC was restarted in 172 patients (23.9%). Median time to OAC resumption was 31 days. The risk of ischemic complication was significantly higher for patients who did not resume OACs (15.0 vs. 5.2%, p<0.01), while the risk of hemorrhagic complications was not (8.1 vs. 6.6%, p=0.48) Among patients with atrial fibrillation (AF, n=566), the risk of mortality and ischemic events were significantly reduced for patients who restarted OACs, while the risk of hemorrhagic complications was not. In propensity analysis of patients with AF, the risk of recurrent ICH was not significantly increased among patients restarting OACs (3.9/100 patient years, 95% C 1.9-5.8 vs. I3.9/100 patient yrs, 95% CI 2.2-5.7, p=0.92)
Majeed et al. 2010	NA	234 patients from 3 centres who had sustained an intracranial hemorrhage	Data pertaining to patients who survived for the first week were	**Primary outcomes:** Recurrent ICH, ischemic stroke, systemic embolism,	Median duration of follow-up was 69 weeks.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Sweden **Retrospective study**		between (ICH or SAH) 2004-2008 who were being treated with warfarin with an INR>1.5 at the time of event. Median age was 76 years, 61% were male.	reviewed (n=177). These included patient characteristics, indication for warfarin treatment, risk score for stroke in patients with atrial fibrillation, additional antithrombotic treatment, and location of bleeding. From the follow-up period after ICH the outcomes and timing of outcomes of patients who resumed warfarin therapy were compared to those who did not. Data were collected through hospital records and family physician	TIA, venous thromboembolism and death	59 patients resumed warfarin treatment after a median of 5.6 weeks. 18 patients had a recurrent ICH. Of these, 8 patients had restarted warfarin. The overall risk of ICH recurrence associated with resumption of warfarin use was significantly increased (HR=5.57, 95% CI 1.80-17.25, p=0.003). The risk of recurrent ICH associated with resumption of warfarin by time was; 1-35 days, HR=4.13; 36-63 days, HR=4.46, ≥64 days: not estimable as there were no ICHs in the sample. The authors suggested the optimal time to restart warfarin following ICH is between 10- and 30-weeks post event, given a treatment horizon of 3 years
Statins					
Ziff et al. 2019 **UK** **Systematic review & meta-analysis**	All of the observation studies had a risk of bias, across ≥1 domain. Among the RCTs, 5 were at low risk of bias across all domains.	51 studies (15 RCTs, 36 observational), including 1 324 450 patients with a previous ischemic or hemorrhagic stroke. Mean/median age ranged from 60.3 to 86.8 years.	The outcomes of patients taking a statin (47.1% of sample) were compared with those on placebo (52.8%).	**Primary outcome:** ICH **Secondary outcomes:** Ischemic stroke, any stroke, all-cause mortality and poor functional outcome	Average length of follow-up was 1.7 years. Patients receiving statins had significantly more diabetes, hypertension, hyperlipidemia and coronary artery disease than controls and were more often receiving anticoagulant and antiplatelet drugs. In patients with previous ICH (n=15 studies), statins did not significantly increase the risk of recurrent ICH (RR=1.04, 95% CI 0.86 to 1.25). The risks of all-cause mortality and poor functional outcome were reduced significantly with statin therapy (RR=0.49, 95% CI 0.36-0.67 and RR=0.71, 95% CI 0.67-0.75). In patients with previous ischemic stroke (n=29 studies), statins did not significantly increase the risk of recurrent ICH (RR=1.36, 95% CI 0.96 to 1.96). The risks of recurrent ischemic stroke, any stroke, all-cause mortality and poor functional outcome were all reduced significantly with statin therapy.

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Ribe et al. 2019 **Denmark** **Retrospective study**	NA	All individuals living in Denmark since 1980 who were alive on January 2004, ≥50 years, with no history of stroke since 1995.	The outcomes of persons who initiated statin therapy (n=519,894) were compared with those who never initiated statin therapy (n=1,222,185) for primary stroke prevention, were examined using a propensity score matched design	**Primary outcome:** ICH	The mean number of days spent at risk in the study was 1,330.2 days for statin users and 1,416.2 days for non-users. Participants were followed for up to 10 years. Over the study period, the risk of ICH was significantly lower among statin users (0.25% vs. 0.03%, HR=0.85, 95% CI 0.80-0.90). Statin users and non-users had similar ICH risk during the first six months after statin initiation (HR=0.98, 95% CI: 0.80–1.21); however, beyond 6 months, statin users had a significantly lower risk of stroke (6 months-1 year, HR=0.65, 95% CI 0.55–0.78;1-2 years, HR= 0.78, 95% CI 0.69–0.90; 2-10 years, HR= 0.72, 95% CI: 0.66–0.78) in models adjusted for age, sex, and calendar period, socioeconomic position, comorbidity.
McKinney & Kostis 2012 **USA** **Meta-analysis**	NA	31 RCTs (n=182,803 patients) examining the use of statins for stroke prevention that reported the risk of ICH as on outcome. Mean age of patients was 62.6 years, 67% were male. Mean baseline LDL chol for both groups was 137±25 mg/dL	Trials comparing high vs. low-dose statins (n=6) and any statin vs. control or usual care (n=25 trials).	**Primary outcomes:** ICH, total stroke rate and all-cause mortality	Mean duration of follow-up was 46±18 months Using the results from all trials, any statin use was not associated with a significantly increased risk of ICH (0.39% vs. 0.35%, OR=1.08, 95% CI 0.88-1.32, p=0.47). In subgroup analysis of primary prevention trials (n=14) the risk of ICH was not significantly increased with statin use (OR=0.86, 95% CI 0.75-1.23, p=0.77). In the analysis including secondary prevention studies, statin therapy was not associated with a significant increase in the risk of ICH (OR=1.26, 95% CI 0.91-1.73, p=0.54)
Hakam et al. 2011 **Canada** **Meta-analysis**	NA	42 studies (23 RCTs [48% primary prevention; 52% secondary prevention] and 19 observational studies) including 248,391 participants.	Studies examined the use of statins for stroke prevention and included the risk of ICH as on outcome.	**Primary outcome:** ICH	Among the RCTs, there was 526,518 patient-years of follow-up. Median follow-up per trial was 3.9 years. Statins were not associated with an increased risk of ICH (RR=1.10; 95% CI 0.86 –1.41). Among the 12 cohort studies, there was 219,459 patient-years of follow-up. Median follow-up was 3.0 years; Statins were not associated with an increased risk of ICH (RR=0.94, 95% CI 0.81-1.10)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Among the 6 case-control studies, the risk of ICH was not increased significantly (RR=0.60; 95% CI 0.41– 0.88).
Baigent et al. 2010 **UK** **Systematic review & meta-analysis** **Cholesterol Treatment Trialists (CTT)**	NA	26 RCTS in which the treatment aim was solely the reduction of LDL cholesterol, sample sizes of at least 1,000 were used and treatment was continued for at least 2 years. All trials included both men and women. In 14 trials, none of the participants had prior vascular diseases.	Evaluation of more intensive vs. less intensive regimens of statin therapy (5 trials, n=39,612) and the effectiveness of statin therapy vs. control condition (21 trials, n=129,536) Treatment contrasts (dose of statin) in the more vs. less intensive trials were: 80 vs. 40 mg, 80 vs. 20 mg, 80-10 mg, 40-80 mg vs. 20-40 mg Treatment contrasts in the statin vs. control trials ranged from 10-80 mg statin. Control conditions were placebo, usual care and no treatment	**Primary outcomes:** Cause-specific mortality, major coronary event (coronary death or non-fatal myocardial infarction), coronary revascularization (angioplasty or bypass grafting), or stroke	**More intensive vs. less intensive statin therapy (n=5 trials)** Median duration of follow-up was 5.1 years. The mean reduction in LDL cholesterol was 0.51 mmol/L. There was a significant reduction in the risk of stroke (RR=0.72, 95% CI 0.66-0.78, p<0.0001). The rate ratio (RR) associated with each 1 mmol/L reduction in LDL-chol, for hemorrhagic stroke was 1.39 (95% CI 0.70 − 2.74, p=0.30 **Statin vs. Control (n=21 trials)** Median duration of follow-up was 4.8 years. In these trials, the mean reduction in LDL cholesterol was 1.07 mmol/L. The rate ratios (RR) associated with each 1 mmol/L reduction in LDL-chol, for hemorrhagic stroke was 1.10, 95% CI 0.91 − 1.34, p=0.30 (n=15 trials). Overall, the risk reduction of hemorrhagic stroke was not significantly reduced (RR= 1.12, 95% CI 0.93 − 1.35, p=0.20, n=20 trials).
Amarenco & Labreuche 2009 **France** **Meta-analysis**	NA	24 RCTs (n=165,792 patients) including participants aged ≥18 years, with masked assessment of outcomes, with at least 1,000 patients enrolled and data were available for stroke events. Mean age of patients was 63 years, 73% were male	Trials comparing high vs. low-dose statins and any statin vs. control or usual care for stroke prevention	**Primary outcomes:** All stroke, fatal stroke and hemorrhagic stroke events	Mean duration of follow-up ranged from 0.3-6.7 years. There were 137 hemorrhagic strokes among patients in the active treatment group and 171 in patients in the control group. Using the results from 11 trials, statin therapy was not associated with a significant reduction in the risk of hemorrhagic stroke (RR=1.03, 95% CI 0.75-1.41). In subgroup analysis using the results from 2 secondary prevention trials (SPARCL and HPS-including patients with prior cardiovascular disease), statin therapy was associated with a significantly

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					increased risk of hemorrhagic stroke (RR=1.73, 95% CI 1.19-2.50). In subgroup analysis of primary prevention studies (n=9), statin use was not associated with a significant reduced risk of hemorrhagic stroke (RR=0.81, 95% CI 0.60-1.08)
Amarenco et al. 2006 ***Stroke Prevention by Aggressive Reduction in Cholesterol (SPARCL)*** **Goldstein et al. 2008** **International** **RCT**	Concealed Allocation: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	4,732 individuals with previous stroke/TIA (ischemic or hemorrhagic) that occurred 1 – 6 months prior to enrolment, and with LDL between 2.6-4.9 mmoL/L and no known history of coronary heart disease. The mean age at baseline was 63 years. 60% were male.	Participants were randomly assigned to receive either 80 mg/day atorvastatin or matching placebo for the duration of the study. Patients were assessed at 1, 3 and 6 months then every 6 months thereafter.	**Primary outcome:** Fatal or nonfatal stroke events. **Secondary outcomes:** Stroke or TIA, major coronary event, major cardiovascular event, acute coronary event, any coronary event, revascularization procedure, or any cardiovascular event	The median duration of follow-up was 4.9 years. LDL-chol was decreased from 3.43 to 1.58 mmol/L, for persons in the atorvastatin group but was unchanged for those in the placebo group (3.45 mmol/L). There were fewer fatal/nonfatal strokes among persons in the atorvastatin group (11.2% vs. 13.1%, p=0.05). The associated 5-year absolute risk reduction was HR=0.84, 95% CI 0.71-0.99, p=0.03. The risk of hemorrhagic stroke was higher for patients in the statin group (55 vs. 33, HR=1.66 95% CI 1.08-2.55, p=0.020). **Additional reporting (Goldstein et al.)** Independent risk factors for hemorrhagic stroke included treatment with atorvastatin (HR=1.69, 95% CI 1.10-2.60, p=0.02), male gender, previous hemorrhagic stroke and stage 2 HTN (HR=6.19, 95% CI 1.47-26.11, p=0.01)
***Heart Protection Study (HPS)* 2002** **UK** **RCT**	Concealed Allocation: ☑ Blinding: Patient: ☑ Assessor ☑ ITT: ☑	20,536 adults, 40–80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/Land considered to be at high-risk of death from coronary disease within the next 5 years due to a history of existing coronary disease, or occlusive disease of non-coronary arteries, or diabetes or treated hypertension.	Following a run-in treatment (4 weeks of placebo, then 4–6 weeks of a fixed dose of 40 mg simvastatin daily) participants were randomized to receive 40 mg of simvastatin or placebo for 5 years.	**Primary outcome:** All-cause mortality, mortality associated with CHD. **Secondary outcomes:** Non-coronary causes of death, major coronary events, major vascular events and coronary or non-coronary revascularizations and non-fatal or fatal strokes of any type	The mean duration of follow-up was 5 years. The average difference in LDL-chol levels between groups over the study period was -1.0 mmol/L (2.3 vs. 3.3 mmol/L). While treatment with simvastatin was associated with reduction in risk of any stroke (RR=0.75, 95% CI 0.66-0.85, p<0.0001), the incidence of hemorrhagic stroke was not significantly reduced (0.5% vs. 0.5%, RR=0.95, 95% CI 0·65-1.40 p=0·80).

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Lifestyle (Alcohol Consumption and Stroke Risk)					
O'Donnell et al. 2016 **Canada (International)** **INTERSTROKE Phase 2** **Case-control study**	NA	Participants were recruited from 32 countries from 2007-2015. Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women. 13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA)	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples. Alcohol use was classified as: never or former, low intake, moderate intake, and high (>14 drinks/week in women or >21 drinks/ week in men) or episodic heavy (>5 drinks in one episode at least once/month) intake	**Primary outcome:** The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)	Low or moderate ETOH intake was associated with significantly higher odds of stroke compared with former/never drinkers. The odds were highest for hemorrhagic stroke (OR=1.43, 99% CI 1.17-1.74) High or heavy episodic drinking was associated with significantly higher odds of hemorrhagic stroke compared with former/never drinkers (OR=2.44, 99% CI 1.64-3.63; PAR 9.8%, 99% CI 6.4-14.8%)
O'Donnell et al. 2010 **Canada (International)** **INTERSTROKE Phase 1** **Case-control study**	NA	Participants were recruited from 22 countries from 2007-2010. Cases were 3,000 persons admitted to hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% women 3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA)	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake, psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples. Alcohol intake was classified as never/former drinker, moderate drinker (1-30 drinks/month), >30 drinks/month or binge	**Primary outcome:** The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) Results were adjusted for age, sex, and region	Moderate alcohol consumption was associated with reduced risk of ischemic stroke and increased risk of hemorrhagic stroke compared with never/former drinkers. All stroke: OR=0.90, 99% CI 0.72-1.11, PAR 3.8%, 99% CI 0.9-14.4% Hemorrhagic stroke: OR=1.52, 99% CI 1.07-2.16, PAR 14.6%, 99% CI 8.5-24.0% >30 drinks/month or binge drinking was associated with an increased risk of stroke compared with never/former drinkers. All stroke: OR=1.51, 99% CI 1.18-1.92 Hemorrhagic stroke: OR=2.01, 99% CI 1.35-2.99

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
			drinker (>5 drinks/day at least once/month).		
Zhang et al. 2014 **China** **Systematic review & meta-analysis**	NA	27 prospective studies including 1,425,513 adult participants. 14 studies included only men, 3 included only women, 9 included both sexes and in one study the sex distribution was not reported	The risk of cardiovascular outcomes and ETOH consumption were explored across 4 exposure categories (no intake, low intake <15 g/day moderate 15-30 g/day and heavy). Information on ETOH intake was obtained using self-administered questionnaires and food frequency questionnaires.	**Primary outcome:** Total stroke, hemorrhagic stroke, ischemic stroke and stroke mortality	Duration of follow-up ranged from 6-35 years. Compared with no intake, the risks of hemorrhagic stroke given increasing levels of ETOH intake were not significantly increased: Low: RR=0.96, 95% CI 0.74-1.24 Moderate: RR=1.21, 95% CI 0.85-1.73 Heavy: RR=1.29, 95% CI 0.98-1.71 Low-to-moderate alcohol intake was not associated with hemorrhagic stroke risk, but an alcohol intake of ≥45 g/day was associated with an increased risk (p for non-linear trend=0.008)
Patra et al. 2010 **Canada** **Systematic review & meta-analysis**	NA	26 studies (cohort n=17 and 9 case-control), published from 1980-2009, were included.	The relationship between ischemic or hemorrhagic stroke and alcohol consumption (any vs. abstinence) was examined, as was a dose-response relationship. When number of drinks was reported, the conversion to grams was based on conversion factors that varied from 8-12 grams/serving.	**Primary outcome:** Sex-specific stroke mortality and morbidity	The risk of both hemorrhagic and ischemic stroke was j-shaped in women and linear in men. Risk of hemorrhagic stroke (women) 1 drink/day vs. none: mortality: RR=0.89, 95% CI 0.52-1.52, morbidity: RR=0.69, 95% CI 0.54-0.89, 7 drinks/day vs. none: mortality: RR=3.66, 95% CI 2.16-6.19, morbidity: RR=2.03, 95% CI 1.19-1.74. Risk of hemorrhagic stroke (men) 1 drink/day vs. none: mortality: RR=1.09, 95% CI 1.06-1.12, morbidity: RR=1.10, 95% CI 1.06-1.14 7 drinks/day vs. none: mortality: RR=1.79, 95% CI 1.48-2.15, morbidity: RR=1.91, 95% CI 1.47-2.47.
Lifestyle (Smoking and Stroke Risk)					
O'Donnell et al. 2016 **Canada (International)** **INTERSTROKE Phase 2**	NA	Participants were recruited from 32 countries from 2007-2015. Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical	**Primary outcomes:** The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)	Smoking was not associated with an increased risk of hemorrhagic stroke (OR=1.14, 99% CI 0.95-1.36, PAR 3.6%, 99% CI 0.9-13.0%)

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
Case-control study		stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women. 13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA)	examinations and blood and urine samples. Smoking status was classified as current or never/former		
O'Donnell et al. 2010 **Canada (International)** **INTERSTROKE Phase 1** **Case-control study**	NA	Participants were recruited from 22 countries from 2007-2010. Cases were 3,000 persons admitted to hospital within 5 days of acute stroke (78% ischemic stroke, 22% ICH). Mean age was 61 years. 37% women. 3,000 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA).	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, BMI, physical activity, alcohol intake, psychological stress, depression, diet) were collected using questionnaires, physical examinations and blood and urine samples. Smoking status was classified as current or never/former.	**Primary outcomes:** The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR) Results were adjusted for age, sex, and region	Smoking was associated with an increased risk of stroke. All stroke: OR=2.09, 99% CI 1.75-2.51, PAR 18.9%, 99% CI 15.3-23.1% Hemorrhagic stroke: OR=1.45, 99% CI 1.07-1.96, PAR 9.5%, 99% CI 4.2-20.0%
Peters et al. 2013 **Australia & US** **Systematic review & meta-analysis**	NA	81 prospective cohort studies, published from 1966-2013, including the results from, 3,980,359 persons, reporting sex-specific risk of current smoker vs. non-smokers.	Dose-response relationship (<10, 10-20, >20) and stroke subtype (ischemic vs. hemorrhagic) were also examined.	**Primary outcomes:** Combined fatal/nonfatal incident stroke, expressed as relative risk (RR) and a ratio of RR in women/men (RRR). Variables adjusted for in the individual studies included: age, race, education blood pressure, diabetes, serum cholesterol, alcohol intake, physical activity.	Duration of the included studies ranged from 6-40 years. There were 42,401 strokes. The prevalence of current smoking ranged from 8% to 59% in men and from 1% to 51% in women. Most studies reported higher smoking rates among men. The risk of stroke was higher in current smokers compared with non-smokers. Women: RR=1.83, 95% CI 1.58-2.12 Men: RR=1.67, 95% CI 1.49-1.88 The risk was not significantly different between the sexes (RRR=1.06, 95% CI 0.99-1.13, p=0.10). The risk of stroke was higher in former smokers compared with never smokers:

Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings and Recommendations
					Women: RR=1.17, 95% CI 1.12-1.22 Men: RR=1.08, 95% CI 1.03-1.13 The risk was not significantly different between the sexes (RRR=1.10, 95% CI 0.99-1.22) The risk of stroke was higher in women who smoked >20 cigarettes/day compared with men: <10 cigs: RRR=0.94, 95% CI 0.67-1.22 10-20 cigs: RRR=0.91, 95% CI 0.67-1.22 >20 cigs: RRR=1.31, 95% CI 1.00-1.72 The risk of hemorrhagic stroke was significantly increased in women who smoked compared with men who smoked (RRR=1.17, 95% CI 1.02-1.34, p=0.02).
Lifestyle (Physical Activity and Stroke Risk)					
O'Donnell et al. 2016 **Canada (International)** **INTERSTROKE Phase 2** **Case-control study**	NA	Participants were recruited from 32 countries from 2007-2015. Cases were 13,447 persons admitted to hospital within 5 days of first acute stroke and 72 hours of admission to hospital (77% ischemic stroke, 23% ICH). Mean age was 62.2 years. 40.4% of cases were women. 13,472 controls were matched for age and sex and were recruited from the community or hospitals (in-patient or outpatient, unrelated to treatment for stroke or TIA)	All key vascular risk factors (hypertension, DM, smoking, waist-to-hip ratio, diet, physical activity, alcohol intake, psychosocial factors, cardiac causes and ApoB:ApoA1) were collected using questionnaires, physical examinations and blood and urine samples. Physically active individuals were defined as being regularly involved in moderate or strenuous leisure activity ≥ 4 h or more per week.	**Primary outcomes:** The odds of all stroke, ischemic stroke and intracerebral hemorrhagic stroke (ICH) and population attributable risk (PAR)	Compared with persons who were not physically active, the risk of ICH was significantly lower among those who were (OR=0·63, 99% CI 0·48 to 0·81, PAR=34·6, 99% CI 21·3 to 50·7).

Abbreviations

CI Confidence interval	ICH Intracerebral hemorrhage
ITT Intention-to treat analysis	N/A Not assessed
OR Odds Ratio	PAR Population Attributable Risk
RCT Randomized controlled trial	

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