Non-traumatic intracerebral hemorrhage in young adults

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Disclosures :

- Dr. Tatlisumak serves/has served on scientific advisory boards for Bristol Myers Squibb, Inventiva Pharma, and Portolo Pharm. He has received speaker's honorarium from Argenx.
- Has given lectures at educational activities arranged or sponsored by pharmaceutical industry and has organized several academic educational activities / conferences which received support from pharmaceutical industry.
- Dr. Tatlisumak has received research support from the Sigrid Juselius Foundation, European Union, Sahlgrenska University Hospital, University of Gothenburg, and Wennerström's Foundation. He has been granted international patents: new therapeutic uses (method to prevent brain edema and reperfusion injury) and thrombolytic compositions (method to prevent post-thrombolytic hemorrhage formation).
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This lecture is largely based on the systematic review article:

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“with repeated updates”

Nontraumatic intracerebral haemorrhage in young adults

Turgut Tatlisumak[1,2], Brett Cucchiara[3], Satoshi Kuroda[4], Scott E. Kasner[5] and Jukka Putaala[2]*

Abstract | Nontraumatic intracerebral haemorrhage (ICH) is a common subtype of stroke with a poor prognosis, high mortality and long-term morbidity. The incidence of ICH increases with age. ICH has not been widely investigated in young adults (herein defined as aged ~18–50 years) despite an annual incidence of ~5 per 100,000 individuals. Furthermore, ICH characteristics differ between young and elderly patients. Risk factors for ICH are surprisingly common in young adults, in whom ICH is often caused by structural lesions or hypertension, and only rarely by anticoagulation therapy and cerebral amyloid angiopathy (which are common predisposing factors in elderly patients). High short-term mortality (17% at 3 months) and long-term mortality (>25% at 10 years) persist even in contemporary series from high-income countries, and long-term disability is very common. Thus, an aggressive approach to identifying treatable underlying conditions and preventing ICH recurrence is indicated in young patients, although treatment strategies have generally not been investigated specifically in this age group. This narrative Review summarizes existing knowledge on the epidemiology, risk factors, causes, diagnosis, treatment and outcomes of ICH in young adults. We provide comparisons with the population of elderly patients with ICH and discuss challenges for future research.

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Nontraumatic intracerebral haemorrhage (ICH) in young adults is an uncommon but dreaded disease. A young adult patient with ICH is usually defined as aged between 18 years and 50 years, although the precise age range differs between studies and experts. ICH in young adults differs from that in older individuals in several respects, including the spectrum of risk factors, triggers and underlying causes. Furthermore, death or permanent disability is surprising and highly devastating in young and otherwise healthy individuals — who are often building a career and establishing a family, might have small children to look after or might even be pregnant at the time of ICH. Even among patients with fair recovery, many will not be able to return to work. Apart from the economic and social consequences for the patient, ICH in young adults can also generate high costs for society associated with either early retirement from work owing to illness or disability or the need for permanent institutional care.

Several excellent reviews have been published on ICH in general populations of patients[1–3]. However, nontraumatic ICH in young adults differs from that in elderly individuals in several key respects, and in-depth guidance for physicians on the approach to diagnosis and treatment of ICH in young adults is lacking. Such guidance is long overdue as, to the best of our knowledge, this narrative Review is the first on this topic to be published in the English language. Several excellent reviews are also available on individual diseases associated with ICH in young adults, such as arteriovenous malformations[4], cerebral venous thrombosis[5], moyamoya vasculopathy[6] and cerebral vasculitides[7]. However, these articles lack a holistic focus on the young adult who presents with ICH. This comprehensive Review addresses several points where crucial evidence-based data are missing; we hope that drawing attention to these areas will help to stimulate future research. Most novel data in the field of ICH in young adults have come from genetic studies, which have found numerous previously unknown genetic loci linked to ICH-causing diseases. Large collaborative teams are also conducting comprehensive genome-wide association studies in patients with ICH. These studies are likely to bring novel insights to disease mechanisms that could, in the long run, change clinical practice.

In this narrative Review, we provide a comprehensive overview of reported studies that investigated the epidemiology, risk factors, causes, diagnosis, management and outcomes of nontraumatic ICH in young adults. Most data on this topic come from the 13 largest

Why concept of ICH in young adults?

- Young adult non-traumatic ICH population is usually defined as patients between 18 and 50 years of age.
- The spectrum of risk factors, triggers, underlying causes, treatments, and outcomes differ from that in older subjects.
- Death (loss of life-years) or permanent disability (loss of quality-adjusted life-years) is more surprising and devastating in a young otherwise healthy individual who is often building a career, establishing a family, may have small children under his/her custody, mortgage, or may even be pregnant at the time of ICH.
- Even in cases with fair recovery, many patients will not be able to return to work and become sick-pensioned or remain unemployed.
- Apart from economic and social consequences to the patients and their families, the disease may also produce high costs to the society if followed by sick-retirement or permanent institutional care.

ICH guidelines deliver only very limited guiding for young patients

Guidelines

European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage

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Background **Intracerebral hemorrhage (ICH) accounted for 9% to 27% of all strokes worldwide in the last decade, with high early case fatality and poor functional outcome. In view of recent randomized controlled trials (RCTs) of the management of ICH, the European Stroke Organisation (ESO) has updated its evidence-based guidelines for the management of ICH.**
Method **A multidisciplinary writing committee of 24 researchers from 11 European countries identified 20 questions relating to ICH management and created recommendations based on the evidence in RCTs using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.**
Results **We found moderate- to high-quality evidence to support strong recommendations for managing patients with acute ICH on an acute stroke unit, avoiding hemostatic therapy for acute ICH not associated with antithrombotic drug use, avoiding graduated compression stockings, using intermittent pneumatic compression in immobile patients, and using blood pressure lowering for secondary prevention. We found moderate-quality evidence to support weak recommendations for intensive lowering of systolic blood pressure to <140 mmHg within six-hours of ICH onset, early surgery for patients with a Glasgow Coma Scale score 9–12, and avoidance of corticosteroids.**
Conclusion **These guidelines inform the management of ICH based on evidence for the effects of treatments in RCTs. Outcome after ICH remains poor, prioritizing further RCTs of interventions to improve outcome.**

Key words: anticoagulation, antiepileptic treatment, antihypertensive treatment, intracranial hemorrhage, intracranial pressure, management

Introduction

The worldwide burden of hemorrhagic stroke [i.e. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH)] has increased between 1990 and 2010 by 47%, as demonstrated in a systematic epidemiological review of 119 studies from high-, low-, and middle-income countries (1). In high-income countries, the incidence, mortality, disability adjusted life years (DALYs) lost, and mortality-to-incidence ratio decreased by 19%, 38%, 39%, and 27%, respectively (Fig. 1). In contrast, the incidence of hemorrhagic stroke increased by 6% in low- and middle-income countries, and the mortality rate decreased by 23%, DALYs lost by 25%, and mortality-to-incidence ratio by 36% (Fig. 1).

Guideline

EUROPEAN STROKE JOURNAL

European Stroke Journal
1–80

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Sage

European Stroke Organisation (ESO) and European Association of Neurosurgical Societies (EANS) guideline on stroke due to spontaneous intracerebral haemorrhage

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Abstract

Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) affects ~3.4 million people worldwide each year, causing ~2.8 million deaths. Many randomised controlled trials and high-quality observational studies have added to the evidence base for the management of people with ICH since the last European Stroke Organisation (ESO) guidelines for the management of spontaneous ICH were published in 2014, so we updated the ESO guideline. This guideline update was

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Stroke

AHA/ASA GUIDELINE

2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the Neurocritical Care Society

Steven M. Greenberg, MD, PhD, FAHA, Chair; Wendy C. Ziai, MD, MPH, FAHA, Vice Chair; Charlotte Cordonnier, MD, PhD; Dar Dowlatshahi, MD, PhD, FAHA; Brandon Francis, MD, MPH; Joshua N. Goldstein, MD, PhD, FAHA; J. Claude Hemphill III, MD, MAS, FAHA; Ronda Johnson, MBA; Kiffon M. Keigher, MSN, ACNP-BC, RN, SCRN; William J. Mack, MD, MS, FAHA*; J. Mocco, MD, MS, FAHA†; Eileena J. Newton, MD; Ilana M. Ruff, MD‡; Lauren H. Sansing, MD, MS, FAHA; Sam Schulman, MD, PhD; Magdy H. Selim, MD, PhD, FAHA; Kevin N. Sheth, MD, FAHA*§; Nikola Sprigg, MD; Katharina S. Sunnerhagen, MD, PhD; on behalf of the American Heart Association/American Stroke Association

Key Words: AHA Scientific Statements ■ cerebral amyloid angiopathy ■ cerebral hemorrhage ■ intracranial hemorrhage ■ prevention ■ recovery ■ treatment

TOP 10 TAKE-HOME MESSAGES FOR THE MANAGEMENT OF PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE GUIDELINE

1. The organization of health care systems is increasingly recognized as a key component of optimal stroke care. This guideline recommends development of regional systems that provide initial intracerebral hemorrhage (ICH) care and the capacity, when appropriate, for rapid transfer to facilities with neurocritical care and neurosurgical capabilities.
2. Hematoma expansion is associated with worse ICH outcome. There is now a range of neuroimaging markers that, along with clinical markers such as time since stroke onset and use of antithrombotic agents, help to predict the risk of hematoma expansion. These neuroimaging markers include signs detectable by noncontrast computed tomography, the most widely used neuroimaging modality for ICH.
3. ICHs, like other forms of stroke, occur as the consequence of a defined set of vascular pathologies. This guideline emphasizes the importance of, and approaches to, identifying markers of both microvascular and macrovascular hemorrhage pathogeneses.
4. When implementing acute blood pressure lowering after mild to moderate ICH, treatment regimens that limit blood pressure variability and achieve smooth, sustained blood pressure control appear to reduce hematoma expansion and yield better functional outcome.

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AHA Stroke Council Scientific Statement Oversight Committee members, see page e337.
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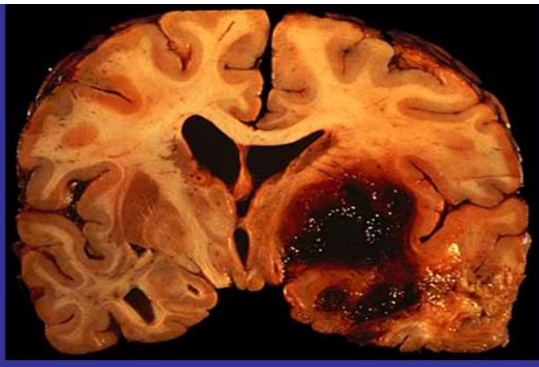
Epidemiology



- ICH forms 10–38% of all stroke among young adults (recent data from GBD suggest 28% globally)
- ICH:IS ratio is 1:1.5-2 in younger adults and decreases to 1:5-6 by aging
- Overall ICH incidence is approx. 25/100 000 person years
- <45 y: 2/100 000, increases to 10-fold at 45-54 years, and ~20-fold thereafter
- Overall incidence of ICH has not declined unlike ischemic strokes
- There is a significant increase in the incidence of ICH in young people (20-64 y) in low- and middle-income countries as well as among 18-44-yo people in the USA
- Prevalence of ICH doubled between 1990 and 2013 in this age group
- ICH is roughly double among Asians compared to black and white people. Indigenous nations (e.g. aboriginals in Australia) also have higher rates of ICH.

Risk factors of ICH in young adults

- It is not always clear whether a factor is a risk factor or cause
- A large number of risk factors exist for ICH, however, they are not explicitly studied in young people
- Hypertension (OR 5.7), diabetes (OR 2.4), menopause (OR 2.5), smoking (OR 1.6), alcohol over 2 drinks /day (OR 2.2), and caffeine in large amounts (OR 1.7) were associated with ICH in young adult Americans 18 to 49 years of age (Feldmann E et al, Stroke 2005)
- Another study reported cocaine use (OR 6), hypertension (OR 5.2), alcohol use (OR 1.9) as independent risk factors among 18-45 year-old African Americans (Qureshi A et al, Ethn Dis 2001)
- Several series of consecutive patients showed high frequencies of illicit drug use among young ICH patients
- Virtually only pregnancy and post-partum period are specific risk factors exclusive to the young adults
- Genetic factors likely play larger role among young patients than in the elderly

Etiological classification of ICH: SMASH-U

- Several etiological classifications for ischemic stroke (TOAST, ASCO-D, CCSS)
- Prior ICH classifications were e.g.: traumatic versus non-traumatic, spontaneous versus non-spontaneous, primary versus secondary, supratentorial vs infratentorial, deep (non-lobar or basal ganglionic) vs superficial (lobar, cortical), large vs small, regular- vs irregular-shaped, with or without intraventricular hemorrhage.
- We described a comprehensive classification system for ICH in over 1000 unselected ICH patients (SMASH-U, Meretoja A et al, Stroke 2012)
- S: Structural (3-mo mortality rate: 4%)
- M: Medication (54%)
- A: Amyloid angiopathy (22%)
- S: Systemic disease (44%)
- H: Hypertension (33%)
- -
- U: Undetermined (30%)
- SMASH-U showed high inter-rater agreement ($\varkappa$=0.89) and good correlation with 3-month mortality ($P < 0.001$) in ~1000 consecutive ICH patients with a 3-mo mortality rate of 32%
- Not yet validated specifically in young adult ICH patient populations
- A new version presented lately: “SMASH-UP” where P is standing for “posterior reversible encephalopathy syndrome/reversible cerebral vasoconstriction syndrome” (Sariyeva et al, JAHA 2024)

Studies (>20 patients & detailed descriptions) on ICH in young adults

Study	Country	Study period and setting	No of patients	Age, years	Male %	Lobar/Mixed/IVH %	Angio/MRI %	Causes (reported with accuracy enabled by the data presented)	Early mortality
Kalita, 2014	India	2001-2010 unicenter, retrospect	404[e]	16-50 (mean 41.6)	76.2%	16.6% NR 2.0%	NR NR	HTN 79.2%, coagulopathy 4.0% anticoagulants 3.5%, AVM 2.5%, CVT 2.2%, cavernoma 1.0%, mycotic aneurysm 0.7%, thrombocytopenia 0.7%, vasculitis 0.5%, liver cirrhosis 0.5% undetermined 9.2%	25.2% @1mo
Menon, 2023	India	2015-2020 unicenter, retrospect	344	18-50 (mean 42.9)	78.5%	13.1% NR 5.2%	NR	HTN 70%, the rest were undetermined cause tumors, traumas, vasc malformations, and coagulopathies were excluded	21.8%@90day
Koivunen, 2015	Finland	2000-2010 unicenter, retrospect	336[b]	16-49 (median 42)	59.5%	20.9% 19.4% 36.1%	60.7% 42.3%	HTN 25.0%, AVM 13.4%, cavernoma 10.7%, CVT 3.0%, illicit drugs 3.0%, liver disease 2.1%, vasculitis 1.8%, tumor 1.8%, hematologic malignancy 1.5%, anticoagulants/thrombolytics 1.5%, diabetic microangiopathy 1.2%, eclampsia 0.6%, essential thrombocythemia/thrombocyte dysfunction 0.6%, moyamoya 0.3%, von Willebrand's disease 0.3%, HELLP 0.3%, RCVS 0.3% epithelioid hemangioendothelioma 0.3%, capillary telangiectasia 0.3%, PRES 0.3%, undetermined 32.1%	14.9% in-hospital 16.4% @1mo 17.0% @3mo
Lai, 2005	Taiwan	2000-2001 unicenter, retrospect	296[b]	15-45 (mean 37.0)	75.7%	25.0% 2.0% 3.0%	30.7% NR	HTN 46.7%, vascular malformations (not specified) 16.9%, alcohol intoxication/smoking 8.8%, tumor 6.1%, coagulopathy 5.4%, other 1.7%, undetermined 14.5%	24.0% in-hospital
Chen, 2021	Taiwan	2009-2019 unicenter, retrospect	259	16-45 (mean 36.4)	70.7%	NR NR NR	NR NR	HTN 42.9%, structural vasculopathy 28.6%, undetermined 21.6%	18.1% 1-year mortality
Ruiz-Sandoval, 1999	Mexico	1986-1997 unicenter, retrospect	200[c]	15-40 (mean 27.0)	53.5%	55.0%, 1.5%, 4.0%	NR NR	AVM 33.5%, cavernoma 16.0%, HTN 11.0%, CVT 5.0%, illicit drugs 3.5%, preeclampsia 3.5%, undetermined 20.5%	12.5% in-hospital
Enriquez, 2020	Philippines	2014-2019, unicenter, retrospect	185	19-49 (mean 41.0)	71.9%	27.0%, NR, 1.1%	NR NR	HTN 73.0%, AVM/aneurysm 12.4%, sympathomimetic agents 7.6%, thrombocytopenia 2.2%, cancer 2.2%, anticoagulants 1.1%	8.7% in-hospital
Fuh, 1994	Taiwan	1986-1992 unicenter, retrospect	170[d]	15-45 (mean 34.5)	65.3%	41.8% 2.9% 5.3%	42.9% 0%	HTN 37.6%, AVM 20.0%, coagulopathy 7.5%, aneurysm 1.8%, alcohol intoxication 1.8%, illicit drugs 1.8%, moyamoya 1.2%, infective endocarditis 1.2%, preeclampsia/eclampsia 1.2%, tumor 0.6%, SLE 0.6%, undetermined 24.7%	34.1% in-hospital
Hassan, 2024	Somalia	2019-2022, unicenter, retrospective	168	16-50 (mean 35)	59%	35% NR 1.8%	NR	HTN 35.7%, CVT 15%, substance abuse 13.7%, AVM 6%, AC-treatment 4.2%, thrombolysis 2.4%, eclampsia 4.2%, cavernoma 1.8%, renal failure 3.6%, undetermined 13.7%	28% in-hospital
Del Brutto, 1999	Ecuador	1986-1996 unicenter, retrosp/prospect	151[e]	15-44 (mean 33.4)	60.9%	41.7% 2.6% 6.6%	41.1% 15.2%	HTN 39.7%, aneurysm 10.6%, AVM 9.9%, alcohol intoxication 4%, preeclampsia/eclampsia 3.3%, cavernoma 1.3%, anticoagulants 1.3%, endocarditis 0.7%, idiopathic thrombocytopenic purpura 0.7%, illicit drugs 0.7%, undetermined 27.8%	22.5% @1mo
Kirkman, 2012	UK	2006-2010 unicenter, prospect	111	18-40	58.6%	61.3% 3.6% NR	53.2% NR	AVM 10.8%, HTN 10.8%, aneurysm 9.0%, illicit drugs 9.0%, cavernoma 7.2%, head trauma 7.2%, hemorrhagic infarction 5.4%, vasculitis 4.5%, CVT 1.8%, pregnancy 3.6%, tumor 3.6%, coagulopathy 2.7%, undetermined 27.0%	8.1% @1mo
Gedansky, 2019	USA	Unicenter, retrospect	110	18-50 (median 45.0)	62.7%	NR NR NR	12.7% NR	HTN 82.7%, AVM+cavernoma 5.5%	20.9%, in-hospital
Awada, 1998	Saudi Arabia	1981-1995 multicenter, retrospect	107[f]	0.5-45 (mean 28.6)	64.5%	61.7% 2.8% NR	54.2% 9.3%	AVM 23.4%, HTN 19.6%, coagulopathy 15.9%, aneurysm 8.4%, blood malignancy 8.4%, coagulation factor deficiency 2.8%, pregnancy/delivery 2.8%, vasculitis 0.9%, liver disease 1.9%, ITP 1.9%, DIC 0.9%, endocarditis 0.9%, illicit drugs 0.9%, brain tumor 0.9%, undetermined 26.2%	27.1% in-hospital
Rutten-Jacobs, 2014	Netherlands	1980-2010, unicenter, prospect	98[a]	18-50 (mean 38.0)	50.0%	59.0% NR	NR NR	HTN 26.8%, AVM 21.6%, cavernoma 5.2%, medication 5.2%, coagulopathy 3.1%, illicit drugs 2.1%, septic embolism 1.0%, multiple	20.4% @1mo

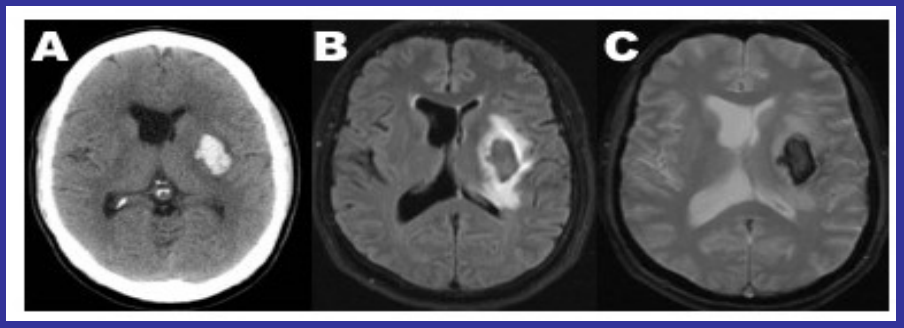
Etiologic characteristics of ICH in young adults: data from 19 large studies

- We found 19 large studies (including over 20 patients; only 1 was a multicenter study) with altogether 3250 patients (66% males)
- Largest series included 404, 344, and 336 patients
- Significant differences in methodologies and age distribution between studies
- Hypertension seems to be the leading cause in Indian and Asian patient populations whereas structural lesions (particularly AVM) lead (or are equal to hypertension) among white people
- Cavernous angioma was the most common cause of brainstem ICH in one study (Ruiz-Sandoval JL et al, Stroke 1999)
- Amphetamines and cocaine were the most common illicit drugs reported
- The proportion of undetermined etiology ranged between 0% and 41% with a mean of 22% (including patients who died before diagnostic studies could be completed)
- In general, the better the patients were investigated, the higher the chances to find a definite cause
- Simultaneous multiple ICH were found in ~6% (half of that in the unselected ICH populations). Lesser usage of AC agents and extreme rarity of amyloid angiopathy likely explain this difference

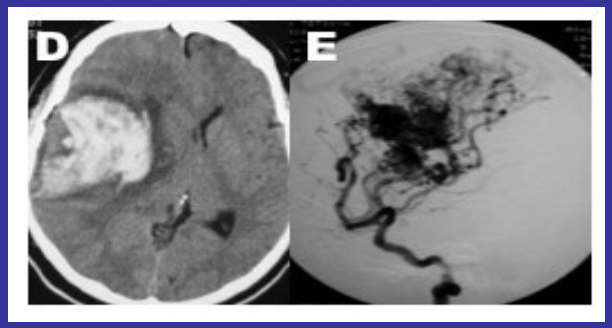
Causes of ICH in young adults reported in the literature grouped according to SMASH-U*

STRUCTURAL LESIONS	**Arteriovenous malformation, aneurysm (and associated diseases such as fibromuscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome, polycystic kidney disease), cavernoma, venous angioma (developmental venous anomaly), dural arteriovenous fistula, capillary telangiectasia, moyamoya vasculopathy, primary and secondary (metastatic) tumors of the central nervous system, von Hippel-Lindau disease, developmental venous anomalies, dolichoectasia, intracranial dissection**
MEDICATION	**Anticoagulants, antiplatelets, thrombolytics, SSRIs, illicit drug abuse (amphetamine, methamphetamine, cocaine, crack, heroin, phencyclidine, methadone, ephedrine, pseudoephedrine, phenylpropanolamine, pentozocine)**
AMYLOID ANGIOPATHY	**Icelandic and Dutch forms of hereditary cerebral hemorrhage with amyloidosis**
SYSTEMIC DISEASE	**Severe liver disease, renal insufficiency, glomerulonephritis, HIV/AIDS, endocarditis/septic embolism, pregnancy and post-partum period, eclampsia, vasculitides, RCVS, PRES, CVT, connective tissue disorders, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease), lightning stroke, heat stroke, hematological diseases and coagulopathies (severe anemias, hemophilia, leukemia, lymphoma, von Willebrand's disease, thrombocytopenias, polycythemia vera, sickle-cell disease, DIC), snake venom**
HYPERTENSION	**Primary and secondary (e.g. pheochromocytoma)**
UNDETERMINED	**No clear cause could be detected after adequate investigations or the patient could not be properly investigated**

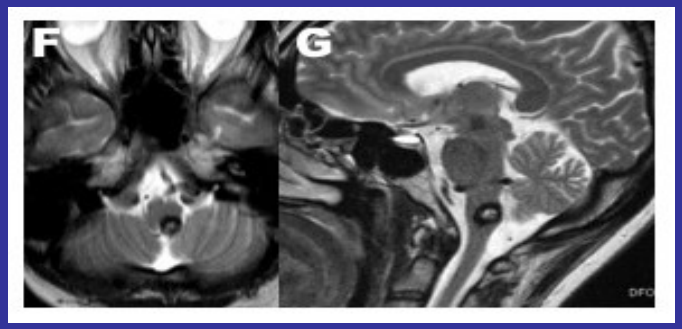
* SMASH-U classification of non-traumatic ICH (Meretoja A et al, Stroke 2012)



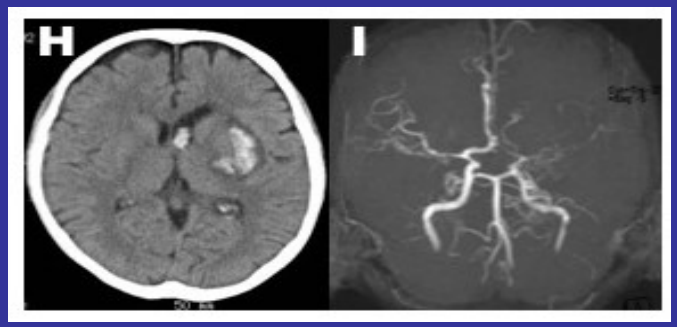
Hypertensive hemorrhage. Computed tomography demonstrated a fresh deep left putaminal ICH in a 43-year-old male with untreated hypertension (A). MRI shows a single solid hematoma with early-developing edema in FLAIR (B) and T2* images (C) and no other old or new hemorrhages. No other etiology or risk factors could be detected. Electrocardiogram showed left ventricular hypertrophy.



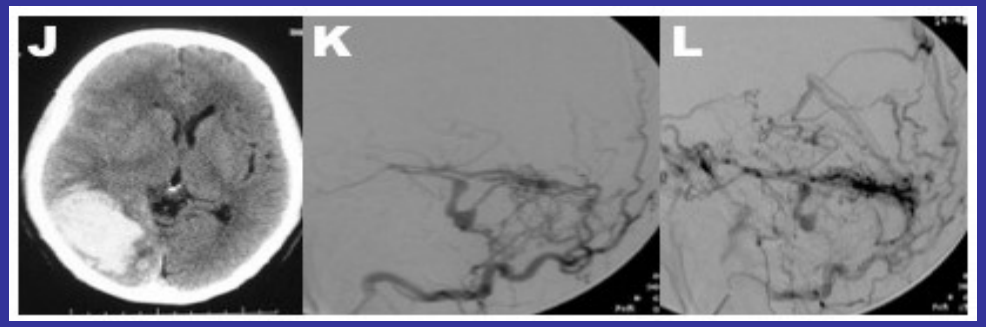
Arteriovenous malformation. 25-year-old male with massive right frontal ICH (D). Cerebral angiography demonstrates a large vascular nidus in the same territory (E). The arteriovenous malformation is fed by middle cerebral and middle meningeal arteries (E). He underwent acute hematoma evacuation and later to extirpation of arteriovenous malformation.

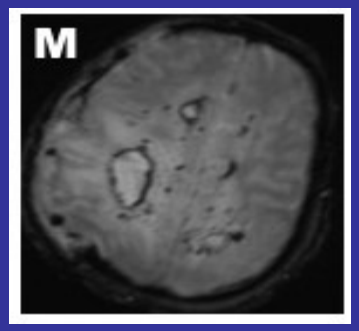


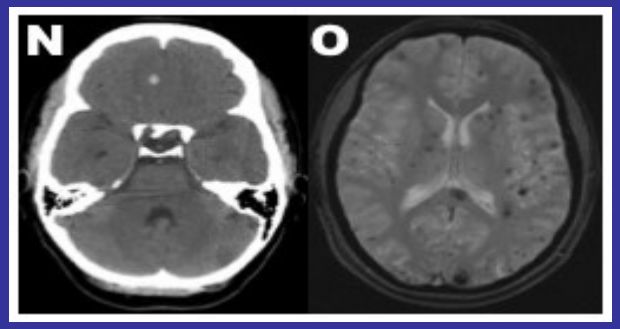
Cavernoma. A 48-year-old woman with ICH in medulla oblongata caused by a cavernoma (F and G).

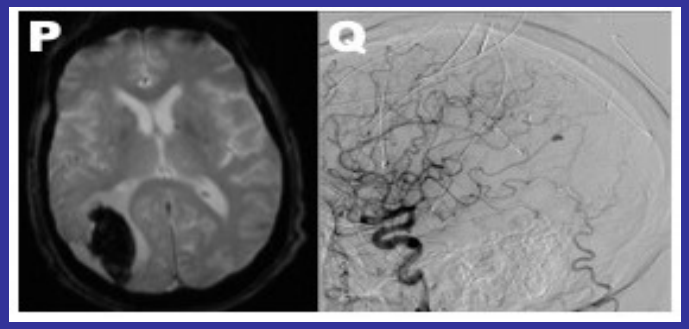


Moyamoya. A 28-year-old female developed left putaminal hemorrhage (H). MR angiography revealed left-sided unilateral moyamoya angiopathy (I).







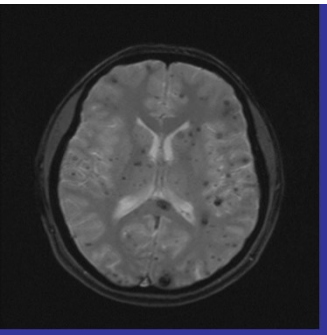


AV fistula. 42-year-old man with massive right temporo-occipital ICH (J). Cerebral angiography disclosed a dural AV-fistula between the right occipital artery and transverse-sigmoid sinus (K). Note the aggressive retrograde drainage into the vein of Labbe and superficial middle cerebral veins (L).

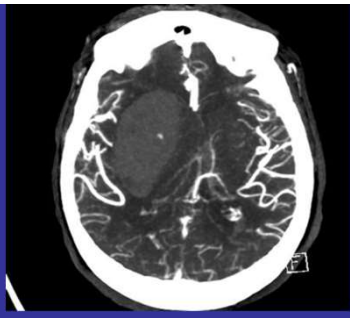
Cerebral vasculitis. Biopsy-proven in a young woman presenting with multiple bilateral ICHs on susceptibility-weighted MRI (M).

Cavernomatosis. A 36-year-old woman arriving with severe headache and vomiting and with 2 small ICHs in brain CT imaging (N). MRI shows hundreds of cavernomas with the typical moth-eaten brain appearance (O). She developed similar episodes later. Family history was negative for ICH.

Endocarditis and mycotic aneurysm. A young man with history of intravenous drug abuse came with a right parietal ICH (P) and found to harbor a mycotic aneurysm in cerebral angiography (Q). The underlying cause was endocarditis.



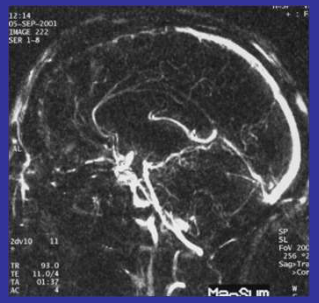
Diagnostics - 1



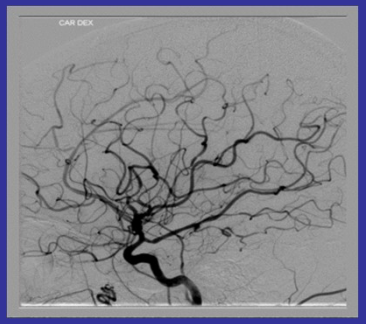
- The clinical presentation of ICH in a young patient reflects the underlying cause, location(s), and volume of the bleeding - as in older patients.
- Some data suggest that the younger the age the less severe the neurological symptoms/signs, which might reflect the larger proportion of structural causes.
- Routine laboratory testing on admission should include complete blood count, glucose, electrolytes, renal and liver function tests, CRP, PT with INR, APTT.
- Specific coagulation and toxicology studies should be done in selected patients.
- A positive toxicology screen should not be considered a definitive exclusive explanation for the ICH (many with active illicit drug use also harbor an alternative ICH cause).
- Blood cultures: if there is a clinical suspicion for infectious endocarditis.
- An electrocardiogram should be performed to screen for left ventricular hypertrophy, another indicator of chronic hypertension-related end-organ damage, and to evaluate for other concomitant cardiac comorbidities.
- Chest x-ray?

Clinical features suggesting potential underlying cause of ICH

Clinical history or examination finding	Possible ICH mechanism	Diagnostic testing
Illicit drug use (amphetamines, cocaine, other stimulants)	Induced hypertensive ICH Drug-associated toxic vasculopathy/vasculitis Reversible cerebral vasoconstriction syndrome	Urine toxicology screen
Injectable illicit drug use	Infectious endocarditis	Urine toxicology screen Blood cultures
Sickle cell disease	Moyamoya syndrome	Hemoglobin electrophoresis
Headache for days to weeks preceding acute presentation	Cerebral vein thrombosis Hemorrhagic brain tumor/metastasis Reversible cerebral vasoconstriction syndrome	Advanced imaging
History of VTE or hypercoagulability	Cerebral vein thrombosis	Advanced imaging
Current or former malignancy	Hemorrhagic brain tumor/metastasis	Advanced imaging
Migraine with aura with stereotyped aura localizing to anatomic region where ICH occurred	Arteriovenous malformation	Advanced imaging
Prior history of hemorrhage in same location	Cavernoma	Advanced imaging
Fever at presentation or recent/concurrent bacterial infection	Infectious endocarditis	Sedimentation rate Blood cultures
Family history of ICH	Familial cavernoma syndrome Hereditary hemorrhagic telangiectasias COL4A mutations	Genetic testing and counselling
Younger age, lobar/posterior fossa location, absence of small vessel disease	Arteriovenous malformation	Advanced imaging
Pulsatile tinnitus or bruit	Arteriovenous fistula Cerebral venous thrombosis	Advanced imaging
Hemophilia or other inherited coagulopathy	ICH associated with coagulopathy	PT/APTT Specialized coagulation testing
Anticoagulant use	ICH predisposed by anticoagulation or due to acquired coagulopathy	PT/APTT, thrombin time, INR, anti-Factor Xa level, specific concentration assays



Diagnostics - 2



- Neuroimaging is the cornerstone of ICH diagnostics.
- CT is preferable in the ER and MRI when time constraints are less important.
- Many perform hyperacute CTA/CTV immediately after identification of an ICH on non-contrast head CT. Alternatively, MRA/MRV combined with brain MRI.
- CT has ≥ sensitivity for acute ICH compared to MRI.
- Advantages of an MR-based imaging strategy include the ability to identify cavernomas and chronic microhemorrhages, underlying mass lesions such as tumors, better characterization of microvascular disease burden, and the ability to visualize thrombus directly in the venous sinuses or cortical veins.
- MRI is logistically much more challenging to obtain at most centers, especially in acute setting, and more susceptible to motion artifact in uncooperative patients.
- Both CTA and MRA have good sensitivity (~95%) for identification of AVMs compared to catheter angiography. They are also very sensitive for identification of cerebral venous thrombosis.

Diagnostics - 3

- Non-invasive studies are less reliable for identifying reversible cerebral vasoconstriction syndrome (RCVS), an important and increasingly recognized cause of ICH in young patients.
- Both false-negative and false-positive studies for RCVS are seen with CTA and MRA.
- Dural AV-fistulas may also frequently be missed on non-invasive vascular imaging.
- Most experts recommend catheter angiography in young patients with unexplained ICH and negative non-invasive vascular imaging.
- This includes patients with subcortical ICH, as young patients have a high rate of harboring an alternative mechanism even with ICH in this location. In one series of 200 young patients with ICH, 37% with subcortical basal ganglia hemorrhage had a specific non-hypertensive cause identified *(Ruiz-Sandoval JL et al, Stroke 1999)*.
- Whether and in which patients with comprehensive but negative initial imaging angiography should be repeated, is a common clinical dilemma. Vascular malformations may be compressed by mass effect from the acute hematoma and therefore not seen on initial angiography, but become apparent 4-8 weeks later. Patients with RCVS may have initially normal angiography which becomes abnormal on repeat study 3-7 days later.

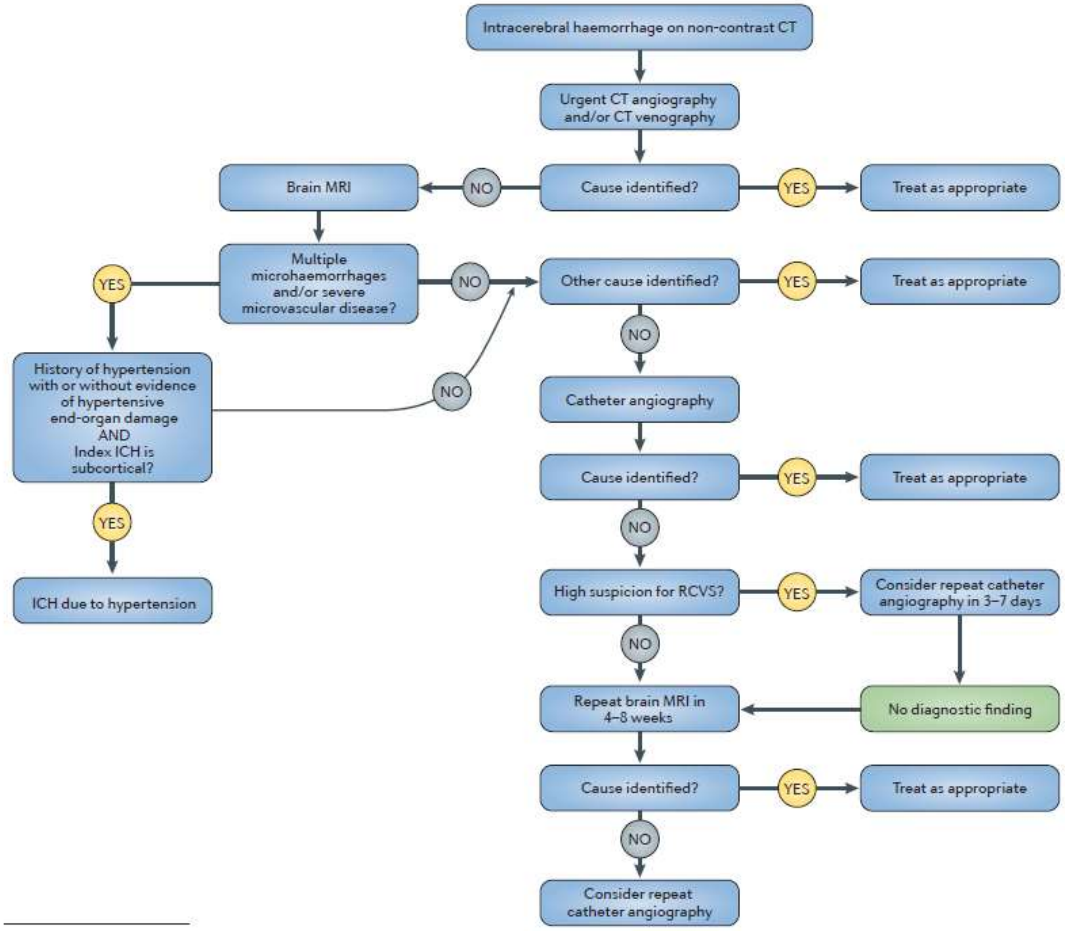


Figure 1 | **An approach to the diagnosis of intracerebral haemorrhage in young adults (aged 18–50 years).** ICH, intracerebral haemorrhage; RCVS, reversible cerebral vasoconstriction syndrome.

Tatlisumak T, Cucchiara B, Kuroda S, Kasner SE, Putaala J. Nature Rev Neurology, 2018

4.2. Diagnostic Assessment for ICH Pathogenesis

Recommendations for Diagnostic Assessment for ICH Pathogenesis Referenced studies that support recommendations are summarized in Data Supplement 15.

COR	LOE	Recommendations
1	B-NR	1. In patients with lobar spontaneous ICH and age <70 years, deep/posterior fossa spontaneous ICH and age <45 years, or deep/posterior fossa and age 45 to 70 years without history of hypertension, acute CTA plus consideration of venography is recommended to exclude macrovascular causes or cerebral venous thrombosis.[117,118]
1	B-NR	2. In patients with spontaneous IVH and no detectable parenchymal hemorrhage, catheter intra-arterial digital subtraction angiography (DSA) is recommended to exclude a macrovascular cause.[119]
1	C-LD	3. In patients with spontaneous ICH and a CTA or magnetic resonance angiography (MRA) suggestive of a macrovascular cause, catheter intra-arterial DSA should be performed as soon as possible to confirm and manage underlying intracranial vascular malformations.[117,118,120–122]
2a	B-NR	4. In patients with (a) lobar spontaneous ICH and age <70 years, (b) deep/posterior fossa ICH and age <45 years, or (c) deep/posterior fossa and age 45 to 70 years without history of hypertension and negative noninvasive imaging (CTA±venography and MRI/MRA), catheter intra-arterial DSA is reasonable to exclude a macrovascular cause.[117,118,120–122]
2a	B-NR	5. In patients with spontaneous ICH with a negative CTA/venography, it is reasonable to perform MRI and MRA to establish a nonmacrovascular cause of ICH (such as CAA, deep perforating vasculopathy, cavernous malformation, or malignancy).[118,123,124]
2a	C-LD	6. In patients with spontaneous ICH who undergo CT or MRI at admission, CTA plus consideration of venography or MRA plus consideration of venography performed acutely can be useful to exclude macrovascular causes or cerebral venous thrombosis.[118]
2b	C-LD	7. In patients with spontaneous ICH and a negative catheter intra-arterial DSA and no clear microvascular diagnosis or other defined structural lesion, it may be reasonable to perform a repeat catheter intra-arterial DSA 3 to 6 months after ICH onset to identify a previously obscured vascular lesion.[125]

Greenberg et al, AHA Guidelines for spontaneous ICH 2022

Cerebrovascular disease
Research paper

Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score

Nina A Hilkens [1], Charlotte J J van Asch [2, 3], David J Werring [4], Duncan Wilson [4], Gabriël J E Rinkel [2], Ale Algra [1, 2], Birgitta K Velthuis [5], Gérard A P de Kort [5], Theo D Witkamp [5], Koen M van Nieuwenhuizen [2], Frank-Erik de Leeuw [6], Wouter J Schonewille [7], Paul L M de Kort [8], Diederik W J Dippel [9], Theodora W M Raaymakers [10], Jeannette Hofmeijer [11], Marieke J H Wermer [12], Henk Kerkhoff [13], Korné Jellema [14], Irene M Bronner [15], Michel J M Remmers [16], Henri Paul Bienfait [17], Ron J G M Witjes [18], H Rolf Jäger [19], Jacoba P Greving [1], Catharina J M Klijn [2, 6] the DIAGRAM study group

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Abstract

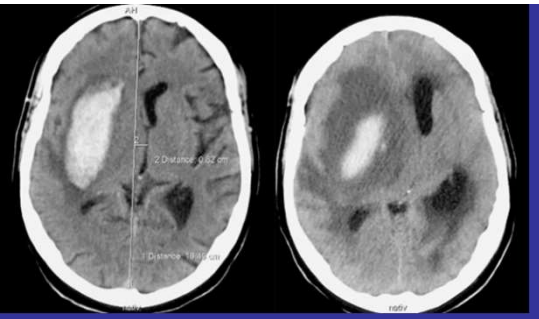
Objective A substantial part of non-traumatic intracerebral haemorrhages (ICH) arises from a macrovascular cause, but there is little guidance on selection of patients for additional diagnostic work-up. We aimed to develop and externally validate a model for predicting the probability of a macrovascular cause in patients with non-traumatic ICH.

Methods The DIagnostic AngioGRAphy to find vascular Malformations (DIAGRAM) study (n=298; 69 macrovascular cause; 23%) is a prospective, multicentre study assessing yield and accuracy of CT angiography (CTA), MRI/ magnetic resonance angiography (MRA) and intra-arterial catheter angiography in diagnosing macrovascular causes in patients with non-traumatic ICH. We considered prespecified patient and ICH characteristics in multivariable logistic regression analyses as predictors for a macrovascular cause. We combined independent predictors in a model, which we validated in an external cohort of 173 patients with ICH (78 macrovascular cause, 45%).

Results Independent predictors were younger age, lobar or posterior fossa (vs deep) location of ICH, and absence of small vessel disease (SVD). A model that combined these predictors showed good performance in the development data (c-statistic 0.83; 95% CI 0.78 to 0.88) and moderate performance in external validation (c-statistic 0.66; 95% CI 0.58 to 0.74). When CTA results were added, the c-statistic was excellent (0.91; 95% CI 0.88 to 0.94) and good after external validation (0.88; 95% CI 0.83 to 0.94). Predicted probabilities varied from 1% in patients aged 51–70 years with deep ICH and SVD, to more than 50% in patients aged 18–50 years with lobar or posterior fossa ICH without SVD.

Conclusion The DIAGRAM scores help to predict the probability of a macrovascular cause in patients with non-traumatic ICH based on age, ICH location, SVD and CTA.

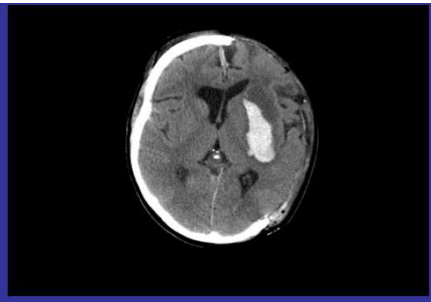
Complication rates for DSA are less than 1% with most complications being arterial puncture site hematoma and transient neurological deficits. In young individuals, lesser complications may be expected. However, which patients should undergo DSA carries substantial uncertainty...



Acute medical treatment

- All young ICH patients except those with clearly hopeless prognosis should be treated in organized stroke units/neurointensive care.
- Reverse ongoing anticoagulation…..(Vit K antagonists =>Vit K + 4-factor PCC; FXa inhibitors => andexanet; dabigatran => idarucizumab) ?
- Initial management includes supportive care and aggressive treatment of increased intracranial pressure.
- Corticosteroids and prophylactic anti-epileptic agents should be avoided.
- Pro-coagulants should be used in research settings only.
- Anticoagulation in CVT patients seems reasonable even in presence of single or multiple ICH.
- The role of aggressive antihypertensive treatment remains controversial. Probably target systolic goal of 140-160 mmHg in the acute phase in patients with high blood pressure is reasonable.
- Although most glucose, temperature, RR, reversal of AC, avoiding early withdrawal of care, etc. single treatment trials did not show clear benefits, applying all of them simultaneously (care bundle approach) may be beneficial.
- Patients with massive bleeding and inevitably progressing to brain death should be considered for organ donation if this is consistent with patient's and family's wishes.

Acute surgical treatment



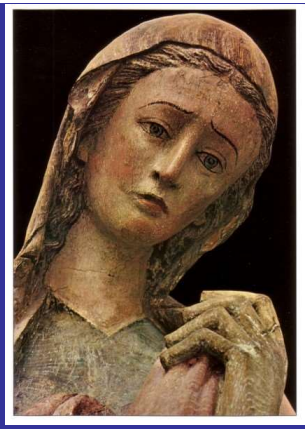
- Current guidelines do not specifically give instructions on young ICH patients.
- Major trials (STICH and STICH II) on hematoma evacuation in acute ICH did not show benefit. Young patients were not separately analyzed/reported (younger than 65 years were reported without benefit being detected).
- ENRICH (minimally invasive surgery) trial showed some benefit in lobar, but not deep hematomas. SWITCH trial (decompr craniectomy vs standard care; n ~200, med age 61) reported a trend for benefit in 18-75 yo deep ICH patients.
- A critical and comprehensive evaluation of surgical approaches are summarized in ESO ICH guidelines 2025
- Despite that, young ICH patients with large hematomas and decreased level of consciousness are frequently treated surgically.
- Two observational studies showed independent and robust associations between surgical hematoma evacuation and lower mortality in young ICH patients *(Lai S et al, Eur J Neurol 2005; Koivunen R et al, Stroke 2014)*.
- *Koivunen R et al (Stroke 2014)* also did a propensity-score-matching showing 3 times higher risk for 3-month mortality with conservative treatment.

Secondary prevention

- Strategies to prevent recurrent ICH should be targeted at the underlying ICH mechanism.
- In hypertensive ICH, a target syst pressure of ≤130 mmHg and/or diast pressure of ≤80 mmHg. The benefit of BP lowering seems more robust in younger patients (Law MR et al, BMJ 2009).
- Antithrombotic agents should be avoided. Cessation of smoking, alcohol use, and illicit drugs is advised.
- In case of CVT, products containing estrogen should be stopped.
- The risk of recurrent ICH due to AVM is 18% in the first year (Mast H et al, Lancet 1997), with recurrent hemorrhages conveying high mortality and dependency (26% and 39%, respectively; Laakso A et al, Neurosurgery 2011). AVM can be treated with endovascular embolization, neurosurgery, stereotactic radiotherapy, or combinations of these (Ogilvy C et al, Stroke 2001; Derdeyn C et al, Stroke 2017).
- In patients with moyamoya vasculopathy, rebleeding occurs at an annual rate of 7% (Kobayashi E et al, J Neurosurg 2000). Extracranial-intracranial bypass surgery may reduce the risk of rebleeding (Miyamoto S et al, Stroke 2014).
- Brainstem cavernomas presenting with ICH carry a 5-year hemorrhage risk of 31% (Horne M et al, Lancet Neurol 2015). Neurosurgical excision – when feasible – should be preferred over stereotaxic radiosurgery (Li C et al, PLOS One 2015).
- Similarly, dural AV fistula especially in presence of cortical venous reflux should be treated with either endovascular or neurosurgical approach.


OUTCOMES

Outcomes: early mortality



- Most deaths occur during the first weeks due to neurological complications
- In-hospital mortality varies from 8.7% to 34%
- 1-month mortality (case fatality) varies from 8% to 26%
- 3-month mortality was 17% in a recent study (Koivunen R et al, Stroke 2014)
- Independent factors associated with early mortality include female gender, increasing NIHSS score, decreased level of consciousness, size of bleeding, infratentorial hematoma location, multiple hemorrhages, higher leukocyte count, hyperglycemia, clustering of medical complications (infections, venous thrombosis, arrhythmia, renal failure, hyperglycemia, electrolyte imbalances), and structural causes
- Ethnic group may alter ICH mortality due to various reasons, including socioeconomic status, comorbid vascular conditions, and distribution of underlying causes
- Asian series had higher mortality rates and deep ICH locations in line with hypertension being the dominant cause (Kalita J et al, J Neurol Sci 2014; Lai S et al, Eur J Neurol 2005; Fuh JL et al, J Stroke Cerebrovasc Dis 1994)
- Disparity in stroke mortality seems to be particularly profound for ICH with American Indians, Asians, indigenous nations, and Hispanics carrying each about a 1.5-times higher risk of death
- African-Americans have a five-fold risk of death compared to whites (Chong JY and Sacco RL, J Thromb Thrombolysis 2005)

Outcomes: long-term mortality

- After 6-17 months of follow-up, mortality ranging from 12.5% to 38.9% was reported, the highest numbers coming from the oldest studies.

- All cause mortality was 27.6% at 9.7 years *(Koivunen R et al, Eur J Neurol 2015), 31.4% at 11.3 years (Rutten-Jacobs LC et al, J Neurol 2014)* and 35.0% at 8.2 years (Verhoeven JI et al, Eur Stroke J 2021).

- Long-term standard mortality ratio was nearly 5-fold *(Rutten-Jacobs LC et al, J Neurol 2014)* and 13-fold (Verhoeven JI et al, Eur Stroke J 2021) compared to the background population of the same age.

Outcomes: recurrence

- Two earlier studies found high recurrence rates: 4.9 to 9% with 8 to 17 months of follow-up *(Ruiz-Sandoval JL et al, Stroke 1999 and Del Brutto OH et al, Funct Neurol 1999)*
- In solely hypertensive ICH, recurrence rate was 15.4% at a mean of 19 months follow-up (Ruiz-Sandoval JL et al, Stroke 2006)
- Two more recent studies *(Rutten-Jacobs LC et al, J Neurol 2014 and Koivunen R et al, Eur J Neurol 2015)* showed consistent cumulative risks of recurrent ICH at 10 years (11.2-12.2%), with 1-year and 5-year risks of 1.9% and 8.4%, respectively. In both of these studies recurrent bleeding in most cases was caused by a structural malformation known at the time of index ICH (AVM, cavernoma, moyamoya).
- The risk of ischemic stroke after ICH was about a half of that compared with recurrent ICH in the Finnish study (*Koivunen R et al, Eur J Neurol 2015)*

Outcomes: chronic consequences

- Post-ICH epilepsy was diagnosed at cumulative rates of 22.9% and 31% (23% with recurrent seizures) in about 10 years of follow-up (Koivunen R et al, Eur J Neurol 2015; Arntz R et al, PLOS One 2013) , but in only 7.6% in a 5-year follow-up in a more recent study (Verburgt E et al, JAMA Neurol 2025).
- In a Finnish study with 131 survivors aged ≤50 years at the time of index ICH, 75.8% were independent (mRS 0-2), 51.1% were completely recovered or had mild symptoms only (mRS 0-1), while 25.2% were moderately or severely disabled (mRS 3-5) after median follow-up of 9.7 years *(Koivunen R et al, Eur J Neurol 2015)*. A Dutch study with 67 ICH patients of the same age range showed that 50.7% of all patients were independent after a mean of 9.1 years *(Synhaeve NE et al, Stroke 2014)*.
- A structured interview used validated scales to assess mood, pain, sleep problems, and cognition in 130 young ICH survivors. Of these, 23% suffered from depression, 40% had symptoms of anxiety, and 47% reported fatigue. Mild, moderate, and severe pain was reported by 51%, 7.7%, and 0.8% of the patients, respectively. Degree of disability was associated with depression, anxiety, and pain (Koivunen R et al, Acta Neurol Scand 2015).
- Roughly half of young ICH survivors are able to return to work at some point of time, with younger patients having better odds (Koivunen R et al, Acta Neurol Scand 2015; Maaijwee N et al, Neurology 2014).

Conclusions

- Limited systematic data exist on this topic, most studies having retrospective design
- ICH in young adults is an uncommon but a serious disease
- Presentation is similar to that in older patients, but less severe
- Structural causes are more common than that in the elderly patients and require surgery
- There are several risk factors and causes behind which need to be carefully explored
- Diagnostics require special expertise and extensive (repeated) imaging
- Acute surgery may be beneficial in young patients
- Long-term outcomes are not benign

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- Anu Eräkanto

5.2. Hemostasis and Coagulopathy

5.2.1. Anticoagulant-Related Hemorrhage

Recommendations for Anticoagulant-Related Hemorrhage
Referenced studies that support recommendations are summarized in Data Supplements 18 and 19.

COR	LOE	Recommendations
1	C-LD	1. In patients with anticoagulant-associated spontaneous ICH, anticoagulation should be discontinued immediately and rapid reversal of anticoagulation should be performed as soon as possible after diagnosis of spontaneous ICH to improve survival.[162]
VKAs		
1	B-R	2. In patients with VKA-associated spontaneous ICH and INR ≥2.0, 4-factor (4-F) prothrombin complex concentrate (PCC) is recommended in preference to fresh-frozen plasma (FFP) to achieve rapid correction of INR and limit HE.[163]
1	C-LD	3. In patients with VKA-associated spontaneous ICH, intravenous vitamin K should be administered directly after coagulation factor replacement (PCC or other) to prevent later increase in INR and subsequent HE.[164,165]
2b	C-LD	4. In patients with VKA-associated spontaneous ICH with INR of 1.3 to 1.9, it may be reasonable to use PCC to achieve rapid correction of INR and limit HE.[162,164]
DOACs		
2a	B-NR	5. In patients with direct factor Xa inhibitor–associated spontaneous ICH, andexanet alfa is reasonable to reverse the anticoagulant effect of factor Xa inhibitors.[166,167]
2a	B-NR	6. In patients with dabigatran-associated spontaneous ICH, idarucizumab is reasonable to reverse the anticoagulant effect of dabigatran.[168]

Recommendations for Anticoagulant-Related Hemorrhage (Continued)

COR	LOE	Recommendations
2b	B-NR	7. In patients with direct factor Xa inhibitor–associated spontaneous ICH, a 4-F PCC or activated PCC (aPCC) may be considered to improve hemostasis.[169–171]
2b	C-LD	8. In patients with dabigatran- or factor Xa inhibitor–associated spontaneous ICH, when the DOAC agent was taken within the previous few hours, activated charcoal may be reasonable to prevent absorption of the DOAC.[172–174]
2b	C-LD	9. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, aPCC or PCCs may be considered to improve hemostasis.[175,176]
2b	C-LD	10. In patients with dabigatran-associated spontaneous ICH, when idarucizumab is not available, renal replacement therapy (RRT) may be considered to reduce dabigatran concentration.[177]
Heparins		
2a	C-LD	11. In patients with unfractionated heparin (UFH)–associated spontaneous ICH, intravenous protamine is reasonable to reverse the anticoagulant effect of heparin.[178]
2b	C-LD	12. In patients with low-molecular-weight heparin (LMWH)–associated spontaneous ICH, intravenous protamine may be considered to partially reverse the anticoagulant effect of heparin.[178]

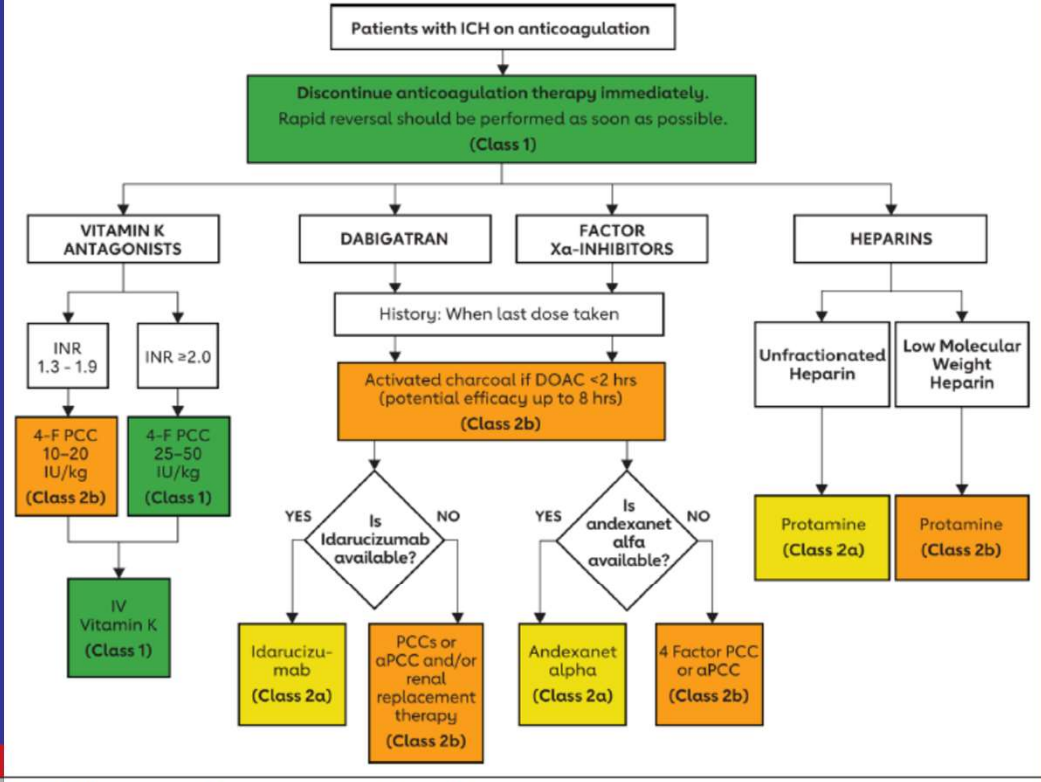

Figure 2. Management of anticoagulant-related hemorrhage.
aPCC indicates activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; INR, international normalized ratio; and PCC, prothrombin complex concentrate.