# Management of High Blood Pressure in Intracerebral Haemorrhage

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## 12.1 Introduction

Intracerebral haemorrhage (ICH) is a devastating disease with the highest rate of mortality among the major pathological stroke subtypes. ICH is also the major contributor to disability-adjusted life years lost among all neurologic disorders [1]. Hypertension is the most important modifiable risk factor for both primary and recurrent ICH [2].

Early blood pressure (BP) elevation is observed in the majority of patients with ICH [3]. High BP appears to play a critical role in the pathogenesis of ICH, since it has been shown to be strongly related to haematoma growth [4–6] and subsequent poor clinical outcomes [7–11]. Therefore, acute BP alteration might be of clinical relevance in this cerebrovascular disorder.

In fact, recent clinical trial evidence suggests that BP lowering immediately after ICH may be an important treatment target to prevent haematoma expansion and may be associated with better outcomes [12].

## 12.2 Epidemiology

ICH is a less common subtype of stroke than cerebral ischaemia, accounting for 9–33 % of all acute cerebrovascular events/strokes worldwide, but is associated with higher mortality rates and poorer functional outcomes. Haemorrhagic stroke is especially common in Asia, particularly in Japan and China, and in African

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populations, where it constitutes up to 20–33 % of all strokes [13]. In Caucasians, ICH accounts for approximately 9–15 % of all strokes [14]. The incidence of ICH rises with age and therefore the number of ICH is expected to increase substantially in the near future. ICH is associated with high early and late mortality and morbidity. The case fatality rate is 40 % at 1 month, rising to 54 % at 12 months [15, 16]. About 50 % of survivors will be permanently disabled, with only a minority of ICH patients being independent of long-term care at 12 months [17–19].

Most patients receive no warning signs before ICH. Occasionally, some patients with vascular malformations may present with recurrent, usually localized, headaches or seizures.

Among vascular risk factors, elevated BP is well established as the major contributor to ICH, with a much stronger association with ICH than with ischaemic stroke [20, 21]. BP values are linearly associated with the risk of ICH. The higher the BP, the greater the increased risk of haemorrhagic stroke and recurrent stroke, both haemorrhagic [22] and ischaemic [20, 21].

In general, hypertensives have a 2–3 times higher relative risk of ICH than non-hypertensive subjects [23]. High BP is a much stronger predictor of ICH in younger adults than in older subjects [24]. Discontinuation of antihypertensive therapy is also associated with a significantly greater risk of ICH [25].

## 12.3 Pathophysiology

Pathogenetically, arterial small vessel disease (so-called arteriolosclerosis), cerebral amyloid angiopathy and haemostatic and coagulation disorders – either due to intrinsic systemic or other diseases or to medications – are the leading causes of ICH in the elderly, while vascular malformations, venous disease, acute hypertensive crises or aneurysms are more likely to explain bleeding in younger patients [26, 27]. Cerebral arteriolosclerosis affects the small perforating arteries arising from the large vasculature of the brain and is related mainly, but not exclusively, to chronic uncontrolled hypertension [28]. Hypertension-related ICH tends to be located in the deep structures of the brain (e.g. basal ganglia, thalamus, white matter, pons, cerebellum), although, in rare cases, it may affect the subcortical areas [29].

The percentage of hypertension-related ICH varies between 50 and 70 % in older studies and between 35 and 54 % in more recent studies due to the availability of modern neuroimaging tools allowing other causes of ICH to be diagnosed. However, in about 20 % of ICH cases, no underlying cause is identified with currently available diagnostic tools, and thus they may still be considered cryptogenic [26].

With the advent of modern neuroimaging tools, continued bleeding and haematoma expansion have been demonstrated in one-third of patients with ICH in the first few hours [30] and in a further 10 % in the 3–24 h after stroke onset [31–33]. In ICH associated with anticoagulants, haematoma expansion persists even longer [34]. Haematoma expansion and final lesion volume, determined mainly within the first 24 h after stroke, are the key prognosticators of clinical outcomes in patients

with ICH. However, the adverse effects of peri-haematoma edema [35, 36] and inflammation [37, 38] in the first few days post-stroke may also contribute to overall morbidity and mortality.

## 12.4 BP and Outcomes in ICH

Acutely elevated BP in the first 24 h – the so-called acute hypertensive response (AHR) – occurs in up to 90 % of ICH cases [39–42], whereas pre-existing hypertension (self-reported) with systolic BP (SBP) ≥ 140 mmHg or >160 mmHg is found in 73 % and 60 % of ICH patients, respectively [3]. Stress, pain, increased intracranial pressure and premorbid elevations in BP are associated with AHR in ICH patients [10, 42].

In a recent study by Fisher et al., the first recorded acute-phase SBP was much higher in patients with ICH than in those with ischaemic stroke. Moreover, the first mean SBP after ICH was much higher than premorbid levels, in contrast with findings in patients with ischaemic stroke [43]. Mean SBP also increased steeply in the days and weeks before ICH, but not before ischaemic stroke. SBP appeared to rise substantially after ICH compared with usual premorbid values, and the reported difference between the highest SBP within 3 h of onset was 50 mmHg higher, on average, than the maximum premorbid SBP. Larger acute BP increases during ICH have been reported in Black populations than in Caucasian groups [44].

Rapid BP changes, with a substantial acute BP rise, seem to be specific for the ICH subtype of stroke, while in ischaemic stroke, acute post-event SBP tends to be much closer to premorbid values [43]. A possible explanation may be that ICH causes acute elevations in intracranial pressure more often than ischaemic stroke [45], followed by a reflex increase in systemic BP (the so-called Cushing triad: hypertension, bradycardia and breathing pattern abnormalities) [46]. Raised BP tends to decline spontaneously, primarily in the first few hours after intracerebral bleeding. Consistent with the data mentioned above, in the first 24 h after stroke, BP usually falls much more after ICH than after major ischaemic stroke [43]. However, in a substantial proportion of ICH patients, BP remains increased.

High BP in the acute phase after ICH has been associated with haematoma expansion [5], neurological deterioration and death and dependency [6, 47]. Furthermore, ICH patients with pathologically raised BP have more severe oedema and a higher risk of early stroke recurrence [22, 35, 36]. Therefore, BP-lowering therapy may potentially reduce the ICH-related burden. Not only mean BP values are of clinical importance in ICH patients. In a recent large, prospective randomized trial, BP variations in the first 24 h, and for several days after ICH, have been shown to be independent predictors of a poor outcome [48]. This may reflect the transient character of many individual factors associated with the initial pressor response, with episodic hypertension most likely to be related to the pathomechanisms of ICH triggering and progression. Moreover, raised BP may be both a risk factor and a risk marker for intracerebral bleeding and subsequent intracranial hypertension [8].

Factors associated with a poor outcome after ICH (other than BP) include older age [49, 50], large haemorrhage volume [17, 51–53], reduced level of consciousness [6, 54], extravasation with continued bleeding [49], haematoma expansion [31, 55], hydrocephalus and intraventricular involvement [17, 51, 54]. Patients with ICH are at high risk of other cardiovascular events, including recurrent ICH [56]. Hypertension and older age are important risk factors for ICH recurrence [57, 58]. A deep location of the initial and recurrent haemorrhage is more common in Asians, while in Caucasians, most ICHs (both initial and recurrent) tend to be located more superficially (in the lobes of the brain) [57, 59].

## 12.5 BP Management After ICH

Population-based studies show that most patients present with small ICH that are readily survivable with good medical care [60]. This suggests that excellent medical care probably has a potent, direct impact on ICH morbidity and mortality. The goal of ICH treatment is to prevent and reverse acute brain injury and prevent neurological impairment and disability. The evidence shows that management in an acute stroke unit improves outcomes compared with care on a general ward, reducing mortality and dependency in patients with ICH [61]. This may partially be explained by continuous monitoring of vital functions, including BP, and early treatment of complications by stroke units.

The treatment of acute BP elevation in ICH has been controversial for decades. The theoretical concept justifying early BP lowering in ICH patients is that it attempts to limit cerebral haemorrhage growth, which occurs mainly in the first few hours after stroke onset [12, 62], and to reduce cerebral oedema and minimize the risk of early hypertensive emergencies, including stroke recurrence, in the acute phase of ICH. However, the treatment plan should consider the potential risk of ischaemic injury to peri-haematoma areas or other vascular beds and the potentially higher disability and mortality, especially when the fall in BP in the acute phase is large and rapid [63]. In fact, acute BP-lowering therapy may be associated with ischaemic strokes remote from the primary haematoma in patients with ICH, as evidenced by recent MRI studies [64]. However, there is some evidence showing that reduced metabolism [65] and preserved autoregulation, the two typical features of the peri-haematoma region [66], might prevent any injury associated with SBP lowering. As indicated in recent prospective studies of acute ICH, BP reduction decreases haematoma expansion but has no adverse effect on peri-haematoma blood flow [4, 67–70].

There is also long-standing clinical debate on the optimal BP values in ICH, which should probably depend on coexisting individual factors including age, pre-existing hypertension, intracranial pressure, presumed cause of bleeding and time from stroke onset. The initial data on the effects of BP lowering in ICH were conflicting, with positive [68, 71, 72], neutral [73] and negative [63, 74, 75] effects attributed to SBP reduction. These clinical uncertainties were reflected in the heterogeneous expert-based recommendations for optimal BP lowering in acute ICH (Table 12.1).

**Table 12.1** Suggested previous guidelines recommendations for BP-lowering treatment in patients with acute ICH

| | Start medication | Target |
|---|---|---|
| *ICH* | | |
| American Heart Association [76] | Systolic BP > 200 mmHg or MAP > 150 mmHg<br>Systolic BP > 180 mmHg or MAP > 130 mmHg and possibility of elevated ICP<br>Systolic BP > 180 mmHg or MAP > 130 mmHg and no evidence of elevated ICP | Aggressive reduction in BP<br>Reducing BP while maintaining CPP ≥ 60 mmHg<br>Moderate reduction in BP, e.g. MAP < 110 mmHg or BP <160/90 mmHg |
| International Society of Hypertension [77] | >220/120 mmHg | Up to 20 % reduction |
| Stroke Foundation of New Zealand [78] | >180/100 mmHg | Systolic BP < 180 mmHg or mean BP < 130 mmHg |

*MAP* mean arterial pressure, *ICP* intracranial pressure, *CPP* cerebral pulse pressure

There is now growing evidence supporting the safety of early intensive BP lowering after ICH. Observational studies suggest that more aggressive BP lowering may have a greater effect on reductions in haematoma growth (Table 12.2).

The Antihypertensive Treatment of Acute Cerebral Haemorrhage (ATACH) trial was a small multicentre open-label pilot trial to determine the safety of intravenous nicardipine-based BP lowering in 60 patients with chronic hypertension and SBP > 170 mmHg presenting within 12 h after supratentorial ICH. Patients were enrolled into one of three tiers of increasing BP-lowering intensity (170–200, 140–170, 110–140 mmHg). Aggressive SBP lowering (110–140 mmHg) was well tolerated and safe [79].

The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTRERACT) included over 400 predominantly Chinese patients with acute ICH diagnosed by computed tomography within 6 h of stroke onset, and with SBP in the range of 150–220 mmHg, and no definitive indication or contraindication to BP treatment. Patients were assigned to intensive therapy (target SBP of 140 mmHg) or standard AHA guideline therapy (target SBP of 180 mmHg). After 24 h, SBP decreased to 146 mmHg in the intensive therapy group and to 157 mmHg in the standard therapy group. Mean proportional haematoma growth was lower in the intensive treatment group (13.5 % vs. 36.3 %; $p = 0.04$), although there was no clinical benefit at 90 days but also no higher risk of adverse events or poorer outcomes. An optimum attenuation of haematoma growth was demonstrated at SBP of 130–140 mmHg [4]. This was particularly true for very early intensive blood pressure lowering [67].

Thus, while the ATACH study was the first to prove the feasibility and tolerability of early intensive SBP lowering, the INTERACT found an additional positive effect of this type of therapy, namely, a reduction in haematoma expansion.

The recently completed INTERACT2 study of approximately 2,800 patients with an acute ICH showed improved functional recovery without any harm after

**Table 12.2** Results of studies of blood pressure reduction after intracerebral haemorrhage

| Trial, publication year, country | No. of patients | Mean age (years) (I; C) | Baseline SBP/DBP, mmHg | Intervention period (days) | Outcome assessment | Comments |
|---|---|---|---|---|---|---|
| INTERACT [67], 2010, multiple countries | 404 | 63; 62 | Active: 180/100<br>Control: 181/104 | 7 | Absolute and proportional increases in haematoma and perihaematomal oedema volumes during the first 72 h after intracerebral haemorrhage | Early intensive BP-lowering treatment attenuated haematoma growth over 72 h. No appreciable effects on perihaematomal oedema |
| ATACH [79, 80], 2010, USA | 60 | 62; 59; 65 (First tier, second tier, third tier) | SBP:<br>First tier: 209<br>Second tier: 212<br>Third tier: 201 | 24 h | Neurological deterioration within 24 h and serious adverse events within 72 h | No significant difference was observed in average SBP change at 2 h after treatment initiation between subjects with or without neurological deterioration within 24 h |
| INTERACT2 [12], 2013, multiple countries | 2839 | 63; 64 | Active: 179/101<br>Control: 179/101 | 7 | Combined end point of death and dependency according to the modified Rankin scale at 90 days | Intensive BP lowering did not significantly reduce the rate of the primary outcome of death or severe disability; an ordinal analysis of modified Rankin scores indicated improved functional outcomes with intensive BP lowering |
| SAMURAI [11], 2013, Japan | 211 | 65 (whole group) | SBP: 200 (whole group) | 24 h | Neurological deterioration, haematoma expansion and unfavourable outcome | Increased SBP was associated with an increase in neurological deterioration, an increase in haematoma expansion and an increase in unfavourable outcome |
| SCAST [81], 2011, Northern European countries (haemorrhagic stroke subgroup) | 274 | NA | NA | 7 | Death or disability at 6 months: combination of vascular death, myocardial infarction or stroke during first 6 months | The risk of the composite vascular end point did not differ between treatment groups; analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group |

an intensive strategy of BP lowering in patients with ICH. Exclusion criteria included (1) a clear indication for, or a contraindication to, intensive BP lowering; (2) severe neurological symptoms, concurrent medical conditions, a high likelihood of death within 24 h or massive ICH; and (3) early planned surgical intervention. The aggressive BP control (target SBP <140 mmHg) in very early (<6, mean time to start therapy about 3.7) hours after ICH onset was associated with a reduction in haematoma growth, as demonstrated in the INTERACT study and, more importantly, with safety and better functional outcome, as shown in the ordinal analysis of the dichotomous modified Rankin scale (mRS), although not in the primary outcome, which was the dichotomous mRS (i.e. there was a non-significant 4 % absolute treatment effect ($p = 0.06$) on the primary outcome of death or major disability) [12].

The BP-lowering protocols were based on locally available intravenous agents, as the antihypertensive drugs were not prespecified in the trial. Only one-third of patients achieved the target SBP value within 1 h (half achieved the target by 6 h), and most (75 %) presented with mild-to-moderate (<20 mL) haematomas [82].

Nonetheless, the INTERACT2 study has generally been interpreted as a positive trial, demonstrating both radiological and clinical benefit. Moreover, the more aggressive BP lowering was associated with a better outcome, with an optimal BP target around 130–139 mmHg achieved within the first 6 h [83]. Optimal recovery from ICH was observed in hypertensive patients who achieved the greatest SBP reductions (≥20 mmHg) in the first hour and which were maintained for 7 days [84].

The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement – Intracerebral Haemorrhage (SAMURAI-ICH) evaluated the effects of BP lowering in 211 Japanese patients with ICH and SBP > 180 mmHg [85]. Patients were treated with intravenous nicardipine within 3 h of stroke onset. The aim of the study was to achieve SBP between 120 and 160 mmHg and to maintain it in this range for the first 24 h. BP reduction was related to the reduction in the risk of haematoma expansion in the acute period and neurological deterioration and functional status at 3 months.

In the SCAST trial, over 200 (14 %) patients had ICH. Unfortunately, the treatment of elevated BP with candesartan (mean time to start therapy about 18 h) did not reduce, but increased, the risk of a poor outcome. It might be speculated that, if BP lowering is time dependent in ICH, the BP-altering intervention may have been too late in this trial. Alternatively, candesartan, as an angiotensin receptor blocker, might be not the best option for lowering BP in ICH.

The Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) enrolled patients with a recent stroke (time window 48 h) taking antihypertensive drugs. The majority of participants had ischaemic stroke, although 15 % of patients recruited had an ICH. At the study end point of 2 weeks, the continued treatment group had systolic/diastolic BP that was 13/8 mmHg less than the stop treatment group. However, there were no differences in rates of death and

dependency, the primary end point, or in the rates of serious adverse events, 6-month mortality or cardiovascular events. The continuation of BP-lowering agents did not have any significant efficacy on adverse events. Nevertheless, it should be stressed that the absolute number of ICH subjects enrolled in the trial was relatively small.

Thus, although the available evidence is insufficient to provide accurate guidance on the management of BP in the acute phase of ICH, there is recent evidence supporting very early aggressive BP control during this phase. Consequently, it seems reasonable that urgent initiation of the time-sensitive procedure of BP lowering should be made in the emergency department. Specific protocols for the management of ICH should be developed for more efficient, standardized management of patients with ICH.

## 12.6 Current Guideline Recommendations

The current American Stroke Association [82] and European Stroke Organization [86] guidelines recommend reduction of SBP to <140 mmHg in ICH patients presenting with SBP between 150 and 220 mmHg and with no contraindication to acute BP treatment. Acute lowering of SBP to 140 mmHg is regarded safe and may be effective in improving functional outcomes and may be superior to an SBP target of <180 mmHg. For ICH patients presenting with systolic BP > 220 mmHg, it may be reasonable to consider aggressive BP reduction and frequent BP monitoring. A lower limit for safe reduction is undefined. Short-acting and easily titratable antihypertensive infusions are preferred (Table 12.3).

**Table 12.3** Short and rapidly acting intravenous antihypertensive agents that may be considered for control of elevated BP in patients with ICH

| Agent | Dosing | Onset/duration of action |
|---|---|---|
| Labetalol | 5–20 mg IV bolus every 15 min, up to 2 mg/min IV infusion | 2–5 min/4–6 h |
| Nicardipine | 5–15 mg/h IV infusion | 5–15 min/4–6 h |
| Esmolol | 500 μg/kg IV bolus or 25–300 μg/kg/min IV infusion | 120 s/18–30 min |
| Urapidil | 12.5–25 mg IV bolus or 5–40 mg/h IV infusion | 1–5 min/1–2 h |
| Enalaprilat | 1.25 to 5 mg every 6 h IVP | 15 min/12–24 h |
| Hydralazine | 10–20 mg IV bolus | 10 min/> 1 h |
| Nipride | 0.1–10 μg/kg/min IV infusion | Unset immediately while giving |
| Nitroglycerine | 5–100 mg/min as IV infusion | 2–5 min/5–10 min |

Modified from Aiyagari et al. [87]
*IVP* intravenous push

## 12.7 Future Directions and Ongoing Studies

Further trials are needed to identify the optimal timing and the best drug classes for lowering high BP in ICH. There are no data on drugs specific for ICH patients. In some pivotal trials, the feasibility of calcium channel blockers has been shown. However, the optimal choice of drug and intensity of treatment remain elusive. The benefits (and potential risks) of aggressive BP management may vary according to age and comorbidities.

The ATACH II study – ongoing trial for intensive lowering of elevated BP within 3.5 h with nicardipine IV – will provide information about any differential effect between populations.

Other vascular factors, such as BP variability, the presence of obstructive sleep apnoea [88], obesity, frequent alcohol use [89] and illicit drug use [90], which have been linked to elevated BP and ICH, should also be considered in both the acute and chronic care of ICH patients.

## References

1. Chin JH, Vora N (2014) The global burden of neurologic diseases. Neurology 83:349–351
2. Feigin VL, Forouzanfar MH, Krishnamurthi R et al (2014) Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet 383:245–254
3. O'Donnell MJ, Xavier D, Liu L et al (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 376:112–123
4. Arima H, Anderson CS, Wang JG et al (2010) Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage. Hypertension 56:852–858
5. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T (1997) Predisposing factors to enlargement of spontaneous intracerebral hematoma. Stroke 28:2370–2375
6. Fogelholm R, Avikainen S, Murros K (1997) Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. Stroke 28:1396–1400
7. Vemmos KN, Tsivgoulis G, Spengos K et al (2004) U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med 255:257–265
8. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A (2004) Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. Stroke 35:1364–1367
9. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S (2005) Effects of blood pressure levels on case fatality after acute stroke. J Hypertens 23:1217–1223
10. Zhang Y, Reilly KH, Tong W et al (2008) Blood pressure and clinical outcome among patients with acute stroke in Inner Mongolia, China. J Hypertens 26:1446–1452
11. Sakamoto Y, Koga M, Yamagami H et al (2013) Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the stroke acute management with urgent risk-factor assessment and improvement-intracerebral hemorrhage study. Stroke 44:1846–1851
12. Anderson CS, Heeley E, Huang Y et al (2013) Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 368:2355–2365

13. Tsai C-F, Thomas B, Sudlow CLM (2013) Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. Neurology 81:264–272
14. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V (2009) Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 8:355–369
15. Van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ (2010) Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 9:167–176
16. Poon MTC, Fonville AF, Al-Shahi SR (2014) Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 85:660–667
17. Portenoy RK, Lipton RB, Berger AR, Lesser ML, Lantos G (1987) Intracerebral haemorrhage: a model for the prediction of outcome. J Neurol Neurosurg Psychiatry 50:976–979
18. Barber M, Roditi G, Stott DJ, Langhorne P (2004) Poor outcome in primary intracerebral haemorrhage: results of a matched comparison. Postgrad Med J 80:89–92
19. Tatu L, Moulin T, El Mohamad R, Vuillier F, Rumbach L, Czorny A (2000) Primary intracerebral hemorrhages in the Besançon stroke registry. Initial clinical and CT findings, early course and 30-day outcome in 350 patients. Eur Neurol 43:209–214
20. Eastern Stroke and Coronary Heart Disease Collaborative Research Group (1998) Blood pressure, cholesterol, and stroke in eastern Asia. Lancet 352:1801–1807
21. Lawes CMM, Rodgers A, Bennett DA et al (2003) Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens 21:707–716
22. Arakawa S, Saku Y, Ibayashi S, Nagao T, Fujishima M (1998) Blood pressure control and recurrence of hypertensive brain hemorrhage. Stroke 29:1806–1809
23. Ariesen MJ, Claus SP, Rinkel GJE, Algra A (2003) Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke 34:2060–2065
24. Rapsomaniki E, Timmis A, George J et al (2014) Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet 383:1899–1911
25. Thrift AG, McNeil JJ, Forbes A, Donnan GA (1998) Three important subgroups of hypertensive persons at greater risk of intracerebral hemorrhage. Hypertension 31:1223–1229
26. Meretoja A, Strbian D, Putaala J et al (2012) SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. Stroke 43:2592–2597
27. Yeh S-J, Tang S-C, Tsai L-K, Jeng J-S (2014) Pathogenetical subtypes of recurrent intracerebral hemorrhage: designations by SMASH-U classification system. Stroke 45:2636–2642
28. Sessa M (2008) Intracerebral hemorrhage and hypertension. Neurol Sci 29(Suppl 2):S258–S259
29. Mizukami M, Kin H, Araki G, Mihara H, Yoshida Y (1976) Surgical treatment of primary intracerebral hemorrhage- part 1: new angiographical classification. Stroke 7:30–36
30. Davis SM, Broderick J, Hennerici M et al (2006) Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology 66:1175–1181
31. Brott T, Broderick J, Kothari R et al (1997) Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke 28:1–5
32. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O (1994) Hematoma enlargement in spontaneous intracerebral hemorrhage. J Neurosurg 80:51–57
33. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T (1996) Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke 27:1783–1787
34. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J (2004) Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology 63:1059–1064
35. Gebel JM, Jauch EC, Brott TG et al (2002) Natural history of perihematomal edema in patients with hyperacute spontaneous intracerebral hemorrhage. Stroke 33:2631–2635
36. Carhuapoma JR, Hanley DF, Banerjee M, Beauchamp NJ (2003) Brain edema after human cerebral hemorrhage: a magnetic resonance imaging volumetric analysis. J Neurosurg Anesthesiol 15:230–233

37. Gong C, Hoff JT, Keep RF (2000) Acute inflammatory reaction following experimental intracerebral hemorrhage in rat. Brain Res 871:57–65
38. Xue M, Del Bigio MR (2000) Intracortical hemorrhage injury in rats: relationship between blood fractions and brain cell death. Stroke 31:1721–1727
39. Wallace JD, Levy LL (1981) Blood pressure after stroke. JAMA 246:2177–2180
40. Harper G, Castleden CM, Potter JF (1994) Factors affecting changes in blood pressure after acute stroke. Stroke 25:1726–1729
41. Robinson TG, Potter JF (2004) Blood pressure in acute stroke. Age Ageing 33:6–12
42. Qureshi AI, Ezzeddine MA, Nasar A et al (2007) Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med 25:32–38
43. Fischer U, Cooney MT, Bull LM et al (2014) Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet Neurol 13:374–384
44. Zahuranec DB, Wing JJ, Edwards DF et al (2012) Poor long-term blood pressure control after intracerebral hemorrhage. Stroke 43:2580–2585
45. Qureshi AI, Mendelow AD, Hanley DF (2009) Intracerebral haemorrhage. Lancet 373:1632–1644
46. Fodstad H, Kelly PJ, Buchfelder M (2006) History of the cushing reflex. Neurosurgery 59:1132–1137; discussion 1137
47. Willmot M, Leonardi-Bee J, Bath PMW (2004) High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension 43:18–24
48. Manning L, Hirakawa Y, Arima H et al (2014) Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. Lancet Neurol 13:364–373
49. Becker KJ, Baxter AB, Bybee HM, Tirschwell DL, Abouelsaad T, Cohen WA (1999) Extravasation of radiographic contrast is an independent predictor of death in primary intracerebral hemorrhage. Stroke 30:2025–2032
50. Daverat P, Castel JP, Dartigues JF, Orgogozo JM (1991) Death and functional outcome after spontaneous intracerebral hemorrhage. A prospective study of 166 cases using multivariate analysis. Stroke 22:1–6
51. Tuhrim S, Dambrosia JM, Price TR et al (1991) Intracerebral hemorrhage: external validation and extension of a model for prediction of 30-day survival. Ann Neurol 29:658–663
52. Mayer SA, Sacco RL, Shi T, Mohr JP (1994) Neurologic deterioration in noncomatose patients with supratentorial intracerebral hemorrhage. Neurology 44:1379–1384
53. Leira R, Dávalos A, Silva Y et al (2004) Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology 63:461–467
54. Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC (1994) Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. Neurology 44:133–139
55. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R (1998) Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. Stroke 29:1160–1166
56. Arima H, Tzourio C, Butcher K et al (2006) Prior events predict cerebrovascular and coronary outcomes in the PROGRESS trial. Stroke 37:1497–1502
57. Hanger HC, Wilkinson TJ, Fayez-Iskander N, Sainsbury R (2007) The risk of recurrent stroke after intracerebral haemorrhage. J Neurol Neurosurg Psychiatry 78:836–840
58. Izumihara A, Suzuki M, Ishihara T (2005) Recurrence and extension of lobar hemorrhage related to cerebral amyloid angiopathy: multivariate analysis of clinical risk factors. Surg Neurol 64:160–164; discussion 164
59. Inagawa T (2005) Recurrent primary intracerebral hemorrhage in Izumo City, Japan. Surg Neurol 64:28–35; discussion 35–6
60. Zahuranec DB, Gonzales NR, Brown DL et al (2006) Presentation of intracerebral haemorrhage in a community. J Neurol Neurosurg Psychiatry 77:340–344

61. Langhorne P, Fearon P, Ronning OM et al (2013) Stroke unit care benefits patients with intracerebral hemorrhage: systematic review and meta-analysis. Stroke 44:3044–3049
62. Anderson CS, Huang Y, Wang JG et al (2008) Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol 7:391–399
63. Qureshi AI, Bliwise DL, Bliwise NG, Akbar MS, Uzen G, Frankel MR (1999) Rate of 24-hour blood pressure decline and mortality after spontaneous intracerebral hemorrhage: a retrospective analysis with a random effects regression model. Crit Care Med 27:480–485
64. Kidwell CS, Heiss W-D (2012) Advances in stroke: imaging. Stroke 43:302–304
65. Kim-Han JS, Kopp SJ, Dugan LL, Diringer MN (2006) Perihematomal mitochondrial dysfunction after intracerebral hemorrhage. Stroke 37:2457–2462
66. Powers WJ, Zazulia AR, Videen TO et al (2001) Autoregulation of cerebral blood flow surrounding acute (6 to 22 hours) intracerebral hemorrhage. Neurology 57:18–24
67. Anderson CS, Huang Y, Arima H et al (2010) Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). Stroke 41:307–312
68. Qureshi AI, Palesch YY, Martin R et al (2010) Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. Arch Neurol 67:570–576
69. Koch S, Romano JG, Forteza AM, Otero CM, Rabinstein AA (2008) Rapid blood pressure reduction in acute intracerebral hemorrhage: feasibility and safety. Neurocrit Care 8:316–321
70. Xu M (2011) Effect of blood pressure lowering strategy on the enlargement of hematoma and clinical outcome in patients with acute intracerebral haemorrhage. Chinese J Cerebrovasc Dis 8:23–27
71. Meyer JS, Bauer RB (1962) Medical treatment of spontaneous intracranial hemorrhage by the use of hypotensive drugs. Neurology 12:36–47
72. Suri MFK, Suarez JI, Rodrigue TC et al (2008) Effect of treatment of elevated blood pressure on neurological deterioration in patients with acute intracerebral hemorrhage. Neurocrit Care 9:177–182
73. Itabashi R, Toyoda K, Yasaka M et al (2008) The impact of hyperacute blood pressure lowering on the early clinical outcome following intracerebral hemorrhage. J Hypertens 26:2016–2021
74. Powers WJ (1993) Acute hypertension after stroke: the scientific basis for treatment decisions. Neurology 43:461–467
75. Kuwata N, Kuroda K, Funayama M, Sato N, Kubo N, Ogawa A (1995) Dysautoregulation in patients with hypertensive intracerebral hemorrhage. A SPECT study. Neurosurg Rev 18:237–245
76. Morgenstern LB, Hemphill JC, Anderson C et al (2010) Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 41:2108–2129
77. Bath P, Chalmers J, Powers W et al (2003) International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. J Hypertens 21:665–672
78. Stroke Foundation of New Zealand and New Zealand Guidelines Group (2010) Clinical guidelines for stroke management 2010. Stroke Foundation of New Zealand, Wellington
79. Qureshi AI (2007) Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH): rationale and design. Neurocrit Care 6:56–66
80. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) Investigators (2010) Antihypertensive treatment of acute cerebral hemorrhage. Crit Care Med 38:637–648
81. Sandset EC, Bath PMW, Boysen G et al (2011) The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 377:741–750
82. Hemphill JC, Greenberg SM, Anderson CS et al (2015) Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 46:2032–2060

83. Arima H, Heeley E, Delcourt C et al (2015) Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. Neurology 84:464–471
84. Wang X, Arima H, Heeley E et al (2015) Magnitude of blood pressure reduction and clinical outcomes in acute intracerebral hemorrhage: intensive blood pressure reduction in acute cerebral hemorrhage trial study. Hypertension 65:1026–1032
85. Sakamoto Y, Koga M, Todo K et al (2015) Relative systolic blood pressure reduction and clinical outcomes in hyperacute intracerebral hemorrhage: the SAMURAI-ICH observational study. J Hypertens 33:1069–1073
86. Steiner T, Al-Shahi Salman R, Beer R et al (2014) European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke 9:840–855
87. Grysiewicz RA, Ruland SD (2011) Hypertensive encephalopathy and acute blood pressure management after hemorrhagic stroke. In: Aiyagari V, Gorelick P (eds) Hypertension and stroke. Pathophysiology and management. Humana Press, New York
88. Pontes-Neto OM, Fernandes RMF, Sander HH et al (2010) Obstructive sleep apnea is frequent in patients with hypertensive intracerebral hemorrhage and is related to perihematoma edema. Cerebrovasc Dis 29:36–42
89. Woo D, Sauerbeck LR, Kissela BM et al (2002) Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. Stroke 33:1190–1195
90. Gee P, Tallon C, Long N, Moore G, Boet R, Jackson S (2012) Use of recreational drug 1,3 Dimethylamylamine (DMAA) [corrected] associated with cerebral hemorrhage. Ann Emerg Med 60:431–434