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Celine S. Gathier, MD, PhD [a,b,*], IJsbrand A.J. Zijlstra, MD, PhD [c], Gabriel J.E. Rinkel, MD, FRCPE [b], T. Katrien J. Groenhof, MD, PhD [d], Dagmar Verbaan, PhD [e], Bert A. Coert, MD, PhD [e], Marcella C.A. Müller, MD, PhD [f], Walter M. van den Bergh, MD, PhD [g], Arjen J.C. Slooter, MD, PhD [a,h], Marinus J.C. Eijkemans, PhD [d]

[a] Department of Intensive Care Medicine and UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[b] Department of Neurology and Neurosurgery and UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[c] Department of Radiology, Amsterdam University Medical Center, location AMC, University of Amsterdam, Amsterdam, the Netherlands
[d] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[e] Neurosurgical Center Amsterdam, Amsterdam University Medical Center, location AMC, Amsterdam, the Netherlands
[f] Department of Intensive Care, Amsterdam University Medical Center, location AMC, Amsterdam, the Netherlands
[g] Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.
[h] Department of Neurology, UZ Brussel and Vrije Universiteit Brussel, Brussels, Belgium

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ABSTRACT

Introduction and objective: Blood pressure is presumably related to rebleeding and delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (aSAH) and could serve as a target to improve outcome. We assessed the associations between blood pressure and rebleeding or DCI in aSAH-patients.
Materials and methods: In this observational study in 1167 aSAH-patients admitted to the intensive care unit (ICU), adjusted hazard ratio's (aHR) were calculated for the time-dependent association of blood pressure and rebleeding or DCI. The aHRs were presented graphically, relative to a reference mean arterial pressure (MAP) of 100 mmHg and systolic blood pressure (sBP) of 150 mmHg.
Results: A MAP below 100 mmHg in the 6, 3 and 1 h before each moment in time was associated with a decreased risk of rebleeding (e.g. within 6 h preceding rebleeding: MAP = 80 mmHg: aHR 0.30 (95% confidence interval (CI) 0.11–0.80)). A MAP below 60 mmHg in the 24 h before each moment in time was associated with an increased risk of DCI (e.g. MAP = 50 mmHg: aHR 2.59 (95% CI 1.12–5.96)).
Conclusions: Our results suggest that a MAP below 100 mmHg is associated with decreased risk of rebleeding, and a MAP below 60 mmHg with increased risk of DCI.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a subtype of stroke with high morbidity and mortality. Two major contributors to poor outcome after aSAH are rebleeding [1-5] and delayed cerebral ischemia (DCI) [6,7]. These complications occur at different stages after the initial aSAH, with the highest risk of rebleeding in the first hours to days after ictus, and the highest risk of DCI between the third and 14th day after ictus [8].

Both complications seem to be associated with blood pressure, but previous reports have been scarce and inconsistent. The risk of rebleeding was found to be associated with high blood pressure [9-11], particularly systolic blood pressures (sBP) higher than 150 mmHg [9] or 160 mmHg [10-12]. However, another study observed most sBP values within the normal range of 120–140 mmHg prior to rebleeding [13]. Data on blood pressure and DCI are also limited and conflicting. DCI may occur more often in patients with a fall in blood pressure [14] and was associated with intra-operative hypotension in several studies [15-17] but not in a more recent and larger study [18].

As it is currently not clear whether blood pressure is related to rebleeding or DCI, we aimed to assess the associations between blood pressure in the hours preceding rebleeding and DCI and the occurrence of these events.

* Corresponding author at: University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands.
E-mail addresses: c.s.gathier-4@umcutrecht.nl, c.gathier@etz.nl (C.S. Gathier).

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2. Materials and methods

2.1. Design and patients

This is an observational, multicenter cohort study. We retrieved data on all consecutive aSAH patients aged 18 years or older admitted to the intensive care unit (ICU) of the University Medical Center Utrecht (UMCU) and the Amsterdam University Medical Center (AMC) both in the Netherlands, from May 2003, through May 2011. The reason for not expanding this time period beyond 2011 was that from 2013, both centers participated in the ULTRA study in which patients were randomized to tranexamic acid or placebo in order to investigate the effectiveness of tranexamic acid in preventing rebleeding [19].

We defined an aSAH as either a subarachnoid hemorrhage (CT-proven or CT-negative with positive bilirubin in spinal fluid spectrophotometry performed >12 h after ictus) with a detected aneurysm, or a subarachnoid hemorrhage with a definite aneurysmal bleeding pattern in which the responsible aneurysm could not be verified despite CT-angiography or digital subtraction angiography, as these patients are also at risk of developing rebleeding or DCI [20]. We included only those patients of whom blood pressure data were available during ICU admission.

Criteria for ICU admission were a Glasgow Coma Scale of 8 or lower necessitating intubation and mechanical ventilation, or hemodynamic or respiratory instability necessitating intensive care support. Further, patients could be admitted to the ICU after clipping of the symptomatic aneurysm. Patients not fulfilling admission criteria for the ICU were admitted to a dedicated neuro-medium care unit in both centers. All aSAH patients presenting to the UMCU from 2003 to 2011 and all patients presenting to the AMC from 2003 to 2009 were managed this way. Patients in these periods who were admitted to the neuro-medium care unit were not included in the current study because hourly blood pressures for these patients were not available, restricting us from performing the desired statistical analyses (blood pressures were only assessed and documented every four hours). From 2009 to 2011, all aSAH patients presenting to the AMC were admitted to the ICU regardless of their neurological status, and all of those patients were thus included in the current study.

2.2. Procedures

During ICU admission, all patients were treated according to a standardized protocol that consisted of treatment with enteral nimodipine administered 60 mg 6 times per day, cessation of antihypertensive medication on admission and intravenous administration of fluid aiming for normovolemia. In case nimodipine administration resulted in a mean arterial pressure (MAP) drop of >20 mmHg, the administration was changed to 30 mg 12 times orally per day, and if this blood pressure drop was still observed thereafter, intravenous continuous administration or cessation.

Blood pressure management in the ICU differed slightly between the participating centers. In the AMC, there were no strict upper limits to blood pressure prior to aneurysm occlusion until 2010, although sBP reaching 200 mmHg was usually treated. From 2010, MAP was kept below 135 mmHg prior to aneurysm occlusion. After aneurysm occlusion, MAP was kept above 90 mmHg until 2010, and above 80 mmHg from 2010. In the UMCU, a protocol for blood pressure management was installed in 2008. From that moment, sBP was kept below 180 mmHg prior to aneurysm occlusion. After aneurysm occlusion, MAP was kept above 80 mmHg and sBP was accepted until 220 mmHg and MAP until 130 mmHg.

2.3. Data collection

For all patients, data were collected on age, gender, clinical condition on admission according to the World Federation of Neurological Surgeons (WFNS) scale [21], location of the symptomatic aneurysm, modality and timing of aneurysm treatment, amount of extravasated blood on admission CT assessed with the Hijdra-score [22], occurrence of rebleeding and occurrence of DCI. Clinical condition at admission was dichotomized into good clinical condition (WFNS 1–3) and poor clinical condition (WFNS 4–5). The amount of extravasated blood was also dichotomized at the median for both cisternal (sumscore range 0–30) and ventricular (sumscore range 0–12) blood and added to a total Hijdra sum score.

For analysis on rebleeding, we decided a priori to use both the MAP and sBP. For analysis on DCI, we decided a priori to use the MAP, as MAP is directly related to cerebral perfusion pressure which is an important factor in maintaining adequate cerebral perfusion [23]. Intra-arterial blood pressures were measured continuously and stored in the electronic data servers at both ICUs. From these measurements, only the hourly, nurse-validated blood pressures were extracted for statistical analyses. Since these validated measures can still be inaccurate based on typographical error, outliers based on typographical error were manually removed by CGT blinded for outcome measures. This did not result in the exclusion of patients.

2.4. Endpoints

The primary outcome measures were rebleeding and DCI during ICU admission. All rebleeding and DCI events during hospital admission were assessed, but as blood pressure was only extracted during ICU admission and we were interested in the direct relation between blood pressure and the outcome measures, only the events during ICU admission were used in the analyses. Rebleeding was defined as either definite (CT-proven) or probable (defined as an acute clinical deterioration suspected for rebleeding by the treating physician). For the statistical analyses, both definite and probable rebleeding were combined. DCI was defined as a new clinical deterioration which could not be explained by other causes than DCI, following current consensus criteria [24]. Both outcome events were assessed by one of the researchers (CGT) by manually screening all patient records for the mentioning by the treating physician of either DCI or rebleeding, the mentioning of clinical deterioration, or the performance of additional CT scans without a clear reason mentioned in the patients records but suggesting a possible deterioration in the patient. Subsequently, any other possible reasons for deterioration were assessed by reviewing additional patient records (laboratory results, CT scan results, EEG results when suspicion of a seizure was made by the treating physician). The conclusion of DCI was then made by CGT only in case of exclusion of any other possible cause of the deterioration. In case of any doubt, cases were discussed with other authors. The timing of rebleeding and DCI was estimated based on patients' records and the time of the CT scan performed to rule out other possible causes of the deterioration. Both outcomes were assessed without prior knowledge of the blood pressure during ICU admission.

2.5. Ethics

The ethical review board of the AMC and UMCU approved of the study protocol and waived the need for informed consent (W11_091#11.17.0895 respectively 13–137/C).

2.6. Statistical analyses

Cox proportional hazard analysis with MAP or sBP as time dependent covariate was used to calculate hazard ratios (HR) in two different models for either rebleeding and DCI with corresponding 95% confidence intervals (CI). Adjustments were made for a priori selected possible confounders: age, sex, WFNS-score, aneurysm treatment modality (clipping versus endovascular treatment in the analyses for DCI, treated or not treated in the analyses for rebleeding), treatment center, Hijdra

sumscore and, for analyses on DCI only, rebleeding (prior to development of DCI, time dependent variable). A statistically significant association was concluded when the 95% CI of a hazard ratio did not cross '1'.

For our main analysis, we analyzed the time dependent association between blood pressure and the occurrence of either rebleeding or DCI. We created time-lag blood pressure variables that represented the highest and lowest blood pressure within a certain timeframe preceding every available hourly timepoint. For rebleeding, we assumed that the association between blood pressure and rebleeding would be based on high blood pressures and that this would be a more acute association. Therefore, these time-lag blood pressure variables were based on the highest MAP and sBP in the 1, 3 and 6 h preceding every hourly timepoint. For DCI, we expected that the association between blood pressure and DCI would be based on low blood pressures and that this would be a more gradual association [25,26]. Therefore, these time-lag blood pressure variables were based on the lowest MAP within 12 and 24 h preceding every hourly timepoint. We subsequently investigated the association between each of the time-lag blood pressure variables and the occurrence of rebleeding or DCI respectively. We will explain how Cox regression with these time dependent variables works based on the example of DCI. Take a patient who develops DCI at e.g. hour 36 after admission to the ICU. At that timepoint, the analysis looks at this patient with an event and also all other patients in the dataset who did not yet have an event and had not yet been censored at time = 36 h. These latter patients serve as the controls at that timepoint. Using the time-lag blood pressure variable, the lowest blood pressure in the 12 and 24 h preceding time = 36 h is determined for the DCI patient and the control patients. This is repeatedly performed at all timepoints at which a patient experienced DCI. By comparing the time-lag blood pressure variable between the patients with DCI and all controls at all DCI-times, the association between the time-lag blood pressure variables and DCI can be estimated. Concerning rebleeding, we forwarded the estimated timing of the rebleeding in all patients by one hour, in order to avoid a self-fulfilling prophecy by including increased blood pressure values actually *caused* by the rebleeding.

We also assumed that the effect of blood pressure on the risk of rebleeding or DCI was not the same over the whole range of blood pressures, and was therefore non-linear. The effects were thus modelled using restricted cubic splines, using a reference blood pressure value where the adjusted hazard ratio equals 1.

Censoring is a key characteristic in survival analyses and might influence the relation under study (informative censoring). In our study, censoring might have been informative in certain situations. Patients who died during ICU admission because of a poor clinical condition might have been at increased risk for DCI, which would lead to informative censoring. Therefore, we performed a sensitivity analysis for the possibility of informative censoring using two extremes: scenario 1) all patients who were censored because they died in the ICU developed rebleeding/DCI; scenario 2): all patients who were censored because they died in the ICU were immune for development of rebleeding/DCI. As this study was not designed for prediction of rebleeding or DCI, adding competing event analyses was not deemed necessary.

3. Results

During the study period, 1263 aSAH-patients were admitted to both ICUs. Blood pressure data were not available for 96 of these patients (8%), leaving 1167 aSAH-patients included in the study. Of these 1167 patients, 171(15%) aSAH patients were admitted to the AMC from 2009 to 2011, the period where all aSAH patients were admitted to the ICU of the AMC, regardless of neurological status. Of these 171 patients, 80 (7% of the entire study population) were in a good clinical condition (WFNS 1–3) and would have otherwise been admitted to a neuro-medium care unit.

As shown in Table 1, the mean age of the patients was 56 years (standard deviation 13) and 804 (69%) were female. The primary outcome of rebleeding and DCI during ICU admission was known for all patients. Rebleeding occurred in 45 (4%) patients (36 definite, 9 probable). DCI occurred in 110 (9%) patients. Median time from ictus to rebleeding was 2 days (interquartile range (IQR) 1–4.5) and to DCI 4 days (IQR 2.75–7). Median time between ictus and ICU admission was 1 day (IQR 0–2), with 908 (78%) patients being admitted to the ICU ≤ 48 h after ictus. Median length of ICU stay was 2 days (IQR 0–6). Patients in the AMC were more often coiled and had larger amounts of blood on their initial CT scan as compared to patients in the UMCU. The proportion of patients developing rebleeding or DCI was the same in both centers.

Supplementary table 1 shows the baseline characteristics for patients who did or did not develop rebleeding or DCI. Patients who developed rebleeding more often had a poor WFNS score on admission, had larger amounts of blood on their initial CT scan, were more often not treated for their aneurysm, and more often had an aneurysm in the anterior circulation or an aneurysm that was not detected. Patients who developed DCI more often had a poor WFNS score on admission, larger amounts of blood on the initial CT scan and were more often treated with an endovascular procedure as compared to patients who did not develop DCI in the ICU.

The distributions of MAP and sBP in the first 48 h of ICU admission are shown in Fig. 1. Mean sBP was around 150 mmHg, with distributions ranging from 70 to 230 mmHg and outliers around 250 mmHg. Mean MAP was around 95 mmHg, with distributions ranging from 50 to 140 mmHg and outliers around 150 mmHg.

Table 1
Baseline characteristics.

Variables	Entire study population $n = 1167$	AMC $n = 500$	UMCU $n = 667$
Age in years (mean, SD)	56 (13)	55 (13)	57 (13)
Female (%)	804 (69)	343 (69)	461 (69)
Hypertension*	311 (27)	121 (24)	189 (28)
Antihypertensive drugs**	264 (23)	98 (20)	165 (25)
WFNS score > 3	567 (49)	256 (51)	311 (47)
Aneurysm treatment			
Coil (%)	446 (38)	302 (60)	144 (22)
Clip (%)	453 (39)	108 (22)	345 (52)
Other (%)	7 (0,5)	1 (0)	6 (1)
No treatment (%)	261 (22)	89 (18)	166 (25)
No aneurysm found (%)	46 (4)	17 (3)	29 (4)
Rebleeding (%)***	211 (18)	86 (18)	125 (19)
In the ICU (%)	45 (4)[#]	18 (4)	27 (4)
DCI (%)	255 (22)	136 (27)	119 (18)
In the ICU (%)	110 (9%)	52 (10)	58 (9)
Aneurysm location			
Anterior circulation (%)	780 (67)	323 (65)	457 (69)
Posterior circulation (%)	318 (27)	142 (28)	176 (26)
Not found (%)	69 (6)	35 (7)	34 (5)
Hijdra scores****			
Sum score cisterns > median 24 (%)	527 (45)	256 (55)	271 (42)
Sum score ventricles > median 2 (%)	533 (46)	226 (49)	307 (48)
Total sum score > median 26 (%)	568 (49)	270 (58)	298 (46)
ICH present*****	290 (25)	137 (29)	153 (24)
Length of ICU stay (days) median [IQR]	2 [0–6]	2 [1–6]	2 [1–6]
Time ictus to rebleeding in the ICU (days) median [IQR]	2 [1–4.5]	1 [1–3.5]	2 [1–8]
Time ictus to DCI in the ICU (days) median [IQR]	4 [2.75–7]	4 [2–6.75]	6 [3–9]

AMC: Amsterdam University Medical Center; UMCU: University Medical Center Utrecht; WFNS: World Federation of Neurological Surgeons; ICU: intensive care unit; DCI: delayed cerebral ischemia; ICH: intracerebral hematoma; IQR: interquartile range.
* 38 missing; **:79 missing; *** 10 missing; **** 55 missing; ***** 47 missing.
[#] in 6 patients rebleeding occurred after coiling, in 2 patients rebleeding occurred after clipping.

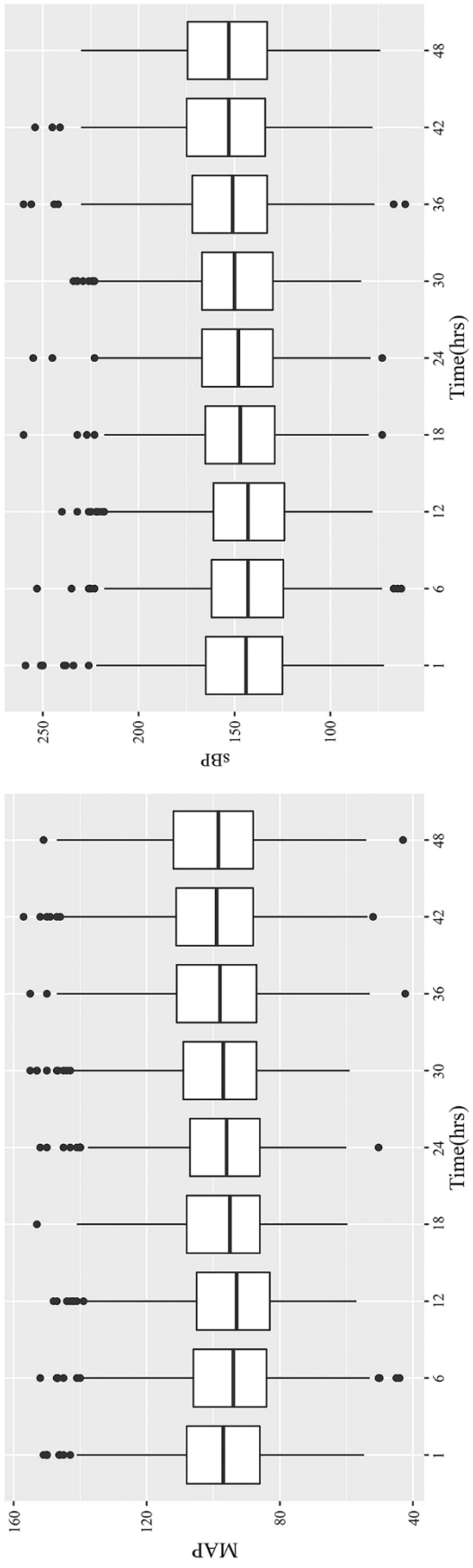


Fig. 1. Distribution of blood pressure in the first 48 h of ICU admission.
MAP: mean arterial pressure, sBP: systolic blood pressure.

3.1. Rebleeding

A MAP below 100 mmHg in the 6, 3 and 1 h before every moment was associated with a decreased risk of rebleeding. The spline curves and aHRs for MAP with corresponding 95% CIs are shown in Fig. 2. No association was found between sBP values and rebleeding. The spline curves and aHRs for sBP with corresponding 95% CIs are shown in Fig. 3

3.2. DCI

A MAP below 60 mmHg in the 24 h before every moment was associated with an increased risk of DCI. No association was found between MAP values in the 12 h preceding every moment and DCI. The spline curves and aHRs with corresponding 95% CI are shown in Fig. 4.

3.3. Sensitivity analyses

The results of the sensitivity analyses are shown in the supplementary material. For rebleeding, the number of events increased to 213 with extreme scenario 1 and decreased to 44 with extreme scenario 2. For DCI, the number of events increased to 298 with extreme scenario 1 and decreased to 105 with extreme scenario 2.

For rebleeding, the direction of the effect for MAP and sBP and rebleeding changed with extreme scenario 1.A MAP below 100 mmHg and a sBP below 150 mmHg in the 6, 3 and 1 h preceding every moment were associated with an increased risk of rebleeding. Further, concerning MAP, a MAP of 130 mmHg and higher in the 6 and 3 h preceding every moment, and a MAP of 150 mmHg and higher in the 1 h preceding every moment were associated with increased risk of rebleeding. Concerning sBP, a sBP of 160, 170 and 180 mmHg was associated with a decreased risk of rebleeding in the 6 and 3 h preceding every moment and a sBP of 160 was associated with a decreased risk of rebleeding in the 1 h preceding every moment. Further, a sBP of 220 mmHg and higher in the 6 and 1 h preceding every moment was associated with increased risk of rebleeding, as well as a sBP of 210 and higher in the 3 h preceding every moment.

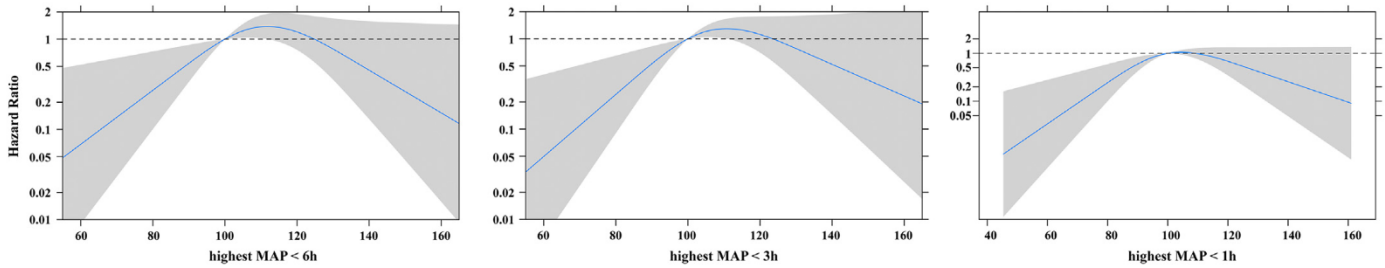
With extreme scenario 2, a sBP of 160 and 170 mmHg in the 3 h preceding every time point became associated with increased risk of rebleeding. For the other analyses, both the direction and the magnitude of the effect for MAP and sBP and rebleeding were unchanged compared to the main analyses.

For DCI, the direction of the effect for MAP and DCI remained unchanged but the magnitude of the effect increased with extreme scenario 1: a MAP of 70 mmHg or lower was associated with increased risk of DCI, both within 24 and 12 h preceding every moment. With extreme scenario 2, the direction of the effect for MAP and DCI changed, but was never associated with the risk of DCI.

4. Discussion

We found that MAP values lower than 100 mmHg in the 6, 3 and 1 h preceding each moment were associated with a decreased risk of rebleeding, and that MAP values below 60 mmHg in the 24 h preceding each moment were associated with an increased risk of DCI.

Previous studies showed conflicting results concerning rebleeding, as some reported an association between high sBP values and rebleeding [9-12,27], while others did not [28,29]. In our study, we found that lower MAP values were associated with decreased risk of rebleeding, which seems biologically plausible. However, the inverted U-shape curve for rebleeding (with higher MAP values also trending towards lower rebleeding risk) seems to lack biologically plausibility. Even though we adjusted for aneurysm securement as a possible confounder, a modelling effect cannot be fully excluded. However, we would like to stress that, as 95% confidence intervals of these hazard ratios all cross '1' and are very wide, there is actually no evidence from our



Highest MAP < 6 h (mmHg)	aHR	95% CI
60	0.07	0.01 – 0.52
70	0.14	0.03 – 0.62
80	0.27	0.10 – 0.73
120	1.20	0.76 – 1.90
130	0.78	0.36 – 1.70
140	0.45	0.13 – 1.58
150	0.26	0.05 – 1.51
160	0.15	0.02 – 1.47

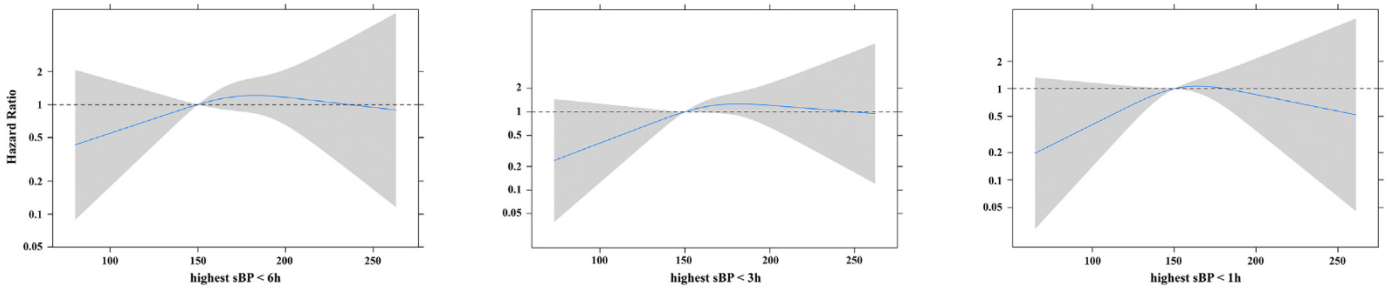
Highest MAP < 3 h (mmHg)	aHR	95% CI
60	0.05	0.01 – 0.40
70	0.11	0.02 – 0.51
80	0.24	0.09 – 0.65
120	1.12	0.71 – 1.77
130	0.78	0.34 – 1.80
140	0.52	0.15 – 1.87
150	0.35	0.06 – 1.97
160	0.23	0.03 – 2.09

Highest MAP < 1 h (mmHg)	aHR	95% CI
60	0.03	0.00 – 0.28
70	0.09	0.02 – 0.41
80	0.24	0.10 – 0.59
120	0.68	0.35 – 1.34
130	0.42	0.13 – 1.34
140	0.25	0.05 – 1.34
150	0.16	0.02 – 1.35
160	0.09	0.01 – 1.36

Fig. 2. Risk of rebleeding per MAP value in the 6, 3 and 1 h preceding every moment.
MAP: mean arterial pressure.
The non-linear effect is presented graphically, with blood pressure values (X-axis) plotted against the adjusted hazard ratio (Y-axis), using a reference value of 100 mmHg MAP for an adjusted hazard ratio of 1.

data that higher MAP values are associated with a lower risk of rebleeding.

Concerning DCI, the association between impaired cerebral autoregulation and DCI is well established [30-37]. However, the association between blood pressure and DCI is not. In one study, a drop in sBP was observed more often in patients who developed DCI as compared to those who did not [14] and treating hypertension resulted in increased risk of DCI [38,39]. However, in another study, MAP in the three days before DCI was actually higher in patients who developed DCI as compared to those who did not [40]. Intraoperative hypotension was associated with vasospasm [17] or DCI [16] in some studies, and a recent small matched case-control study suggested that DCI could be prevented by keeping intraoperative sBP above 95 mmHg, diastolic blood pressure above 50 mmHg and MAP above 62 mmHg [41]. However, intraoperative hypotension was found not associated with DCI in another study [18], and a more recent large observational study of 1099 patients

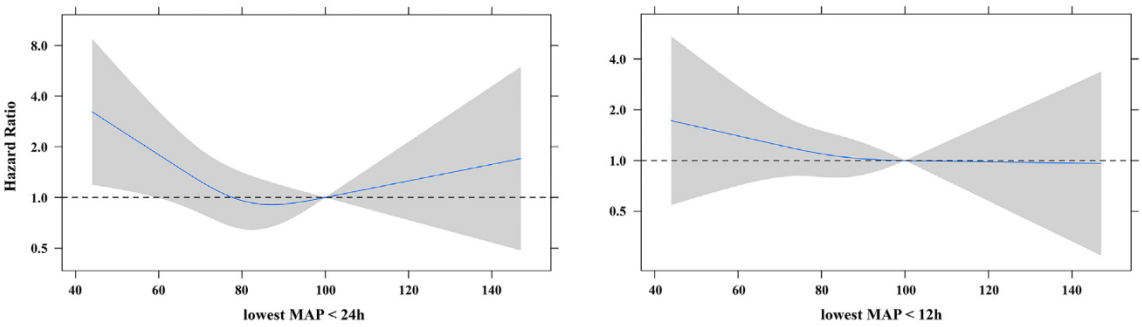


Highest sBP < 6 h (mmHg)	aHR	95% CI
120	0.70	0.36 – 1.36
130	0.79	0.51 – 1.22
140	0.89	0.72 – 1.10
160	1.10	0.93 – 1.31
170	1.18	0.88 – 1.57
180	1.21	0.84 – 1.73

Highest sBP < 3 h (mmHg)	aHR	95% CI
120	0.58	0.30 – 1.14
130	0.70	0.46 – 1.09
140	0.85	0.69 – 1.04
160	1.14	0.98 – 1.32
170	1.23	0.96 – 1.57
180	1.26	0.90 – 1.76

Highest sBP < 1 h (mmHg)	aHR	95% CI
120	0.61	0.34 – 1.08
130	0.74	0.53 – 1.05
140	0.88	0.76 – 1.02
160	1.06	0.94 – 1.19
170	1.06	0.82 – 1.36
180	1.01	0.65 – 1.57

Fig. 3. Risk of rebleeding per sBP value in the 6, 3 and 1 h preceding every moment.
sBP: systolic blood pressure.
The non-linear effect is presented graphically, with blood pressure values (X-axis) plotted against the adjusted hazard ratio (Y-axis), using a reference value of 150 mmHg sBP for an adjusted hazard ratio of 1.



Lowest MAP < 24 h (mmHg)	aHR	95% CI
50	2.59	1.12 – 5.96
60	1.79	0.99 – 3.24
70	1.25	0.81 – 1.93

Lowest MAP < 12 h (mmHg)	aHR	95% CI
50	1.59	0.61 – 4.20
60	1.40	0.71 – 2.76
70	1.23	0.80 – 1.90

Fig. 4. Risk of DCI per MAP value in the 24 and 12 h preceding every moment.
MAP: mean arterial pressure, DCI: delayed cerebral ischemia.
The non-linear effect is presented graphically, with blood pressure values (X-axis) plotted against the adjusted hazard ratio (Y-axis), using reference value of 100 mmHg MAP for an adjusted hazard ratio of 1.

showed no association between intraoperative hypotension and poor outcome after aSAH [42]. The association we found between MAP of 60 mmHg or lower and an increased risk of DCI is therefore difficult to put in perspective against these previous conflicting results, and is further complicated by the varying definitions of blood pressure and varying statistical analyses that have been used. It is plausible however that a MAP below 60 mmHg would increase the risk of DCI, as maintaining a constant cerebral blood flow through cerebral autoregulation may become impaired with MAP below 60 mmHg [43,44].

With the sensitivity analysis for extreme scenario 1, several changes in the association between blood pressure and the outcome events were seen, probably due to the fact that the number of outcome events increased substantially when all patients who died during ICU admission were added. For rebleeding, this resulted in two changes: both higher MAP values (over 130 mmHg) and higher sBP values (over 210 mmHg) as well as lower MAP values (below 100 mmHg) became associated with an increased risk of rebleeding. Concerning lower MAP values associated with rebleeding: as extreme scenario 1 assumes that all patients who died in the ICU also had suffered a rebleeding, it is more likely that we are observing the association between lower blood pressures and an increased risk of death. Concerning higher MAP and sBP values now being associated with increased risk of rebleeding, this is probably mainly related to the substantial increase in case numbers with all patients who died in the ICU now representing a rebleeding case.

For DCI, an increased association was found for low MAP values and increased risk of DCI which we feel is again more likely the reflection of the fact that we are observing the association between low blood pressure and risk of death.

The most important strength of this study is that we were able to assess the time-dependent relation between blood pressure and rebleeding or DCI in a precise way, as we were able to collect extensive data on blood pressures in an hourly fashion in a large study population and could accurately time all the events of rebleeding and DCI.

Our study has several limitations. First, we included only aSAH patients who were admitted to the ICU. We did include 80 (7% of entire study population) patients to the ICU of the AMC during 2009–2011 that were in good clinical condition who would have otherwise not been admitted to the ICU during the previous time period of 2003–2009, but these patients were managed just the same as aSAH patients in poor clinical condition concerning their blood pressure management. As blood pressures are kept within strict limits in the ICU, we were only able to assess the variation in blood pressure within these limits. Further, ICU treatment comes with other issues that might influence blood pressure, such as tube irritation and sedation. This makes our results less generalizable to an aSAH population not admitted to the ICU.

Second, median length-of-stay in the ICU was quite short (2 days), which could have influenced the frequency of the outcome events of DCI or rebleeding during ICU admission.

Third, as we defined DCI as a clinical deterioration with exclusion of other causes, it might have been that certain cases of DCI were missed, particularly in patients with high WFNS scores.

Fourth, we had no information on blood pressure levels prior to ICU admission. Especially for patients who developed rebleeding or DCI shortly after ICU admission, these blood pressure levels might have been important for assessing the association between blood pressure and the outcome event.

Fifth, as lower intravascular volume status is associated with development of DCI, this could have served as a potential confounder in the analyses concerning DCI. Unfortunately, we had no data available on fluid balances, and intravascular assessment of the intravascular volume state (for instance via echocardiography) was not routinely performed in the participating centers during the included time period. We were therefore unable to adjust for this potential confounder in a standardized way.

Sixth, outliers in validated blood pressure values were manually removed, blinded for outcome measures. However, as this did not result in the exclusion of patients, we feel that this will not have majorly impacted our results.

Seventh, our series included 96 patients in whom no aneurysm was detected despite having an aneurysmal bleeding pattern. These patients might have lower risk of rebleeding. However, as these patients only made up 8% of our entire study population, we felt it not useful to add a sensitivity analyses with and without these patients.

Another possible limitation is that our dataset was rather old and spans a long (9-year) period, which might impair generalizability to current patients. However, as the presence or absence of an association between blood pressure and rebleeding or DCI will not change in time,

we feel that the rather old dataset will not have had a major influence on our results.

We excluded 96 patients because of missing blood pressure data. However, as this was only a small proportion (8%) of all patients and the occurrence of rebleeding or DCI occurs independent of the availability of blood pressures, we do not feel that this has affected our results.

There were some baseline differences between the two centers. However, the proportion of patients developing rebleeding or DCI did not differ. By adding treatment center as a variable to adjust for in our analyses, we have tried to take these in-between center differences into account.

5. Conclusion

Our observational data suggest that a MAP below 100 mmHg is associated with decreased risk of rebleeding, and a MAP below 60 mmHg with an increased risk of DCI. Whether lowering MAP below 100 mmHg will prevent rebleeding, or avoiding a MAP below 60 mmHg will prevent DCI could be subject of future prospective research.

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Author's contributions

C.S. Gathier designed, drafted, revised and performed data acquisition for the work.

IJ.A.J. Zijlstra performed data acquisition for the work and made a substantial contribution to the interpretation of the data and revision of the work.

G.J.E. Rinkel designed the work and made a substantial contribution to the interpretation of the data and revision of the work.

T. K. J. Groenhof performed data acquisition for the work and made a substantial contribution to the interpretation of the data and revision of the work.

D. Verbaan made a substantial contribution to the interpretation of the data and revision of the work.

M.C.A. Müller made a substantial contribution to the interpretation of the data and revision of the work.

B.A. Coert made a substantial contribution to the interpretation of the data and revision of the work.

W.M. van den Bergh made a substantial contribution to the interpretation of the data and revision of the work.

A.J.C. Slooter designed the work and made a substantial contribution to the interpretation of the data and revision of the work.

M.J.C. Eijkemans made a substantial contribution to the interpretation of the data and revision of the work.

Declaration of Competing Interest

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3. G.J.E. Rinkel reports no conflict of interest.
4. T. K. J. Groenhof reports no conflict of interest.
5. D. Verbaan reports no conflict of interest.
6. M.C.A. Müller reports no conflict of interest.
7. B.A. Coert reports no conflict of interest
8. W.M. van den Bergh reports no conflict of interest.
9. A.J.C. Slooter reports no conflict of interest.
10. M.J.C. Eijkemans reports no conflict of interest.

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