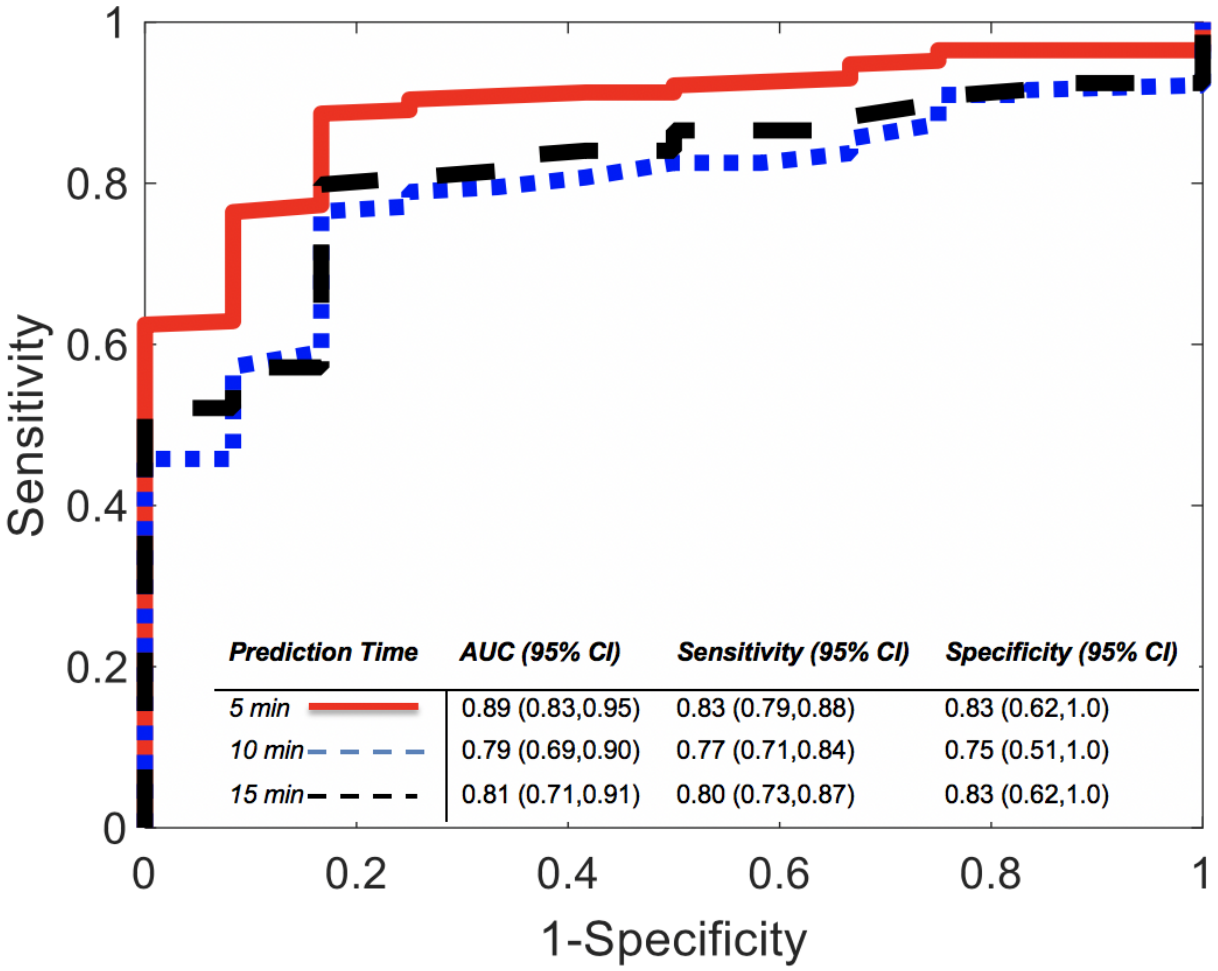
Supplementary Online Content

Wijnberge M, Geerts BF, Hol L, et al. Effect of a machine learning–derived early warning system for intraoperative hypotension vs standard care on depth and duration of intraoperative hypotension during elective noncardiac surgery: the HYPE randomized clinical trial [published online February 17, 2020]. *JAMA*. doi:10.1001/jama.2020.0592

This supplementary material has been provided by the authors to give readers additional information about their work.

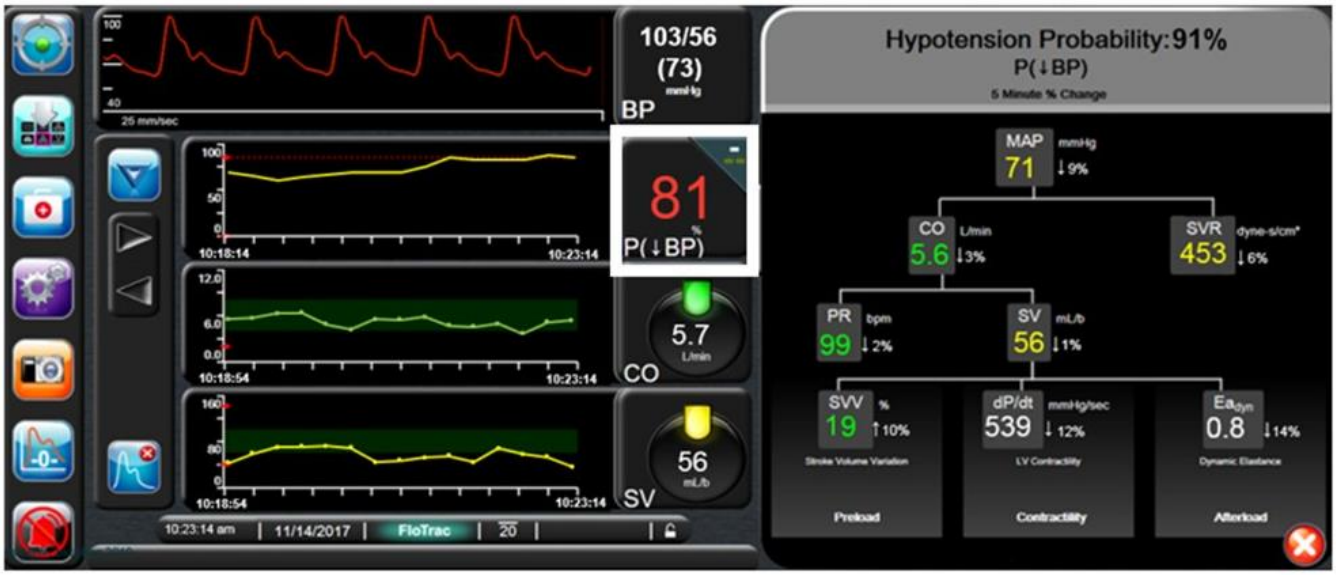
eFigure 1. Performance of the Early Warning System in the Observational Study Group (ROC Analysis)



Receiver under the operating curve (ROC) plot in the observational study group.
In this figure we show the performance of the early warning system in our observational study population (n=40 patients, including 360 hypotensive events and 183 hours of surgery). The exact same methods were used as published by Hatib et al.[1] First the early warning system (the hypotension prediction index) Youden Index was calculated at the three timepoints. The Youden Index at 5 minutes prior to hypotension was 50, the Youden Index at 10 minutes prior to hypotension was 39 and the Youden Index 15 minutes prior to hypotension was 40. Second the ROC curves were plotted at 5, 10 and 15 minutes before a hypotensive event. The sensitivity and specificity at these specific time points were calculated. Of note, these results should be interpreted with caution due to the limited sample size.

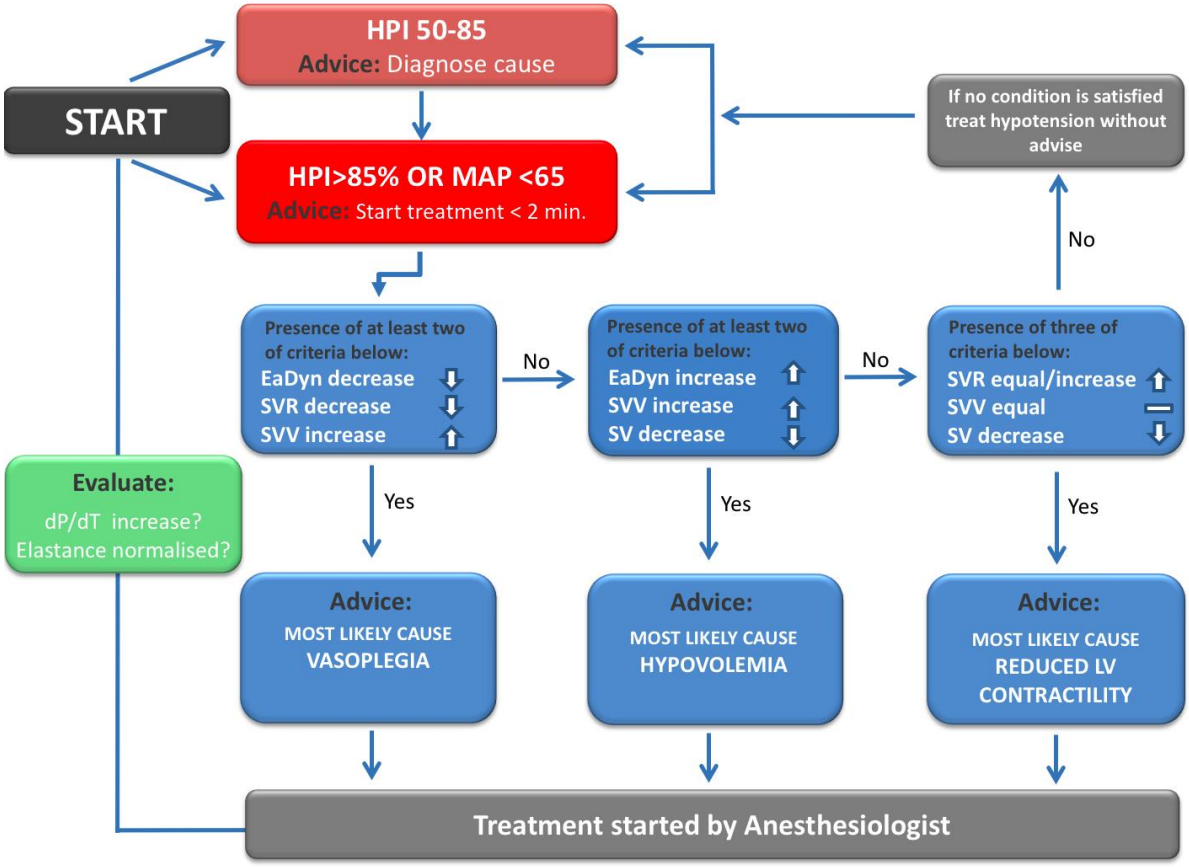
1. Hatib F, Jian Z, Buddi S, et al. Machine-learning Algorithm to Predict Hypotension Based on High-fidelity Arterial Pressure Waveform Analysis. *Anesthesiology.* 2018;129(4):663-674.

eFigure 2. HemoSphere Monitor and Secondary Screen



The early warning system is able to predict hypotension before it occurs. An early warning alarm value (the red number in the figure) above 85 translates approximately to an 85% chance of hypotension to occur in the following minutes. The variables in the secondary screen provide information about the underlying cause of the (predicted) hypotension. These variables include: mean arterial blood pressure (MAP), cardiac output (CO), systemic vascular resistance (SVR), pulse rate (PR), stroke volume (SV), stroke volume variation (SVV), a measure of left ventricular contractility from an arterial pressure waveform (dP/dt) and dynamic arterial elastance (Eadyn). Interpretation of these variables requires in depth hemodynamic knowledge, knowledge that anesthesiologists possess. Furthermore, the attending anesthesiologist is provided with a diagnostic flowchart to help diagnose the underlying cause. Every 20 seconds, the early warning system alarm value (visible in the figure as the red number 81) is recalculated. When the early warning system alarm value exceeds 85%, an alarm indicates that a patient may be trending towards a hypotensive event (MAP < 65 mmHg). The attending anesthesiologist will then use the variables on the second screen and the hemodynamic diagnostic guidance and treatment flowchart (eFigure 3) to diagnose and treat the underlying cause of the predicted hypotension.

eFigure 3. Hemodynamic Diagnostic Guidance and Treatment Protocol Explanation



The hemodynamic variables continuously inform the anesthesiologist about the patient's hemodynamic status. When the early warning system alarm exceeds the value 85 or if the Mean Arterial blood Pressure (MAP) drops below 65 mmHg, the treating anesthesiologist actively searches for the underlying cause of the predicted hypotension. Broadly, hypotension can be caused by a preload (hypovolemia), contractility or afterload (vasoplegia) problem. The behavior of the various hemodynamic variables over time can be screened and by making combinations (presence of at least two or three criteria) the most likely cause of hypotension can be diagnosed. For example, the combination of an increase (arrow up) in stroke volume variation, and a decrease (arrow down) in systemic vascular resistance results in the diagnosis of vasoplegia.

The suggested treatment advice for vasoplegia are vasopressors, the suggested treatment advice for hypovolemia are fluids (crystalloid of colloids) and the suggested treatment advice for reduced contractility is to administer inotropes. If more than one underlying cause was present based on the criteria the advice was to treat both underlying problems and administer a combination of treatments. The anesthesiologists were free to choose the dose of the fluids and drugs they wanted to administer.

The hemodynamic diagnostic guidance and treatment protocol was based on previous research published[1]

1. Pinsky M Protocolized cardiovascular management based on ventricular-arterial couping. In: Functional Hemodynamic Monitoring. Update in Intensive Care and Emergency Medicine. Springer-Verlag, Berlin, 381 - 395. ISBN 3540223495

eTable 1. Observational Study Baseline Characteristics

Patient characteristics	Observational study(n=40)
Male, No.(%)	20 (50)
Age, years	67 [59 - 72]
Male, No. (%)	20 (50)
Female, No. (%)	20 (50)
BMI, kg/m^2	24 [22 – 27]
ASA classification, No.(%)[a]	
1 – normal, healthy	2 (5)
2 – mild systemic disease	24 (60)
3 – severe systemic disease	13 (33)
4 – life-threatening disease	1 (3)
WHO classification, No.(%)[b]	
0 – fully active	12 (30)
1 – ambulatory and light work	20 (50)
2 – ambulatory but unable to work	7 (18)
3 - >50% confined to bed or chair	0 (0)
4 –Totally confined to bed or chair	1 (3)
MAP outpatient clinic, mmHg	100 [92 – 110]
MAP day before, mmHg	97 [92 -107]
MAP before induction, mmHg	98 [90 – 111]
Type of surgery, No.(%)	
Gynaecological	3 (8)
Gastrointestinal	36 (90)
Pancreas	*12 (33)*
Oesophagus	*14 (39)*
Other	1 (3)
Surgical approach, No.(%)	
Laparotomy	16 (40)
Laparoscopic	6 (15)
Conversion	4 (10)
Combined	14 (35)
Duration of surgery, min[c]	272 [197 – 377]
Duration of anesthesia, min[d]	323 [238-436]

Prior to launching the RCT, a short observation study was conducted to ensure to control group was a representative sample of standard care in our hospital. The data collected including time-weighted average in hypotension was collected (see eTable 2). The only difference in methods between the control group in the RCT and the short observational was that the anesthesiologist was not aware of the aim of the study (to assess hypotension) in the observational study group.

ASA= American society of Anesthesiologists. WHO= World Health Organization. MAP= mean arterial pressure. Continuous data are presented as median with interquartile range [IQR]. Categorical data are given as number with percentages.

[a] The ASA classification was defined as ASA 1: a normal healthy person, ASA 2: a patient with mild systemic disease, ASA 3: a patient with severe systemic disease, ASA 4: a patient with severe systemic disease that is constant threat to life. [1,2]

[b] The WHO classification was defined as WHO 0: Fully active, able to carry on all pre-disease performance without restriction, WHO 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work, WHO 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, WHO3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours, WHO4: Complete disabled. Cannot carry on any self-care. Totally confined to bed or chair.[3,4]

[c] duration of surgery was calculated in minutes form the time of incision until closure of the surgical wound.

[d] duration of anesthesia was calculated in minutes from administration of first anesthetic drug (sufentanil, lidocain, propofol) until extubation. If extubation was not in the operation room but at the ICU of PACU the time of leaving the operation room was noted as end of anesthesia.

1. Doyle DJ, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). In: *StatPearls.* Treasure Island (FL): StatPearls Publishing. StatPearls Publishing LLC.; 2019.
2. Knuf KM, Maani CV, Cummings AK. Clinical agreement in the American Society of Anesthesiologists physical status classification. *Perioperative medicine (London, England).* 2018;7:14.
3. Federici S, Bracalenti M, Meloni F, Luciano JV. World Health Organization disability assessment schedule 2.0: An international systematic review. *Disability and rehabilitation.* 2017;39(23):2347-2380.
4. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American journal of clinical oncology.* 1982;5(6):649-655.

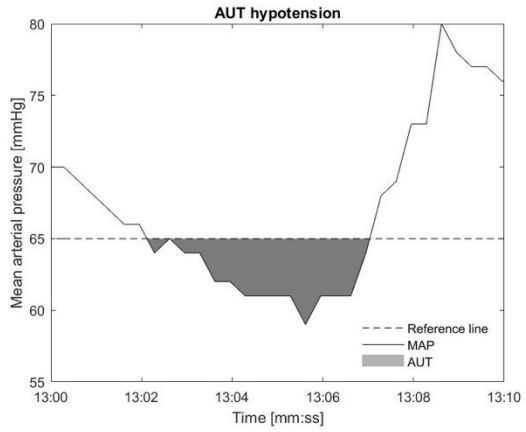
eTable 2. Observational Study vs Control Group RCT

	Observational study	Control group RCT	Median differences with 95%CI[a]	P-value[b]
Primary endpoint Hypotension				
Time-weighted average in hypotension, mmHg	0.44 [0.16 – 0.76]	0.44 [0.23 – 0.72]	-0.5 (-0.22 to 0.14)	.48
Hypotension				
AUT, mmHg*min[c]	80.00 [27.92 – 248.96]	142.17 [64.67 – 258.92]	35.58 (-21.00 to 86.50)	.24
Incidence	6.00 [2.00 – 11.00]	8.00 [3.50 – 12.00]	2.00 (-1.00 to 5.00)	.22
Total time, min	17.50 [7.58 – 47.58]	32.67 [11.50 – 59.67]	6.17 (-5.33 to 19.00)	.31
% of time	8.89 [2.71 – 16.83]	10.34 [4.59 – 15.55]	0.86 (-3.13 to 4.46)	.67
Hypertension				
TWA, mmHg	0.01 [0.00 – 0.22]	0.05 [0.00 – 0.13]	0.00 (0.00 to 0.05)	.39
AAT, mmHg*min[c]	1.92 [0.00 – 54.67]	13.33 [0.00 – 44.25]	2.17 (0.00 to 13.33)	.20
Incidence	1.00 [0.00 -1.75]	1.00 [0.00 -2.00]	0.00 (-1.00 to 0.00)	.18
Total time, min	0.83 [0.00 – 5.17]	3.00 [0.00 – 6.83]	0.33 (0.00 to 2.33)	.24
% of time	0.30 [0.00 – 2.80]	0.85 [0.00 – 1.91]	0.00 (-0.20 to 0.76)	.45
Treatment behavior				
Reaction time, seconds[d]	95.5 [42.8 – 170.7]	87.3 [53.0 – 172.5]	-1.8 (-18.9 to 16.6)	.86
Post-hoc endpoints				
Treatments				
Incidence treatments[e]	5.00 [2.00 – 7.75]	9.00 [3.50 – 13.00]	3.00 (1.00 to 6.00)	**.02**
Early warning system alarms				
TWA, HPI	4.03 [2.10 – 6.78]	4.31 [2.50 – 5.79]	0.13 (-1.12 to 1.50)	.87
AAT, HPI*min[c]	908.67 [423.83 – 2255.67]	1231.00 [701.50 – 1966.33]	160.17 (-301.33 to 599.33)	.46
Incidence	9.50 [6.00 – 14.00]	11.00 [8.00 – 14.50]	1.00 (-2.00 to 4.00)	.44
Total time, min	95.83 [43.00 – 187.50]	116.33 [68.33 – 170.33]	13.00 (-26.33 to 50.67)	.39
% of time	41.96 [22.99 – 59.11]	41.14 [23.93 – 56.35]	-0.65 (-12.44 to 9.40)	.89

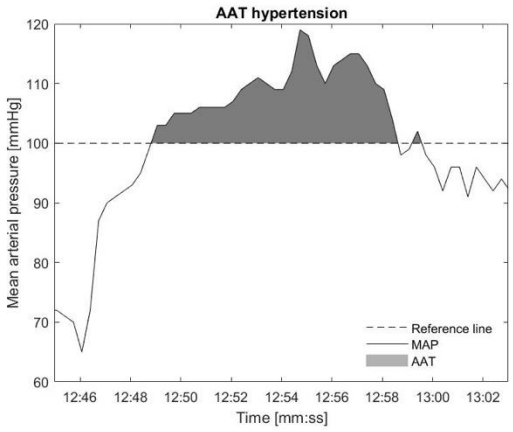
Prior to launching the RCT, a short observation study was conducted to ensure to control group was a representative sample of standard care in our hospital. The only difference in methods between the control group in the RCT and the short observational was that the anesthesiologist was not aware of the aim of the study (to assess hypotension) in the observational study group. There are no significant differences in hypotension or hypertension endpoints between the observational study group and the control group. This table illustrates that our control group was indeed a representative sample of standard care.
All endpoints are medians per patient. The incidence of hypotension, hypertension and early warning system alarms presents the median number of events per patient. Continuous data are presented as median with interquartile range [IQR] and median differences with their 95% confidence intervals (CI). HPI= hypotension prediction index, the variable of the early warning system illustrating the prediction of hypotension. MAP = mean arterial pressure. TWA = time-weighted average. AUT = area under the threshold. AAT = area above the threshold. [a] The median differences and their 95% confidence intervals were calculated with the Hodges-Lehmann method [b] The p-value was measure with the Mann-Whitney U test [c] See eFigure 4 for illustration of the AUT and AAT [d] In the intervention group, the reaction time was measured as the time (in seconds) from the onset of the early warning system alarm until treatment. In the control group, reaction time was defined as the time from start of hypotension untill treatment.
[e]Treatment incidence was calculated as the median treatments related to hypotension or the alarm.

eFigure 4. AUT and AAT to Calculate TWA

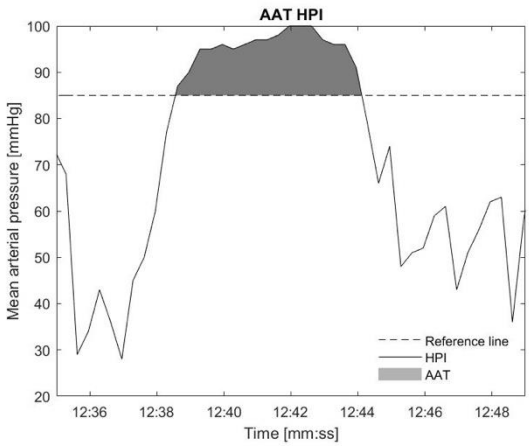
A.



B.



C.



Not only the time spent in hypotension but also the severity (minimum MAP reached) of hypotension is important for associations with postoperative outcome.[1] The time-weighted average (TWA) in hypotension combines the time and depth of hypotension and is therefore a good outcome parameter. To calculate the TWA of hypotension the area under the threshold (AUT) is needed. The AUT is calculated as the 'depth of hypotension below the threshold – defined as a Mean Arterial blood Pressure (MAP) of 65 mmHg' x 'time spent below MAP 65 mmHg in minutes'. Subsequently the formula of TWA in hypotension is as follows: 'AUT' / 'total duration operation in minutes'. The area above the threshold (AAT) is required to calculate the TWA in hypertension. The AAT is calculated by multiplying the 'depth of hypertension – defined as a MAP above 100 mmHg' by the 'time spent above a MAP of 100 mmHg in minutes'. The TWA of hypertension is calculated by dividing the AAT by the 'total duration operation in minutes'.

1. Sessler DI, Bloomstone JA, Aronson S, et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *British journal of anaesthesia.* 2019;122(5):563-574.

eTable 3. Adverse and Serious Adverse Events

	Intervention (*n=31 patients*)	Control (*n=29 patients*)	*p*-value[a]
Total number of adverse events	33	30	
Pulmonary complications			.38
Pneumonia	-	2	
Pneumothorax	1	-	
Other	1	1	
Cardiac events			.81
Myocardial infarction	1	-	
Arrhythmia	2	1	
Pericardial effusion	1	1	
Surgical complications			.37
Post-surgical bleeding	2	1	
Mediastinal or abdominal abscess	3	1	
Anastomotic leakage	-	5	
Chylothorax	6	6	
Ileus	4	1	
Wound infection	3	2	
Bile leakage	1	1	
Reoperations	2	1	
Urologic			.99
Increase of > 50% in creatinine	1	1	
Thrombo-embolic event	-	1	.97
Neurologic event			.99
CVA/TIA	-	-	
Postoperative cognitive dysfunction	1	-	
Re-admittance ICU	2	2	.99
Re-admittance hospital	2	1	.99
30-day mortality	-	2	.44

Frequencies are given in numbers. ICU = intensive care unit. [a] P-values were calculated using the Chi-square test

According to our study protocol and local ethical committee guidelines adverse events were defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. Serious adverse events were defined as any untoward medical occurrence or effect that 1. resulted in death 2. was life threatening 3. required hospitalization or prolongation of hospitalization, 4. resulted in persistent or significant disability or incapacity. 5 was a congenital anomaly or birth defect; 6. any other important medical event - that did not result in any of the outcomes listed above- due to medical or surgical intervention. An elective hospital admission was not considered to be a serious adverse event.

Definitions of postoperative outcomes
Pulmonary complications:
Pneumonia; radiologic confirmation of an infiltrate, combined with positive cultures (when available) and clinical signs of infection (above 38.5 degrees Celsius or elevated leucocytes or elevated C-reactive protein). Pneumothorax; collection of air between the visceral and parietal pleural surfaces, requiring drainage. Other was defined as reintubation, pleural effusion (collection of fluid between the visceral and parietal pleural surfaces, requiring drainage) and acute respiratory failure (partial pressure of arterial oxygen<60 mmHg or oxygen saturation <90% while breathing ambient air).

Surgical complications:
Intraoperative surgical complications are defined as any complication that has a lasting harmful effect on the patient and is not part of the normal surgical procedure. Postoperative surgical bleeding was defined as postoperative blood loss requiring blood transfusion and/or leading to hemodynamic instability. Mediastinal abscess was scored when an abscess was identified by radiologic imaging or intraoperative visualization and required interventional or antibiotic treatment. Anastomotic leakages were recorded when they were clinically manifest and confirmed by physical examination, radiologic imaging, or intraoperative/endoscopic visualization. Chylothorax was recorded when elevated levels of triglycerides in intrathoracic fluid ([1 mmolL-1 [89 mg per dL]) were found. Wound infection was defined as a contaminated wound requiring any type of intervention.

Thrombo-embolic complications:
Thrombo-embolic events were recorded when a (pulmonary or other) embolus was detected on computed tomography or by duplex ultrasound.

Neurologic complications
Neurologic events included delirium and cerebrovascular events.

Cardiac complications
Cardiac complications were arrhythmia (any change in rhythm on the electrocardiogram, requiring treatment), myocardial infarction (electrocardiographic changes suggesting myocardial infarction and / or enzyme changes suggesting myocardial infarction), and left ventricular failure (marked pulmonary edema on a chest radiograph).

Urologic complications:
Kidney function disorder was defined as 50% elevation of preoperative creatinine.

eFigure 5. Post Hoc Regression Analysis

In order to post-hoc test for the possible confounding effect of the pre-induction blood pressure on the time-weighted average (TWA) of hypotension, the following statistical procedures were performed.

1. The normality of time-weighted average in hypotension was visually inspected (figure 1 and 2)

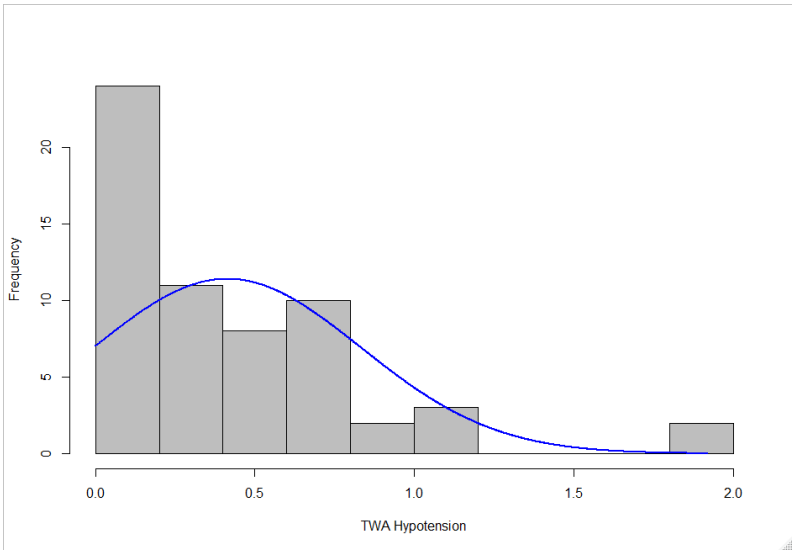


Figure 1. Histogram of the time-weighted average in hypotension

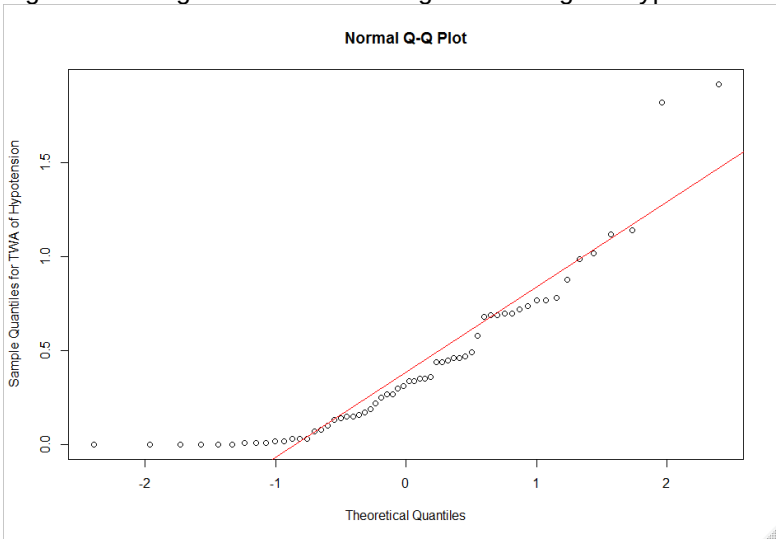


Figure 2. Q-Q Plot of the time-weighted average in hypotension

2. The normality of the pre-induction Mean Arterial Pressure (MAP) was visually inspected (figure 3 and 4)

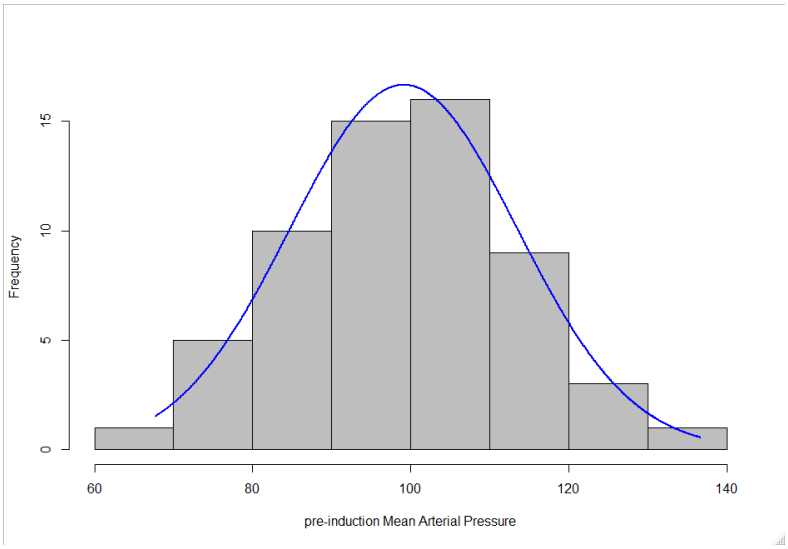


Figure 3. Histogram of the pre-induction MAP

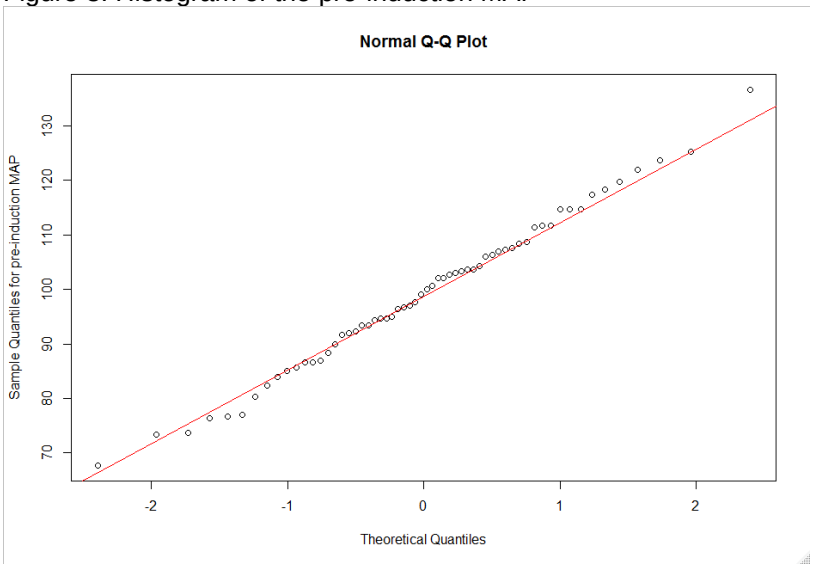


Figure 4. Q-Q Plot of the pre-induction MAP

3. To correct for the non-normality of time-weighted average in hypotension, data was transformed to normality using the box-cox function. Optimum lambda for transformation was calculated at 0.3 (Figure 5)

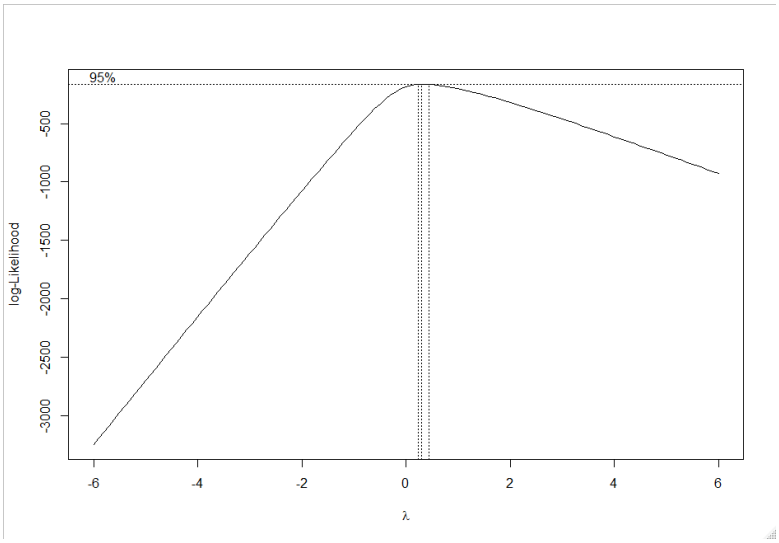


Figure 5. Optimum lambda cut-off for transformation to normality

4. The time-weighted average in Hypotension was log-transformed using the optimum lambda of 0.3. After transformation the normality was inspected visually. (Figure 6 and 7)

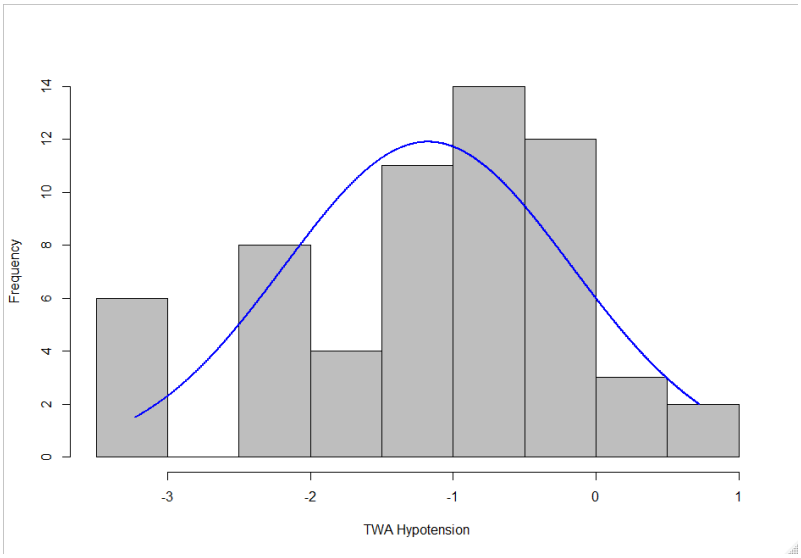


Figure 6. Histogram of the time-weighted average in hypotension after transformation

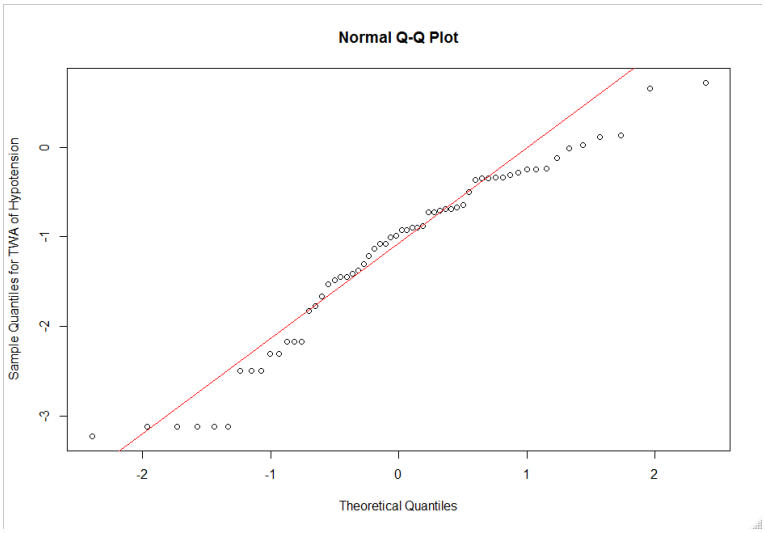


Figure 7. Q-Q Plot of the time-weighted average in hypotension after transformation

5. A linear regression model was composed to assess the effect of the early warning system usage on the time weighted average in hypotension:

```
Residuals:
Min        1Q         Median     3Q         Max
-2.38621   -0.59293   0.05263    0.52641    2.31166

Coefficients:
                        Estimate    Std. Error    t value    Pr(>|t|)
(Intercept)             -0.7368     0.1702        -4.328     6.02e-05 ***
randomized_group        -0.8543     0.2368        -3.607     0.000646 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.9168 on 58 degrees of freedom
Multiple R-squared:  0.1832,    Adjusted R-squared:  0.1691
F-statistic: 13.01 on 1 and 58 DF,  p-value: 0.0006456
```

6. A multi-variate linear regression model was composed to assess the confounding effect of MAP before induction on the relationship between early warning system usage and the time-weighted average in hypotension.

```
Residuals:
Min        1Q         Median     3Q         Max
-2.39984   -0.59703   0.03883    0.52480    2.32360

Coefficients:
                        Estimate    Std. Error    t value    Pr(>|t|)
(Intercept)             -0.853754   0.846990      -1.008     0.317721
randomized_group        -0.864287   0.249087      -3.470     0.000999 ***
MAP_before_induction    0.001232    0.008736      0.141      0.888359
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.9247 on 57 degrees of freedom
Multiple R-squared:  0.1835,    Adjusted R-squared:  0.1549
F-statistic: 6.405 on 2 and 57 DF,  p-value: 0.003095
```

eTable 4. Treatment Choice RCT

	Intervention	**Control**	**Proportional difference (95%CI)[b]**	**p-values[c]**
Total number of treatments [a]	N = 596	N = 258		
Treatment choice No. (%)				
Noradrenaline	263 (44)	102 (40)	0.04 (-0.03 – 0.12)	.21
Ephedrine	38 (6)	37 (14)	0.08 (0.06 – 0.14)	**<.001**
Phenylephrine	110 (19)	61 (24)	0.05 (-0.01 – 0.11)	**.04**
Dobutamine	3 (0.5)	0 (0)	0.01 (-0.00 – 0.01)	.25
Decrease anesthetics	44 (7)	17 (7)	0.01 (-0.03 - 0.04)	.68
-*Sevoflurane*	*42 (7)*	*17 (7)*	0.01 (-0.03 – 0.04)	.81
-*Propofol*	*2 (0.3)*	*0 (0)*	0.00 (0.00 – 0.01)	.35
Decrease analgesics	9 (2)	4 (2)	0.00 (-0.02 – 0.02)	.96
-*Sufentanil intravenous*	*3 (0.5)*	*1 (0.4)*	0.00 (-0.01 – 0.01)	.82
-*Sufentanil epidural*	*2 (0.3)*	*0 (0)*	0.00 (0.00 – 0.01)	.35
-*Bupivacaine epidural*	*1 (0.2)*	*2 (1)*	0.01 (-0.01 – 0.02)	.17
-*Lidocain epidural*	*0 (0)*	*0 (0)*	-	-
-*Ketamin* intravenous	*3 (0.5)*	*1 (0.4)*	0.00 (-0.01 – 0.01)	.82
Fluid bolus	96 (16)	16 (6)	0.10 (0.06 – 0.14)	**<.001**
-*Colloid*	*29 (5)*	*3 (1)*	0.04 (0.02 – 0.06)	**.009**
-*Crystalloid*	*67 (11)*	*13 (5)*	0.06 (0.03 – 0.10)	**.004**
Increase speed of fluid infusion	23 (4)	16 (6)	0.02 (-0.01 – 0.06)	.30
Blood products	0 (0)	0 (0)		-
Trendelenburg	9 (2)	5 (2)	0.00 (-0.02- 0.02)	.80

The results are presented as frequencies with percentage (%) [a] Total number of treatments means the total number of treatments for hypotension in the control group (because the early warning system alarm was blinded) and the total number of treatments for the early warning system alarms and hypotension in the intervention arm. [b] Proportional differences were calculated using a two-proportions z-test. [c]P-values were calculated using the Chi-square test

eTable 5. Treatment Behavior Silent Alarms

Early warning system alarms	Intervention (n=31)	Control (n=29)	Proportional difference or median difference (95% CI)[a]	p-value[b]
Total alarms, n	377	356		-
Alarms per patient	11 [7 - 16]	11 [8 – 15]	0 (-4 to 3)	.84
Total treated alarms, n (%)	324 (86%)	117 (33%)	53 (47 to 59)	**< .001**
Treatments per alarm	1 [1 - 2]	0 [0 - 1]	1 (0 to 1)	**< .001**
Time from alarm to first treatment action (seconds)	53 [24 - 99]	161 [73 - 391]	48 [13 to 97]	**< .001**
Time from first alarm to first treatment action (seconds)	57 [22 – 81]	108 [44 - 204]	91 [70 to 117]	**0.01**

This table demonstrates the results of a post-hoc analyses. Results presented in median with IQR [ ], or frequencies with %. This table shows the total number of treatments after a early warning system alarm (referred to as 'alarm') but before hypotension occurred. In the intervention group the alarms were visible to the treating anesthesiologists. In the control group the alarms were not visible to the treating anesthesiologists. The results show that in the control group in 117 out of 356 alarms the treating anesthesiologist started treatment before hypotension occurred. The median time to treatment was significantly longer in the control group. [a.]For continuous data the median differences and their 95% confidence intervals were calculated with the Hodges-Lehmann method. For categorical data the proportional differences were calculated using a two-proportions z-test. [b]Mann-Whitney U test for continuous data and chi-square for categorial data.