Supplement 2

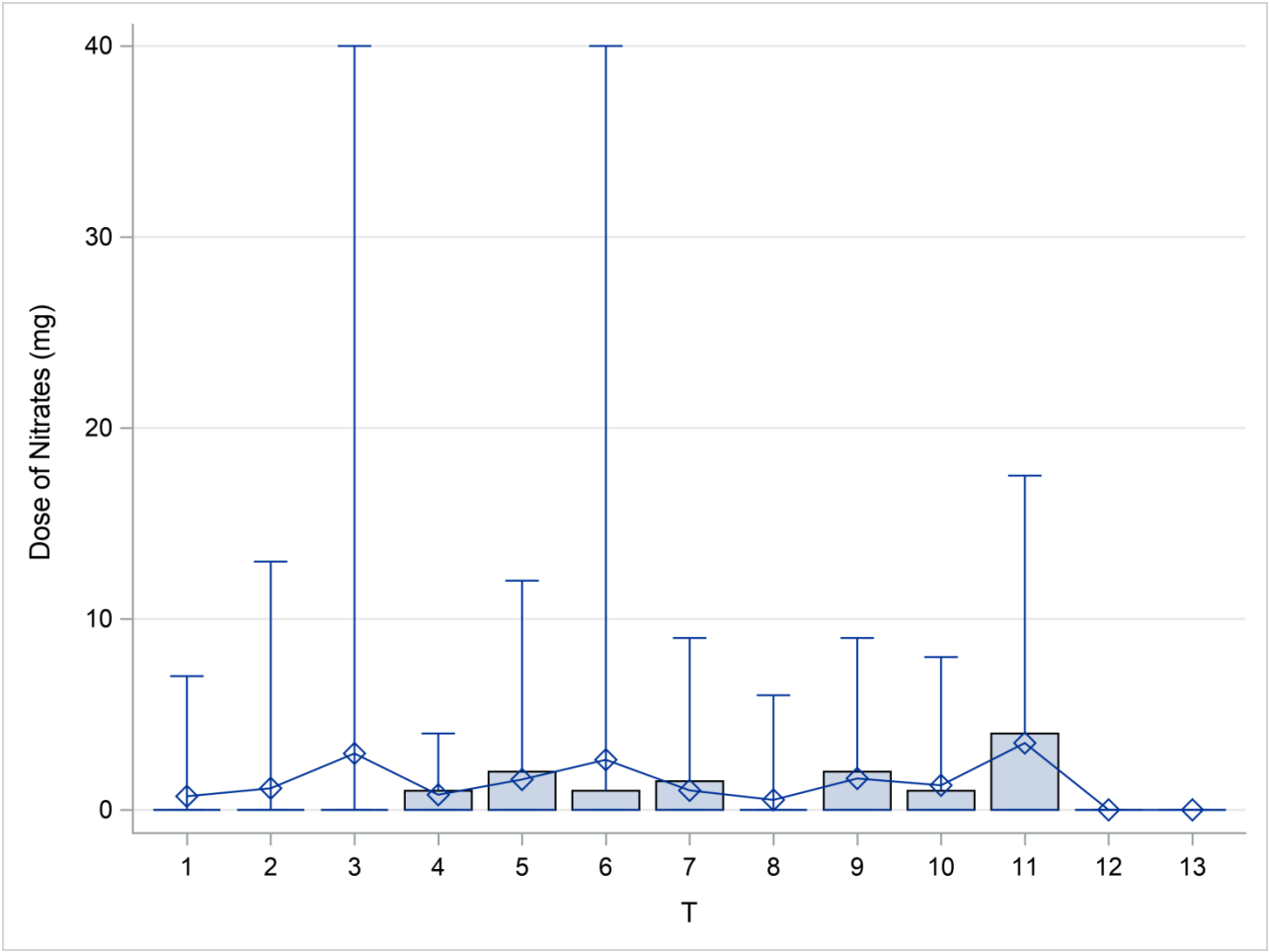
		Number of patients (n) by site and time period															Total by time
Identification number of site		7	8	4	15	10	1	14	12	2	6	5	13	3	11	9	block
Number of participant per block time (n)	10 Dec 18 - 6 Jan 19	6	4	7	7	5	8	7	3	3	6	9	6	11	3	3	88
	7 Jan - 20 Jan 19	4	3	2	0	4	2	3	1	1	2	3	0	2	4	0	31
	21 Jan - 3 Feb 19	4	1	2	4	0	2	2	2	6	2	5	1	6	1	0	38
	4 Feb - 17 Feb 19	1	2	2	3	2	3	1	1	4	1	1	0	3	0	5	29
	18 Feb - 3 Mar 19	4	0	1	3	1	4	0	2	3	3	2	1	2	2	1	29
	4 Mar - 17 Mar 19	2	1	3	2	0	3	3	3	1	2	2	0	5	5	1	33
	18 Mar - 30 Mar 19	4	0	0	0	0	7	3	4	1	3	5	4	0	2	4	37
	1 Apr - 14 Apr 19	3	1	4	3	0	5	2	2	4	1	3	1	5	5	2	41
	15 Apr - 28 Apr 19	2	2	2	1	2	3	1	1	1	2	2	1	1	3	4	28
	29 Apr - 12 May 19	1	1	1	0	0	4	2	1	1	0	2	0	0	0	5	18
	13 May - 26 May 19	0	0	0	3	1	2	2	0	3	0	0	2	4	3	2	22
	27 May - 9 Jun 19	0	0	2	0	3	2	0	0	2	3	1	0	1	0	1	15
	10 Jun - 23 Jun 19	0	2	1	0	0	2	0	0	1	0	1	0	0	0	2	9
	24 Jun - 7 Jul 19	0	0	1	0	1	0	0	1	1	4	2	0	2	0	0	12
	8 Jul - 21 Jul 19	2	0	0	0	0	5	0	1	1	0	0	0	3	0	0	12
	22 Jul - 23 Sep 19	5	5	4	5	5	11	2	5	6	1	1	0	6	2	2 [a]	60
Total by site (n)		38	22	32	31	24	63	28	27	39	30	39	16	51	30	32	502

Usual care period Training period [b] Intervention period

eFigure 1: Study diagram.

[a] Training period only the first two weeks of the period.

[b] Training period was analyzed as intervention period.



eFigure 2: Trend of median dose of given iv nitrates in control groups.
Error bars report extreme values (upper and lower caps), interquartile (box), mean (diamond) and median (bar). All median and lower values are equal to zero.

		Usual-care period				Intervention period			
Center no.	Study week of change from control to intervention	Enrolled	Excluded after enrollment	Included in "as randomized" analysis	Included in sensitivity analysis	Enrolled	Excluded after enrollment	Included in "as randomized" analysis	Included in sensitivity analysis
1	15	22	0	22	22	41	0	41	38
2	21	24	0	24	24	15	0	15	15
3	29	40	0	40	40	11	0	11	11
4	9	11	0	11	11	21	0	21	21
5	25	34	0	34	31	5	0	5	5
6	23	22	0	22	22	8	0	8	8
7	5	6	0	6	6	32	0	32	31
8	7	7	0	7	7	15	0	15	15
9	33	30	0	30	30	2	0	2	2
10	13	12	0	12	12	12	0	12	12
11	31	28	0	28	28	2	0	2	2
12	19	19	1	18	17	9	0	9	9
13	27	16	0	16	15	0	0	0	0
14	17	19	0	19	19	9	0	9	9
15	11	14	0	14	14	17	0	17	17
Total		304	1	303	298	199	0	199	195

eTable 1. Study diagram in primary analysis (as-randomized) and sensitivity analysis (patients that completed the trial).

Variable	n	Intervention	n	Usual care	Adjusted difference	95% CI
At least 1 precipitating factor present in the Emergency Department	199	80 (40.2%)	303	144 (47.5%)	-6.4%	(-20.9% to 8.1%)
At least 1 precipitating factor treated in the Emergency Department	80	47 (58.8%)	144	46 (31.9%)	31.1%	(14.3% to 47.9%)
Suspicion of infection	199	37 (18.6%)	303	51 (16.8%)	5.0%	(-5.7% to 15.7%)
Antibiotics[a]	37	29 (78.4%)	51	22 (43.1%)	19.2%	(-11.2% to 49.7%)
Acute coronary syndrome	199	38 (19.1%)	303	73 (24.1%)	-3.0%	(-14.0% to 8.0%)
Antiplatelet agents[b]	38	8 (21.1%)	73	15 (20.5%)	12.8%	(-16.5% to 42.0%)
Atrial fibrillation > 100 BPM	199	25 (12.6%)	303	48 (15.8%)	-4.2%	(-12.0% to 3.7%)
Antiarrhythmics[c]	25	14 (56.0%)	48	13 (27.1%)	49.9%	(26.7% to 73.0%)

eTable 2: Presence and treatment of suspected precipitating factors in the ED in the primary (as-randomized) analysis.

[a] Numbers and percentage are given among patients with suspicion of infection

[b] Numbers and percentage are given among patients with acute coronary syndrome

[c] Numbers and percentage are given among patients with atrial fibrillation > 100 BPM

Variable	Intervention		Usual Care		Adjusted difference [a]	95%CI
	n		n			
Treatment in the Emergency Department, n(%)						
Diuretics	195	191 (98%)	298	269 (90%)	6.9	(0.6 to 13.2)
dose, mg, median (IQR)	191	40 (40 ; 80)	268	60 (40 ; 80)	-13.0	(-25.4 to -0.6)
iv nitrates [b]	195	187 (96%)	297	73 (25%)	70.8	(61.3 to 80.2)
Cumulative dosing at hour 1, mg, median (IQR)	183	18 (9 ; 30)	53	3 (2 ; 4)	15.0	(8.9 to 21.1)
Cumulative dosing at hour 4, mg, median (IQR)b	184	27 (9 ; 54)	72	4 (2 ; 6)	24.0	(8.5 to 39.4)
Antibiotics	195	38 (20%)	298	37 (12%)	11.5	(2.2 to 20.8)
Antiplatelet agents	195	15 (8%)	298	23 (8%)	0.1	(-8.1 to 8.4)
Dual antiplatelet agents [c]	195	4 (2%)	298	3 (1%)		
Antiarythmics	195	22 (11%)	298	23 (8%)	2.3	(-5.9 to 10.6)
Non-invasive ventilation	195	28 (14%)	298	27 (9%)	8.0	(-3.3 to 19.4)
Emergency Department discharge disposition, n(%)	195		298			
Home		3 (1.5)		15 (5.0)	-3.2	(-9.5 to 3.2)
ED observation unit		95 (48.7)		136 (45.6)	-3.0	(-16.6 to 10.5)
Hospital ward		58 (29.7)		107 (35.9)	3.6	(-9.4 to 16.6)
Intensive care unit[d]		39 (20.0)		38 (12.8)	8.8	(-2.1 to 19.7)

eTable 3: Management in the ED in the sensitivity analysis (patients that completed the trial). IQR, interquartile range;

[a] Differences were adjusted for intervention, time period and cluster size (categorical) as fixed effects and cluster as a random effect.

[b] Cumulative dose of nitrates over the period of time that includes boluses (first hour) and infusion (between first hour and 4th hour), among patients that were treated with nitrates.

[c] Given the small numbers, no analysis was performed for the dual antiplatelet agents variable.

[d] Including cardiac intensive care unit.

Endpoints	Intervention			Usual Care			Unadjusted difference	95%CI	Adjusted difference [a]	95%CI	Adjusted ratio[a]	95% CI	Adjusted risk ratio[a]	95% CI
	n			n										
Primary endpoint,														
median (IQR)														
Days alive and out of hospital at day 30	195	19.0	(0.0 ; 24.0)	298	19.5	(3.0 ; 24.0)	0.5	(-3.3 to 4.3)	-2.1	(-6.7 to 2.6)	0.87	(0.64 to 1.19)		
Secondary endpoints,														
N (%)														
30-day all-cause mortality	195	16	(8.2%)	298	29	(9.7%)	-1.5%	(-7.1% to 4.0%)	3.9%	(-17.3% to 25.2%)			1.16	(0.53 to 2.54)
30-day cardiovascular mortality	195	10	(5.1%)	298	22	(7.4%)	-2.3%	(-7.0% to 2.5%)	2.1%	(-15.5% to 19.7%)			1.12	(0.45 to 2.81)
30-day hospital re-admission	154	22	(14.3%)	234	37	(15.8%)	-1.5%	(-9.3% to 6.3%)	-2.8%	(-29.8% to 24.2%)			0.92	(0.43 to 2.00)
Length of hospital stay, days, median (IQR)	179[c]	8.0	(5.0 ; 21.0)	269[c]	8.0	(5.0 ; 16.0)	0.0	(-1.8 to 1.8)	2.5	(-0.8 to 5.9)	1.23	(0.95 to 1.59)		
2-fold rise in creatinine level[b]	190	2	(1.1%)	286	4	(1.4%)								

eTable 4: Study endpoints in the sensitivity analysis (patients that completed the trial). IQR: interquartile range. RR: risk ratio

[a] Difference, ratios and risk ratios were adjusted for time period and cluster size (categorical) as fixed effects and cluster as a random effect. The difference is expressed as intervention minus control, and the ratio intervention/control.

[b] Given the small numbers, no analysis was performed for the 2-fold rise in creatinine level variable.