CRRT: Clotting or bleeding: which is worse?

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Melbourne

The Achilles' heel of CRRT

- Needs to deliver treatment over the 24 cycle
- Contact with membrane and tubing promotes clotting
- Clotting generate filter loss, costs, red cell loss, much work and decreased therapy

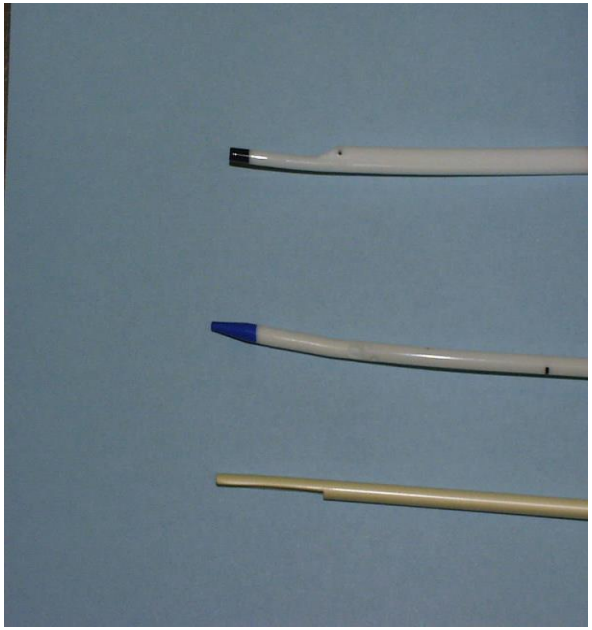
Prevention of clotting

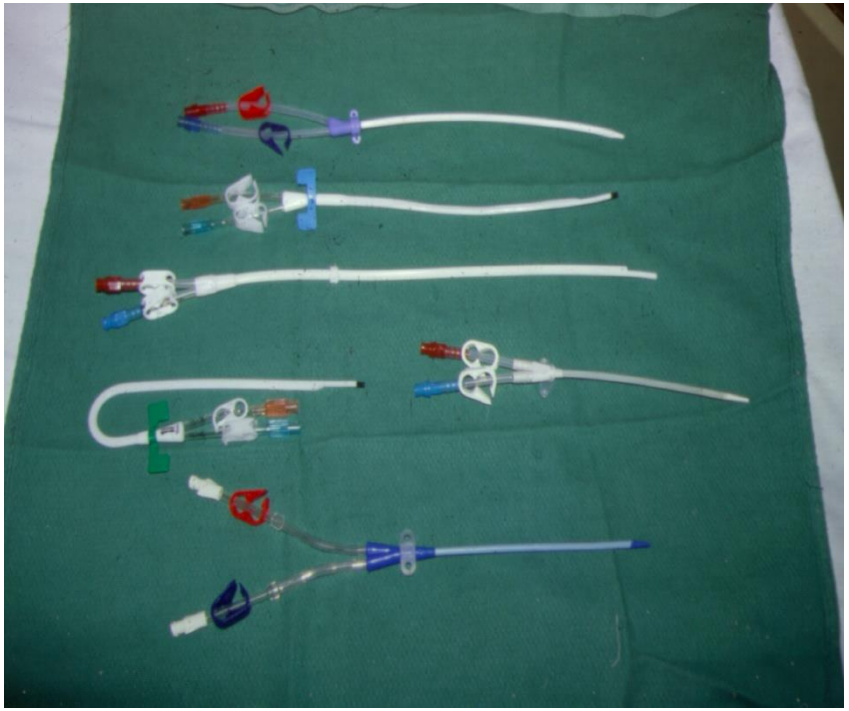
- Several interventions are available to decrease the risk of clotting
- They include filter anticoagulation
- Regional anticoagulation
- Systemic anticoagulation
- Many such interventions **increase the risk of bleeding**
- How should clinicians practice?

Understand circuit mechanics

- The first step in preventing clotting (and bleeding form unnecessary anticoagulation) is to exclude mechanical causes of circuit clotting
- Mechanical problems due to vascular access inadequacy are common and important causes of clotting

Vascular access catheters





BRIEF REPORTS

Automated electronic monitoring of circuit pressures during continuous renal replacement therapy: a technical report

Ling Zhang, Ian Baldwin, Guijun Zhu, Aiko Tanaka and Rinaldo Bellomo

Crit Care Resusc 2015; 17: 51–54

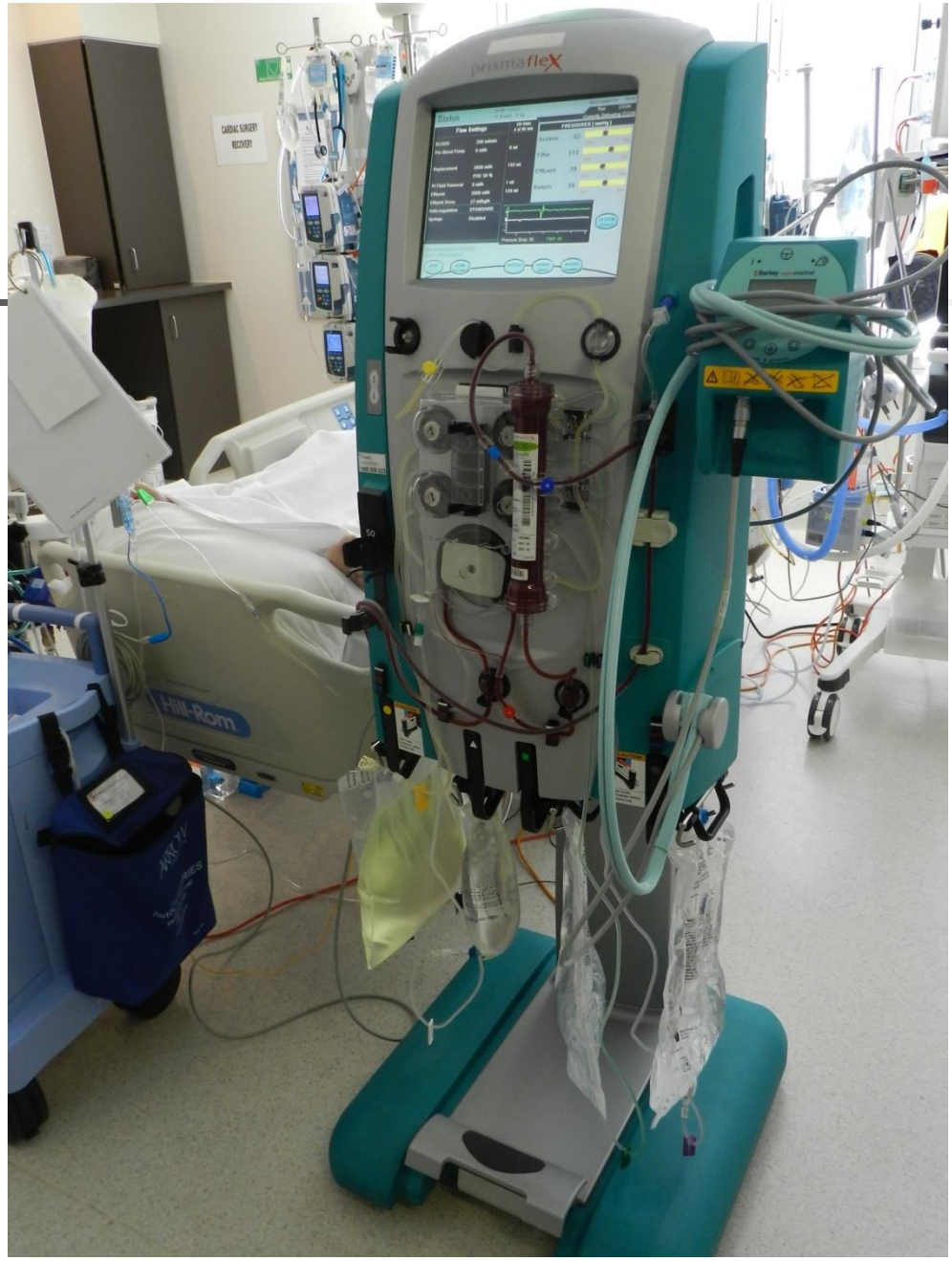
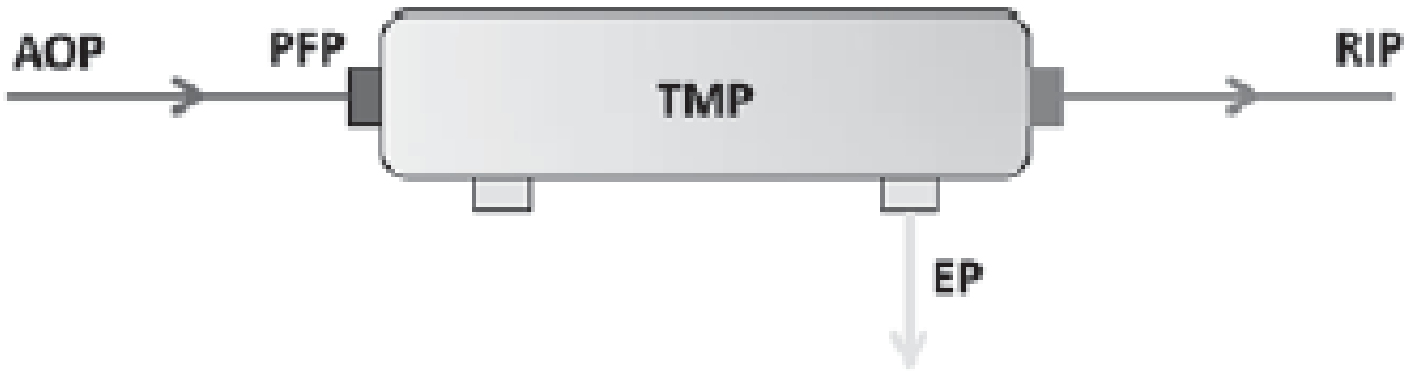
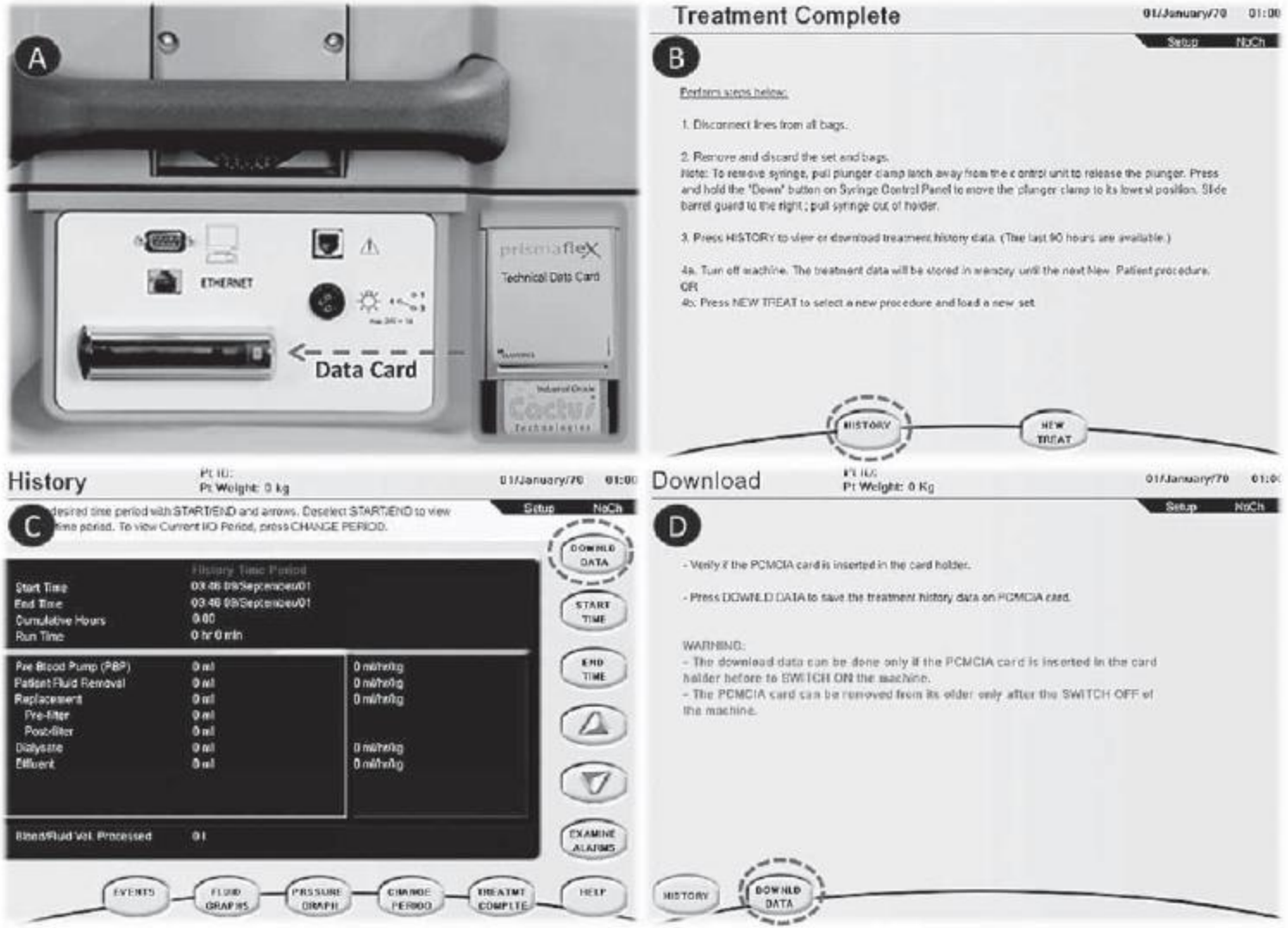

prismaflex
CARDIAC SURGERY
RECOVERY
Hill-Rom

Figure 1. Circuit pressure monitoring during continuous renal replacement therapy

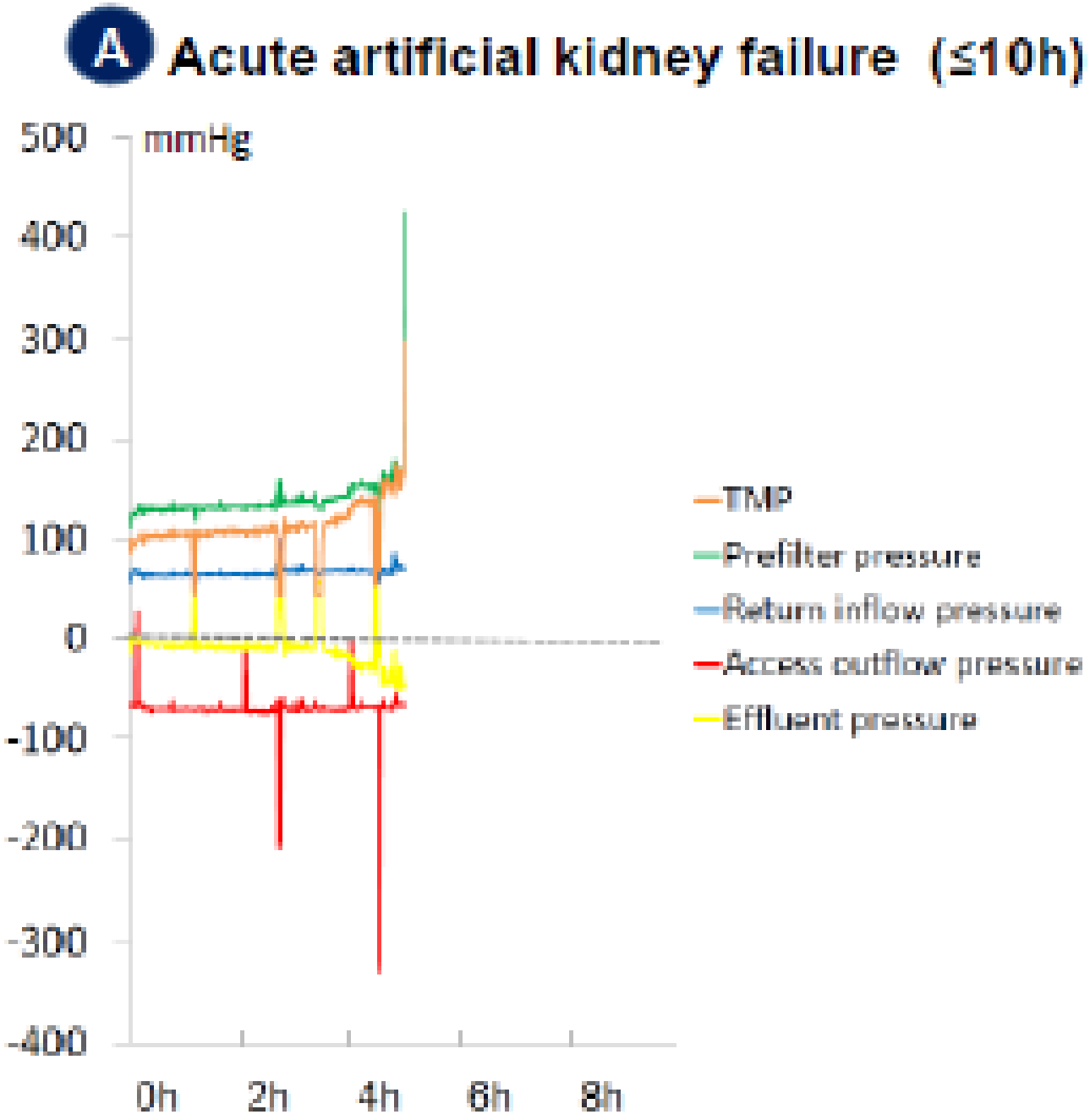


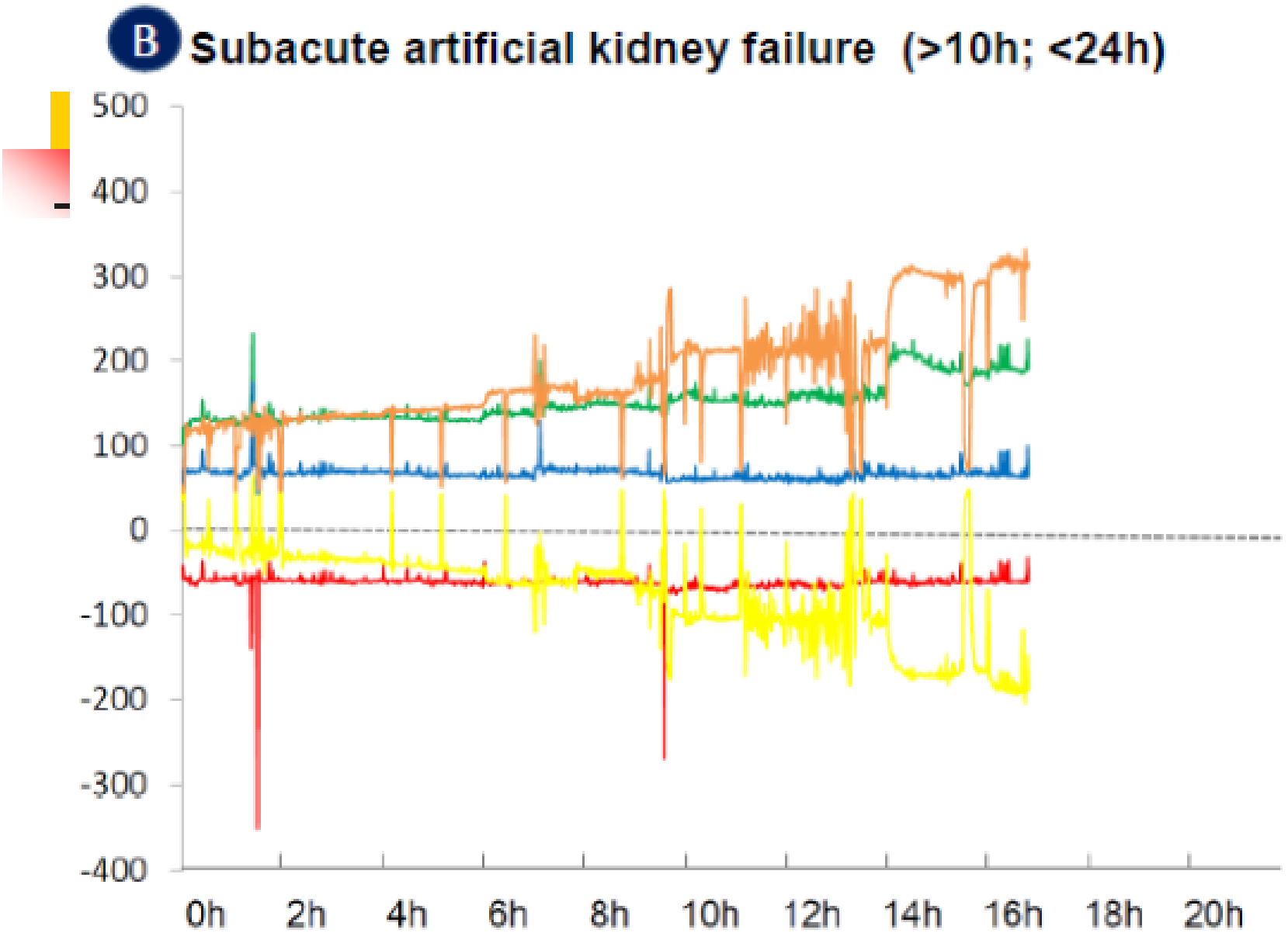
AOP = access outflow pressure. PFP = prefilter pressure.
TMP* = transmembrane pressure. EP = effluent pressure.
RIP = return inflow pressure. * TMP = (PFP + RIP)/2 – EP (mmHg).

Figure 2. Process of downloading the data from the Prismaflex machine

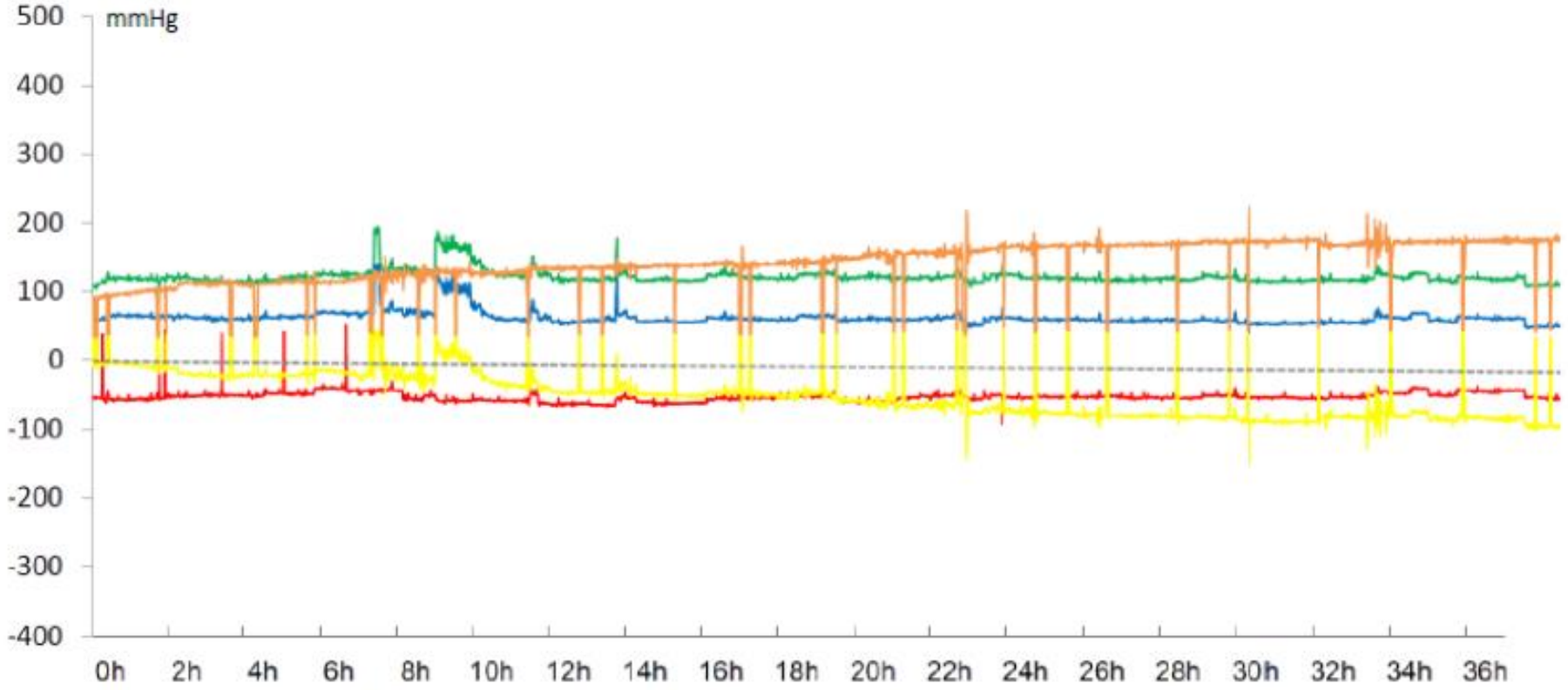


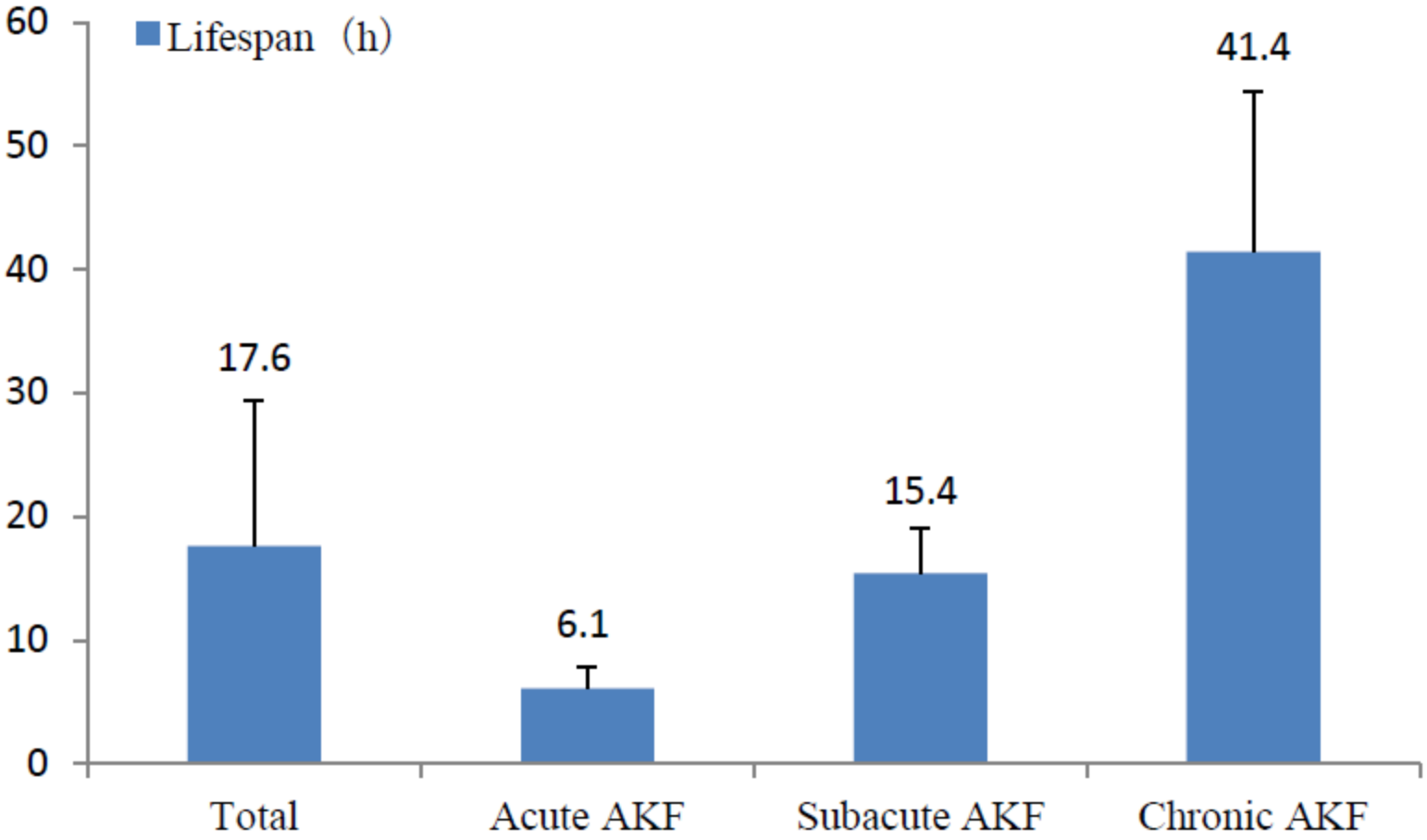
A: insertion of data card reader. B: from the "choose patient" screen, select "last history". C and D: download data.


A
Acute artificial kidney failure (≤10h)
mmHg
500
400
300
200
100
0
-100
-200
-300
-400
0h
2h
4h
6h
8h
TMP
Prefilter pressure
Return inflow pressure
Access outflow pressure
Effluent pressure


B
Subacute artificial kidney failure (>10h; <24h)
500
400
300
200
100
0
-100
-200
-300
-400
0h
2h
4h
6h
8h
10h
12h
14h
16h
18h
20h

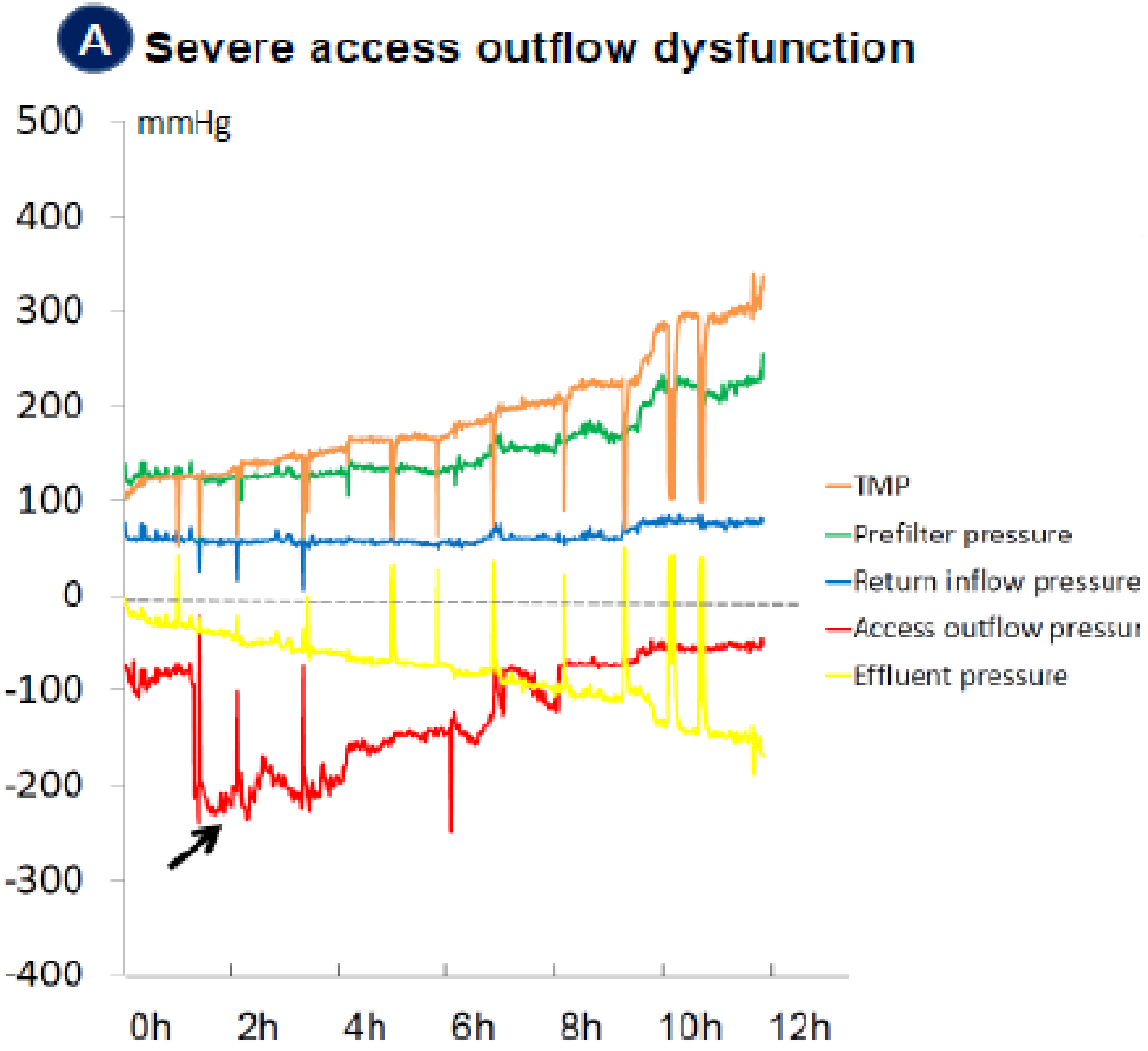
C Chronic artificial kidney failure (≥24h)

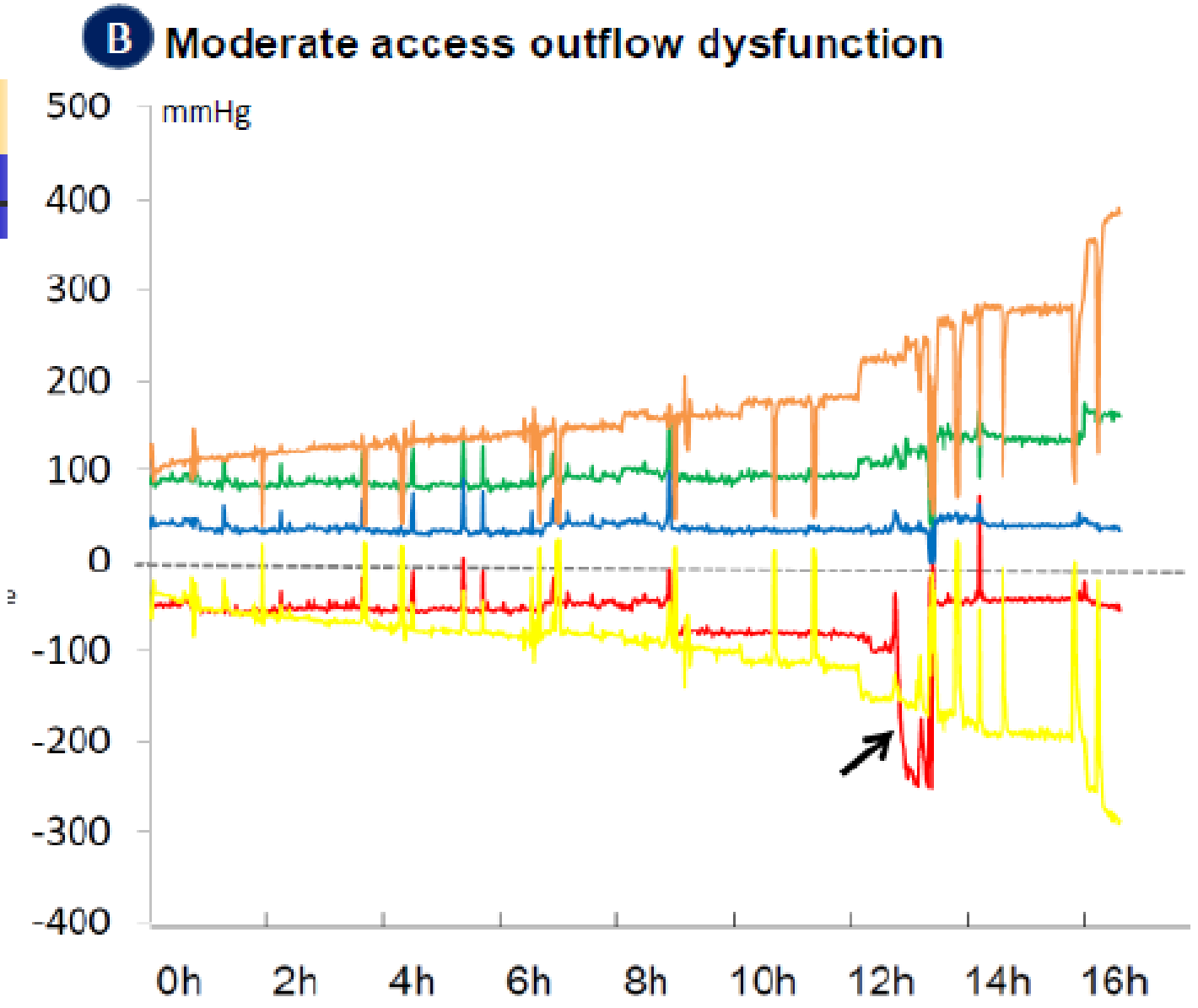




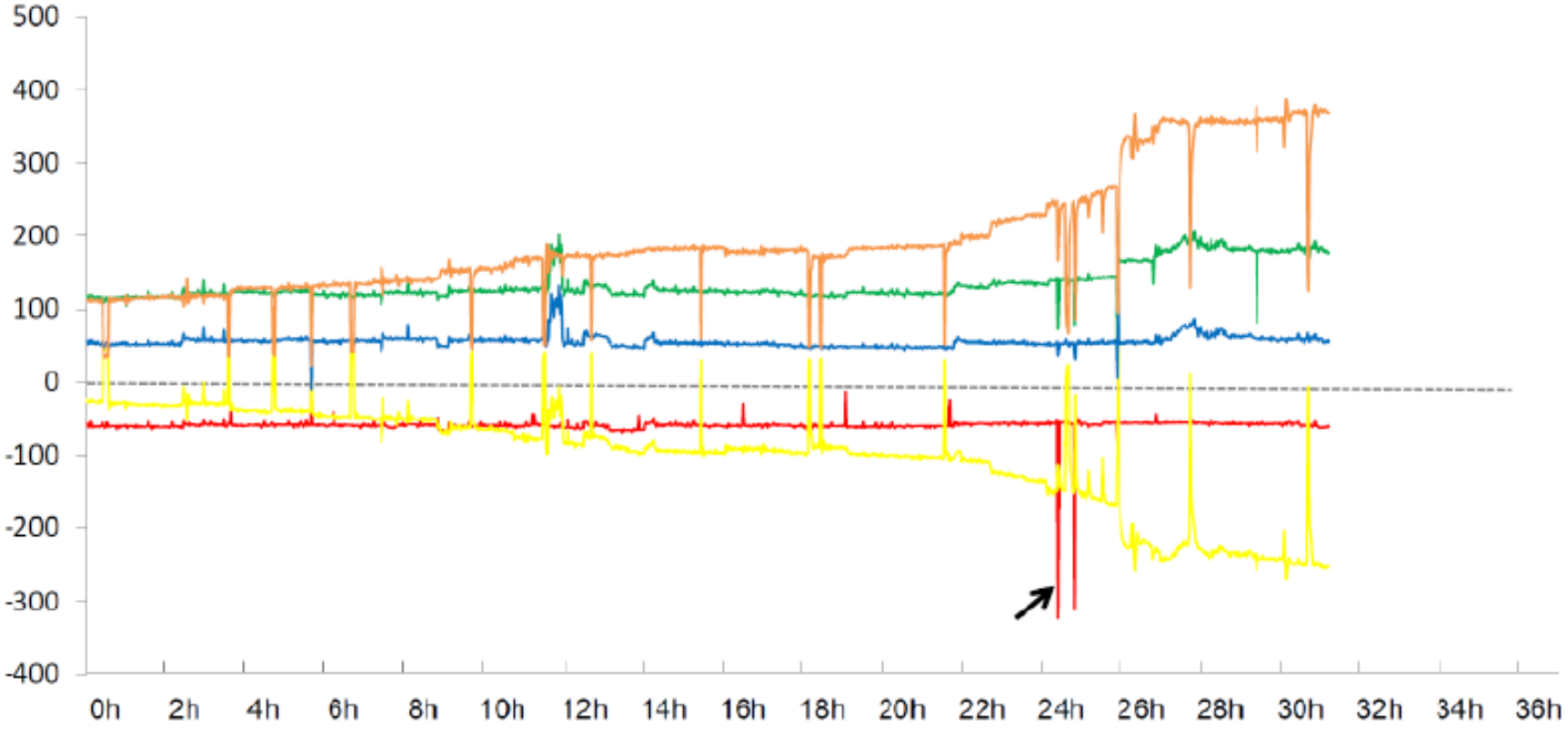
Life

Figure 2 Lifespan of different patterns of artificial kidney failure (AKF)


A
Severe access outflow dysfunction
mmHg
500
400
300
200
100
0
-100
-200
-300
-400
0h
2h
4h
6h
8h
10h
12h
TMP
Prefilter pressure
Return inflow pressure
Access outflow pressur
Effluent pressure


B
Moderate access outflow dysfunction
mmHg
500
400
300
200
100
0
-100
-200
-300
-400
0h
2h
4h
6h
8h
10h
12h
14h
16h

C Mild access outflow dysfunction



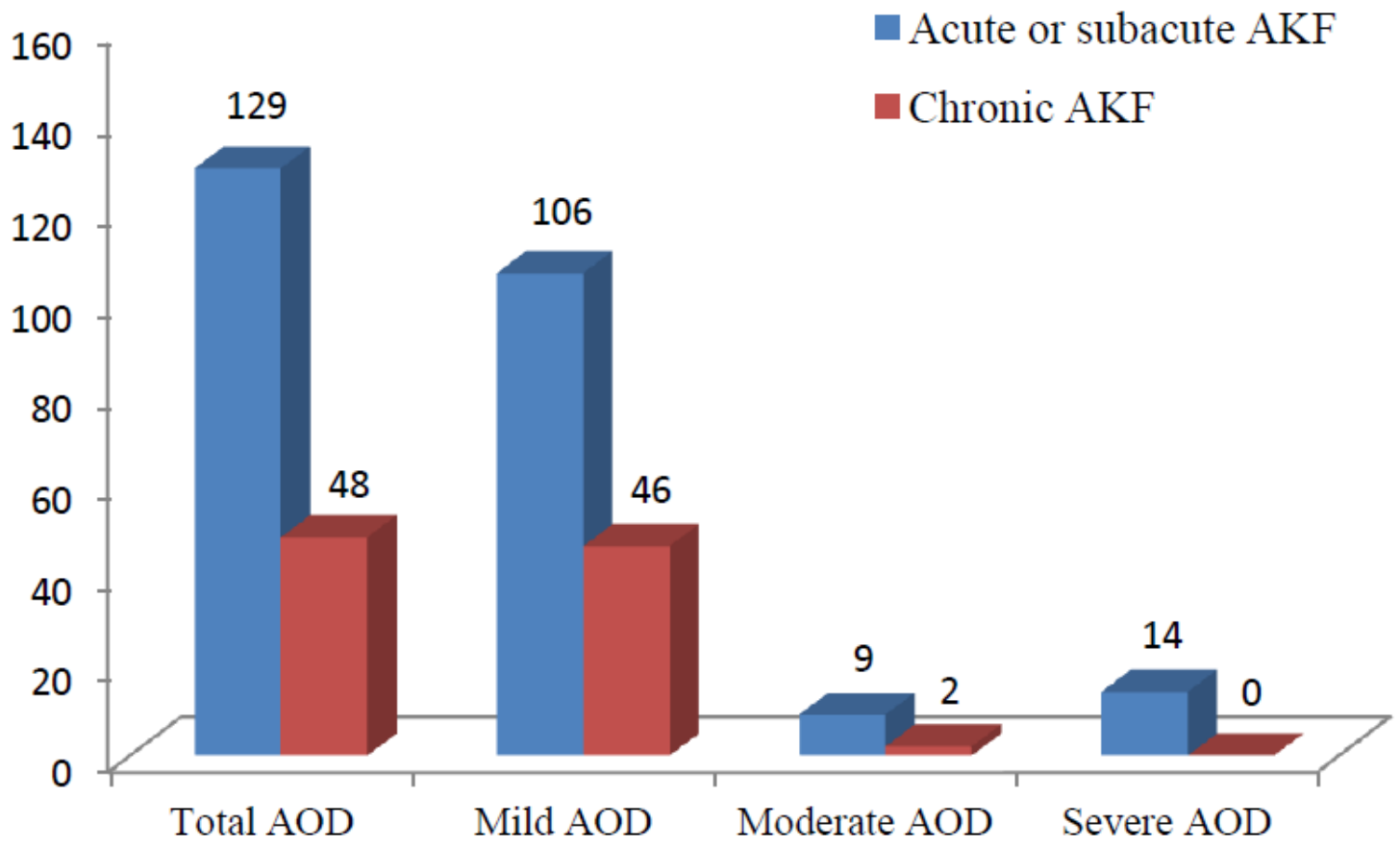


Figure 4 Events of different patterns of access outflow dysfunction (AOD) (per 1000 CRRT hrs)

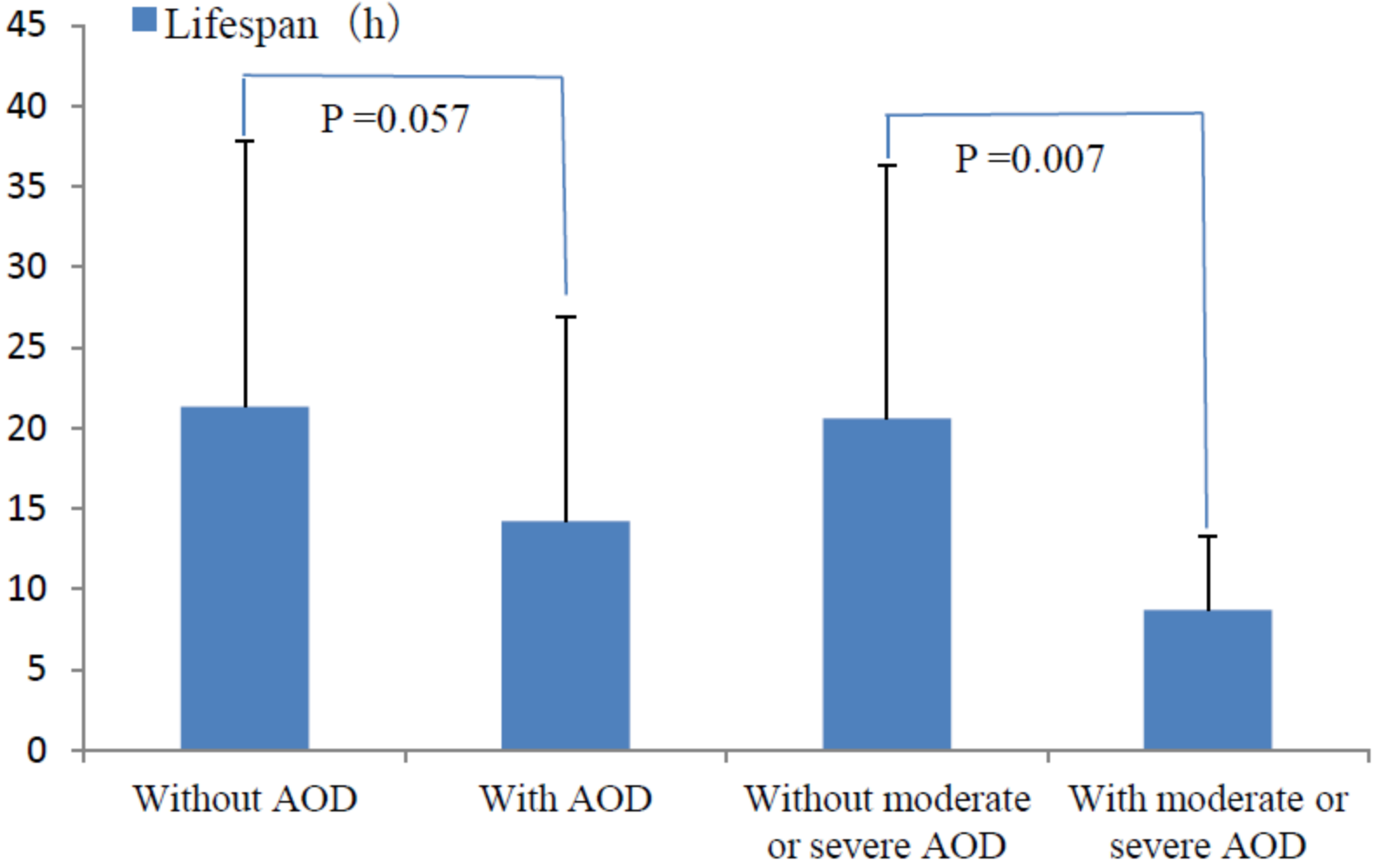


Figure 5 Lifespan in different patterns of AOD

Table 2 Changes of pressures in different patterns of AKF during CRRT

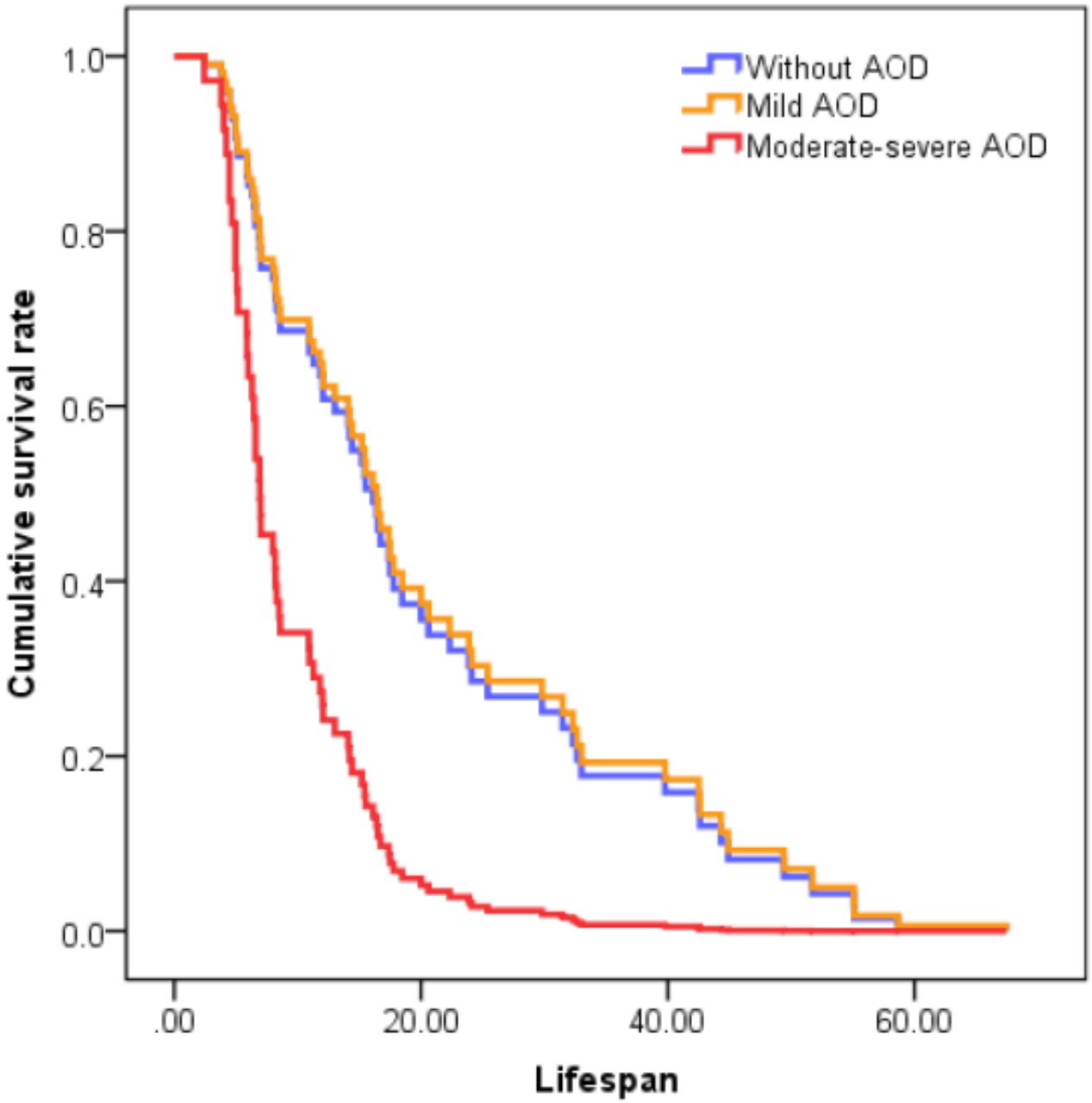
	Acute AKF N =28	Subacute AKF N =30	Chronic AKF N =18	P value
Baseline AOP (mmHg)	-76.0 ± 36.7	-58.9 ± 15.8*	-59.5 ± 8.2*	0.024
Mean AOP (mmHg)	-75.4 ± 22.5	-64.8 ± 2.5	-62.6 ± 7.7*	0.065
AOP variability (mmHg)	26.0 ± 17.6	17.2 ± 12.5*#	8.2 ± 3.6*#	<0.001
Baseline RIP (mmHg)	62.3 ± 9.5	60.5 ± 23.3	66.5 ± 16.3	0.521
Mean RIP (mmHg)	64.8 ± 13.0	61.6 ± 21.6	66.1 ± 10.5	0.643
RIP variability (mmHg)	7.5 ± 3.8	10.3 ± 9.0	10.4 ± 6.2	0.225
Increase in TMP (mmHg/h)	43.4 ± 20.7	15.2 ± 6.8*#	5.1 ± 2.6*#	<0.001
Increase in PFP (mmHg/h)	34.2 ± 18.5	8.7 ± 5.7*#	1.2 ± 1.1*#	<0.001
Decease in PE (mmHg/h)	-29.8 ± 15.2	-12.0 ± 4.1*#	-4.4 ± 2.1*#	<0.001

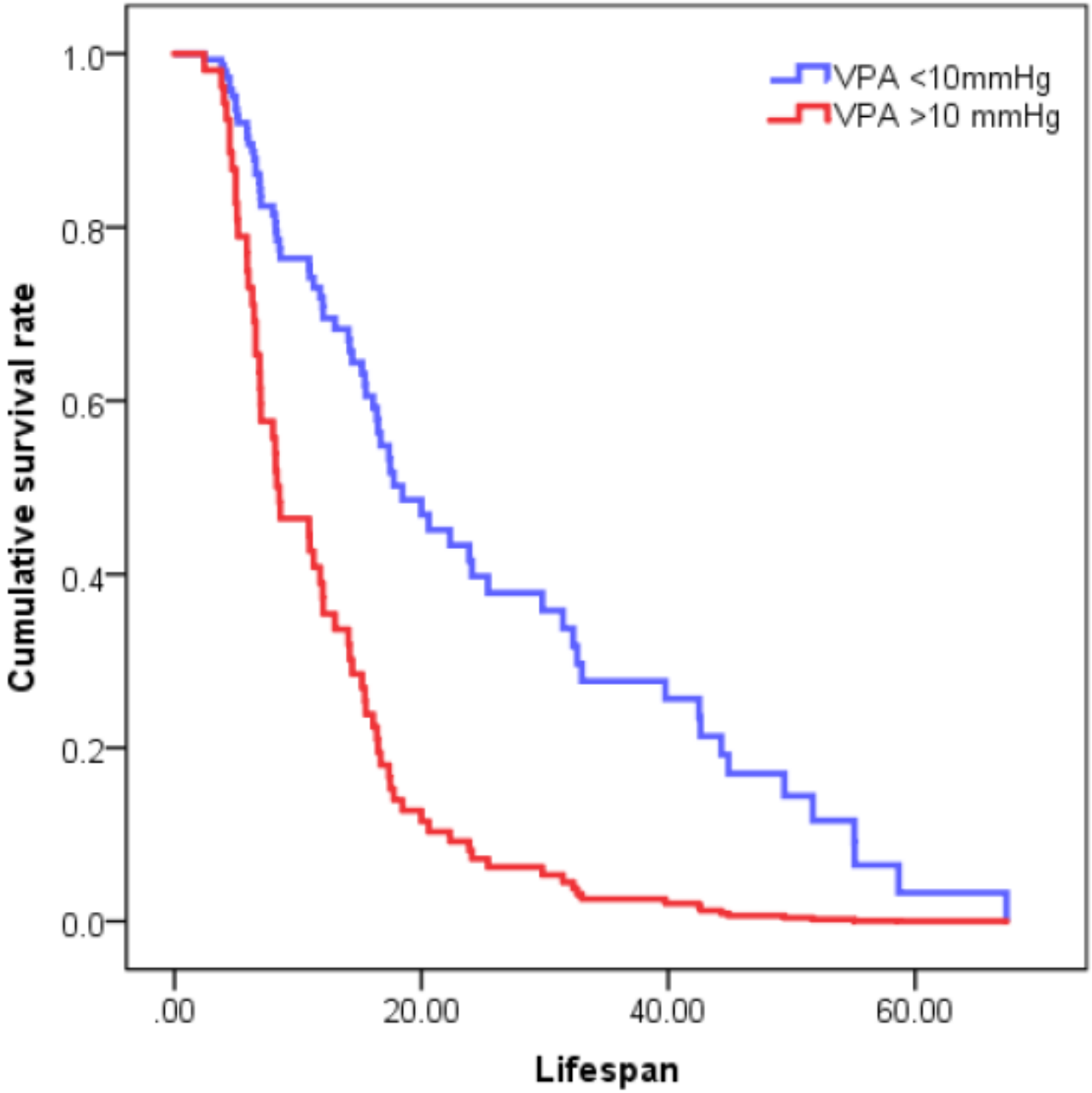
AOP = access outflow pressure; PFP = prefilter pressure; EP = effluent pressure; RIP = return inflow pressure; TMP = transmembrane pressure.

*Significant differences when compared to acute group (P<0.05).

#Significant differences when compared to subacute group (P<0.05).

	Acute or subacute AKF N =58	Chronic AKF N =18	P value
Lifespan (h)	10.6 ± 5.6	42.2 ± 12.3	<0.001
Total AOD events	53 (55.2%)	10 (31.3%)	0.019
Mild AOD	25 (26.0%)	8 (25.0%)	0.907
Moderate-severe AOD	28 (29.2%)	2 (6.3%)	0.008
Baseline AOP（mmHg）	-67.9 ± 29.2	-59.5 ± 8.2	0.232
Mean AOP（mmHg）	-70.2 ± 22.5	-62.6 ± 7.7	0.166
AOP variability（mmHg）	20.5 ± 16.5	8.2 ± 3.6	0.006
AOP >10 mmHg	64 (66.7%)	5 (15.6%)	<0.001
Anticoagulant use in CRRT	54/96	16/32	0.539
CRRT modality （CVVH/CVVHDF）	59/96	23/32	0.288
CRRT dose（L/h）	2.5 ± 0.5	2.3 ± 0.2	0.704
Femoral access position (R)	69/96	20/32	0.318
Hemoglobin（g/l）	84.5 ± 21.4	89.3 ± 20.4	0.271
Platelet（10^9/L）	168.9 ± 75.3	104.6 ± 56.7	<0.001
INR	1.5 ± 0.5	1.5 ± 0.4	0.673
APTT (s)	41.8 ± 10.9	41.7 ± 15.2	0.972


Without AOD
Mild AOD
Moderate-severe AOD
Cumulative survival rate
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
Lifespan


VPA <10mmHg
VPA >10 mmHg
Cumulative survival rate
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
Lifespan

What about anticoagulation? Heparin: the good

- All docs and nurses are familiar with it
- Easy to give
- Cheap
- Can be monitored
- Can be adjusted
- Logical choice if systemic anticoagulation is desired

Heparin: the bad

- Variable effectiveness in achieving adequate filter life
- Can trigger bleeding
- Contraindicated in several patient groups (recent major surgery, liver failure, severe thrombocytopenia, major trauma)
- Can induce HITTS

Regional citrate anticoagulation

- Used in intermittent HD since the 1960s
- Adapted to CRRT in the USA and first reported for CVVHDF in the early 1990s
- Dependent on citrate-based chelation of calcium
- Ionized calcium (Cai) falls and, as Cai is needed for coagulation, clotting is blocked
- The chelated calcium (and magnesium) is removed by filtration and needs to be replaced

Why is RCA not used in everyone?

- Lack of uniformity in RCA “recipes” reported in the literature causes confusion
- Cost and logistics of obtaining custom-made solutions (low Na, no Ca)
- Limited information on RCA for non diffusive CRRT (CVVH)
- Relatively common development of metabolic alkalosis
- Fear of citrate accumulation in selected patients

Why is RCA not used in everyone?

- Concern about the complexity and workload of monitoring calcium levels
- Concern about possible errors when 3 solutions may be administered simultaneously (Ca solution, citrate solution, custom-made low Na and no Ca replacement/dialysate fluids)
- Concern about training of nurses and doctors to do this safely

The data are clear!

(*Crit Care Med* 2015;

A Randomized Controlled Trial of Regional Citrate Versus Regional Heparin Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Adults

David J. Gattas, MD, MMed (ClinEpi), FCICM, FRACP[1,2];
Dorrilyn Rajbhandari, RN Post Grad Dip (Clinical Nursing)[1,2]; Celia Bradford, MD, FCICM[3];
Heidi Buhr, RN, MClinTPrac[1]; Serigne Lo, PhD, AStat[2];
Rinaldo Bellomo, MBBS, MD (Hons), FRACP, FCICM, PG Dip Echo[4,5]

Design: Multicenter, parallel group randomized controlled trial.

Setting: Seven ICUs in Australia and New Zealand.

Patients: Critically ill adults requiring continuous renal replacement therapy.

Interventions: Patients were randomized to receive one of two methods of regional circuit anticoagulation: citrate and calcium or heparin and protamine.

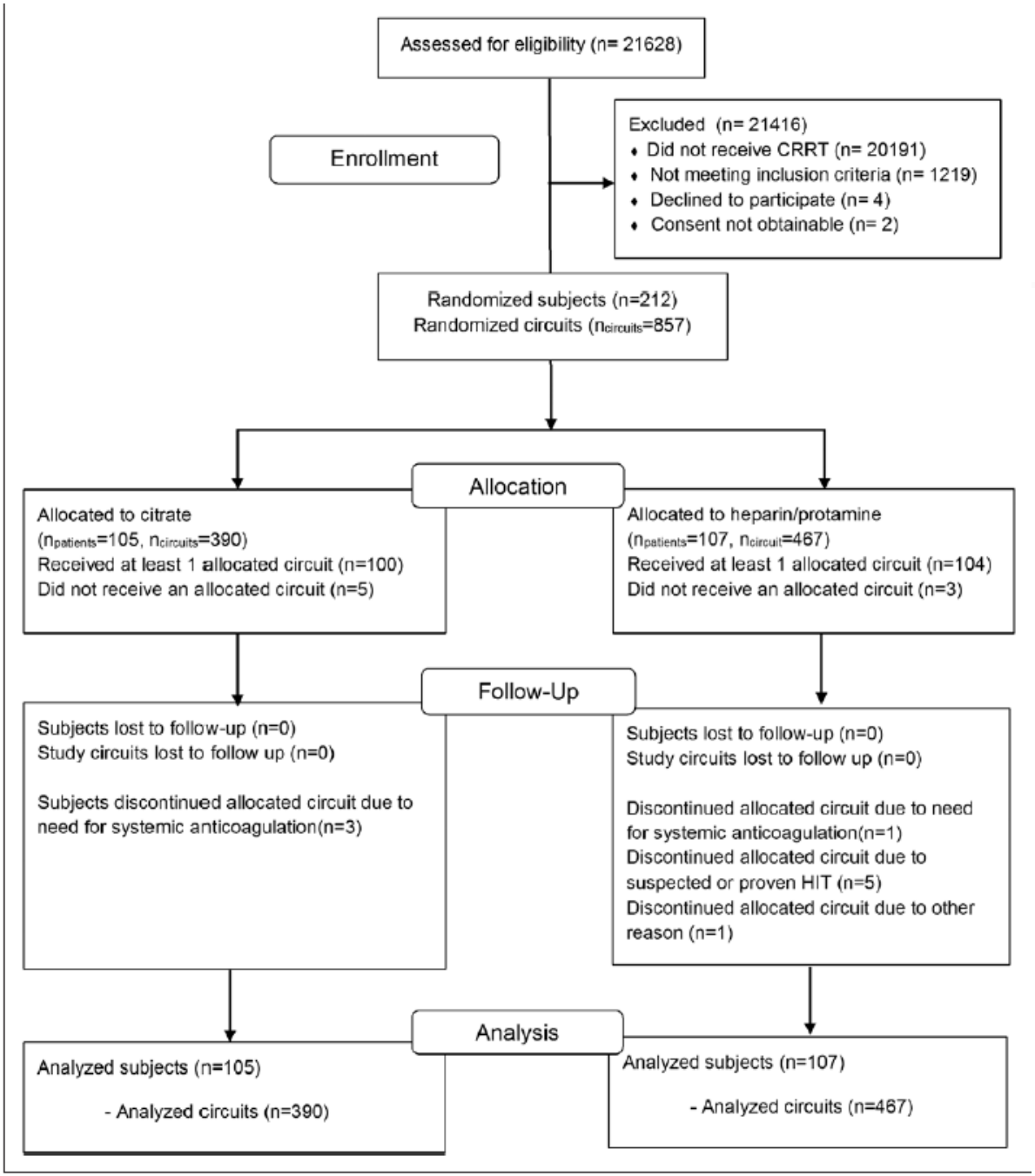

Assessed for eligibility (n= 21628)
Enrollment
Excluded (n= 21416)
♦ Did not receive CRRT (n= 20191)
♦ Not meeting inclusion criteria (n= 1219)
♦ Declined to participate (n= 4)
♦ Consent not obtainable (n= 2)
Randomized subjects (n=212)
Randomized circuits ($n_{circuits}$=857)
Allocation
Allocated to citrate
($n_{patients}$=105, $n_{circuits}$=390)
Received at least 1 allocated circuit (n=100)
Did not receive an allocated circuit (n=5)
Allocated to heparin/protamine
($n_{patients}$=107, $n_{circuit}$=467)
Received at least 1 allocated circuit (n=104)
Did not receive an allocated circuit (n=3)
Follow-Up
Subjects lost to follow-up (n=0)
Study circuits lost to follow up (n=0)
Subjects discontinued allocated circuit due to need for systemic anticoagulation(n=3)
Subjects lost to follow-up (n=0)
Study circuits lost to follow up (n=0)
Discontinued allocated circuit due to need for systemic anticoagulation(n=1)
Discontinued allocated circuit due to suspected or proven HIT (n=5)
Discontinued allocated circuit due to other reason (n=1)
Analysis
Analyzed subjects (n=105)
- Analyzed circuits (n=390)
Analyzed subjects (n=107)
- Analyzed circuits (n=467)

TABLE 1. Baseline Demographic and Clinical Characteristics of the Intervention and Control Groups

Variable	Citrate ($n = 105$)	Heparin ($n = 107$)
Age, yr	66.4 (14.3)	66.8 (14.9)
Male gender, *n*/total (%)	74/105 (71)	72/107 (67)
Weight		
Measured (vs estimated), *n*/total (%)	46/105 (44)	50/107 (47)
Weight (kg)	85.0 (20.6)	84.3 (22.9)
Source of admission to ICU, *n*/total (%)		
Emergency department	24/105 (22.9)	38/107 (35.5)
Hospital ward	27/105 (25.7)	19/107 (17.8)
Operating theatre, elective	31/105 (29.5)	33/107 (30.8)
Operating theatre, emergency	4/105 (3.8)	3/107 (2.8)
Transfer from another hospital	4/105 (3.8)	6/107 (5.6)
Transfer from other ICU	9/105 (8.6)	6/107 (5.6)
Not available	6/105 (5.7)	2/107 (1.9)
Time from ICU admission to randomization (hr)		
Median (interquartile range)	25.1 (44.5)	21.5 (44.0)
APACHE III diagnostic group, *n*/total (%)		
Coronary artery bypass grafts	14/105 (13.3)	13/107 (12.1)
Renal disorders	10/105 (9.5)	7/107 (6.5)
Sepsis with shock, nonurinary	8/105 (7.6)	7/107 (6.5)
Other respiratory diseases	6/105 (5.7)	7/107 (6.5)
Valvular heart surgery	5/105 (4.8)	6/107 (5.6)
Other	62/105 (59.0)	67/107 (62.6)
APACHE II score, mean (SD)	25.6 (7.6)	25.0 (6.9)

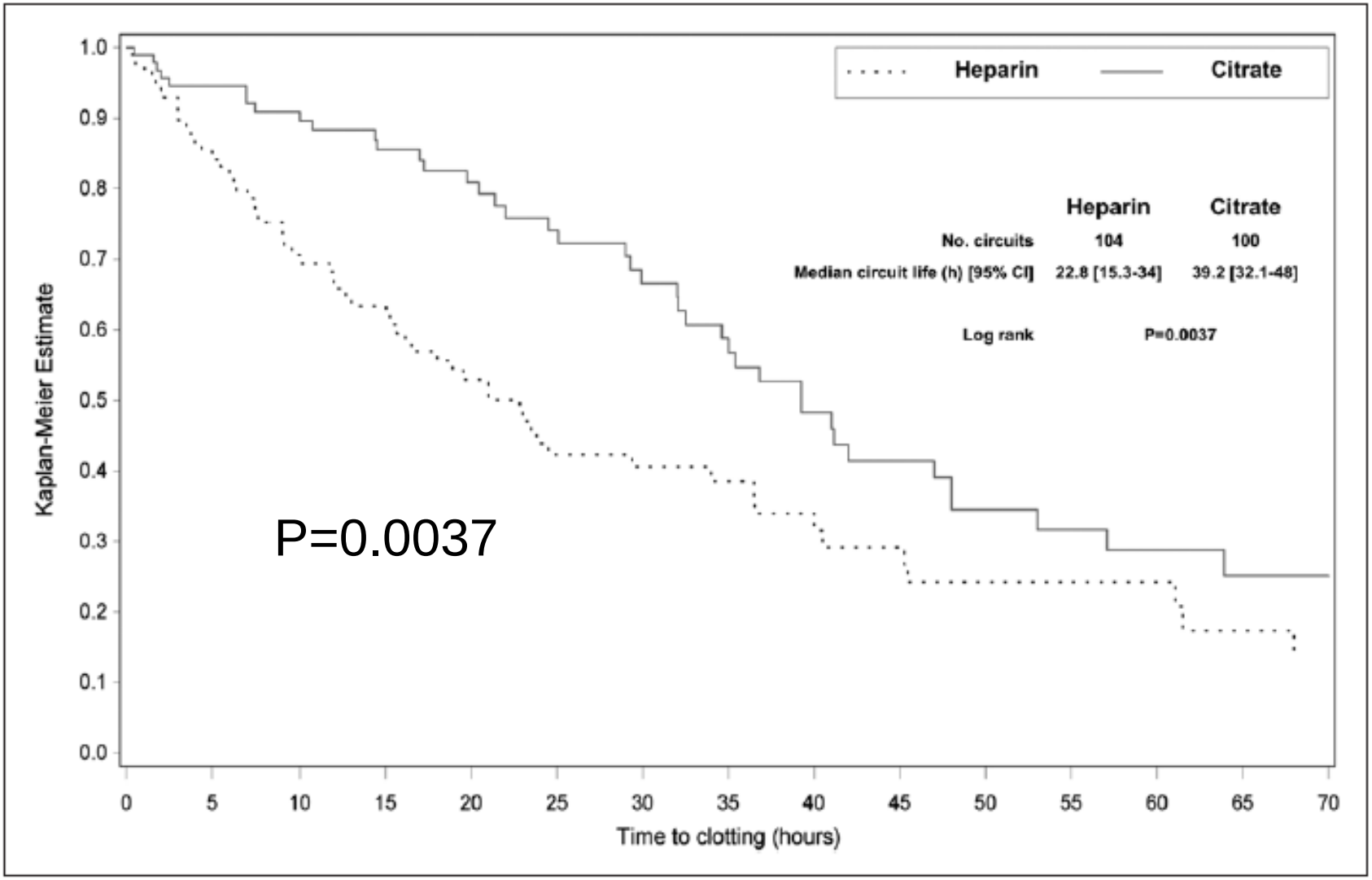


Figure 2. Kaplan-Meier estimate of the probability of continuous renal replacement therapy circuit survival for the first circuit.

For all circuits: HR for clotting 2.03 using frailty model

Schilder et al. Critical Care 2014, 18:472
http://ccforum.com/content/18/4/472

CRITICAL CARE

RESEARCH Open Access

Citrate anticoagulation versus systemic heparinisation in continuous venovenous hemofiltration in critically ill patients with acute kidney injury: a multi-center randomized clinical trial

Louise Schilder[1*], S Azam Nurmohamed[1], Frank H Bosch[2], Ilse M Purmer[3], Sylvia S den Boer[4], Cynthia G Kleppe[5], Marc G Vervloet[1], Albertus Beishuizen[6], Armand RJ Girbes[6], Pieter M ter Wee[1], AB Johan Groeneveld[7] and for the CASH study group

Abstract

Introduction: Because of ongoing controversy, renal and vital outcomes are compared between systemically administered unfractionated heparin and regional anticoagulation with citrate-buffered replacement solution in predilution mode, during continuous venovenous hemofiltration (CVVH) in critically ill patients with acute kidney injury (AKI).

Methods: In this multi-center randomized controlled trial, patients admitted to the intensive care unit requiring CVVH and meeting inclusion criteria, were randomly assigned to citrate or heparin. Primary endpoints were mortality and renal outcome in intention-to-treat analysis. Secondary endpoints were safety and efficacy. Safety was defined as absence of any adverse event necessitating discontinuation of the assigned anticoagulant. For efficacy, among other parameters, survival times of the first hemofilter were studied.

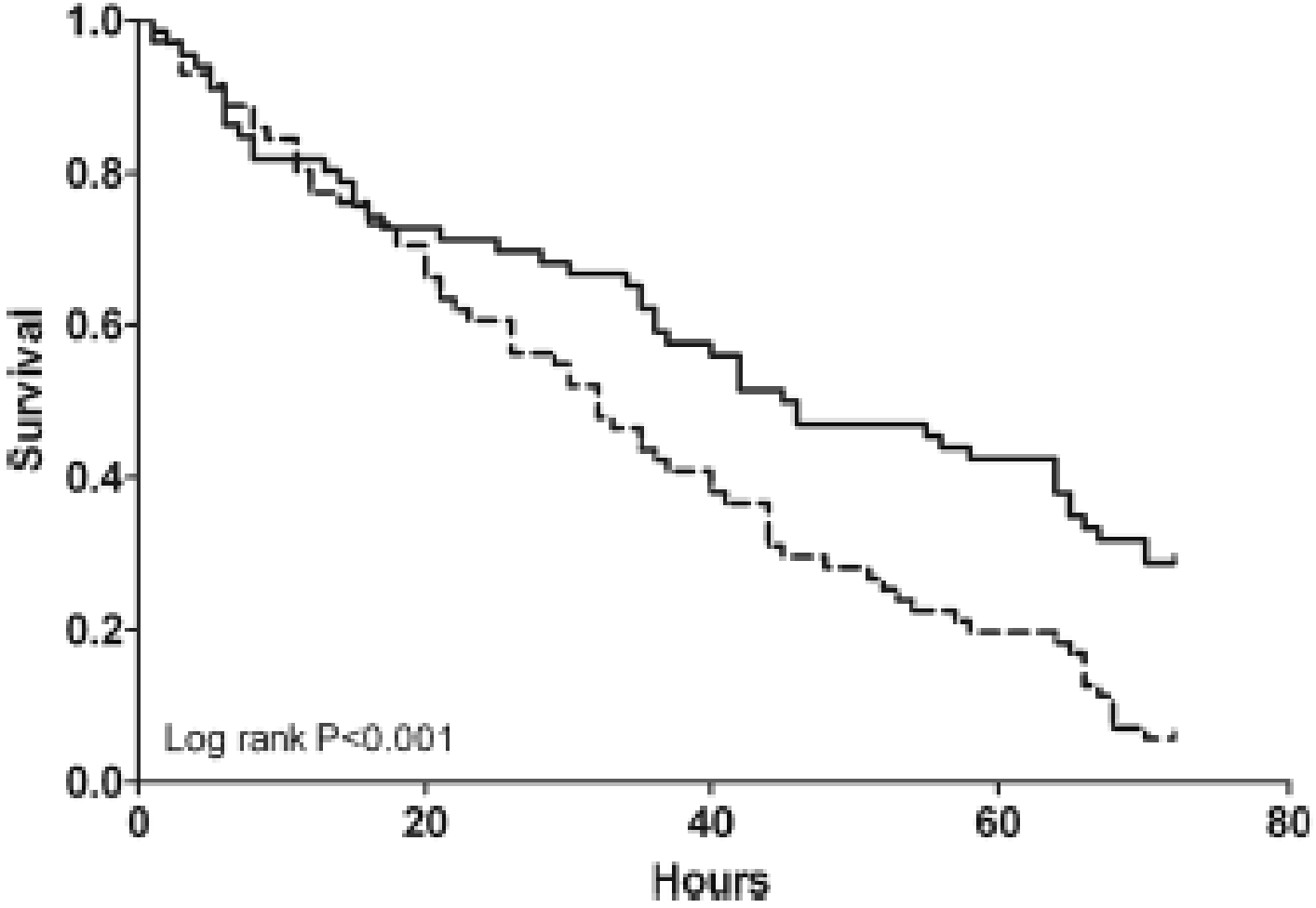


Figure 2 Survival times for the first filter. Continuous line represents citrate, dotted line represents heparin.

Fewer complications

Table 2 Secondary outcomes

	Citrate (n = 66)	Heparin (n = 73)	*P*-value
Safety, discontinuation of study anticoagulant			
Within 72 h	2 (3)	9 (12)	0.06
Bleeding episode	0	2 (22)	
HIT	0	2 (22)	
Frequent filter failure	0	3 (33)	
Citrate accumulation	2 (100)	0	
Miscellaneous	0	2 (22)	
Within 28 days	5 (8)	24 (33)	<0.001
Bleeding episode	0	8 (33)	
HIT	0	6 (25)	
Frequent filter failure	0	7 (29)	
Citrate accumulation	4 (80)	0	
Miscellaneous	1 (20)	3 (13)	
Bleeding episode within 28 days	3 (5)	10 (14)	0.08
Requirement of >2 packed cells	2 (3)	4 (6)	0.68
Metabolic derangements, during first 72 hours of therapy			
pH >7.50	1 (2)	0	1.00
Sodium >150 mmol/L	4 (7)	3 (5)	0.71
Magnesium <0.7 mmol/L	8 (15)	6 (9)	0.40

More filter life

Efficacy, intention to treat			
Survival time first filter, h	46 (1 to 138)	32 (1 to 72)	0.02
Number of filters used within 72 h	1 (1 to 5)	2 (1 to 9)	0.002
Off-time within 72 h, h	1 (0 to 12)	3 (0 to 31)	0.002
Reason for circuit disconnection			0.01
Circuit clotting	16 (24)	35 (51)	
Elective filter change (72 h)	20 (30)	6 (9)	
Catheter dysfunction	4 (6)	8 (12)	
Termination of CWH[1]	10 (15)	10 (12)	
Transport	4 (6)	1 (1)	
Technical problems	8 (12)	5 (7)	
Therapy change[2]	2 (3)	3 (4)	
Miscellaneous	2 (3)	1 (1)	
Total duration of CWH, h	123 (4 to 999)	73 (5 to 672)	0.18

Cheaper overall

Costs			
Total cost of first 72 h of CWH, €	553 (436 to 872)	663 (320 to 1,319)	<0.001
Replacement fluid, €	316 (225 to 366)	429 (119 to 736)	<0.001
Wage nursing staff for filter change, €	19 (19 to 95)	38 (19 to 171)	0.02

Table 2 Secondary outcomes *(Continued)*

Filter sets, €	85 (85 to 425)	170 (85 to 765)	0.02
Heparin, €	0	6.46 (3.84 to 6.74)	<0.001
Calcium glubionate, €	82 (70 to 84)	0	<0.001

Liu *et al. Critical Care* (2016) 20:144
DOI 10.1186/s13054-016-1299-0

Critical Care

RESEARCH Open Access

Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials

Chao Liu†, Zhi Mao†, Hongjun Kang, Jie Hu and Feihu Zhou*

Background: Regional citrate or heparin is often prescribed as an anticoagulant for continuous renal replacement therapy (CRRT). However, their efficacy and safety remain controversial. Therefore, we performed this meta-analysis to compare these two agents and to determine whether the currently available evidence is sufficient and conclusive by using trial sequential analysis (TSA).

Methods: We searched for relevant studies in PubMed, Embase, the Cochrane Library databases and the China National Knowledge Infrastructure (CNKI) Database from database inception until September 2015. We selected randomized controlled trials comparing regional citrate with heparin in adult patients with acute kidney injury (AKI) who were prescribed CRRT.

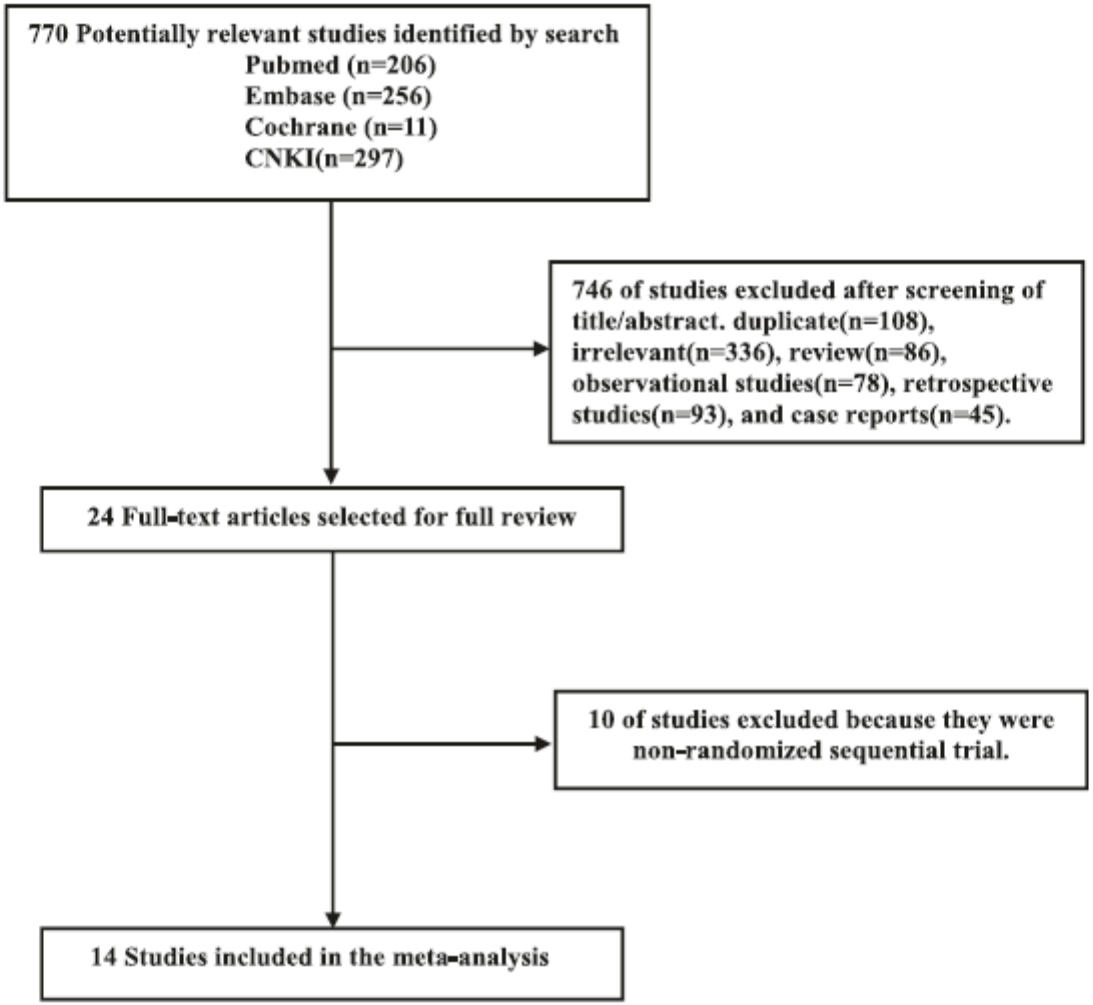
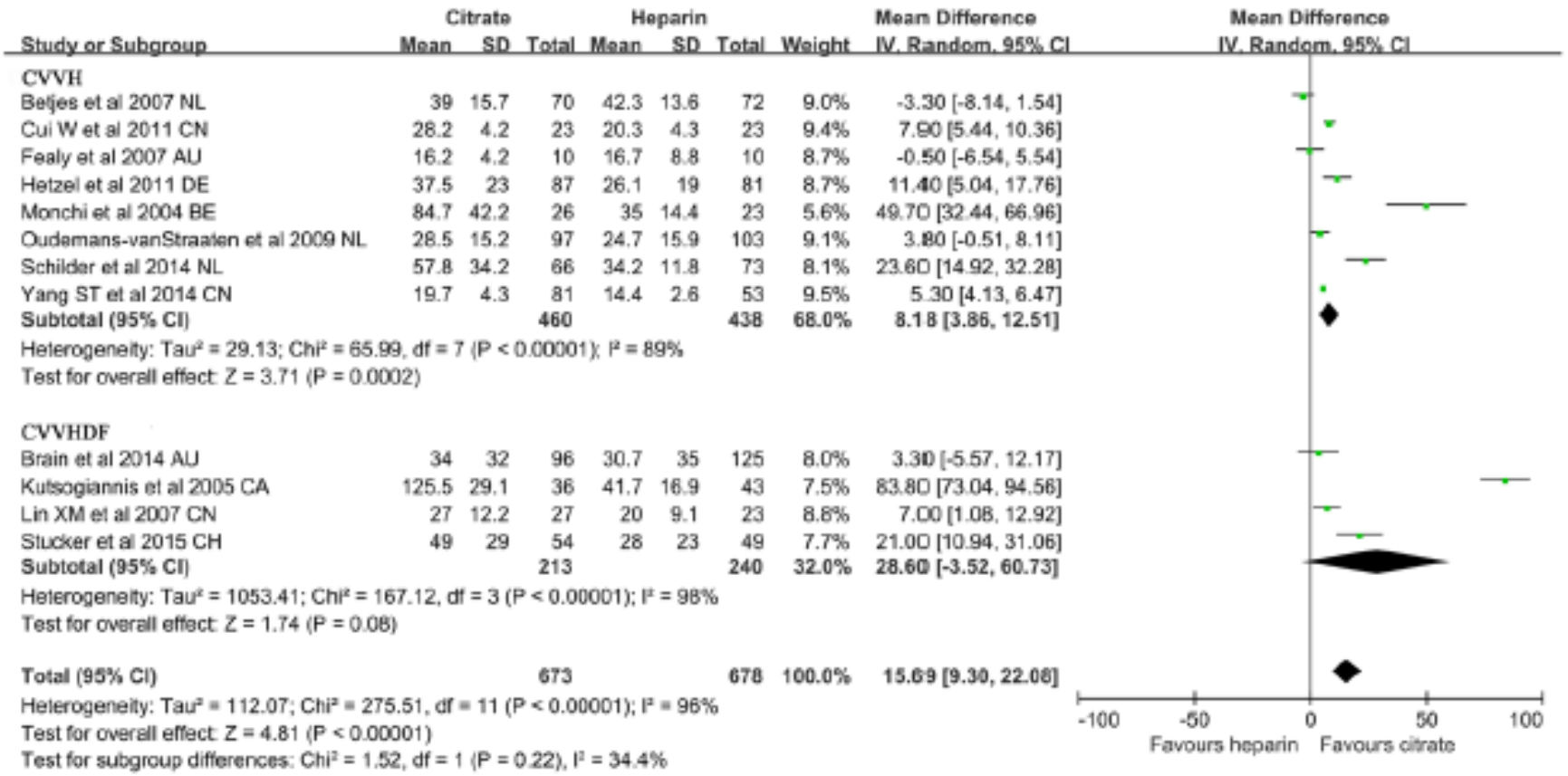


Fig. 1 Flow chart of the study selection. *CNKI* Chinese National Knowledge Infrastructure

Filter life

a



Study or Subgroup	Citrate Mean	Citrate SD	Citrate Total	Heparin Mean	Heparin SD	Heparin Total	Weight	Mean Difference IV, Random, 95% CI
CVVH								
Beljes et al 2007 NL	39	15.7	70	42.3	13.6	72	9.0%	-3.30 [-8.14, 1.54]
Cui W et al 2011 CN	28.2	4.2	23	20.3	4.3	23	9.4%	7.90 [5.44, 10.36]
Fealy et al 2007 AU	16.2	4.2	10	16.7	8.8	10	8.7%	-0.50 [-6.54, 5.54]
Hetzel et al 2011 DE	37.5	23	87	26.1	19	81	8.7%	11.40 [5.04, 17.76]
Monchi et al 2004 BE	84.7	42.2	26	35	14.4	23	5.6%	49.70 [32.44, 66.96]
Oudemans-vanStraaten et al 2009 NL	28.5	15.2	97	24.7	15.9	103	9.1%	3.80 [-0.51, 8.11]
Schilder et al 2014 NL	57.8	34.2	66	34.2	11.8	73	8.1%	23.60 [14.92, 32.28]
Yang ST et al 2014 CN	19.7	4.3	81	14.4	2.6	53	9.5%	5.30 [4.13, 6.47]
Subtotal (95% CI)			**460**			**438**	**68.0%**	**8.18 [3.86, 12.51]**
Heterogeneity: Tau² = 29.13; Chi² = 65.99, df = 7 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 3.71 (P = 0.0002)								
CVVHDF								
Brain et al 2014 AU	34	32	96	30.7	35	125	8.0%	3.30 [-5.57, 12.17]
Kutsogiannis et al 2005 CA	125.5	29.1	36	41.7	16.9	43	7.5%	83.80 [73.04, 94.56]
Lin XM et al 2007 CN	27	12.2	27	20	9.1	23	8.6%	7.00 [1.08, 12.92]
Stucker et al 2015 CH	49	29	54	28	23	49	7.7%	21.00 [10.94, 31.06]
Subtotal (95% CI)			**213**			**240**	**32.0%**	**28.60 [-3.52, 60.73]**
Heterogeneity: Tau² = 1053.41; Chi² = 167.12, df = 3 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 1.74 (P = 0.08)								
Total (95% CI)			**673**			**678**	**100.0%**	**15.69 [9.30, 22.08]**
Heterogeneity: Tau² = 112.07; Chi² = 275.51, df = 11 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 4.81 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.4%								

Table 2 Direct comparison of regional citrate with heparin on adverse events

Adverse events	No. of studies	No. of patients		RR(95%CI)	Heterogeneity	Test for effect (p value)
		Citrate	Heparin		I^2 (p value)	
Bleeding events	10 (11, 13, 24, 25, 27, 28, 29, 32, 33, 34)[a]	405	405	0.31(0.19, 0.51)	0% (0.56)	<0.00001
	3 (12, 26, 31)[b]	140	138	0.23 (0.03, 1.97)	0% (0.75)	0.18
HIT	5 (11, 12, 13, 28, 33)	409	415	0.41 (0.19, 0.87)	0% (0.73)	0.02
Metabolic alkalosis	7(11, 13, 24, 27, 28, 29, 34)	289	301	0.84 (0.47, 1.49)	40% (0.14)	0.55
Hypocalcemia	7 (11, 24, 27, 28, 29, 33, 34)	310	311	3.96 (1.50, 10.43)	0% (1.00)	0.005

CI confidence interval, *HIT* heparin induced thrombocytopenia, *RR* relative risk, [a] citrate versus systemic heparin; [b] citrate versus regional heparin

Conclusions I

- Citrate anticoagulation during CRRT increases filter life and decreases risk of bleeding
- However, it is more complex
- Its implementation demands greater training and a more sophisticated understanding of CRRT & citrate physiology
- **You do not have to choose between bleeding and clotting with citrate: no bleeding and less clotting!**

Conclusion II - So…what to do?

- Understand how both work
- Appreciate risks and advantages
- Educate workforce to use both safely
- Citrate best in most patients
- Heparin best if systemic anticoagulation needed anyway
- Some people cannot receive either heparin or citrate (fulminant liver failure patients)
- **Never forget that more filters are lost because of inadequate vascular access than inadequate anticoagulation!**