Rigshospitalet
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FACULTY OF HEALTH AND MEDICAL SCIENCES
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REGION

The Cooling And Surviving Septic Shock (CASS) study

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On behalf of the CASS trial group
Denmark: The Capital Region, Region Zealand, Central Denmark Region, University of Copenhagen
Holland: Academic Medical Center, Amsterdam

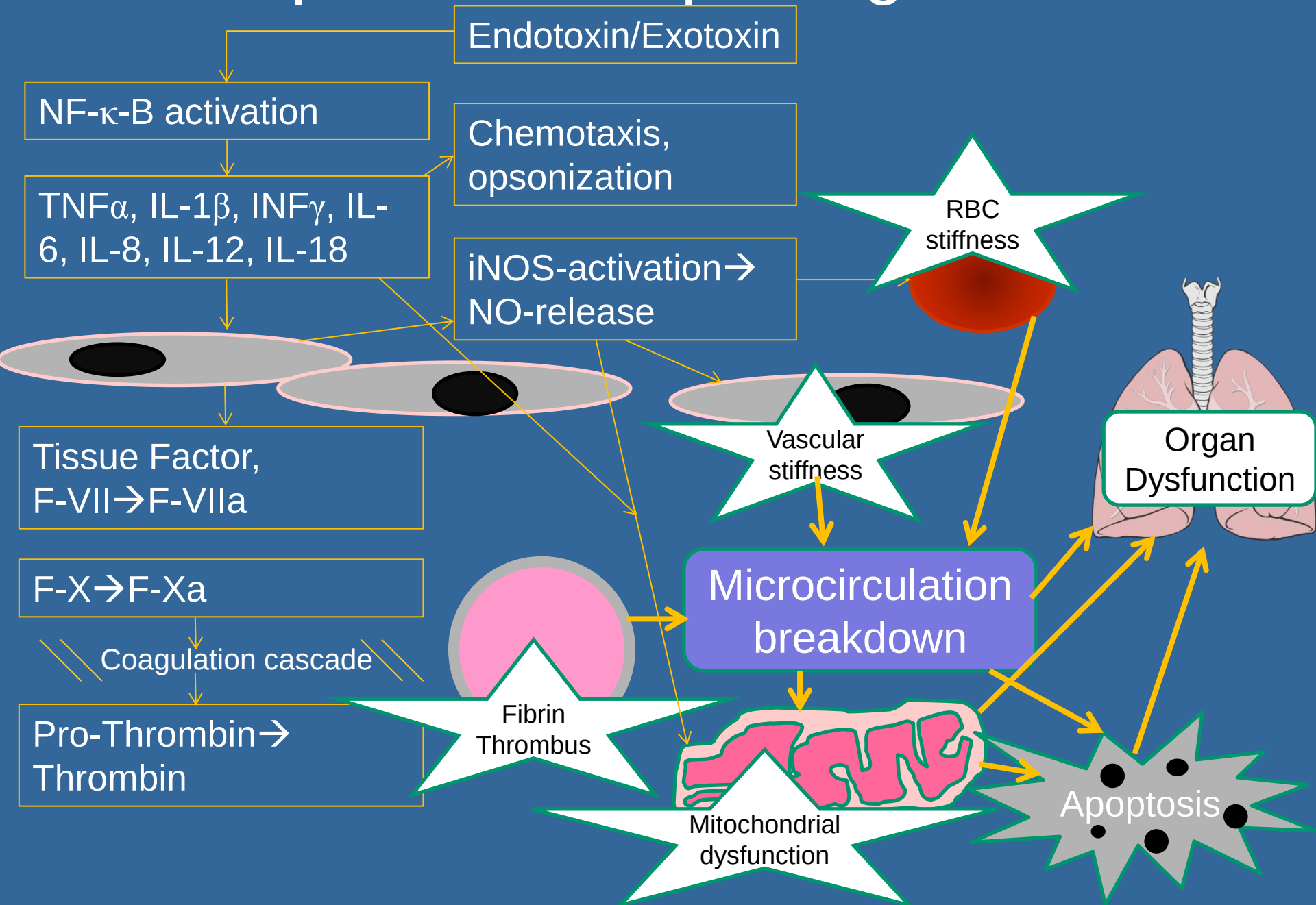
GLOBAL EXCELLENCE IN HEALTH

- **Conflicts of Interest: None**

Septic Shock

- Mortality in septic shock is around 30-50%
- Complex interaction of immune system, hypercoagulation and apoptosis
- Microcirculatory collapse is central in the pathogenesis leading to multi-organ failure and death
- Very high cost for families, health care and society

Septic shock - pathogenesis



Mild Induced Hypothermia

- Action points in the pathogenesis ?

Bacterial growth & Cooling

Food studies:

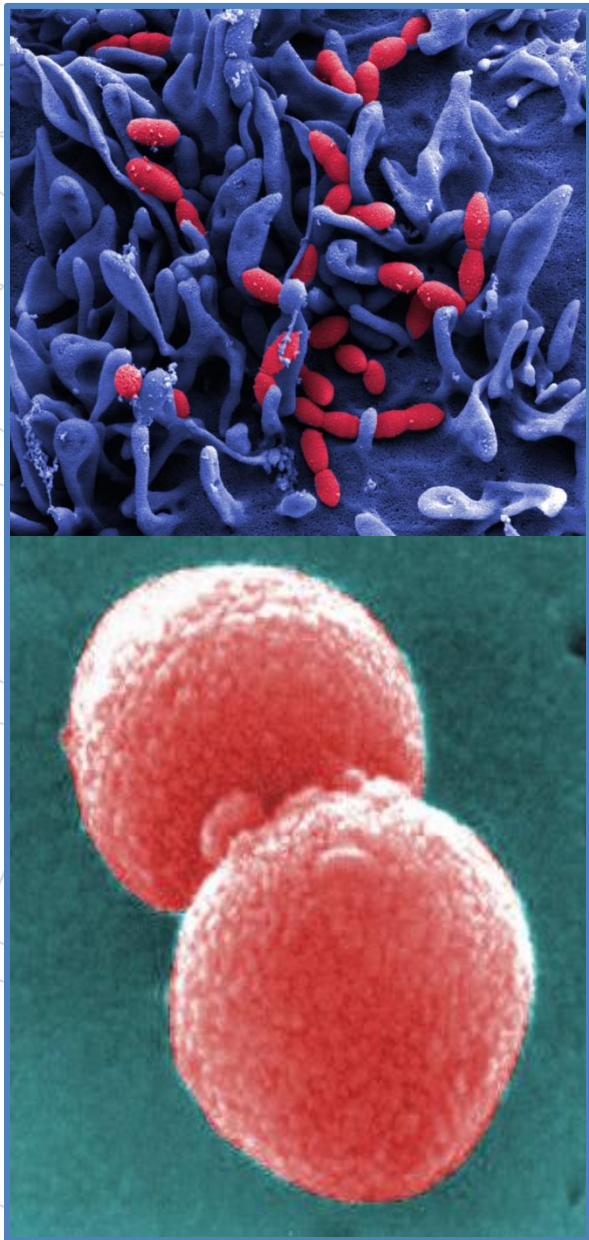
- Optimum bacterial growth at~39^{o}C (102 F)
- Temperature dependent exponential growth of bacteria
- At 33^{o}C (91 F) the amount of bacteria will theoretically reduced ~ 10 times in 6 h

Membre et al. Int J Food Microbiol. 2005

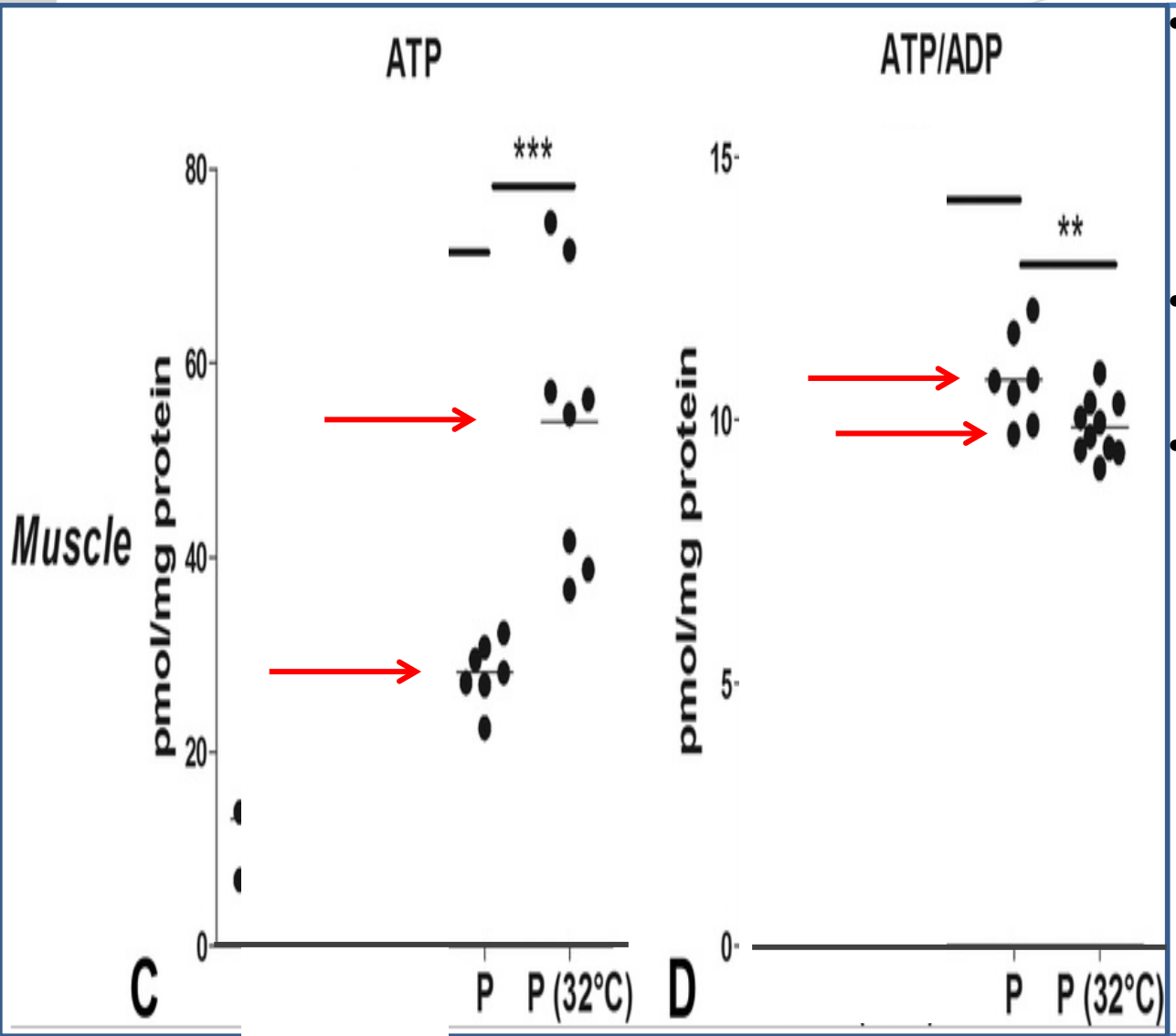
Rat study: 32^{o}C, 90 F):

- Pneumococcal challenge
- No significant decrease in bacteria in lungs
- But: less pneumococcal dissemination to spleen

Beurskens. Crit Care Med. 2012.



Mitochondrial function and Cooling



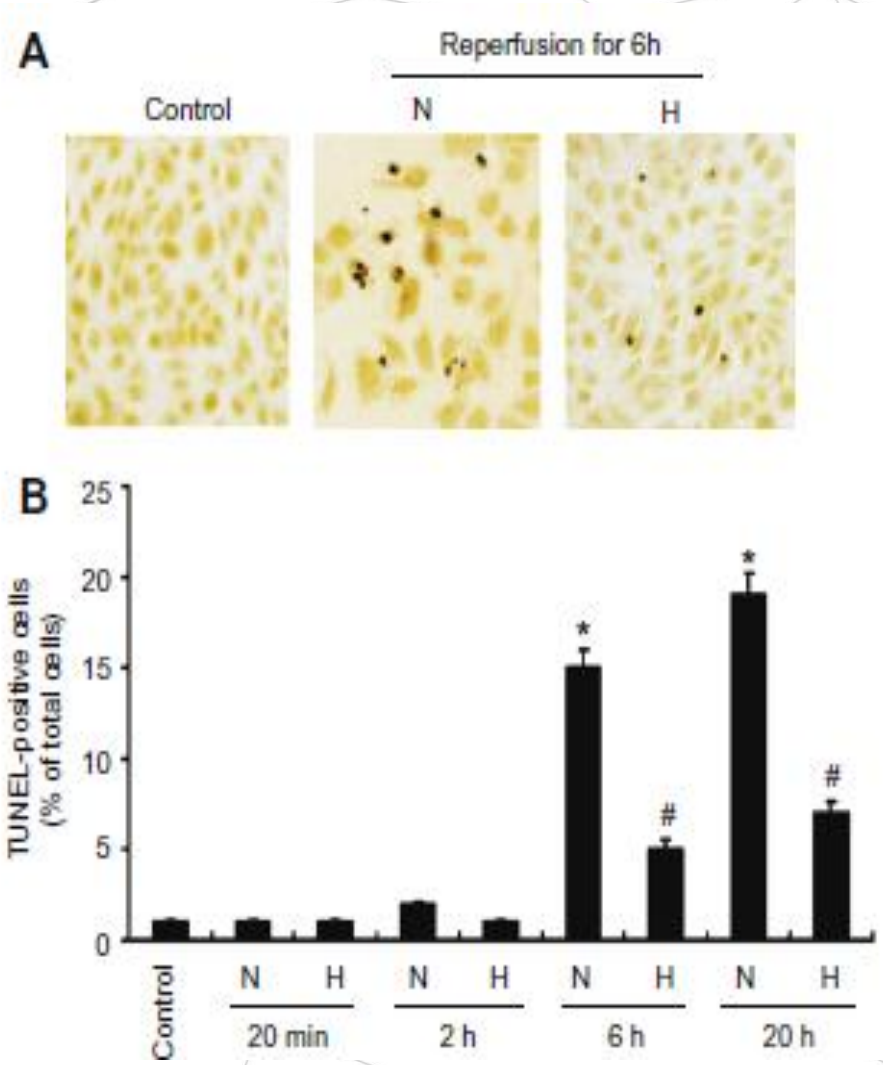
- In male rats with pneumococcal challenge, muscle ATP levels increase substantially and highly significantly ($p<0.0001$)
- Intracellular metabolism seems to be preserved in MIH
- The mitochondrial oxygen consumption drop in pneumococcal sepsis is reversed in MIH (32°C)

*32 °C ~ 90 F

Charlotte Beurskens et al. Crit Care Med 2012

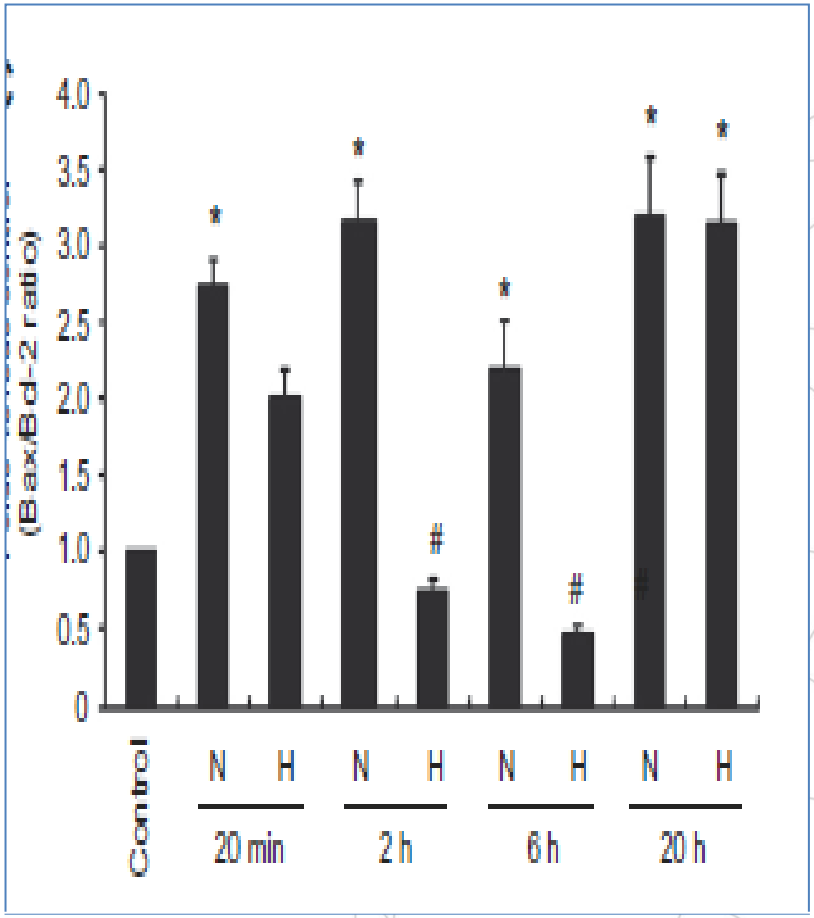
Apoptosis

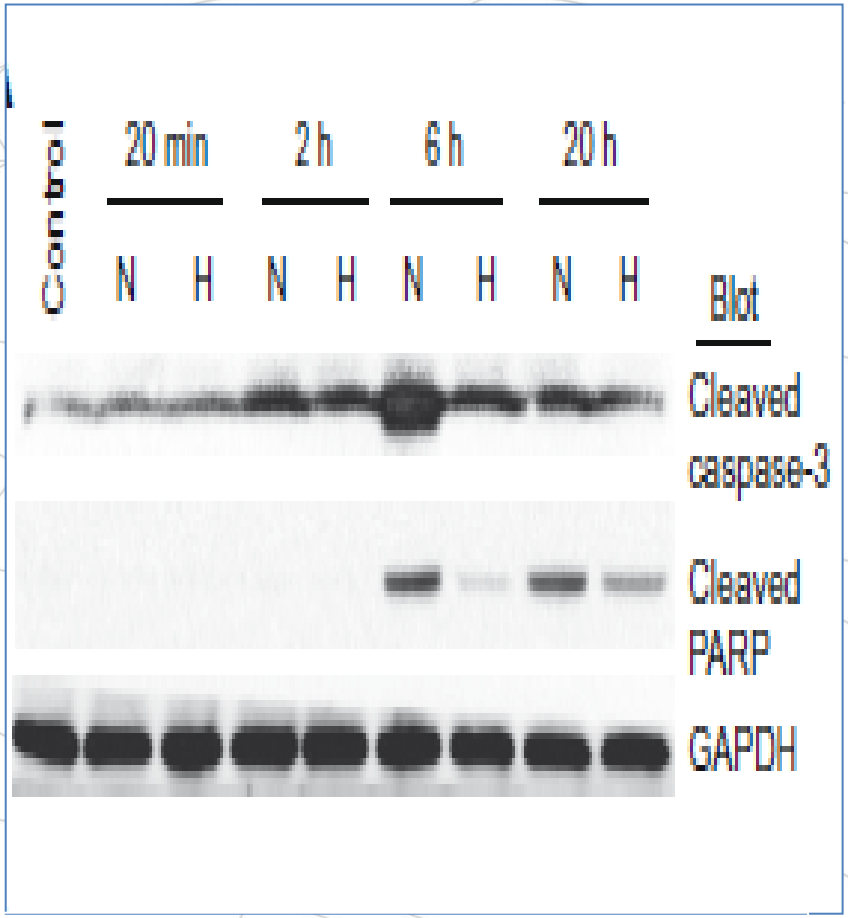
- Human Umbilical Cord cells (HUVEC)
- Ischemia-reperfusion induced apoptosis
- 37°C (98.6 F) vs. 33°C (91.4 F)



Yang et al. FEBS Letters 2009

Apoptosis





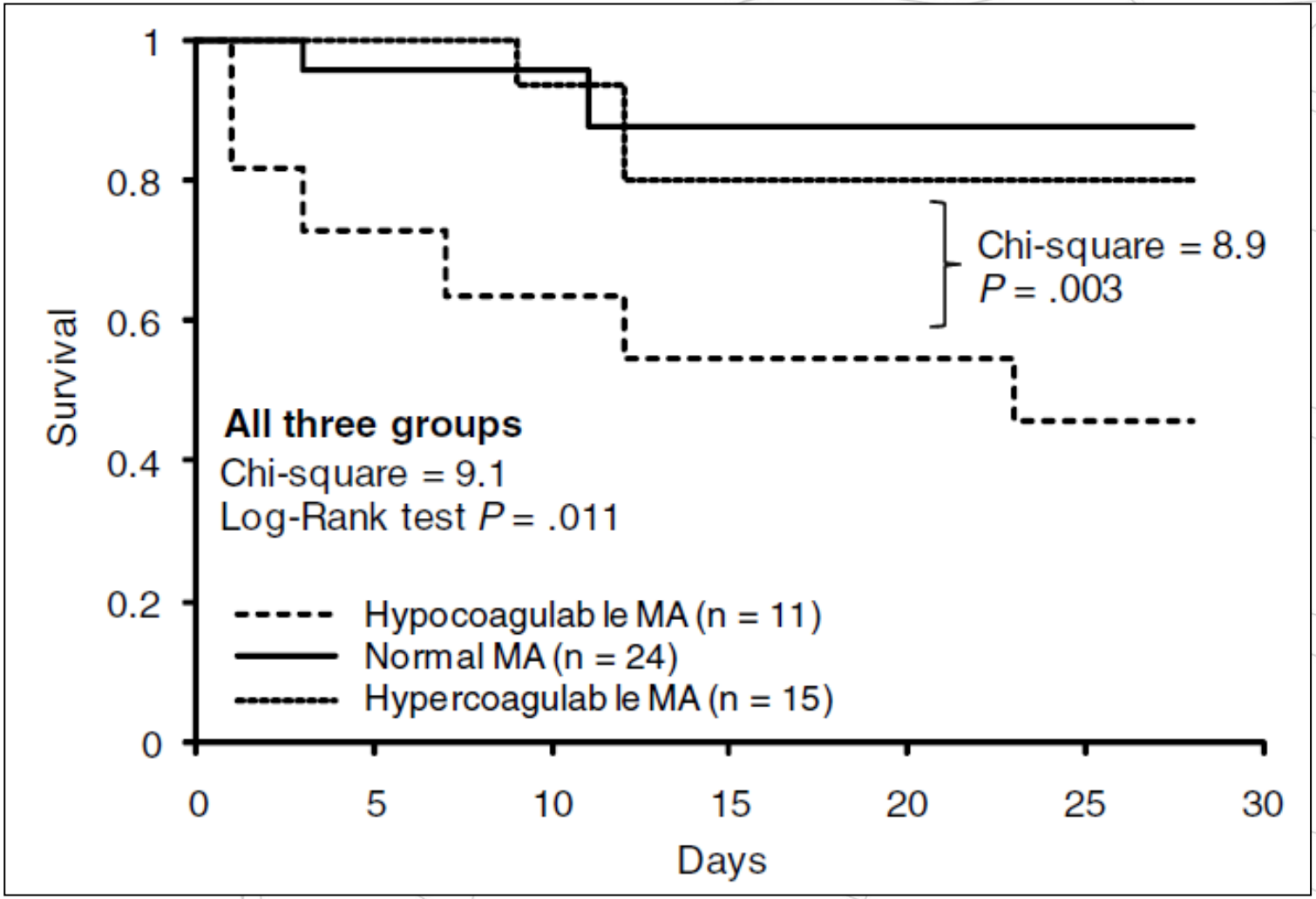
- Reproduced in animal experiments

Yang et al. FEBS Letters 2009

Coagulation and Mild Induced Hypothermia in sepsis

- Effect of MIH on coagulation in sepsis is highly disputed
- No RCT´s have explored this
- Few small observational studies have explored influence of functional coagulaopathy on prognosis

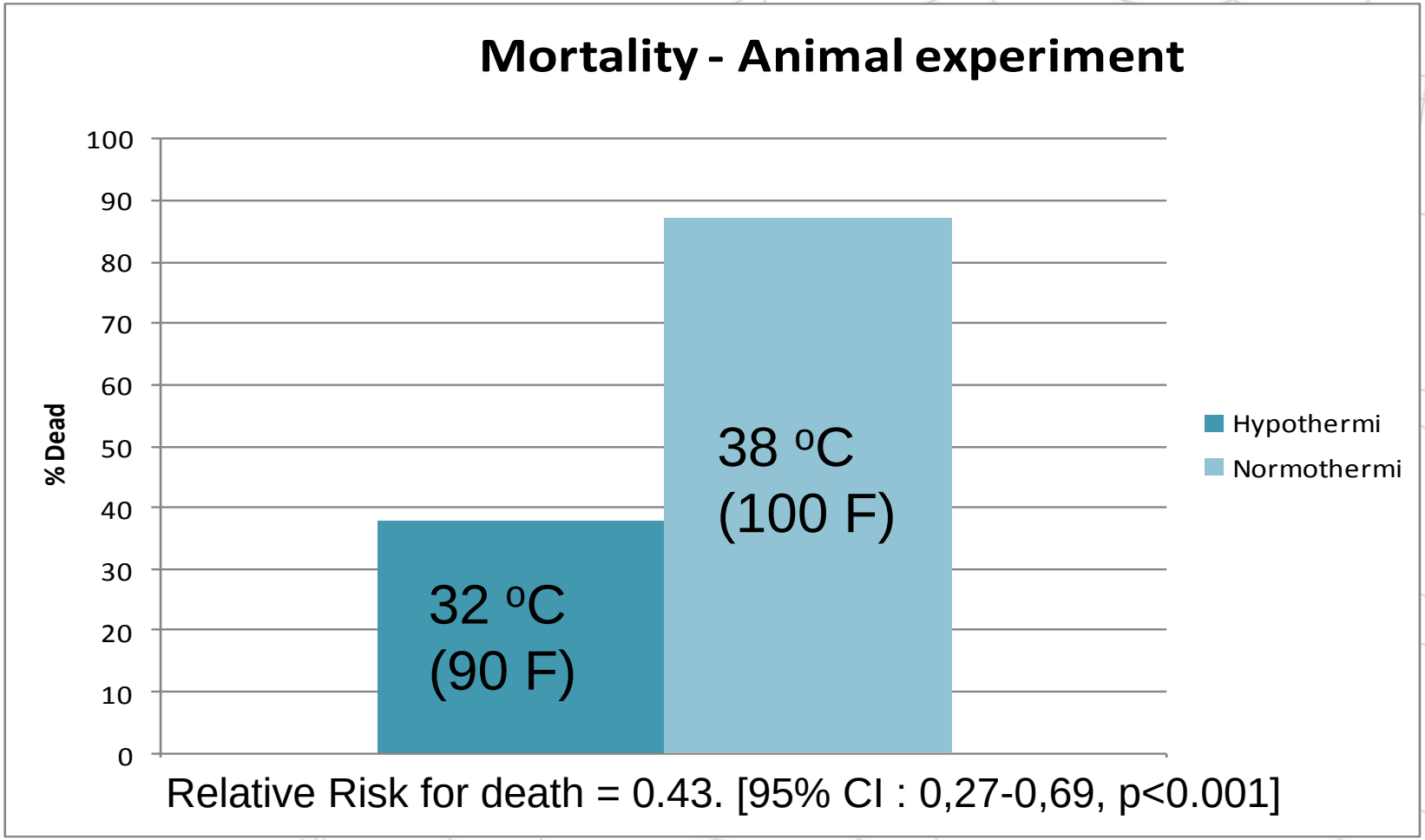
Coagulation - Functional coagulation tests – Thromboelastrography (TEG) in severe sepsis



Ostrowski et al. J crit care 2013

Survival – animal studies

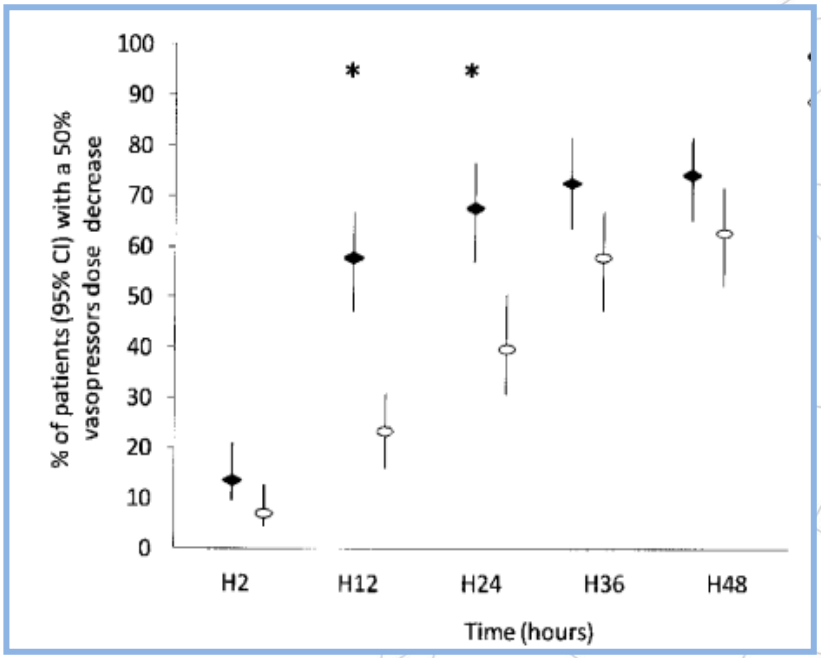
N= 64 rats, Endotoxin challenge.

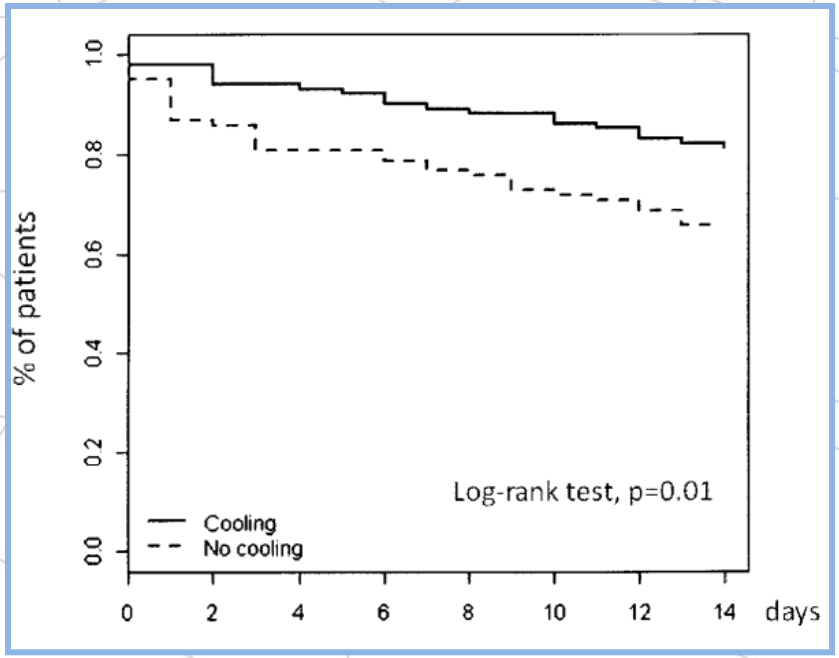


Huet et al. Acta Anaesthesiol Scand 2007

Human study – Shock reversal

External cooling (NB: Normothermia) 48 h. Septic shock. N=200 (101+99). Groups: 36.5 – 37.0 ºC vs. Fever respect



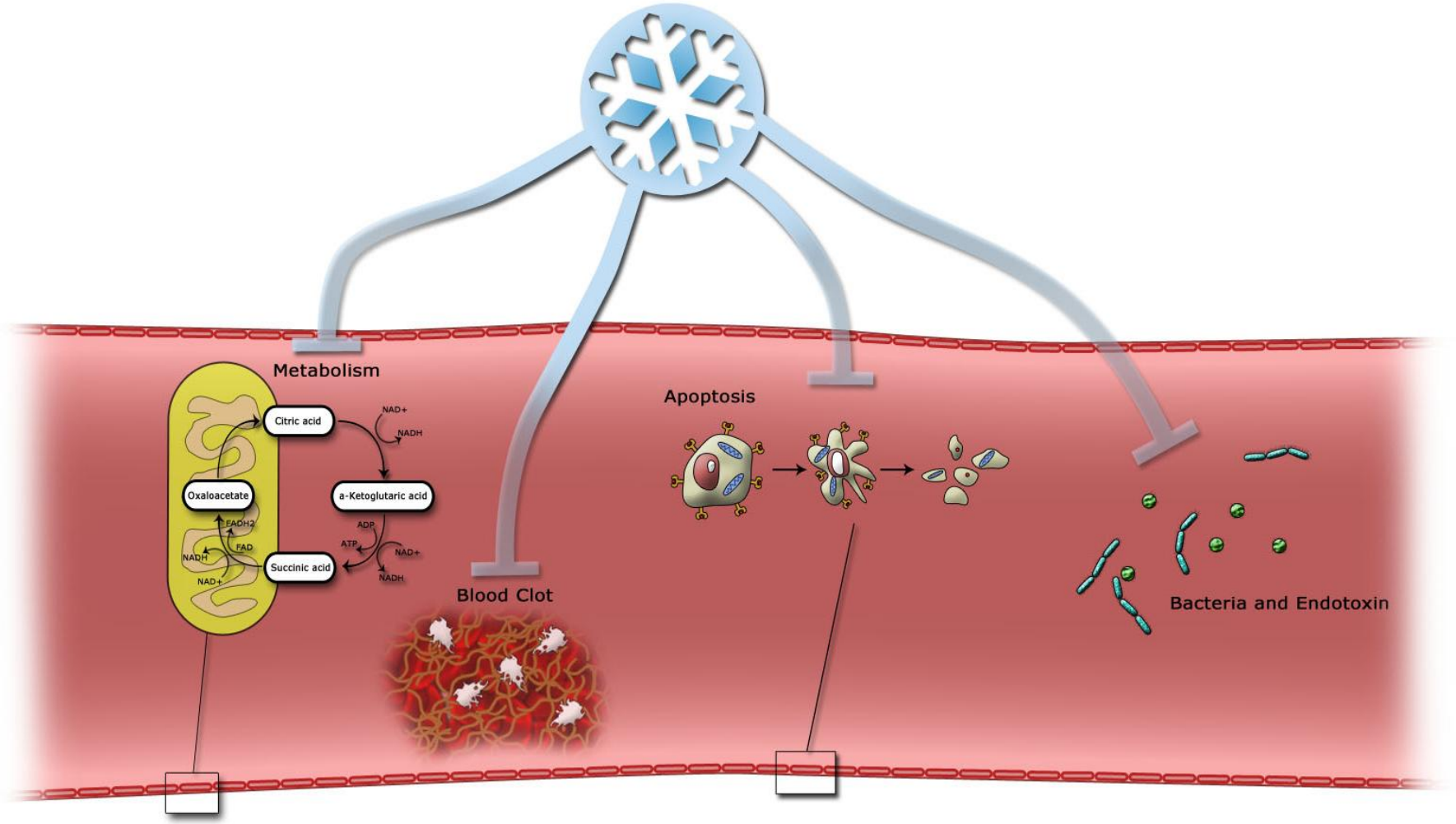


% patients achieving 50% reduction of vasopressor was reached earlier in cooled (normothermic) patients

Tendency towards day-14 mortality lower in normothermia cooled group

Schortgen et al. Am Respir Crit Care Med 2012

Summary – mild induced hypothermia – points of action on sepsis pathophysiology



The CASS trial

- Inclusion of 560 patients at 10 ICUs all across Denmark and The Nederlands
- Investigator-initiated study based on a group of 17 steering committee members
- Data and Safety Monitoring Board (DSMB) consisting of 4 clinical research and biostatistic experts
  (Chairman Henry Masur Chief, Critical Care Medicine Department, National Institutes of Health, USA)
- Well-established coordination center with decades of experience in conducting multicenter trials
- International attention

The CASS trial

560 patients with septic shock

280 patients

Mild Induced Hypothermia (32°C-34°C)

280 patients

Normothermia/ Respect of fever

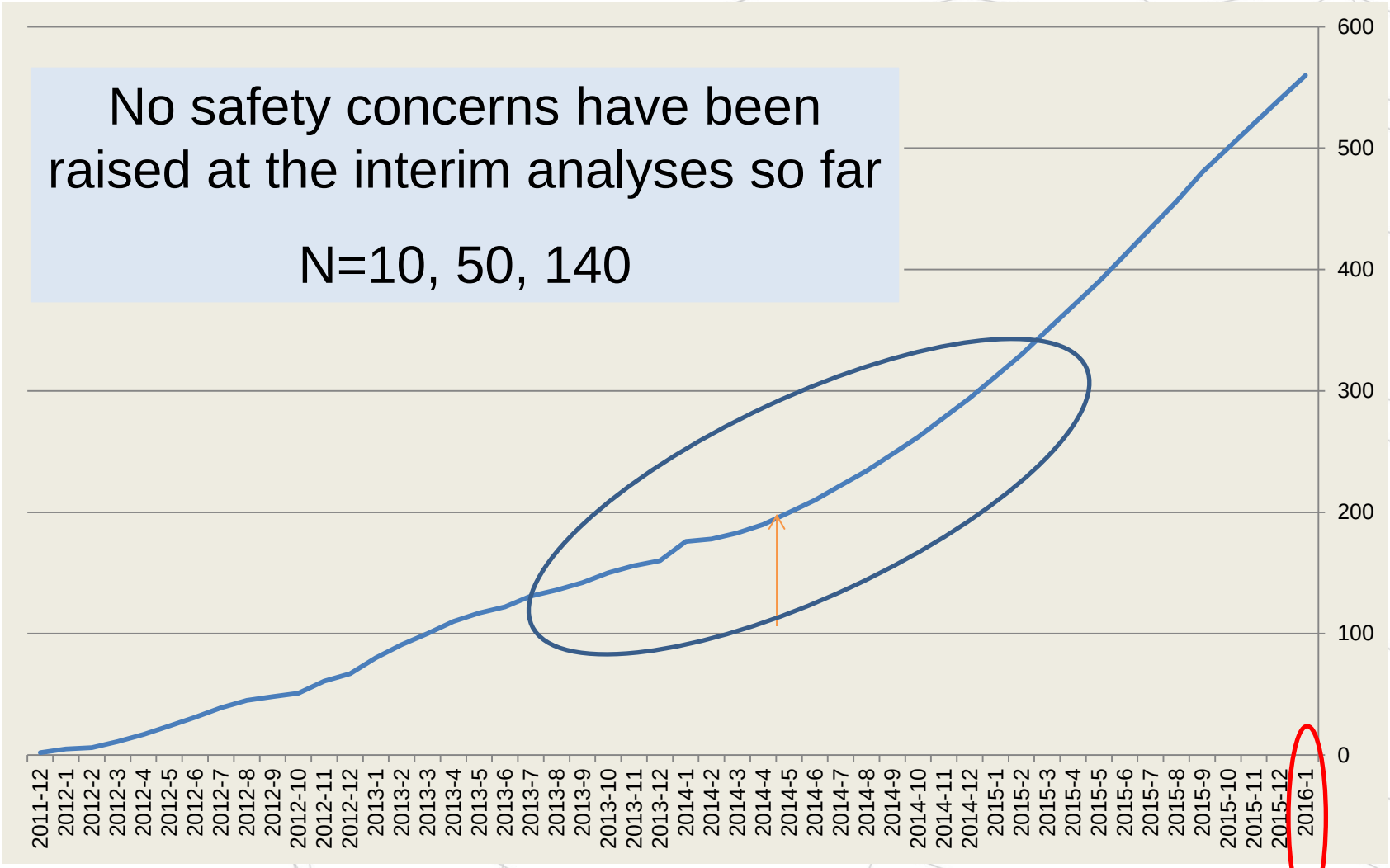
Mild Induced Hypothermia 24 hours + normothermia for 48 hours FU: 30 days

Fever Respect for 24 hours Followed 30 days

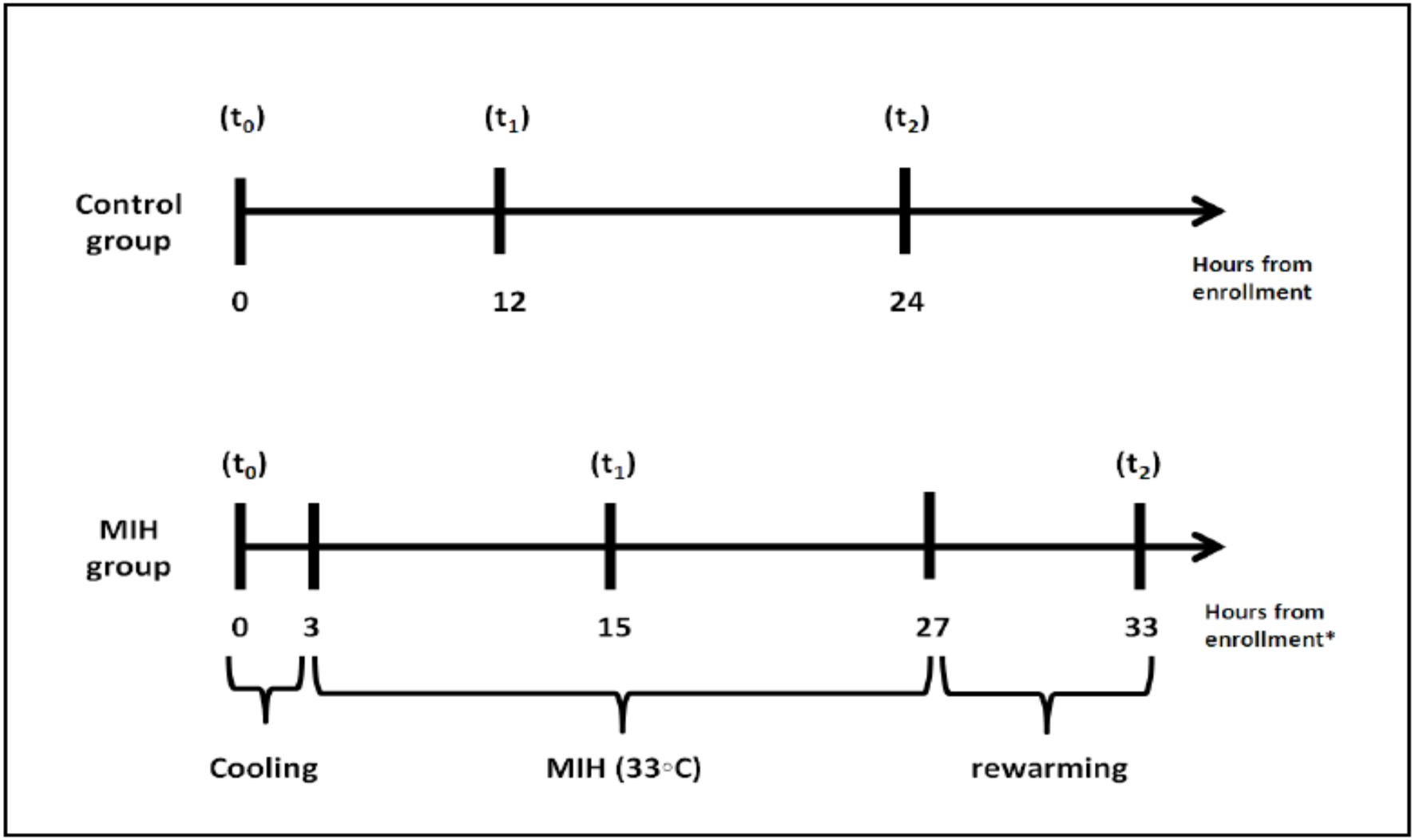
Analysis – Interim and final

N=10, 50, 140, 280, 420, 560

Recruitment – actual and anticipated



Coagulation – Interim data from CASS – on permission from the DSMB – preliminary results



Patient characteristics at baseline

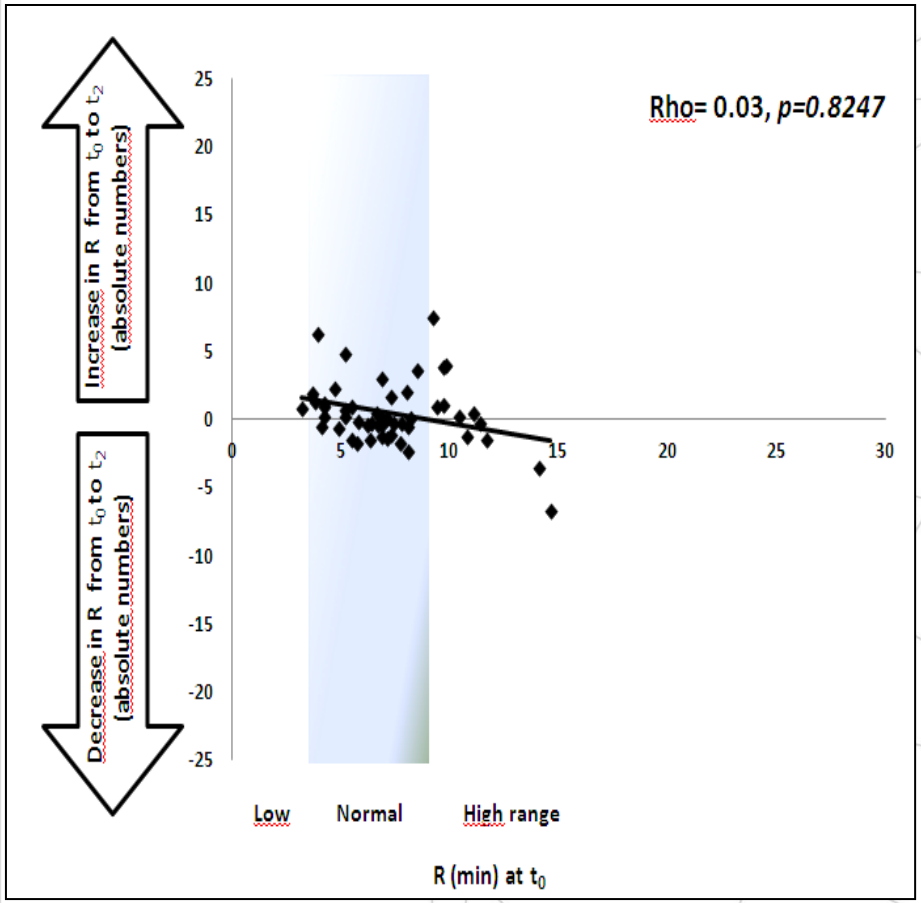
	Control (n=50)	Intervention (n=50)	Total (n=100)
Age - years	67 (58-76)	70 (60-80)	68 (58-78)
Male, %	28 (56)	31 (62)	59 (59)
SOFA score, median	11 (9-14)	11 (9-13)	11 (9-13)
Richmond Agitation-Sedation Scale (RASS), median	-4 (-3 - -5)	-4 (-3 - -5)	-4 (-3 - -5)
MAP , median	64 (55-75)	62 (55-68)	63 (55-72)
Temperature, median	37.2 (36.9-38.2)	37.3 (35.6-38.1)	37.2 (36.5-38.1)

Patient characteristics – baseline

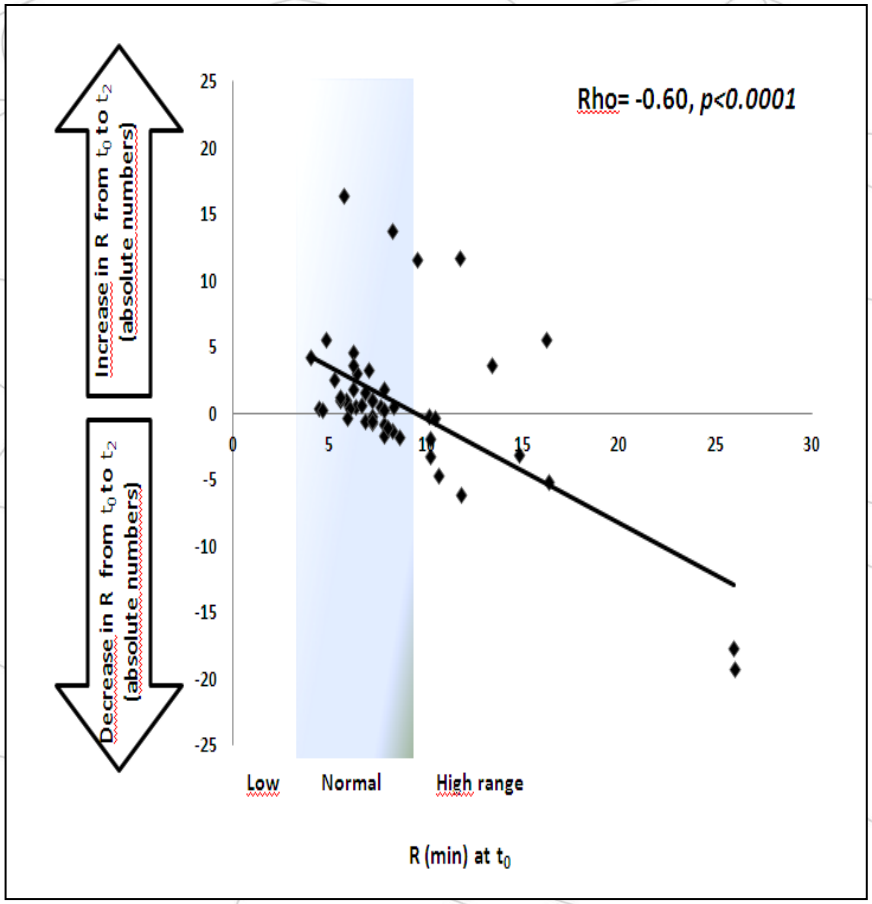
	Control (n=50)	Intervention (n=50)	Total (n=100)
D-dimer (mg/L)	2.7 (1.6-6.6)	4.9 (1.4-7.3)	3.4 (1.4-6.6)
Platelets (x10e9/L)	194 (112-292)	194 (147-318)	194 (140-297)
INR	1.2 (1.0 - 1.4)	1.3 (1.1-1.8)	1.3 (1.1 - 1.5)
Lactate (mmol/l)	1.6 (1.1 - 2.4)	1.6 (1.3-3.2)	1.6 (1.1 - 2.8)
R	6.9 (5.2 - 8.5)	7.2 (6.2 - 10.1)	7.2 (5.8 - 9.3)
Hypocoagulable (MA<51 mm)	1 (2)	2 (6)	3 (3)
Normocoagulable (MA=51-69 mm)	22 (44)	16 (32)	38 (38)
Hypercoagulable (MA>69 mm)	27 (54)	32 (64)	59 (59)

- 60-70% have disturbed functional coagulation at baseline

Correlation between R-time (Baseline) and ΔR-time (BL→day 1)
NB: after re-warming



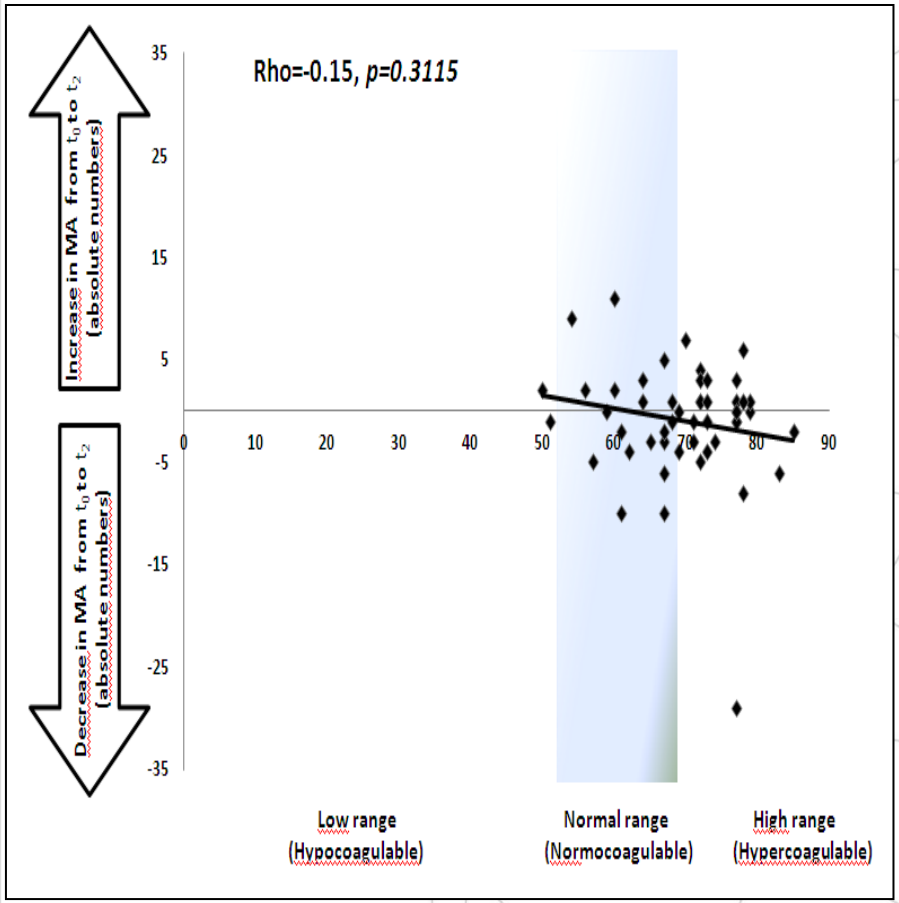
Control



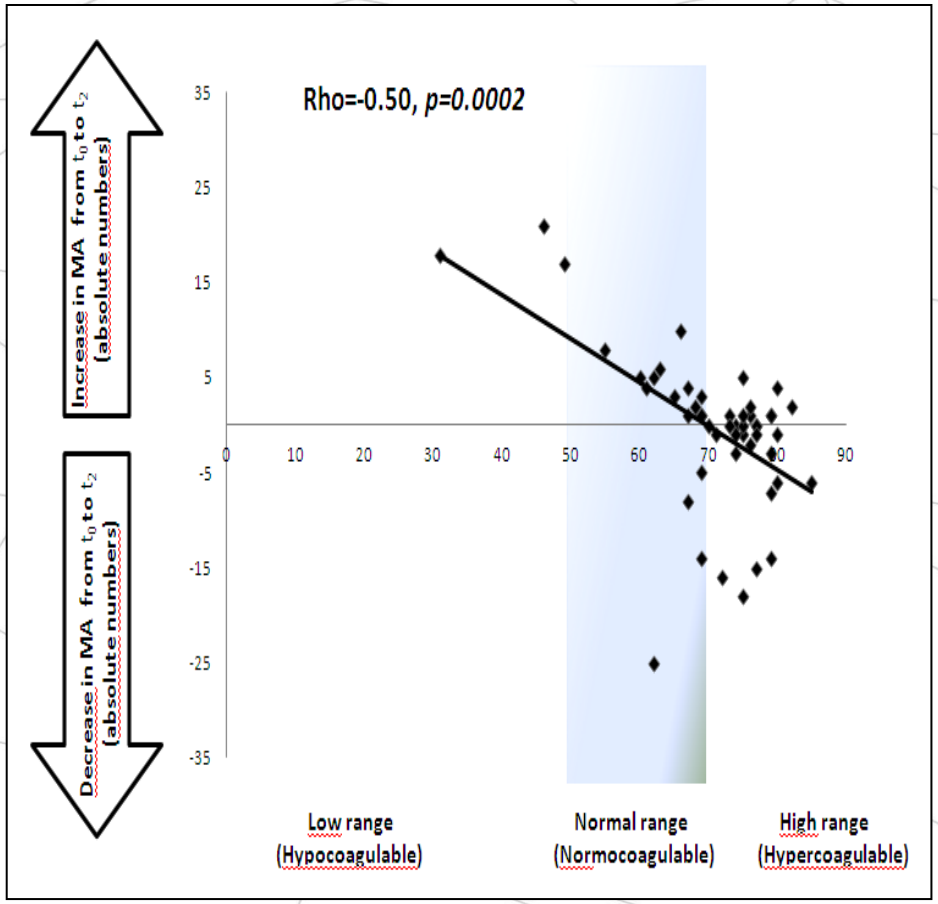
MIH

t_0, baseline, t_2, 24 hours after inclusion (control)/ 24 hours + induction phase (2-4 hours) (MIH)

Correlation between MA* (Baseline) and ΔMA (BL→day 1) NB: after re-warming



Control



MIH

t_0, baseline, t_2, 24 hours after inclusion (control)/ 24 hours + induction phase (2-4 hours) (MIH). * MA=Maximum Amplitude of clot

Conclusions

- Mild induced hypothermia has multiple effects in septic shock
- Bacterial growth and dissemination can be limited to some extent
- Apoptosis can be influenced – seemingly towards reduction
- Animal studies of MIH (not extreme hypothermia, not spontaneous hypothermia) for 24 – 72 hours show generally improved organ function and survival
- Human studies of fever reduction/cooling to normothermia show improved hemodynamics
- Functional coagulation measures seem to be improved during MIH – also when the patient was re-warmed to normothermia
- It remains unclear whether Mild Induced Hypothermia can improve the prognosis in severe sepsis and septic shock
- The CASS trial will bring clarity regarding this – 200 patients are recruited – no safety issues have been detected yet

Thank you !

And thanks to the CASS group @
→CHIP/Rigshospitalet
→Nordsjællands Hospital: Hillerd
→Bispebjerg Hospital
→Herlev Hospital
→Køge Hospital
→Roskilde Hospital
→Horsens Hospital
→Gentofte Hospital
→AMC/Amsterdam

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And:

- Thanks to our dedicated DSMB:
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- Christian Torp-Pedersen (University of Aalborg)
- Court Pedersen (Odense University Hospital)
- Andrew Copas (Royal Free, London)