# 15 YEARS OF CPPOPT
## (FROM 'ART' TO 'TARGET')

Cambridge seminar

January 2017

Marcel Aries

# CONTENT

## 45 MIN HISTORY

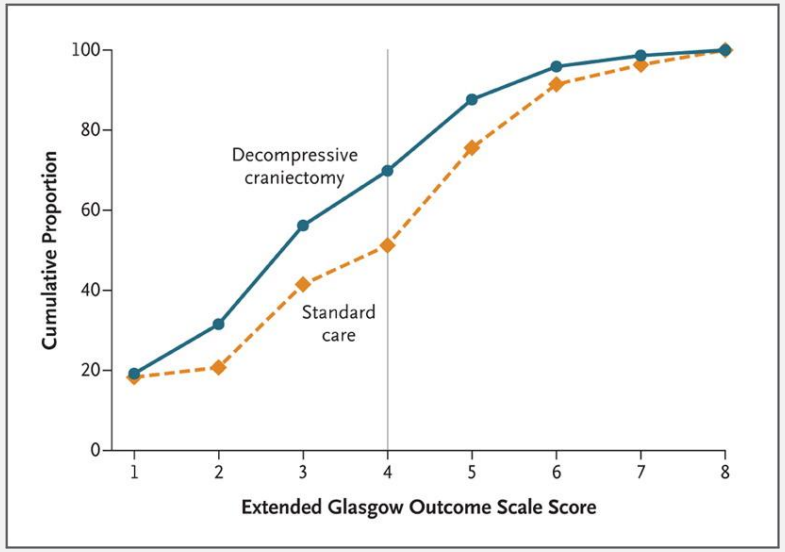
- Traumatic Brain Injury
- CPPopt studies
  - Adults
  - Main results
  - Some comments

## 15 MIN (NEAR) FUTURE

- Intervention study
- Recent (hard) work for that

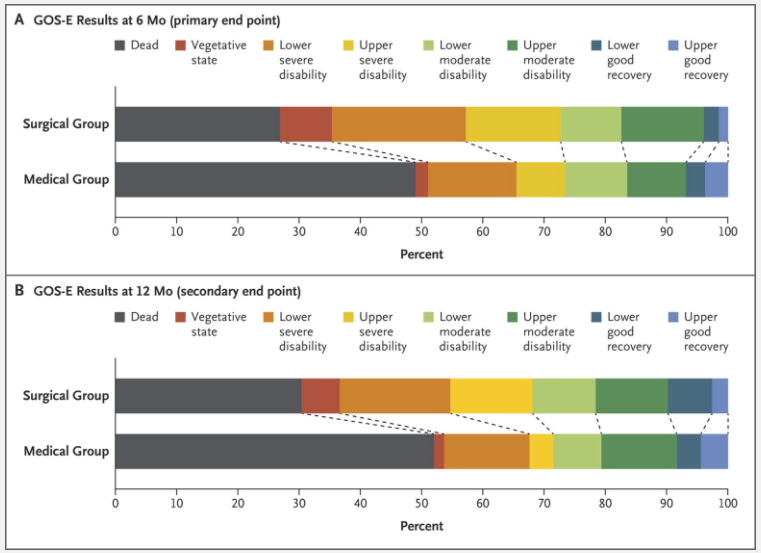
# 2002-2017: TBI

## 2002




Start DECRA

## END 2016

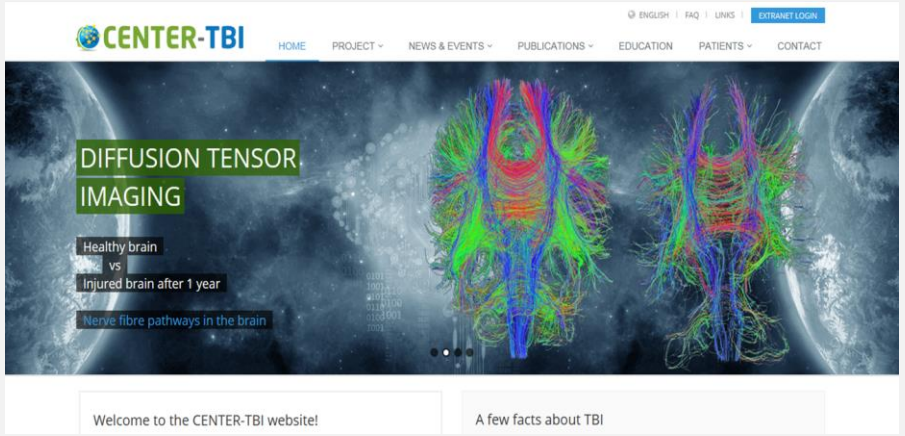



Results of RESCUE ICP

# RETHINKING IDEAS

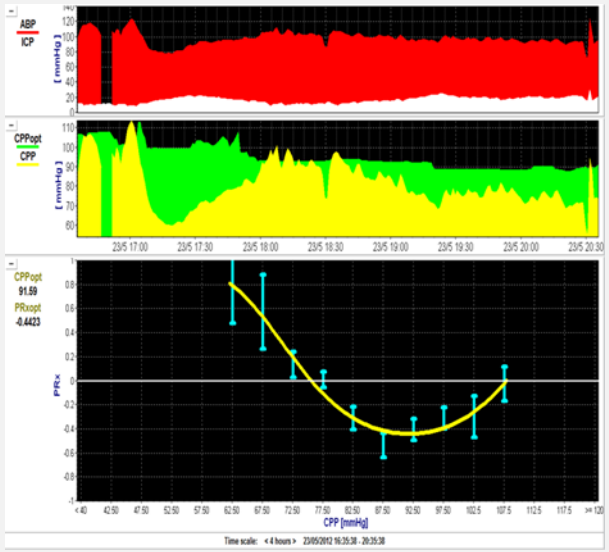
## 2002-2017


## CENTER TBI



# INDIVIDUALISED TREATMENT

## OPTIMAL CPP




## 2002-2017

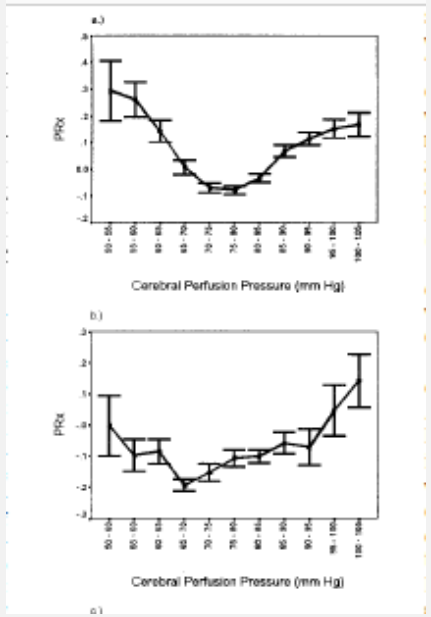
- 'Preparation phase'
- 'Magic bullet'/ 'Holy grail' ?
- Small and careful steps
  - ICP monitoring
  - Feasibility and safety study
- Offline → online analysis →recommendation
- Software challenge

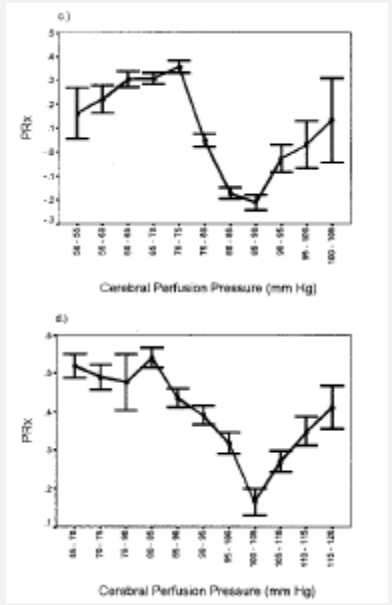
# HISTORY

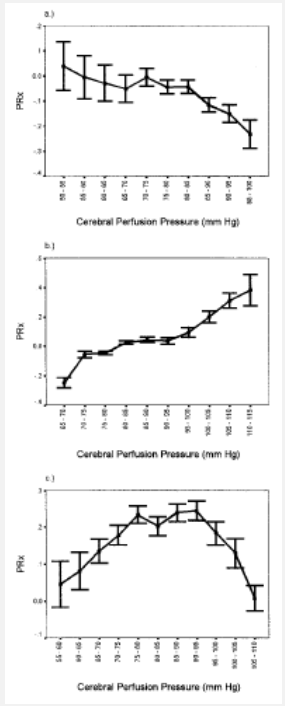
2002: marriage of…..

# STEINER ET AL. (2002)

PRx for CPPopt determination




- PRx-CPP plot  whole recordings
- 60% U shape
- < and > CPPopt related to poor outcome
- Visual determination

# 2006-2008

## CONFIRMATION OF CPPOPT AND RELATION WITH OUTCOME

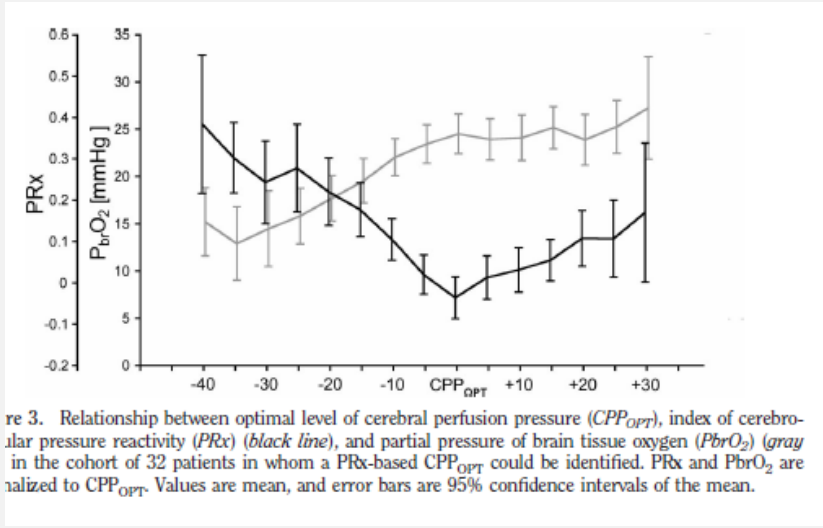
- Balestreri et al. NCC 2006
- Jaeger et al. CCM 2006
- Zweifel et al. Neurosurg focus 2008

## COMMENTS

- Focus on PRx
  - Decompression
  - Therapeutic hypothermia
- Relationship with outcome
  - CPP>CPPopt AND CPP<CPPopt
- 'Proof of concept'
  - Correlation PRx - ORx
  - Correlation PRx - PBtio2

# JAEGER ET AL. 2010

## CPPOPT AND BREAKPOINT OF PBTIO2



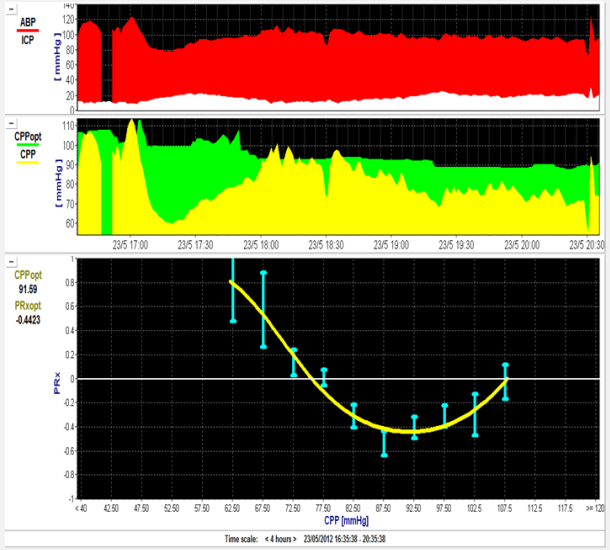

re 3. Relationship between optimal level of cerebral perfusion pressure ($CPP_{OPT}$), index of cerebro-ılar pressure reactivity (*PRx*) (*black line*), and partial pressure of brain tissue oxygen ($PbrO_2$) (*gray* in the cohort of 32 patients in whom a PRx-based $CPP_{OPT}$ could be identified. PRx and $PbrO_2$ are ıalized to $CPP_{OPT}$. Values are mean, and error bars are 95% confidence intervals of the mean.

## COMMENTS

- 'Proof of concept'
- N=38
- Whole recording
- PBTiO2 not targeted?
- Park et al. 2016
- Difficult 'proof of concept'
  - Difficult to measure
  - Local
  - Many contributing factors

# ARIES ET AL. (2012)

## AUTOMATED CALCULATION OF CPPOPT




## COMMENTS

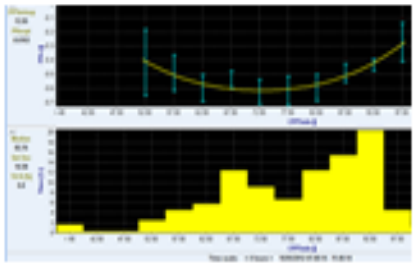
- Automated
- Relationship with outcome
  - No correction for covariates
- 60% of monitoring time a value
- Only 70% (somehow) U-shaped
- High CPPopt values (80)
- Autoregulation status

# WEERSINK ET AL. (2014)

## REASONS FOR CPPOPT ABSENCE

### Main conclusions

1. Results show an association between **absence of CPPopt** and the following physiological and clinical variables:
   - absence of ABP slow waves
   - impaired autoregulation
   - status after decompressive craniectomy
   - not applying muscle paralytics
   - light or moderate sedation
   - high vasopressor use

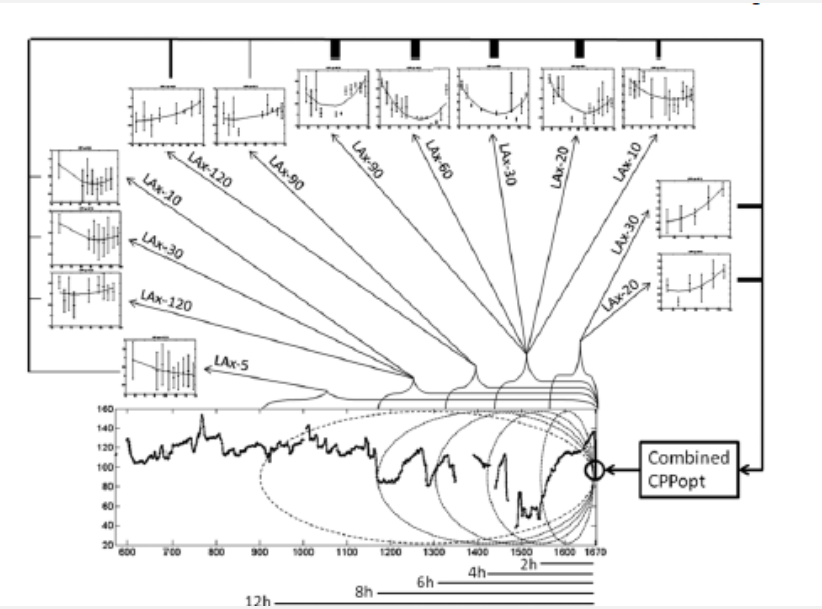


## COMMENTS

- Absence CPPopt?
- Did we incorporate results into CPPopt calculation?
  - 'PRx range to exclude curve'
  - 'Multi-window approach' (confounders)
- Exclude sec decompression patients
- (Threshold for power of slow ABP waves)
- (Confounders)
  - PP Ventilation
  - CVP
  - $CO_2$

# DEPREITERE ET AL. (2013 + 2014)

## CPPOPT CALCULATION IN LEUVEN

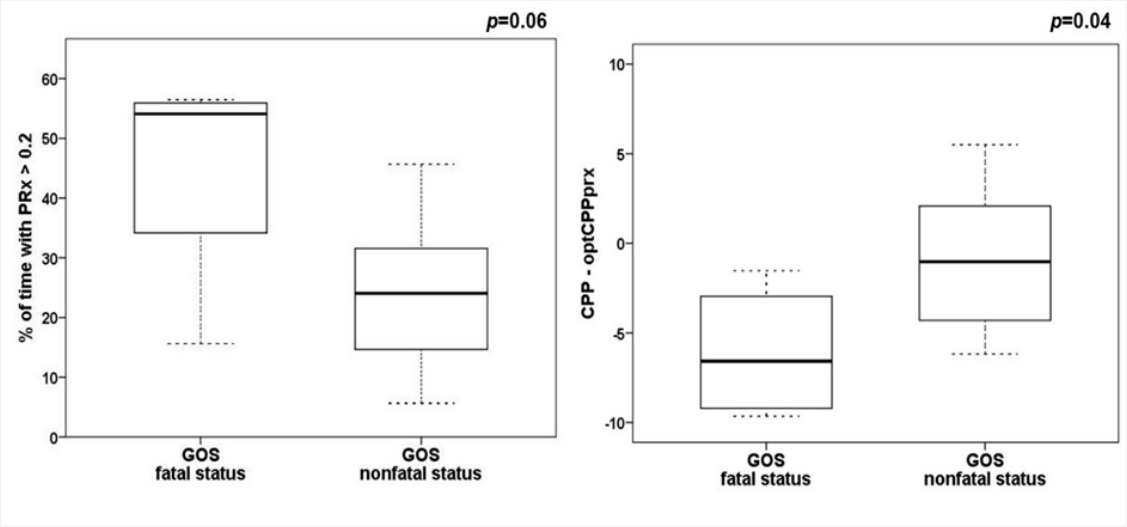



## COMMENTS

- N=180
- CPPopt 95% of monitoring time
- LAx
- Averaged CPPopt
  - 1-24 hrs
  - Weighted (fit/low LAx)
- Indepedent relationship with outcome
  - CRASH covariates

# DIAS ET AL. (2015)

## CPPOPT GUIDED MANAGEMENT AT THE BEDSIDE

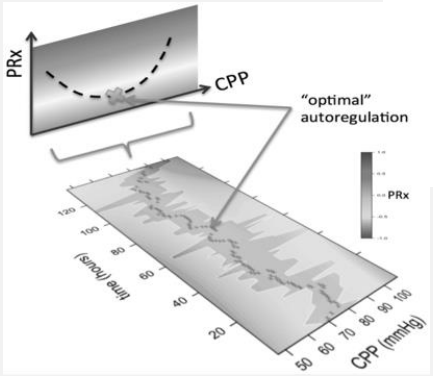


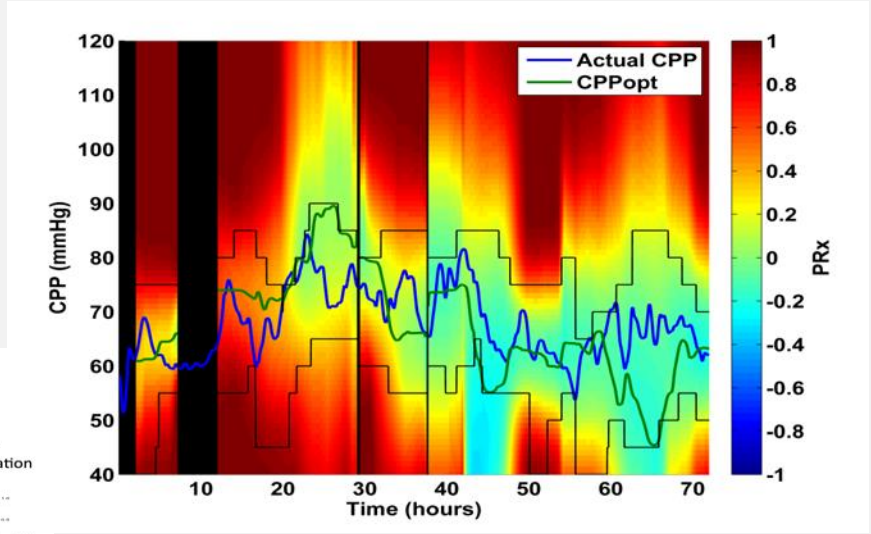

## COMMENTS

- N=18
- CPPopt guided patients!
- CPPopt 59% of time available
- CPP 86 mmHg
- Hypoperfusion?

# WESSELINK ET AL. (2016)

## VISUALISATION OF CPPOPT




## COMMENTS

- Difficult to repeat in different TBI pts
- (time) patterns?
  - How often interventions?
- Needs further exploration
  - With what kind of question?
- Preliminary version ICM+

# UNFINISHED STUDIES (1)

## RETROSPECTIVE MULTICENTER CPPOPT STUDY[1]

- Multivariate day-by-day analysis of CPPopt after TBI
- The CPPopt Multicenter Study Group (n=10)
- **Conclusion**: These retrospective multicenter data show that there is heterogeneity between centers when the association between PRx and derived CPPopt and outcome is considered. However, deviation of CPPopt was significantly correlated with poor outcome in the whole cohort after correction for known prognostic variables.

[1] Boston abstract ICP 2016

## COMMENTS

- Different interpretations of TBI protocols
- CPPopt 60% of time
- Independent relationship with outcome
- CPPopt follows CPP (!)

- Intervention study
  - 3 centres
  - Zeroing ICP/CPP

# UNFINISHED STUDIES (2)

## CPPOPT IN SCANDINAVIA [2]

- CPPopt calculation in Groningen, Cambridge and Uppsala
- Effects of different TBI treatment protocols on CPPopt calculation numbers

## COMMENTS

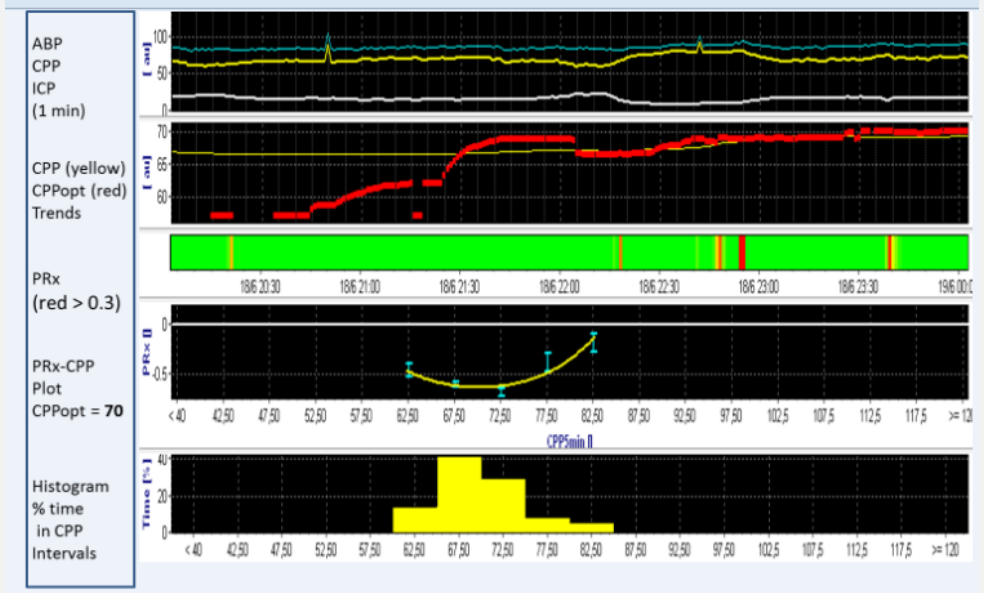
- CPPopt calculation in ODIN software
- CPP = same….. (80)
- Results to come

- Intervention study
  - Medical ethical

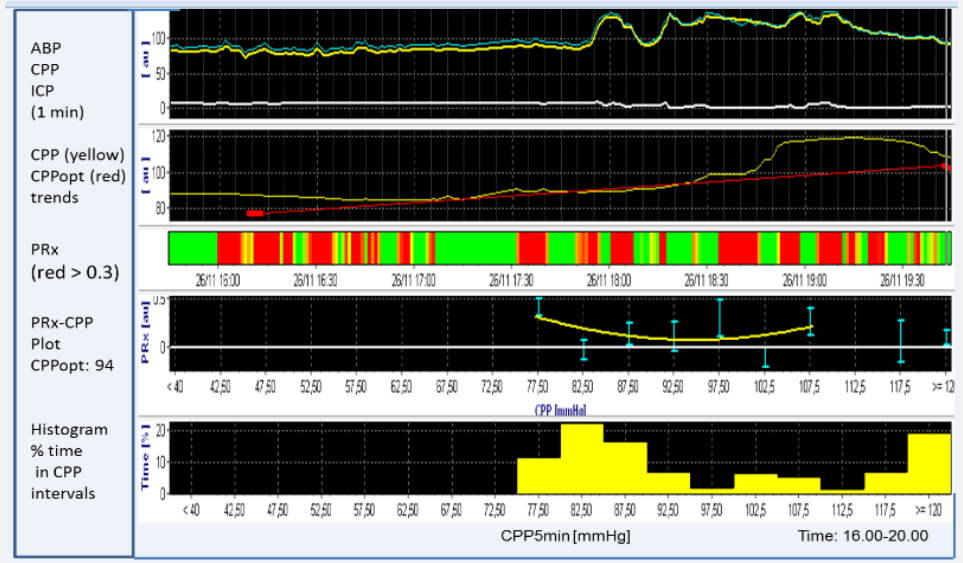
[2] Work in progress

# SURVEY IN AUTOREGULATION CLINICAL EXPERT

## FACE VALIDITY OF CPPOPT



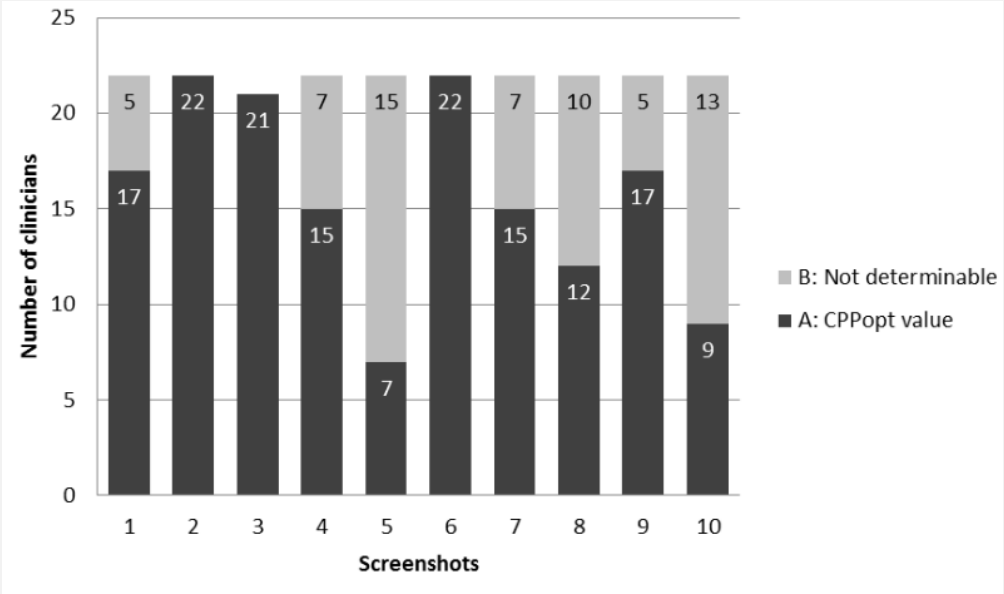

## FACE VALIDITY OF CPPOPT




Thanks to Romy

# SURVEY IN AUTOREGULATION CLINICAL EXPERT

## FACE VALIDITY OF CPPOPT



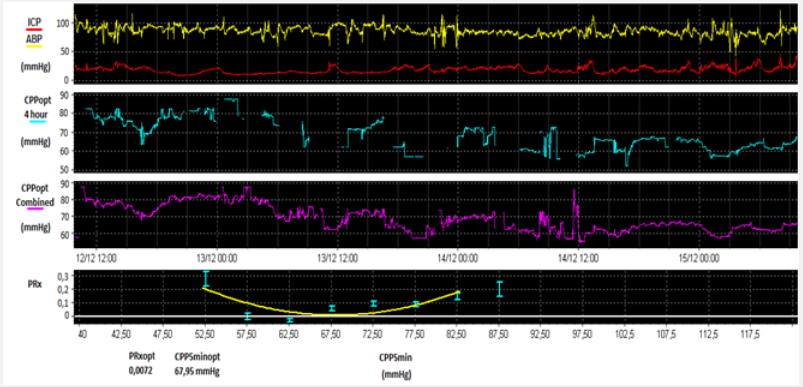

## COMMENTS

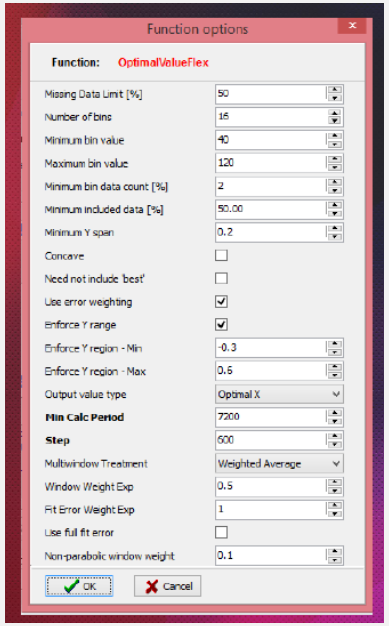
- N= 25 reviewers
- 3 screenshots 'CPPopt' not determinable

- Intervention study
  - 'Reliability/stability' score: too difficult
  - Averaging/smoothing
  - Display PRx-CPP curve

# X. LIU ET AL. (IN PRESS)

## FINDINGS



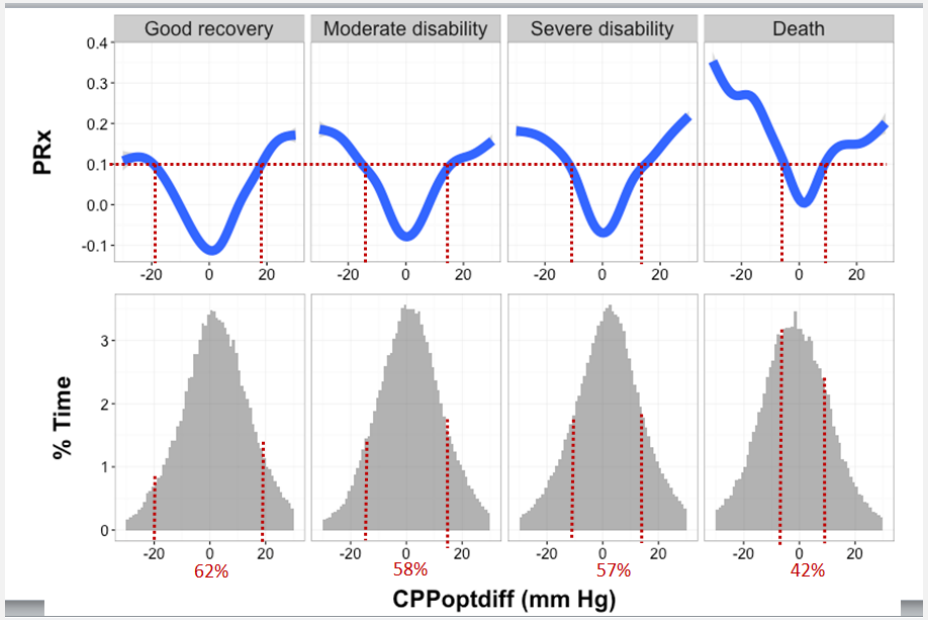

## COMMENTS

- CPPopt yield ≈ 100%
  - Multiwindow (2-8 hrs)
  - Weighting
- Improved variability
- Relationship with outcome

- Intervention study
  - Make choices
  - Legenda !

# DONNELLY ET AL. (IN PREP)

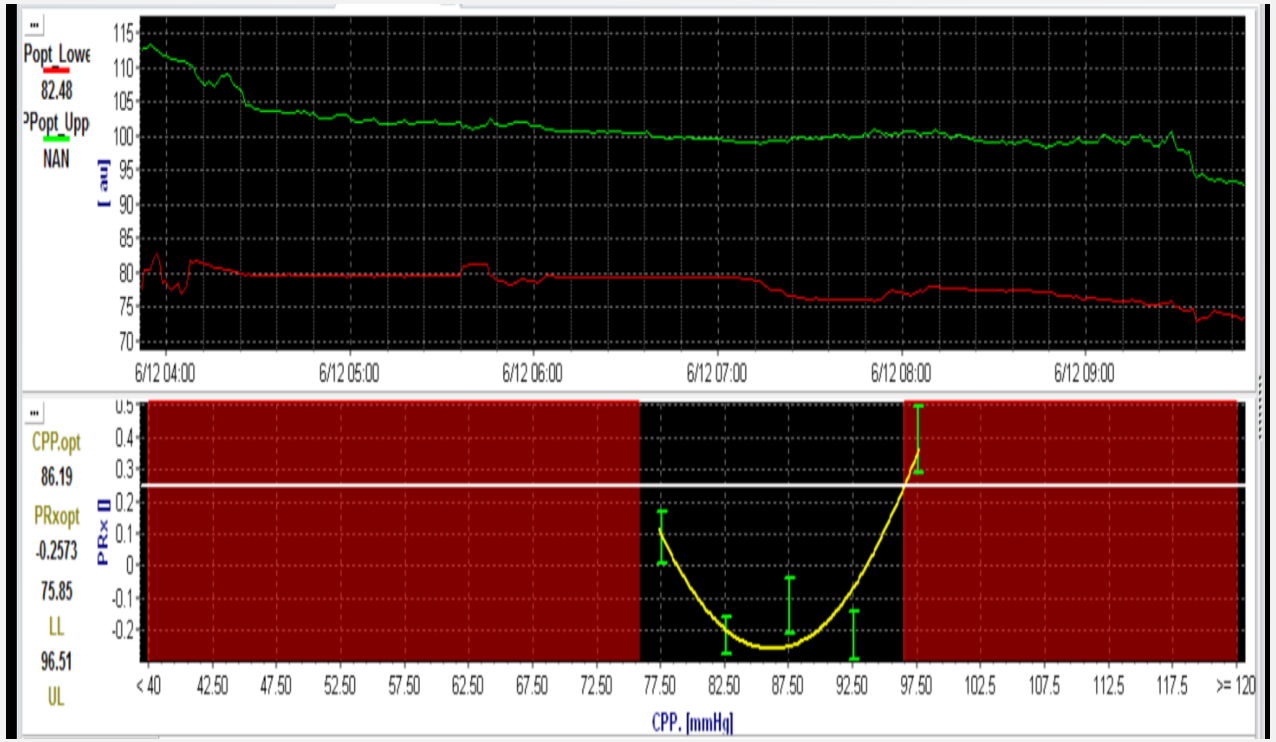
## FINDINGS




## FINDINGS

- Take into account
  - CPP-CPPopt difference
  - Autoregulation status
  - Theshold voor PRx?
- Relationship with outcome

# DONELLY ET AL. (IN PREP)




## COMMENTS

- Automated feature
- Feeds the (oscillating!) discussion
  - Clinical application of CPPopt?
  - Share this information?
- Intervention study
  - Too early

# 2002-2017

## ACHIEVEMENTS

- Nice concept
  - PRx
  - CPPopt
  - Relationship with outcome
  - Tackled many problems
- Good (flexible) infrastructure
- Good network/team
  - Scientists/clinicians
- TBI: 31 publications

## QUESTIONS (SMALL STEPS)

- How does CPPopt behave prospectively?
- Is it safe?
- How do clinicians behave?
- What is good outcome parameter (proof)?

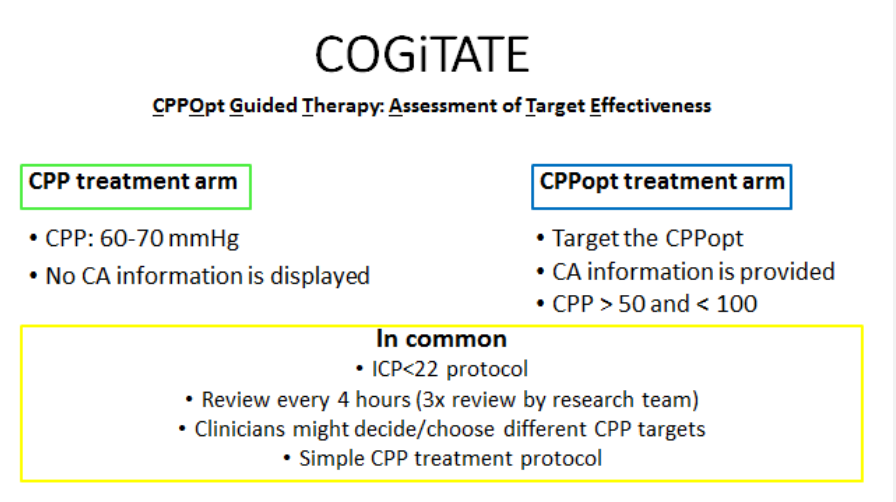
# FUTURE: 3 CENTER RANDOMIZED INTERVENTION STUDY

## FEASIBILITY AND SAFETY STUDY


Covering 5 days after admission

N = 30

## GOGITATE




N = 30

# AFTER (BLOCK) RANDOMIZATION

## CPP ARM

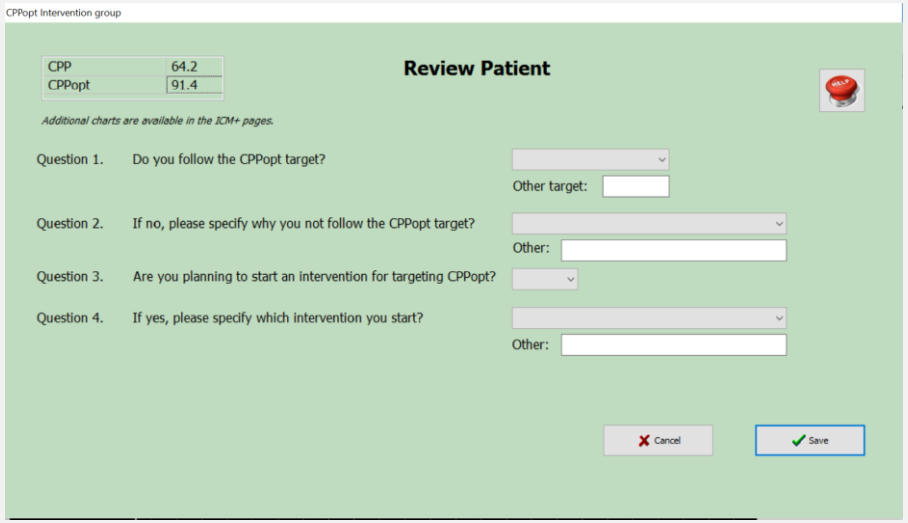
- Start 60-70 mmHg
- Review after 4 hours (60-70), regular 6dd
- ICM+ display:
  - ICP/CPP
  - Other cerebral monitoring

## CPPOPT ARM

- Start 60-70 mmHg
- Review after 4 hours (CPPopt), regular 6dd
- ICM+:
  - ICP/CPP
  - PRx
  - PRx-CPP error bar (6 hr)
  - CPPopt number + trend (multiwindow + weighted) + CPP 5 min trend
  - Other cerebral monitoring
- CPP > 50 and < 100
- If no CPPopt: clinical target

# 4 HOURLY REVIEW

ALERT




ALERT


Thanks to Jeanette and Manuel

# TREATMENT (LOCAL) PROTOCOL

| CPP target | ICP | Action | Interventions |
|---|---|---|---|
| ↑ | > 20 mmHg | Decrease ICP | ICH treatment ↑ |
| ↑ | < 20 mmHg | Increase ABP | Fluids<br>Vasopressor ↑<br>(as per clinician) |
| ↓ | > 20 mmHg | Decrease ABP | Vasopressor ↓ |
| ↓ | < 20 mmHg | Decrease ABP | Vasopressor ↓ |

# OUTCOMES

## MAIN PRIMARY (FEASIBLE)

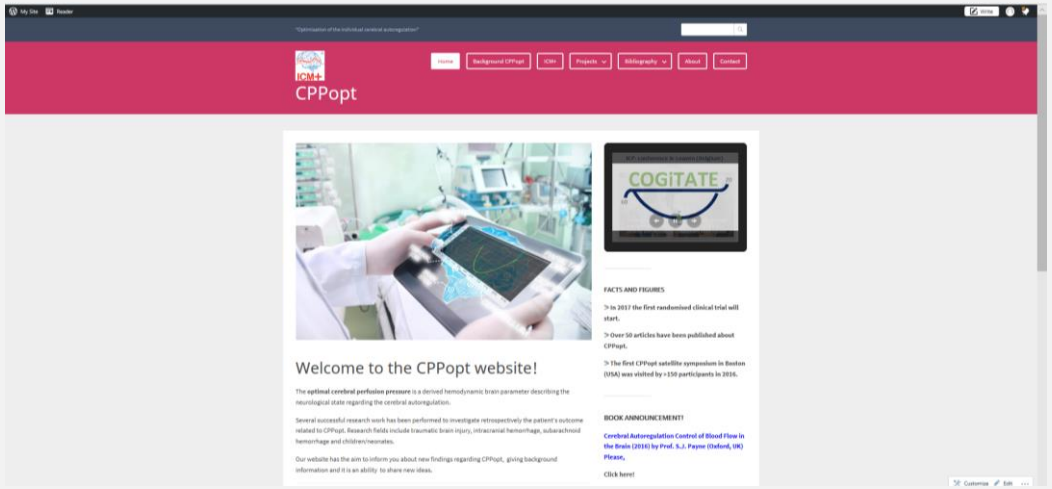
- Percentage of time CPP is within 5 mmHg of CPPopt
- During first 5 days

## MAIN SECONDARY (SAFE)

- Average  treatment intensity level score (TIL) score (> 3 points)
- Many different secondary outcomes
  - Organ damage
  - Physiological parameters
  - Adherence to monitoring protocol
  - Outcome at 6 months

# COMMUNICATION

## WEBSITE

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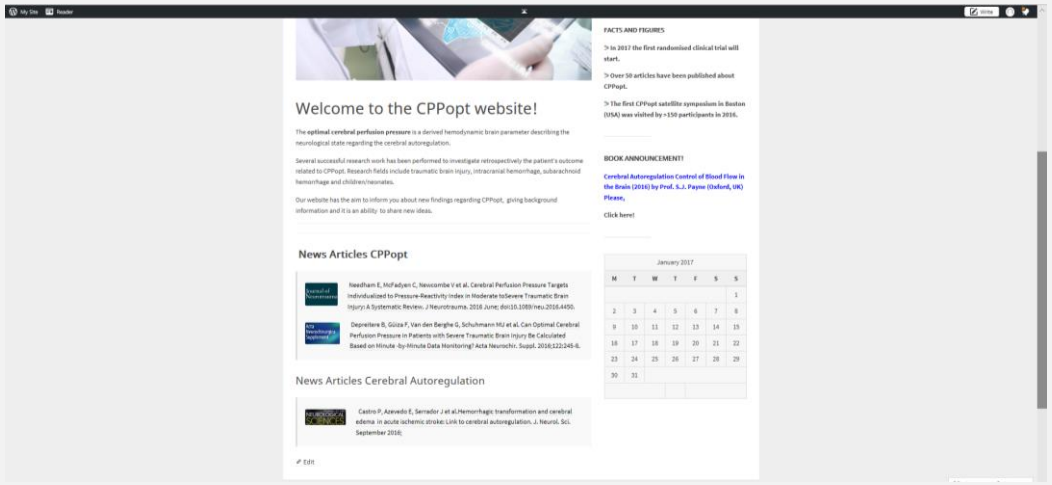
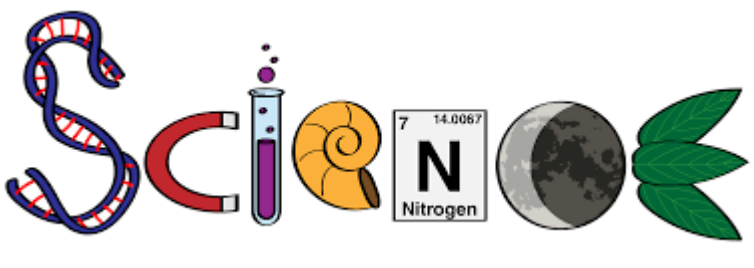



Thanks to Jeanette

- Explanation of CPPopt options
- Powerpoints, etc
- Studies

# SUMMARY

SCIENTISTS




CLINICIANS


Thank you all!!!

# UNCERTAINTIES

- Whole recordings
- ‘Up-to-date’ (4 hr)
- ”Up-to-date” (2-10 hr)

- CPPopt
- CPPopt ‘safe’ range
- CPP Lower Limit of Reactivity (LLR)
- CPP Upper Limit of Reactivity (ULR)
- CPPopt + SD
  - JD
  - JT