INCEPTION trial - randomized study at intensive care department

part II: Bayesian approach - per protocol (PP) analysis

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Colloquium meeting

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Outline

Part 1

INCEPTION trial

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Background information

- Results from the ITT analysis of the INCEPTION trial, comparing extracorporeal with conventional cardiopulmonary resuscitation (ECPR vs CPR) in refractory out-of-hospital cardiac arrest (OHCA) patients, found no statistically significant difference in neurologically favorable survival.
- Since protocol deviations were anticipated, a pre-specified per-protocol analysis was foreseen.
- The PP analysis excluded patients not meeting specific inclusion/exclusion criteria:
  - Time-to-cannulation of more than 60 minutes
  - Achieving a return of spontaneous circulation before hospital arrival
  - Crossovers
- The primary outcome - 30-day survival in a neurologically favorable condition; cerebral performance category (CPC) 1/2 - was analyzed under both a frequentist and Bayesian statistical framework.

PP analysis - rationale

- The main ITT analysis did not find a statistically significant difference between ECPR and CCPR concerning the primary outcome (1-month survival with good cerebral performance)
- The trial applied pre-hospital randomisation and did not require complete elucidation of exclusion criteria prior to randomisation
  - This facilitated timely preparation for ECPR **but**
  - would inevitably lead to the inclusion of patients that would eventually fail to meet inclusion/exclusion criteria
- Since protocol violations could influence the efficacy of ECPR within the ITT analysis, a pre-planned, pre-specified, PP analysis was incorporated in the study protocol
- **AIM**: to evaluate the results of ECPR compared to CCPR in patients congruent with the study protocol

Part 2

PP analysis

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Patient population

- Patients aged between 18 and 70 years suffering a witnessed OHCA with refractory ventricular arrhythmia
- Refractory OHCA was defined as 15 minutes without return of spontaneous circulation (ROSC) despite advanced life support (ALS)
- Exclusion criteria:
  - stable ROSC within 15 minutes of the arrest;
  - terminal heart failure (NYHA III or IV);
  - chronic obstructive pulmonary disease (COPD) GOLD III or IV;
  - oncological disease;
  - pregnancy;
  - bilateral femoral bypass surgery;
  - pre-arrest Cerebral Performance Category (CPC) score of more than 2;
  - multiple trauma (Injury Severity Score more than 15);
  - an advance health care directive prohibiting resuscitation or invasive ventilation;
  - an estimated time to start of cannulation longer than 60 minutes after the initial arrest

PP analysis

- After 15 minutes of ALS, OHCA was deemed refractory, and if patients fulfilled the inclusion criteria based on EMS information, randomization was performed by the hospital staff *before* ED arrival
- To allow for a swift preparation in case of ECPR, not all exclusion criteria had to be ruled out definitely before randomization
- Post-randomization exclusion was not possible based on patients' time of arrival since time-limiting criterion only exists in the intervention
- Patients allocated to ECPR with stable ROSC at ED were included in the ECPR group following the ITT principle, although they did not receive extracorporeal life support (ECLS)
- The patients eligible for the PP analysis were predefined and included only those in whom the allocated protocol was strictly adhered to, thus excluding:
  - Patients in whom ECPR was initiated more than 60 minutes after the start of the arrest
  - Patients with ROSC at the time of ED admission
  - Crossovers, including all patients arriving with ROSC at the ED

Statistical analysis - frequentist

- **Sample size**: Power calculation was based on the ITT analysis for PO: 49 (without dropout) and 55 (with 10% dropout)
- **Methods**: PO and key secondary outcomes analysed via logistic mixed models accounting/checking for:
  - stratification variable (centre)
  - significance of effect-modification of centre
  - relative fit of random intercept and/or slope model (AIC)
  - sensitivity to model specification (e.g. centre correction)
- **Reporting**: for PO and key SOs, adjusted odds ratios (ORs) are reported as effect estimates with 95% confidence intervals (CIs)
- For other outcomes, unadjusted odds ratios are reported
- Time differences were reported in mean differences (MD, minutes) with the corresponding 95% CI
- A significance level of 0.05 was assumed for all frequentist analyses

Statistical analysis - Bayesian

- **PO**: survival with favorable neurological outcome, defined as CPC 1-2, at 30 days
- **Key SOs**: survival with a favorable neurological outcome (CPC 1-2) at 3/6 months
- For PP analysis, Bayesian framework was used to analyse the primary and secondary outcomes to estimate the posterior probability of a potential ECPR benefit based on minimally informative priors:
  - normal distribution of the log OR
  - mean log OR of 0
  - standard deviation of 2
- **Reporting**: Posterior median ORs and posterior mean Absolute Risk Differences (ARD) were presented with corresponding 95% credible intervals (CrI). Different ARD thresholds were considered:
  - 5% minimal clinically important difference (MCID) threshold for shockable OHCA (Nichol et al., 2016)
  - 22% ARD threshold based on original trial protocol (Bol et al., 2019)
- Bayesian analyses were conducted using Markov Chain Monte Carlo sampling (MCMC, 500 burn-in iteration and 10000 iterations saved per chain) via JASP

Part 3

Results

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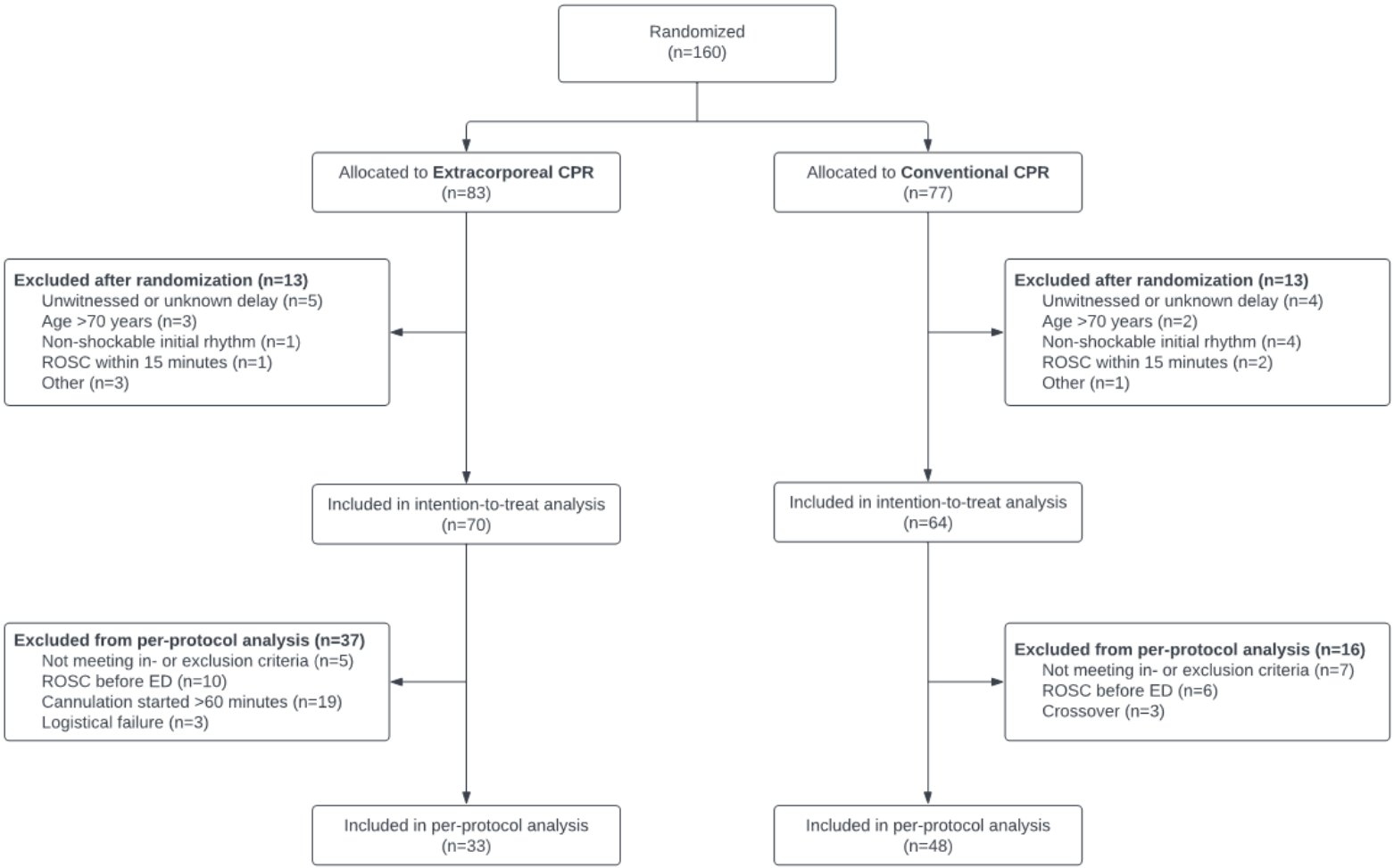
Patients

- Out of the 134 patients enrolled and analyzed according to the ITT principles, 53 in the PP analysis were excluded based on pre-specified criteria
- The PP analysis included 81 patients (ECPR group n=33, CCPR n=48)



Baseline characteristics

Variable	ECPR(obs)	ECPR	CCPR(obs)	CCPR	p-val
Age - yr	33	55(11)	48	56(8)	0.516
Male - sex n(%)	33	30(91%)	48	44(92%)	1
Cause of arrest					
Acute myocardial infarction	33	25(76%)	48	40(83%)	0.577
Dosages and lab values					
pH - arterial	14	6.96(0.18)	24	6.82(0.11)	0.019
lactic acid – mmol/L	28	15(5)	34	14(3)	0.696
partial pressure of oxygen - kPa	30	7(2;8)	37	4(2;7)	0.226

- The mean age (SD) was 55 (11) and 56 (8) years in the ECPR group and CCPR group, respectively (p=0.516)
- There were no statistically significant differences in terms of sex between both groups [male n=30 (91%) vs n=44 (92%) in the ECPR vs CCPR groups, respectively, p=1.000]
- The most frequent cause of arrest was acute myocardial infarction [ECPR n=25 (76%) vs CCPR n=40 (83%), p=0.577]
- Baseline pH at ED arrival differed significantly in the per-protocol analysis population [ECPR 6.96 (0.18]) vs CCPR 6.82 (0.11), p=0.019], although notably there were missing data on 19/33 ECPR patients (58%) and 24/48 CCPR patients (50%)

Intervals between events

Variable	ECPR(obs)	ECPR	CCPR(obs)	CCPR	MD
Start to ED arrival - min	33	31(12)	48	37(10)	-6.3(-11.2;-1.4)
Start to ECLS flow - min	27	69(60;77)			
Cann dur - min	26	20(11;26)			

- There was a significant difference in the time between arrest and ED arrival between the groups [ECPR 31 (12) vs CCPR 37 (10) mins, MD -6.3 mins (95%CI -11.2; -1.4mins)]
- In the ECPR group, ECLS flow was achieved at a median of 69 mins (IQR 60-77 mins) after the initial arrest
- Median cannulation time was 20 mins (IQR 11-26 mins) and successful cannulation and circulatory support was realized in 30/33 ECPR patients (91%)

Primary and secondary outcomes

Variable	ECPR(obs)	ECPR	CCPR(obs)	CCPR	OR	p-val
30-day - n(%)	33	5(15%)	47	4(9%)	1.9(0.4;9.3)	0.450
3-month - n(%)	32	4(13%)	47	3(6%)	2.2(0.4;11.5)	0.362
6-month - n(%)	33	5(15%)	47	4(9%)	1.6(0.3;7.7)	0.551

- Data for the primary outcome were available in all patients in the ECPR group (33/33, 100%), and 47 of 48 patients (98%) in the CCPR group
- Survival with a CPC score of 1 or 2 at 30 days occurred in 5 of 33 (15%) patients in the ECPR group and 4 of 47 patients (9%) in the CCPR group (adjusted OR 1.9; 95% CI 0.4-9.3; p-value 0.450)
- At 6 months, survival with favorable neurological outcome was comparable to 30-day outcomes (adjusted OR 1.6; 95% CI 0.3-7.7; p-value 0.551)
- Additional statistical analyses of the CPC score at different follow-up times showed comparable effect sizes and significance results

Bayesian analysis

- Bayesian analysis was performed under a minimally informative prior (log OR mean=0, SD=2) for the primary outcome (30-day survival in CPC 1-2) and survival with CPC 1-2 at 3 and 6 months
- The posterior probability of the minimal clinically important difference of 5% ARD was 61%, while the estimated posterior probability of an ARD of 10%, and 22% were 34%, and 2%, respectively
- At 3- and 6-month follow-up, the posterior probability of a minimal clinically important ECPR survival benefit was 62% and 61% respectively (median OR 1.9 [95% CrI 0.5-7.4] and 1.8 [95% CrI 0.5-6.7]

Outcome	ECPR	CCPR	median OR	mean ARD	P(5% ARD)	P(10% ARD)	P(22% ARD)
30-day - n(%)	5(15%)	4(9%)	1.8% (0.5;6.7)	7% (-8;21)	61%	34%	2%
3-month - n (%)	4(13%)	3(6%)	1.9% (0.5;7.4)	7% (-8;20)	62%	33%	1%
6-month - n(%)	5(15%)	4(9%)	1.8% (0.5;6.7)	7% (-8;21)	61%	34%	2%

Part 4

Discussion

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Summary

- In this pre-planned, pre-specified, secondary analysis of the INCEPTION-trial on a per-protocol basis, 30-day survival with favorable neurological outcome after refractory shockable OHCA was observed in 15% of ECPR patients versus 9% of CCPR patients. This difference, which persisted at 3- and 6-month follow-up, did not reach statistical significance
- The adjusted OR of 1.9 with a 95% CI that lies mostly above 1, may be consistent with a clinically important benefit of ECPR
- This is compatible with a 62% posterior probability of a clinically important ECPR benefit in the found Bayesian analysis

Discussion

- Per-protocol analyses can provide valuable additional information about the efficacy of an intervention under study when the treatment is strictly delivered according to protocol
- Pre-hospital randomization in ECPR studies provides a true insight in the ITT as preparations for ECPR are started immediately after randomization, but simultaneously results in the inclusion of patients that ultimately do not become ECPR candidates
- In 23% of the enrolled patients, one or more exclusion criteria became apparent after initial inclusion, with the initiation of cannulation more than 60 minutes as the most critical factor (27% of patients in the ECPR group)
- These departues might influence the potential effect of ECPR, which could have been achieved when strict inclusion criteria had been followed

Discussion

- In the ITT analysis, 30-day survival was 20% in patients allocated to ECPR (14/70). However, ECPR was only initiated in 52 (74%) of these patients and 30-day survival in patients receiving ECPR (as-treated) was 9% (5/55)
- Of these, 22 patients (40%) did not adhere to the pre-specified protocol with no survivors, which underlines the poor outcome of ECPR when there is no strict protocol adherence
- The between-group difference for the primary outcome did not reach statistical significance in this per-protocol analysis which, however, may have been affected by a limited sample size
- In these scenarios, as an alternative approach, Bayesian inference allows the estimation of between-group differences at various thresholds without providing a dichotomous judgment about the efficacy of an intervention
- This lead to an estimated the posterior probability of a clinically important ECPR benefit (5% ARD) plausible (61%)

Discussion

- This pre-specified PP analysis might more accurately reflect the outcomes of ECPR for refractory shockable OHCA since ITT analysis applied the concept of pre-hospital randomization, potentially obscuring a true ECPR treatment effect
- PP analyses are subjected to the inherent limitations of studies using post-randomization exclusion, as selection bias may apply
- However, comparison of INCEPTION data with low-flow times and clinical outcomes in case series on ECPR show that the results are in line with most experiences throughout the world
- The estimated mean absolute risk reduction of 7% was not statistically significant but exceeds the minimal clinically relevant treatment effect of 5% absolute risk difference
- Bayesian analysis facilitates intuitive and clinical interpretation of trial results, regardless of a potentially underpowered sample size, and minimally informative priors were used to ensure that posterior probability were based on trial data
- Use of informative priors based on results from other trials would have increased the probability of a positive treatment effect, but would have disregarded the methodological differences amongst the published trials