# The Circulation Improving Resuscitation Care (CIRC) Trial

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CIRC AutoPulse® Clinical Trial

NAKOS prehospital akuttmedisin

Oslo universitetssykehus

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# Conflict of Interest

- Dr. Herken employed by ZOLL Medical Corp.
- Trial funded by ZOLL
  - ZOLL and Principal investigator developed the trial protocol with
    - Study investigators
    - Staff at Data Coordinating Center
    - Statistical consultants
- Investigators' institutions received funding from ZOLL

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# Mechanical Chest Compression

- May overcome poor compression quality
- Advantages
  - Reduces provider fatigue
  - Can be used in confined spaces
  - Safely deliver compressions during transport
  - Can be used during interventions
  - Bridge to more advanced procedures

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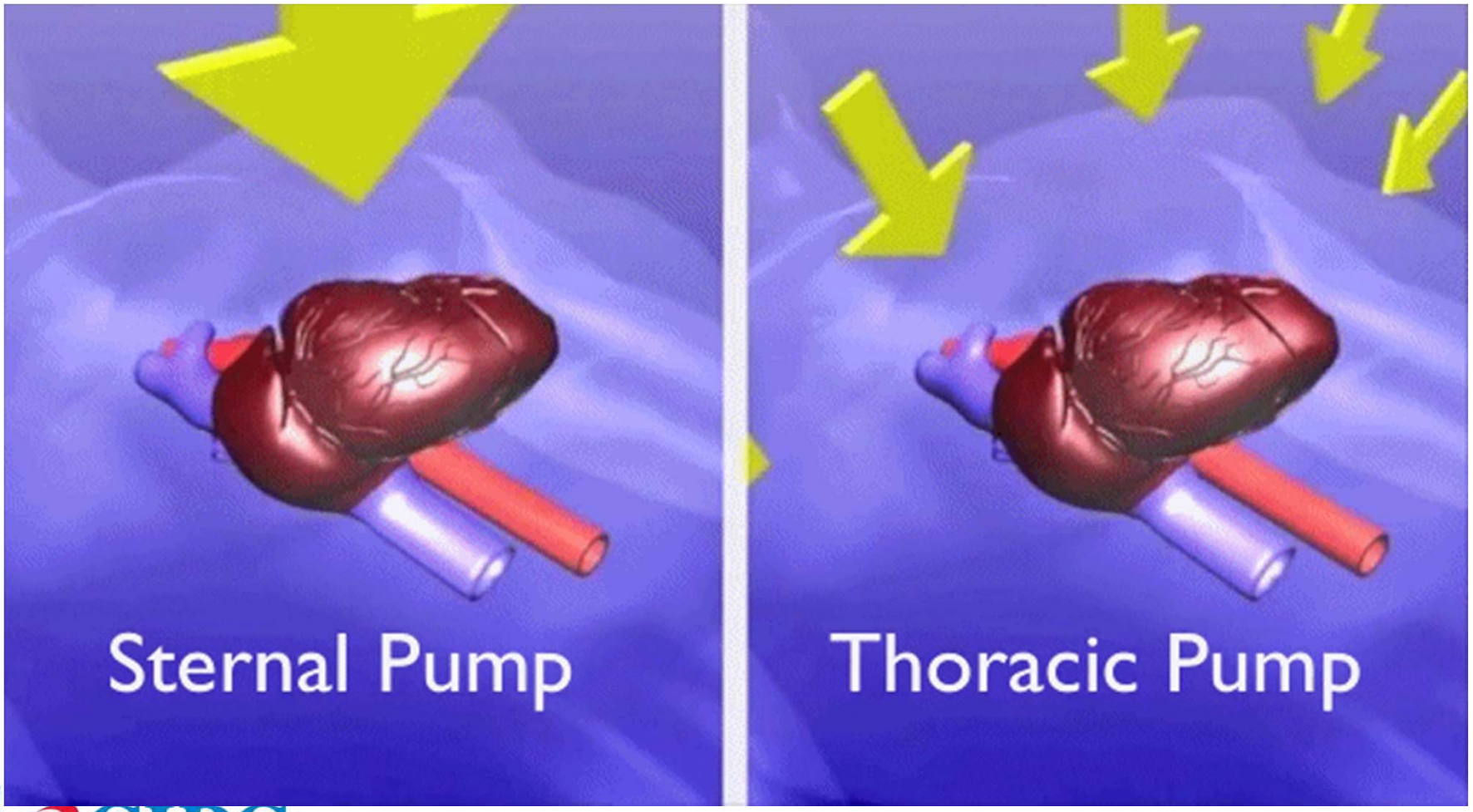
# Mechanisms for Creating Blood Flow during CPR

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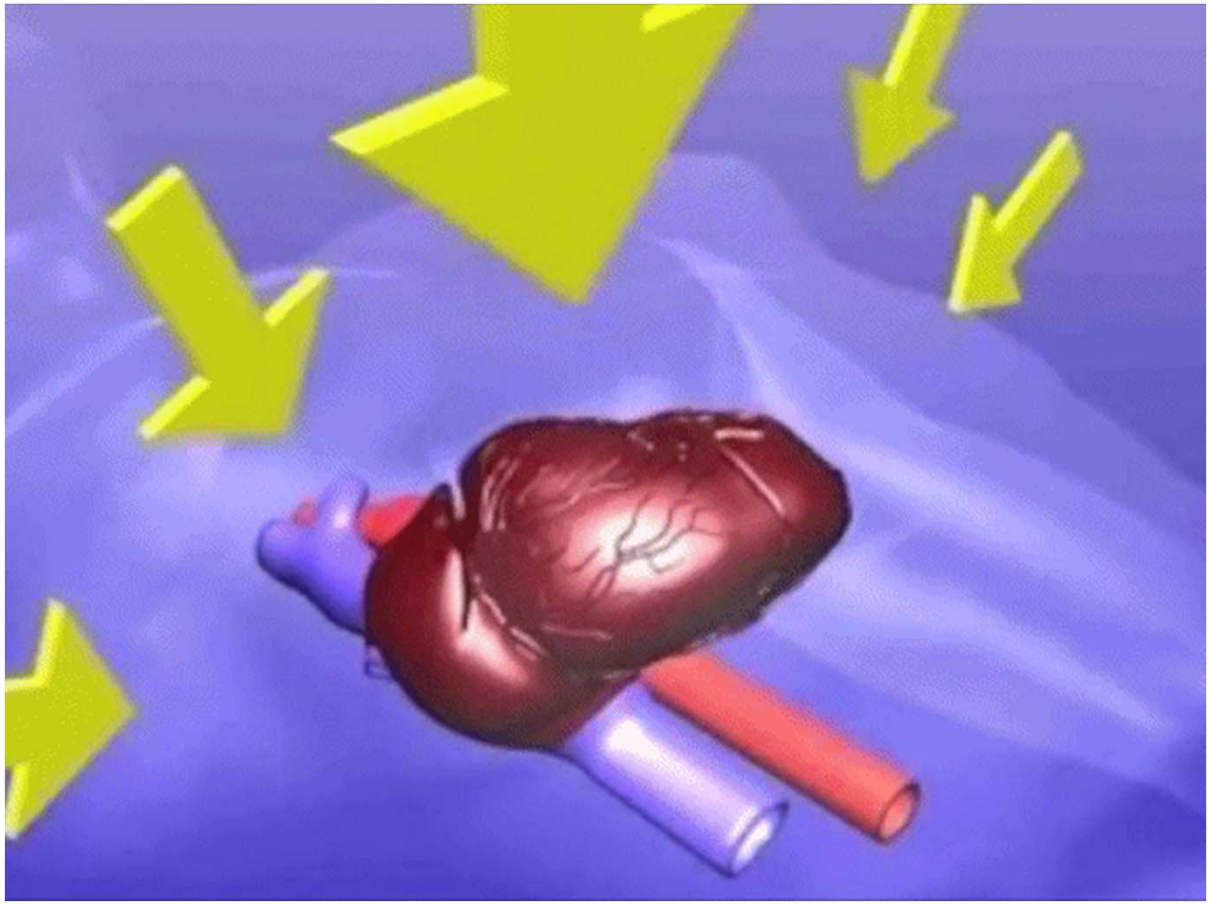
# Load Distributing Band CPR



The Load Distributing Band uses both sternal and thoracic pump mechanisms to create blood flow during CPR

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# Statistics for dummies

- We perform a study in a small part of the world and talk about our results as it was the world we had studied

p* 

p 

- The world probability is p, but the probability we have found is p*
- We need a measure to visualize how much these probabilities diverge
- A Confidence Interval (CI) describe how much p* (an estimate of a probability) diverge from p (the true probability)

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# Statistics for dummies

- Mean is a reasonable estimate (however, uncertain) for expectation of something we would like to know
- If we create an interval around mean that with great probability will include our expected value it will be our CI and will be a measure of the uncertainty of mean
- The smaller the CI is, the more reliable is our results in reflecting the real world

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# Statistics for dummies

- Odds – is possibilities, (deutch: chancen)
  - ratio
- Confidence – believe in, (deutch: vertrauen, norwegian: tillit)
  - interval
  - It measure the margin of error of a measure and is reported as %.
  - A 95% CI include the true value with a probability of 0.95.

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# Study Device

- Load Distributing Band
- Battery powered
- Reduces AP chest diameter by 20%
- 30:2 or continuous compressions
- Rate 80 $min^{-1}$


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# AutoPulse/LDB Research

- Shown to improve hemodynamics*
- Pre-hospital survival studies conflict
  - 3 retrospective studies found improved outcome ‡
  - 1 RCT (ASPIRE) stopped early#
    - No difference in 4 hour survival
    - Cerebral performance worse at discharge

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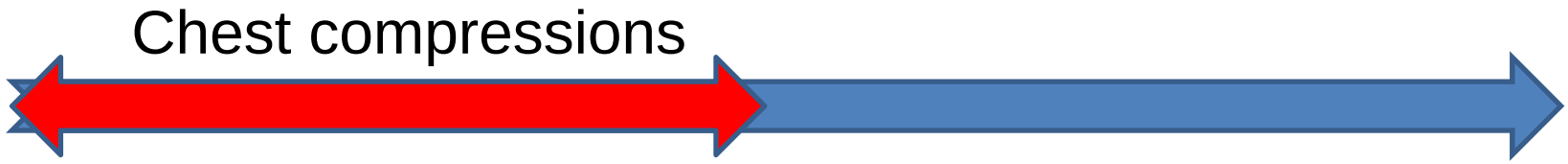
*Ikeno F 2006; Duchateau FX 2010; Timerman 2004; Halperin 2004
‡Casner 2005; Ong 2006; Krep 2007;
#Hallstrom 2006

# CPR fraction




Start CPR

End CPR

Total CPR time is 10 min, chest compressions for 5 min
CPR fraction is 50%

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# CIRC Trial Objectives

- Compare iA-CPR vs. M-CPR
  - Primary endpoint:
    - Survival to hospital discharge
  - Secondary endpoints:
    - ROSC to ED
    - 24 hour survival
  - Safety endpoint:
    - mRS score

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# Published Methods Papers

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

## Design of the Circulation Improving Resuscitation Care (CIRC) Trial: A new state of the art design for out-of-hospital cardiac arrest research☆,☆☆

E. Brooke Lerner[a,*], David Persse[b], Chris M. Souders[b], Fritz Sterz[c], Reinhard Malzer[d], Michael Lozano Jr.[e,f], Mark Westfall[g,h,i,j,k], Marc A. Brouwer[l], Pierre M. van Grunsven[m], Anne Whitehead[n], Jan-Aage Olsen[o],

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[b] Houston Fire Department and the Baylor College of Medicine,
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[d] Vienna City Administration, Municipal Department 70, Emerg
[e] Department of Emergency Medicine, Lake Erie College of Oste
[f] Hillsborough County Fire Rescue, Tampa, FL, United States
[g] Gold Cross Ambulance Service, Menasha, WI, United States
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[l] Heart Lung Center, Department of Cardiology, Radboud Univer
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[o] National Competence Centre of Emergency Medicine, Oslo Uni
[p] ZOLL Medical Corporation, Chelmsford, MA, United States

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Simulation and education

## Advanced life support performance with manual and mechanical chest compressions in a randomized, multicentre manikin study☆

Oystein Tomte[a,b,*], Kjetil Sunde[a,b], Tonje Lorem[a,c], Bjorn Auestad[d], Chris Souders[e,f], Jeff Jensen[g], Lars Wik[a,c]

[a] Institute for Experimental Medical Research, Surgical Division, University of Oslo, Norway
[b] Department of Anaesthesiology, Division of Emergency Medicine, Ullevål University Hospital, Oslo, Norway
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[g] ZOLL Medical Corporation, MA, USA

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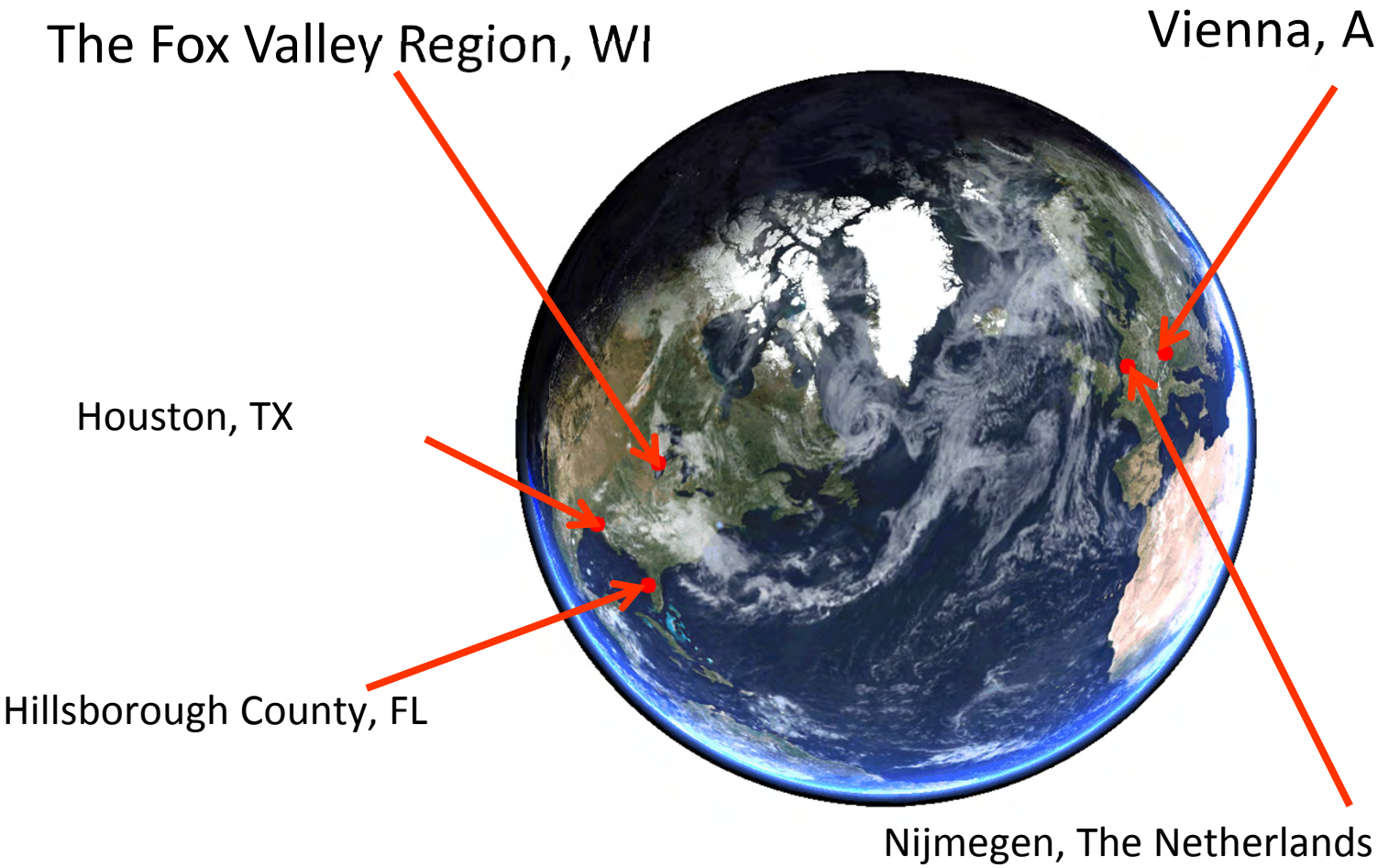
# Setting

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# PI Trial Requirements

1. High quality manual CPR
2. Monitor CPR process in both arms
3. Standardized training

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# Provider training

- 4 hour standardized training
  - Review study protocol
  - Review CPR process
  - Pit Crew deployment strategy
  - Written and practical examination


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# Verification of Protocol Adherence

- Formal simulation study*
  - Full Megacode simulation
  - Validation of protocol and training program
- Evaluated protocol compliance
- Evaluated CPR quality
  - AutoPulse AND manual compressions
- Used to guide refresher training curriculum

*Tømte Ø et al Resuscitation 2009

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# Trial Phases

- Three distinct study phases


Deployment and usage of the AutoPulse for every OHCA*

Randomization and adherence to full study protocol for each OHCA*

Randomization and adherence to full study protocol for each OHCA – Data included in analysis

***Transition based on predefined measures of protocol compliance according to monitoring of the CPR process**

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# Subject Inclusion

- 18 years of age or older
- OHCA of presumed cardiac etiology
- Randomization after M-CPR initiated

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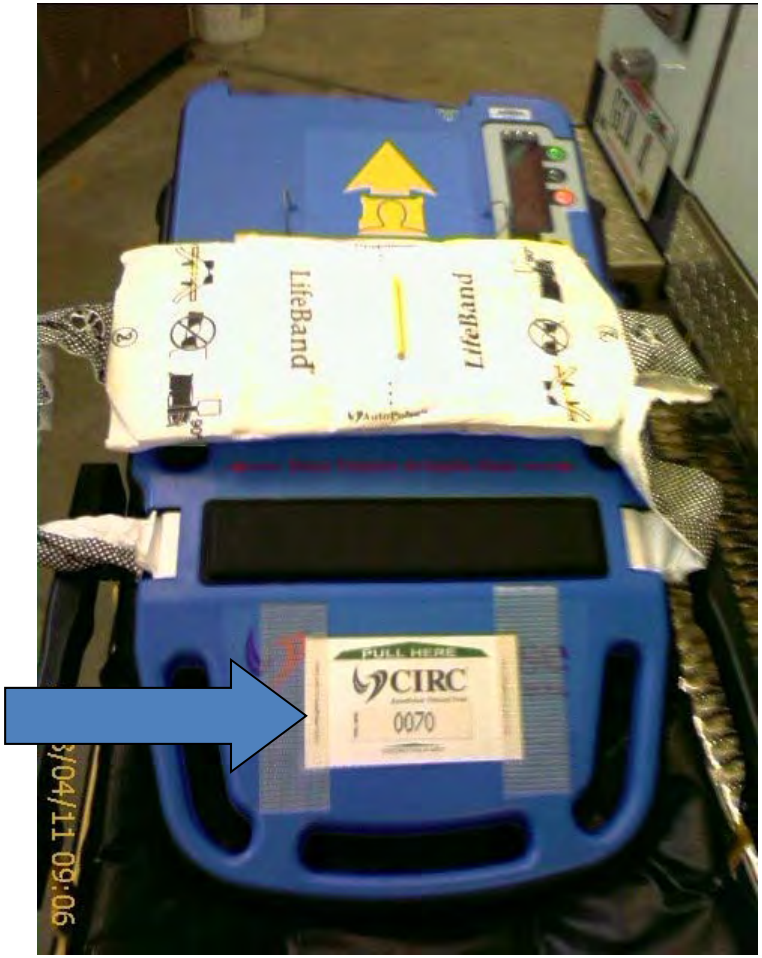
# Randomization Procedure

- Confirm cardiac arrest
- Verify need for CPR
- Start manual compressions
- Determine trial eligibility
- Open randomization envelope
- Treat per randomization card

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# Subject Exclusion

- Known or apparent pregnancy
- Do Not Resuscitate orders
- Too big for the AutoPulse
- Prisoner or ward of the state
- Prior application of a mechanical chest compression device
- Randomizing EMS unit arrived ≥16 minutes after emergency call

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# Determination of Inclusion/Exclusion

- Best estimate of EMS providers
  - No treatment delay
- Some cases excluded after enrollment
  - Except for patient size
  - Retrospective exclusion monitored by DSMB

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# Data Analysis

- Group Sequential Double Triangular Test
- Powered to determine superiority, inferiority, or equivalence
  - Two-sided significance level 5%
  - Power 97.5%
- Equivalence defined as OR 95%

  CI fully between 0.69 and 1.44

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# Vil bruk av AutoPulse ved hjertestans utenfor sykehus øke hands-off tiden?

Jan-Åge Olsen, MD og PhD-stipendiat,
Nasjonalt Kompetansesenter for Prehospital Akuttmedisin (NAKOS), Oslo Universitetssykehus og Universitetet i Oslo, Institutt for klinisk medisin

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NAKOS prehospital akuttmedisin

Oslo universitetssykehus

# Impedanse

- En kjent høyfrekvent, lav amplitude, vekselstrøm blir sendt gjennom brystkassen mellom defibrillator-padsene.
- Resulterer i spenning gjennom brystkassen som måles vha Ohms lov
- Ved hjelp av prosessering og programvare kan man få frem kurver som analyseres

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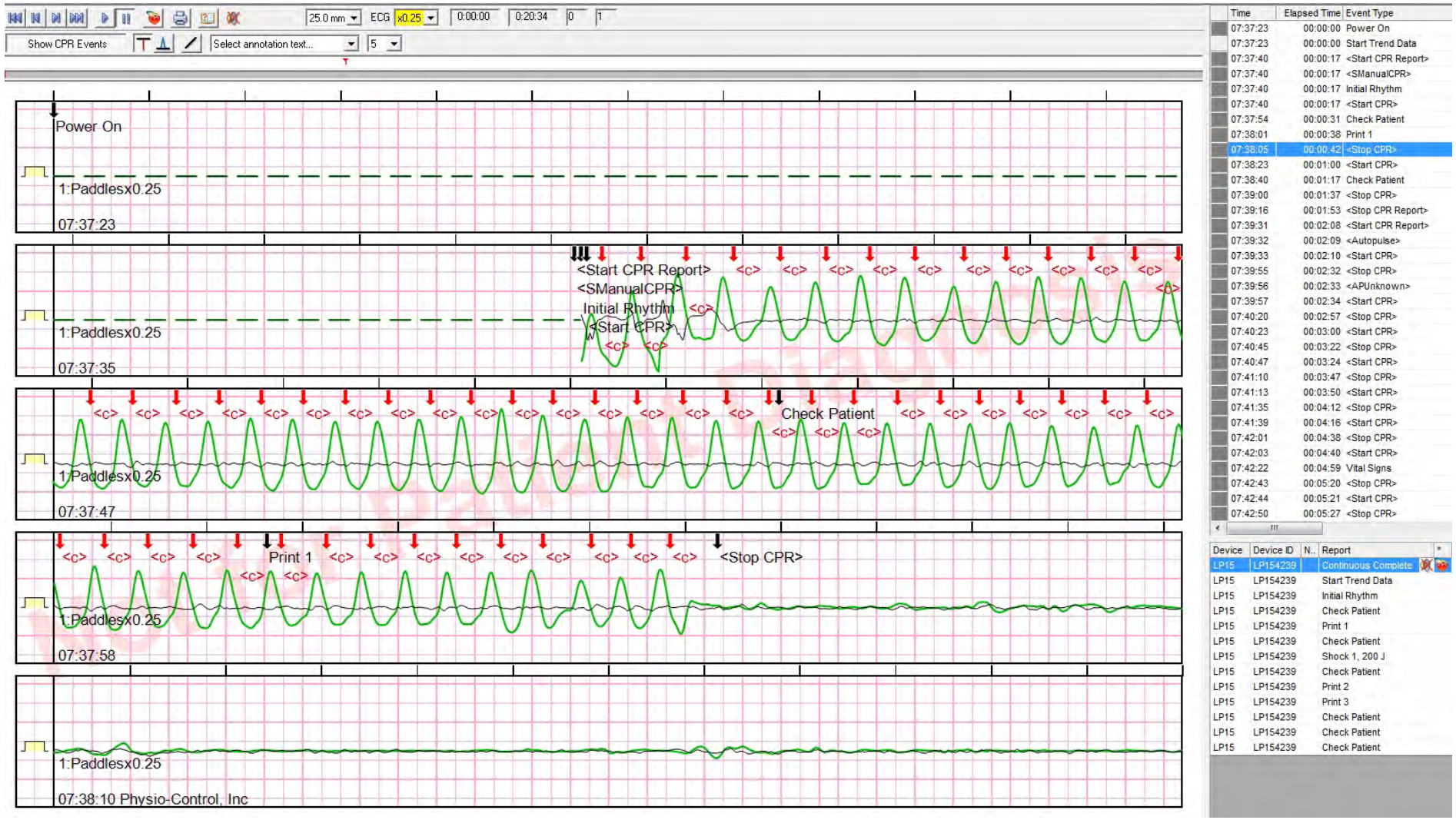


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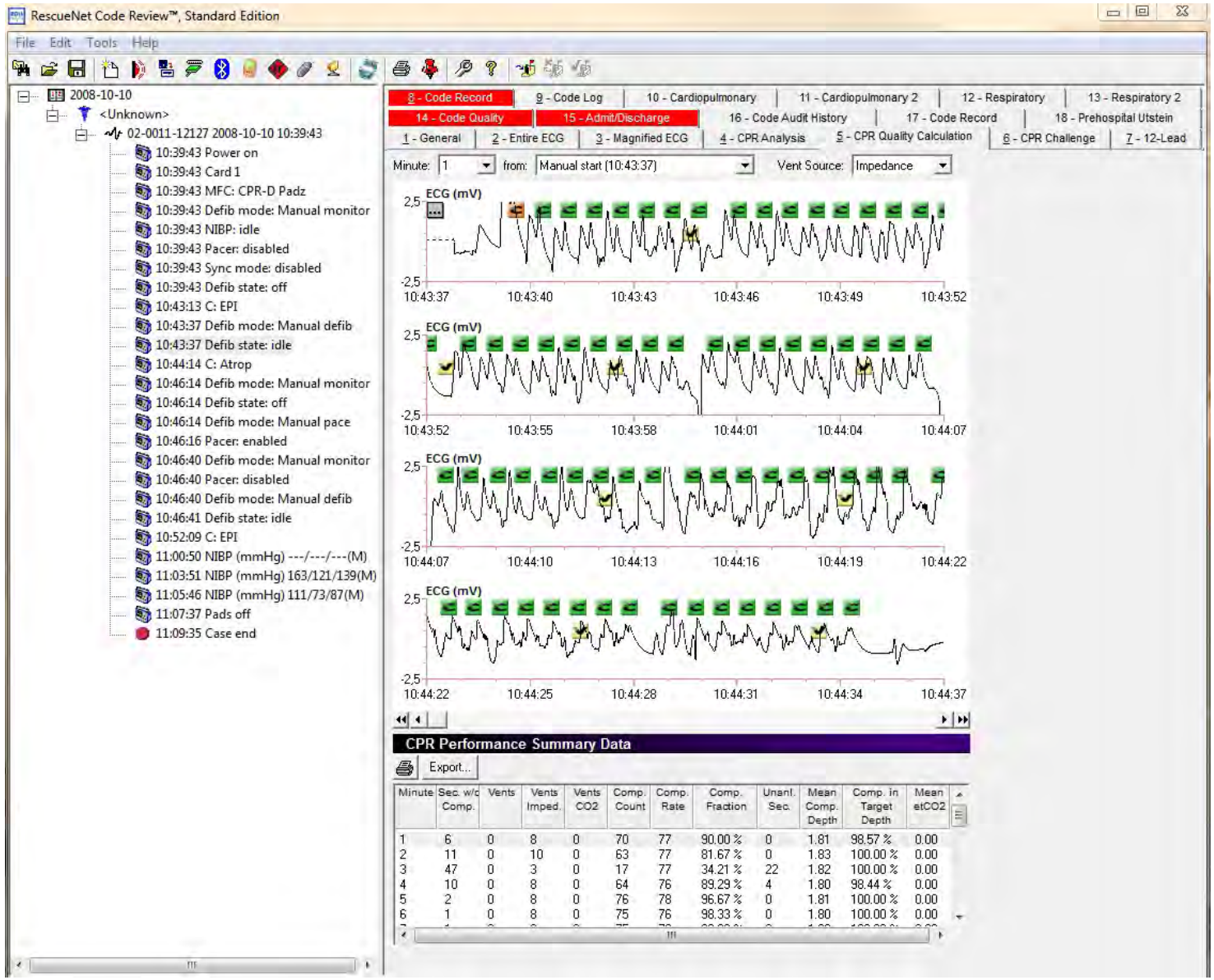
# Physio-Control Code-Stat™ 9.0

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Zoll RescueNet Code Review™ (utvikler-versjon)

# Bruk av elektroniske defibrillatordata

- Physio-Control defibrillatorer: Bruk av transthorakal impedanse validert for kompresjoner.[1] Ikke for ventilasjoner under pågående kompresjoner.[2]
- Zoll defibrillatorer buker impedanse for å tolke ventilasjoner og akselerometer-data for kompresjoner

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[1] Stickney RE, Marx R, Olsufka M, et al. Accurate measurement of chest compressions from thoracic impedance signals. Circulation 2005; 112(17):II-326. Abstract.
[2]Losert H, Risdal M, Sterz F, et al: Thoracic impedance changes measured via defibrillator pads can monitor ventilation in critically ill patients and during cardiopulmonary resuscitation. Crit Care Med 2006; 34:2399–2405

# Metode

- En annoteringsalgoritme ble utviklet for en enhetlig tilnærming. Denne basert på tidligere erfaring[1] og publiserte metoder for å analysere elektroniske data.
- Pause i kompresjoner definert som mer enn 1.5 sekunder mellom to kompresjoner.[2]

[1]Stecher FS, Olsen JA, Stickney RE, et al. Transthoracic impedance used to evaluate performance of cardiopulmonary resuscitation during out of hospital cardiac arrest. *Resuscitation.* Dec 2008;79(3):432-437.
[2]Kramer-Johansen J, Edelson DP, Losert H, et al. Uniform reporting of measured quality of cardiopulmonary resuscitation (CPR). *Resuscitation.* Sep 2007;74(3):406-417.

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# Metode, forts.

- Kontinuerlig EKG og akselerometer- eller impedanse data ble analyser for å bestemme
  - Antall kompresjoner per minutt
  - Antall ventilasjoner per minutt
  - Tiden det tok før Autopulse var i bruk i iA-HLR-armen
  - Antall sjokk
  - Om det ble defibrillert gjennom kompresjoner
- Defibrillering gjennom kompresjoner – minst 50% av defibrilleringene måtte skje mens Autopulse komprimerte

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# Metode, forts.

- HLR-fraksjon ble regnet ut for de første 5, 10 og 20 minuttene
- Deskriptiv statistikk og 95% konfidensintervall ble beregnet

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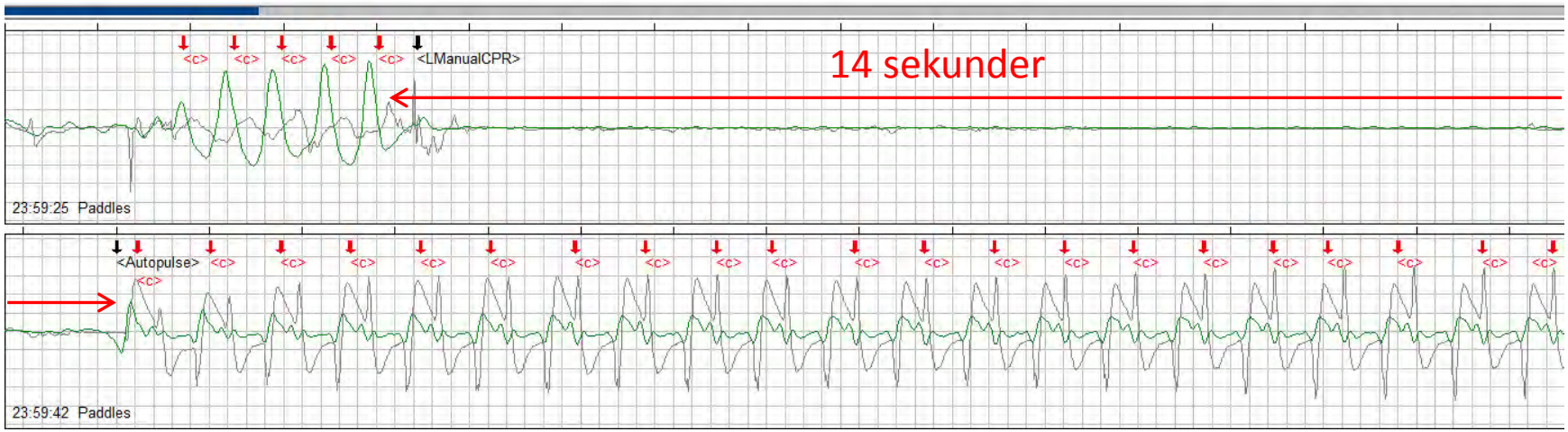
# Tid fra siste manuelle kompresjon til første Autopulse-kompresjon




x1.0, 25 mm

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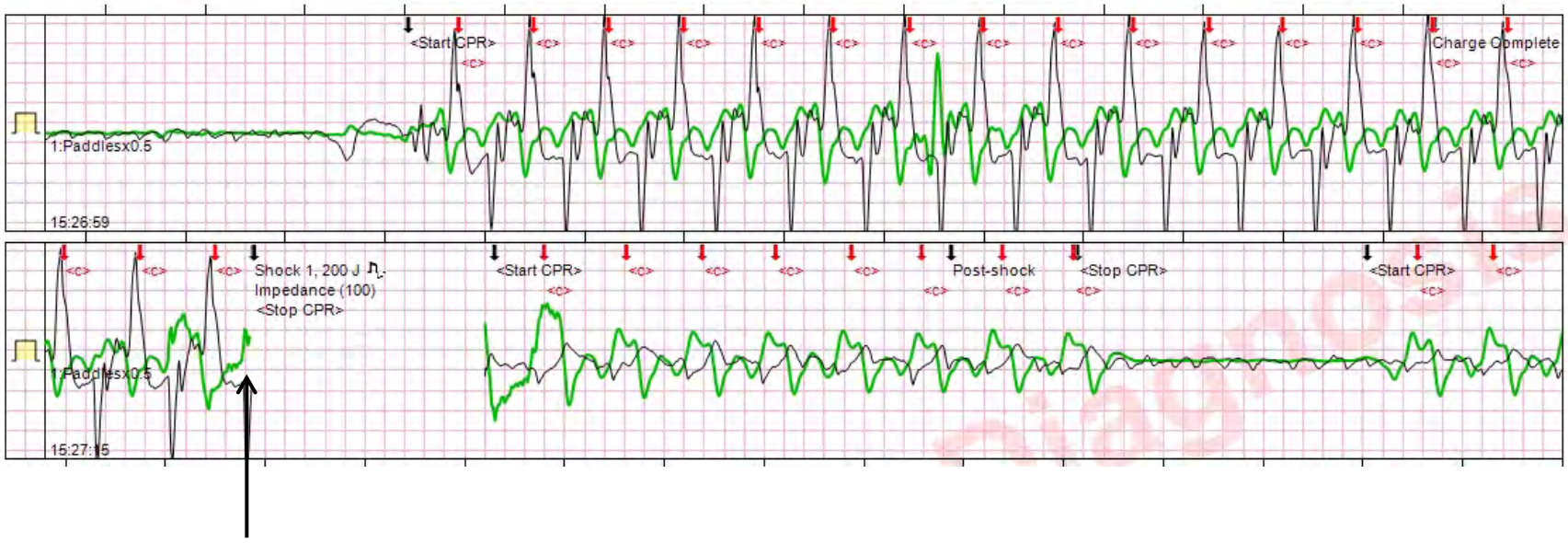
# Sjokk under pågående HLR




Sjokk gis

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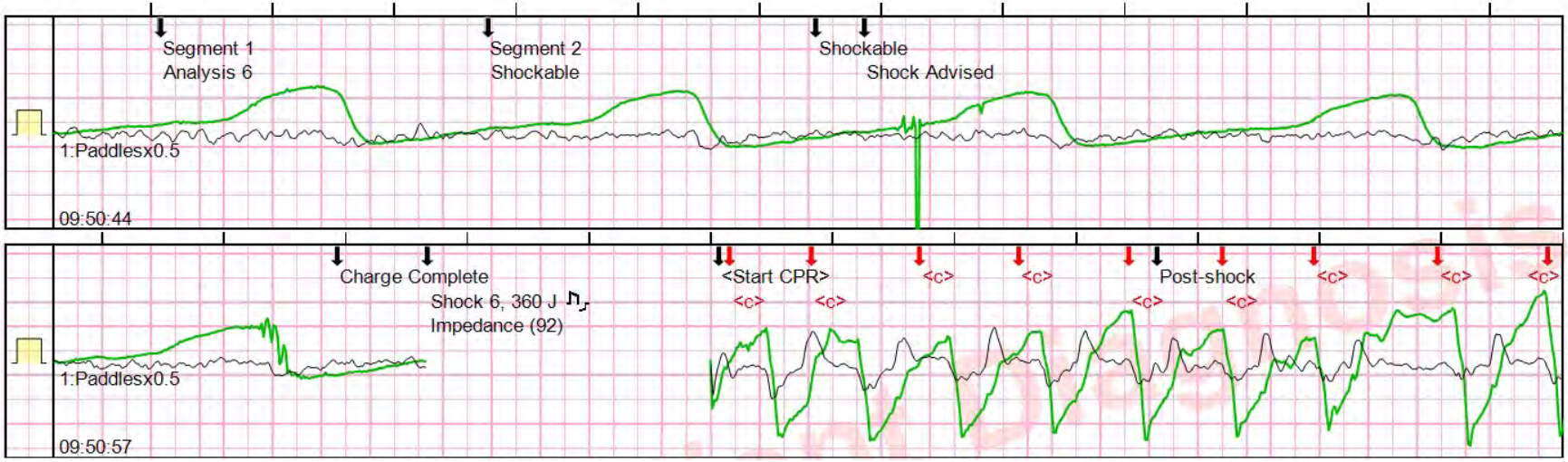
# Autopulse startes etter sjokket

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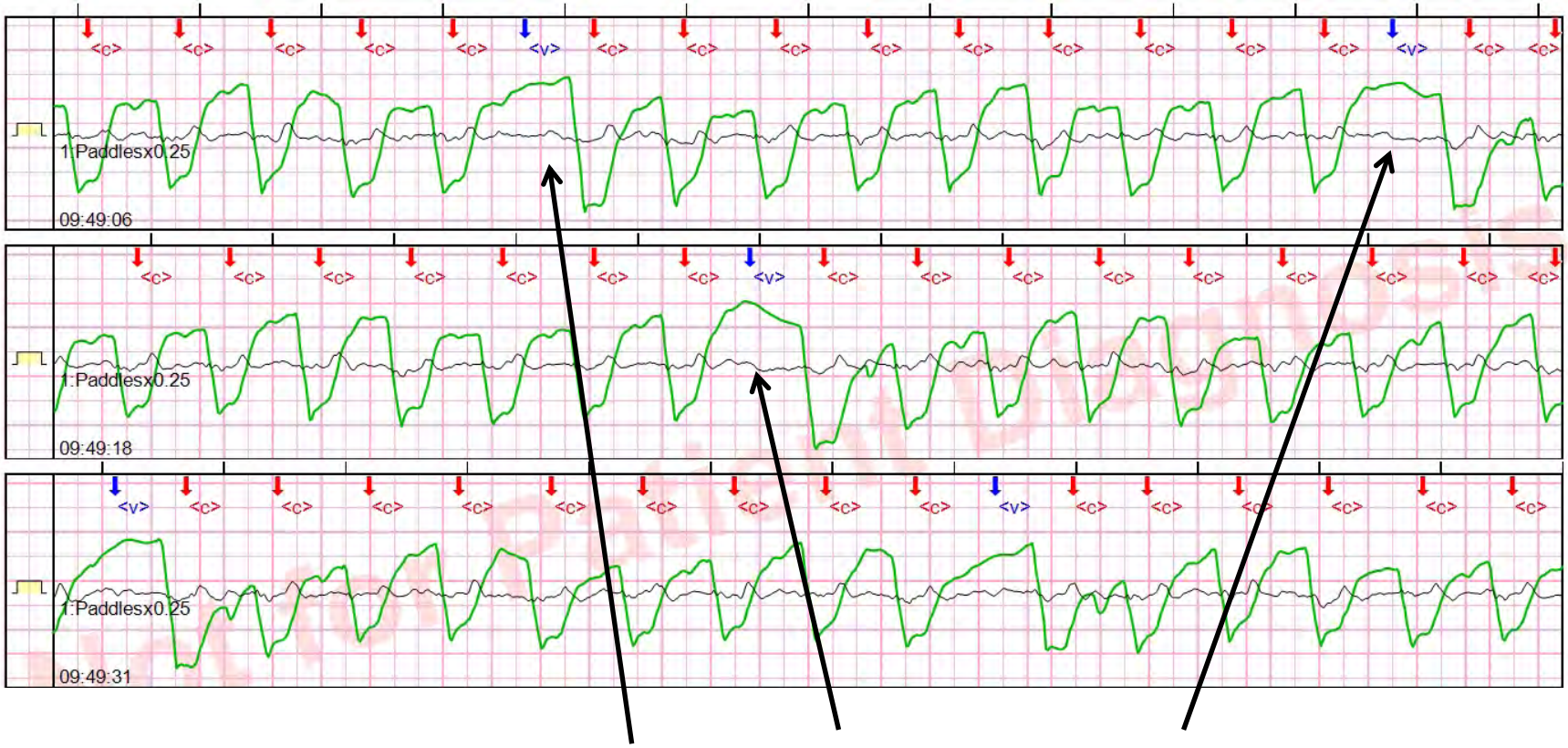
# Kontinuerlig Autopulse




En litt lenger pause mellom 2 kompresjoner slik at man får ventilert.

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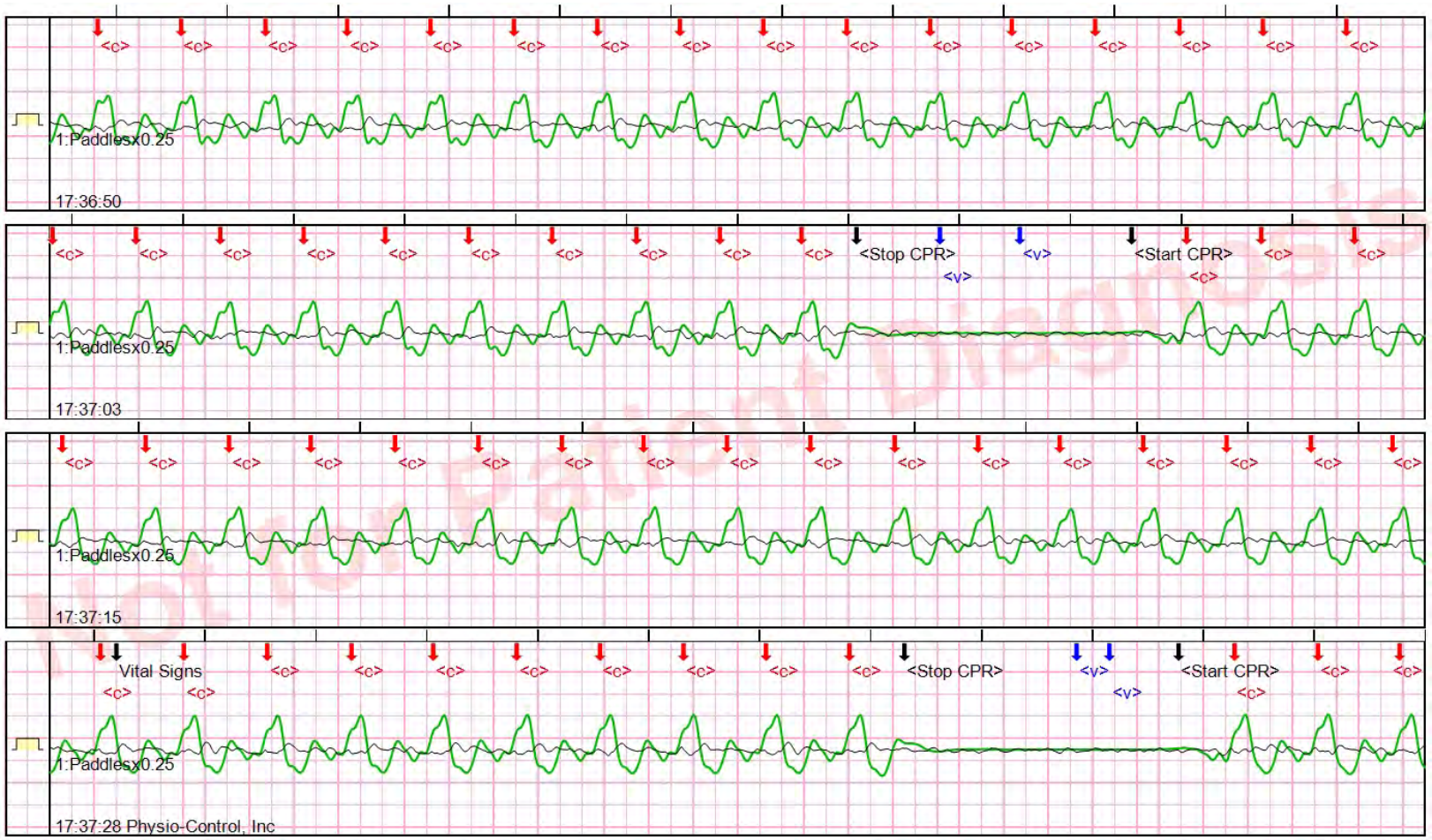
# Autopulse, 30:2

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# Resultater

| | M-HLR (n=2024) | iA-HLR (n=2017) |
|---|---|---|
| Tid fra defibrillator på til første registrerte kompresjon (sekunder) | 61 ± 127 | 65 ± 139 |
| HLR-fraksjon | | |
| Ved 10 minutter | 79,7% ± 10,1% | 78,5% ± 9,4% |
| Ved 20 minutter | 80,2% ± 9,1% | 80,4% ± 8,3% |
| Antall kompresjoner per minutt første 10 minutter | 89,2 ± 17,4 | 66,3 ± 10,7 |
| Antall ventilasjoner per minutt første 10 minutter | 8,8 ± 4,7 | 6,8 ± 3,4 |

Elektroniske data tilgjengelig for 96% av episodene

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# Resultater

| | M-HLR (n=2024) | iA-HLR (n=2017) |
|---|---|---|
| Defibrillerte pasienter (%) | 40% | 38% |
| Median antall defibrilleringer i episoder med defibrillering | 3 | 2 |

- Median tid fra siste manuelle kompresjon til første Autopulse-kompresjon 29 sekunder (IQR 17-43)
- I 74% av iA-HLR episodene ble det sjokket gjennom kontinuerlig kompresjoner

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# Diskusjon

| | HLR-fraksjon, 5 min | HLR-fraksjon, 10 min |
|---|---|---|
| Ong, Manuell arm[1] | 72% ± 20% | 69% |
| CIRC Manuell arm[x] | 79,0% ± 12,3% | 79,7% ± 10,1% |
| Ong, LDB arm[1] | 60% ± 20% | 69,5% |
| CIRC iA-HLR[x] | 74,7 ± 12,7% | 78,5% ± 9,4% |

[x]HLR-fraksjon for første 20 minutter

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[1]Ong ME, Annathurai A, Shahidah A, et al. Cardiopulmonary resuscitation interruptions with use of a load-distributing band device during emergency department cardiac arrest. *Annals of emergency medicine.* Sep 2010;56(3):233-241.

# Begrensninger elektroniske data

- Ingen kompresjonsdybde fra elektroniske data fra Physio-Controls maskiner
- Bare analysert første 20 minutter av episodene for HLR-fraksjon (10 minutter for ventilasjoner)

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# Problemområder

- Svært mye manuelt arbeid. Softwaren brukt i denne studien er fortsatt under utvikling
- Estimert 10 millioner museklikk bare for selve annoteringene.
- Anta 1 museklikk per sekund:  Man vil sitte og klikke i 115 dager (dag og natt)

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# Takk til

- Lars Wik (hovedveileder)
- Petter Andreas Steen (biveileder)

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# Results

- 9,068 calls with presumed cardiac arrest
  - 4315 excluded at time of EMS response:
    - 3467 No CPR attempted (Dead On Arrival - DOA)
    - 245 Non-cardiac etiology
    - 275 Met exclusion criteria
    - 328 Missed enrollment
  - 522 excluded post enrollment
    - 10.4% M-CPR
    - 11.0% iA-CPR
- 4,231 included subjects
    - 50.4% (2132) M-CPR
    - 49.6% (2099) iA-CPR

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# General Characteristics by Arm

| | M-CPR n=2132 | iA-CPR n=2099 |
|---|---|---|
| **Age** | 65.6 ±16.0 | 65.7±16.4 |
| **Male gender** | 61% | 61% |
| **Public location of OHCA** | 13% | 14% |
| **Bystander witnessed** | 37% | 37% |
| **Bystander CPR** | 49% | 47% |
| **Shockable initial rhythm** | 24% | 21% |
| **Response interval [min]** | 6.6 ± 3.0 | 6.7 ± 2.9 |
| **Prehospital epinephrine** | 91% | 93% |
| **Hospital hypothermia*** | 12% | 10% |
| **PTCA/ PCI*** | 6% | 4% |
| **Time from arrival to termination/transport [min]** | 36.1 ± 14.1 | 37.3 ± 14.3 |
| **Initial rhythm VF/ VT average time from defib on to first shock [min]** | 3.5 ± 4.0 | 4.6 ± 4.8 |
| **Time from defib on to first recorded compression(s)** | 61 ± 127 | 65 ± 139 |

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*calculated based on total included in the arm

# Results: Adverse Events

- Medical monitor received 34 adverse event reports
  - 28 were determined to be unexpected
  - 26 of those were serious
- DSMB reviewed all 34 cases
  - No new risks identified
  - No safety concerns

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# Results: Effectiveness Endpoint

- Equivalent survival to hospital discharge
  - Primary Endpoint
  - OR 1.06, 95% CI 0.83 - 1.37
    - Adjusted for covariates (age, witnessed arrest, initial cardiac rhythm, and enrollment site) and interim analysis
    - Within pre-defined equivalence region (0.69 - 1.44)

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# Results: Effectiveness Endpoint

| | **M-CPR (n=2132)** | **iA-CPR (n=2099)** | **Unadjusted OR** (95% CI) | **Adjusted OR** (95% CI) |
|---|---|---|---|---|
| **Survival to Hospital Discharge** | **11.0%** | **9.4%** | **0.84 (0.69 – 1.02)** | **1.06 (0.83 - 1.37)** |
| **Survival to 24h** | 25.0% | 21.8% | 0.84 (0.72 – 0.96) | |
| **Sustained ROSC** Survival to ED | 32.3% | 28.6% | 0.84 (0.74 – 0.96) | |

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# Results: Safety Endpoint

- No difference in mRS scores ≤3
  - Adjusted OR 0.80, 95% CI 0.47 - 1.37 (n.s.)

| | **M-CPR** | **iA-CPR** |
|---|---|---|
| **Discharge mRS** | (n=233) | (n=196) |
| **Score of 0 -3** | 48.1% | 44.4% |
| **Score of 4 -5** | 26.2% | 25.5% |
| **Unknown score** | 25.8% | 30.1% |

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# Subgroup Analysis

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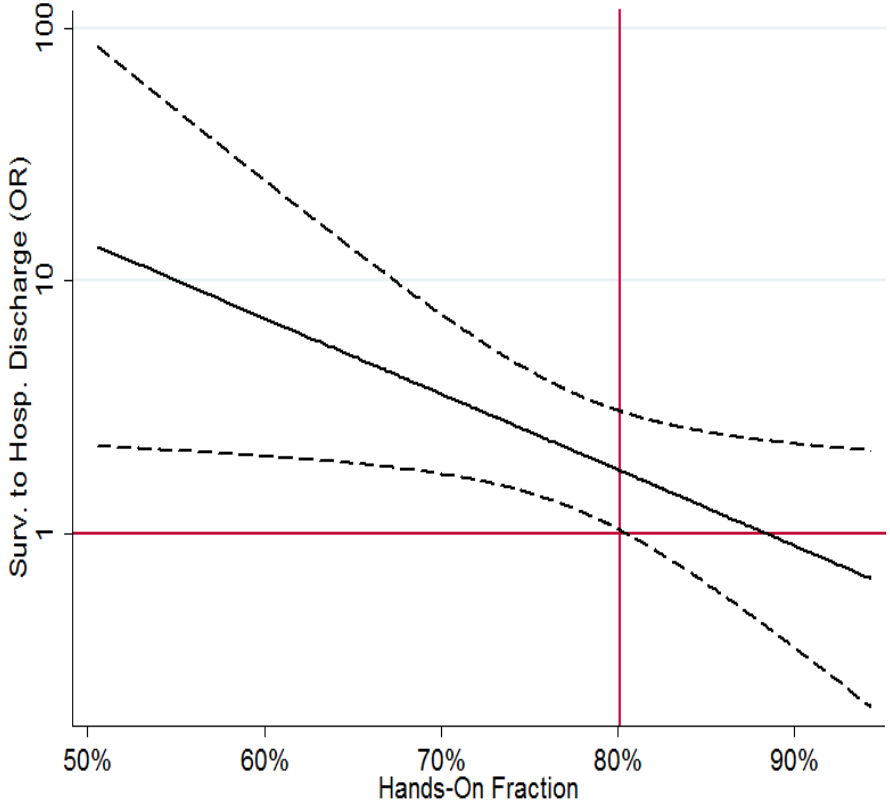
# Subgroup Analysis

- Witnessed Arrests with VF/VT
- Survival higher for iA-CPR if CPR fraction <80%
- No survival difference with higher CPR fractions.
- Example: CPR fraction 70% OR 3.4, 95% CI 2–7.4

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# Discussion - Methods

- Three study phases
  - Consistent study practices
- Training and compliance monitoring
  - High CPR fraction in both arms
  - High overall survival rate (10.2%)
- Patient level randomization
  - Equivalent subject characteristics
- Good patient tracking
  - 98% cases with digital ECG data files
  - 12 cases missing primary endpoint data

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# Discussion - Results

- Equivalence
  - Study powered to show true statistical equivalence.
  - At least as good as high-quality M-CPR
- iA-CPR may solve practical problems
  - CPR in confined spaces
  - CPR with limited number of rescuers
  - CPR during transport

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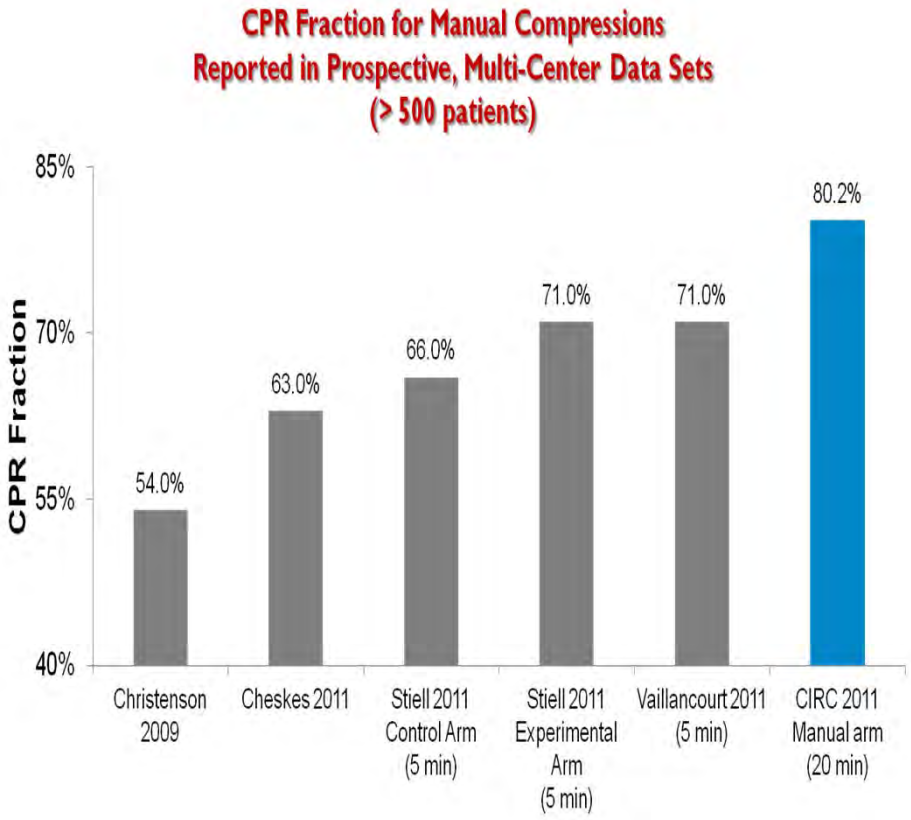
# Discussion - Results

- CPR fraction
  - ~80% CPR Fraction in both arms
    - Higher than most CPR fractions reported for other large RCTs.
  - High CPR fraction hard to achieve and maintain
  - Sub-analysis demonstrated that at more typical "clinical" CPR fractions iA-CPR may be better than M-CPR

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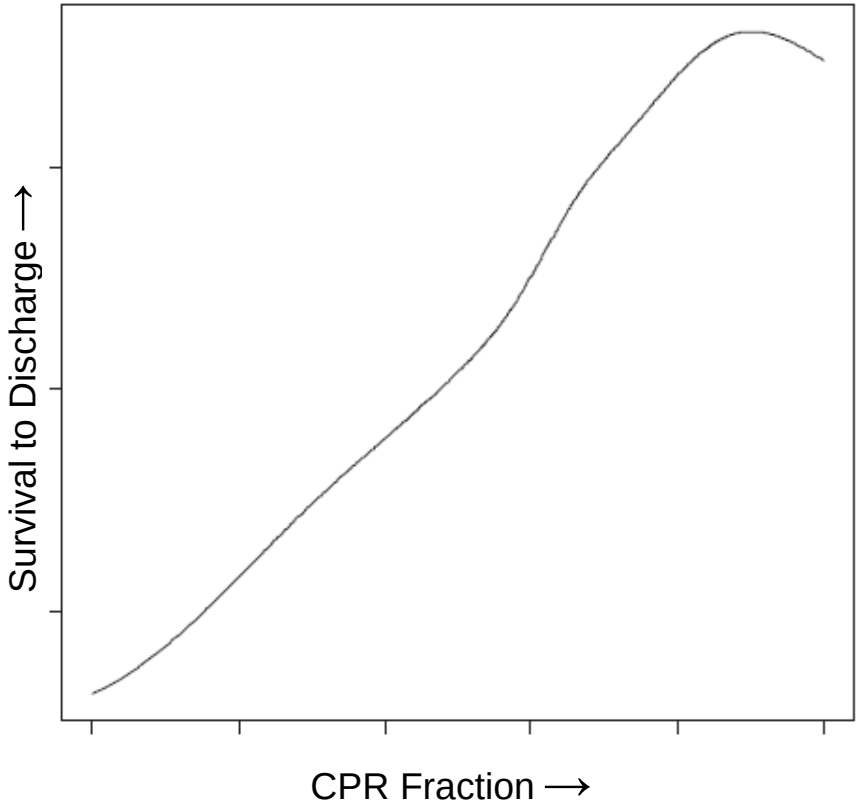
# CPR Fraction Predicts Survival

- The Resuscitation Outcomes Consortium (ROC) reports the CPR Fraction to independently predict survival in cardiac arrest patients.
- CPR Fraction was employed as the primary marker of CPR quality during the CIRC trial.




Christenson J. et al. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. *Circulation.* 2009;120:1241-1247.

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# Limitations

- Post-resuscitation care not standardized
- Clock Synchronization
- CPR fraction only quality measure
- Arrival at patient side same defibrillator on

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# Conclusions

- CPR quality was good for both groups
- It is possible to achieve High quality manual CPR that saves lives
- Compared to high quality M-CPR:
  - iA-CPR resulted in statistically equivalent survival to hospital discharge
  - No difference in neurologic status at discharge

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