# Adaptive versus conventional cardiac resynchronization therapy in patients with heart failure

## Primary results from the AdaptResponse global randomized trial

Bruce L. Wilkoff, MD
Cleveland Clinic, Cleveland, OH
@LEADconnection1

*LEADconnection.org®*

Bruce L. Wilkoff, MD; David Birnie, MD, MB, ChB; Christophe Leclercq, MD, PhD; Michael R. Gold, MD, PhD; Ahmad S. Hersi, MD, MBA, FRCPC; Kengo Kusano, MD, PhD; Wilfried Mullens, MD, PhD; Bart Gerritse, PhD; Janelle van Wel, PhD; Gerasimos Filippatos, MD for the AdaptResponse Investigators

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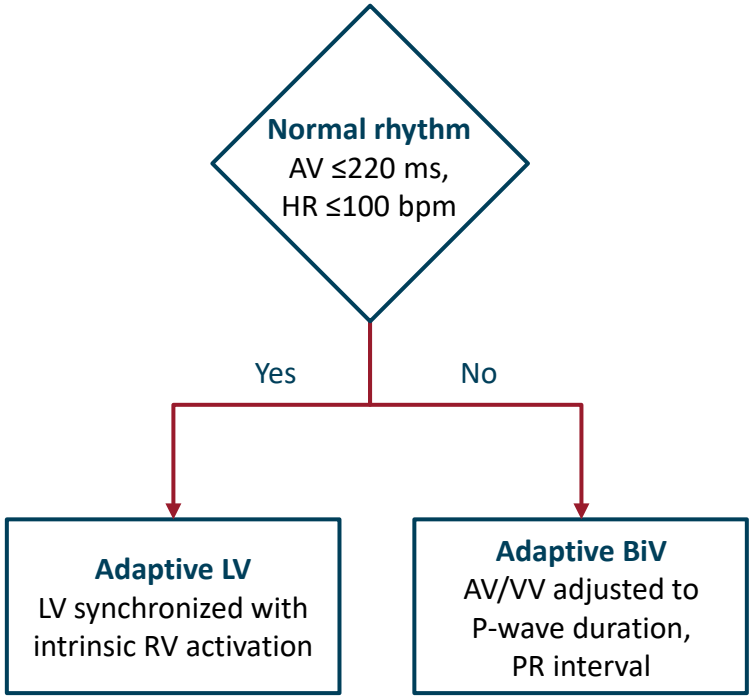
# Background

- CRT improves quality of life while reducing HF symptoms, hospitalizations, and mortality among patients with a prolonged QRS duration, symptomatic HF, and reduced ejection fraction.[1]
- However, up to 30% of patients have been classified as nonresponders using traditional dichotomous CRT response classification.[2]
- Pacing only the left ventricle has been hypothesized to be superior to biventricular pacing when there is intact conduction to the right ventricle.[3]

[1] Glikson, et al. Eur Heart J. 2021;42(35):3427-520.
[2] Mullens, et al. J Am Coll Cardiol. 2009/53(9):765-73.
[3] Vernooy, et al. Nat Rev Cardiol. 2014;11(8):481-93.

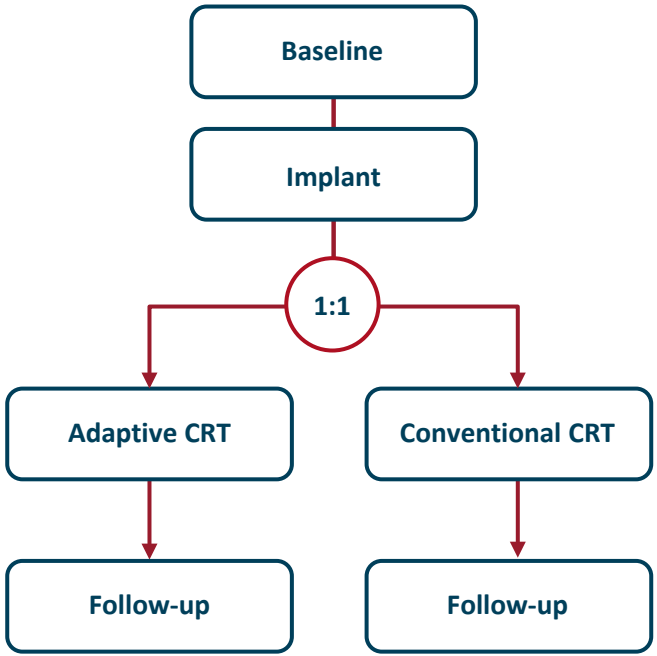
# AdaptivCRT algorithm

- Dynamic algorithm to achieve fusion pacing and optimize resynchronization
- Regularly measures patient's conduction system to adjust therapy: Adaptive LV or BiV pacing
- Adaptive LV reduces unnecessary RV pacing, increasing battery longevity
- Prior studies suggested a benefit in clinical outcomes[1,2], particularly among patients with intact AV conduction and LBBB.[3,4]




[1]Starling, et al. *JACC: Heart Failure*. 2015;3(7):565-72. [2]Singh, et al. *J Cardiovasc Electrophysiol.* 2020;31(4):825-33. [3]Birnie, et al. *Heart Rhythm*. 2013;10(9):1368-74. [4]Yamasaki, et al. *Int J Cardiol.* 217;240:297-301.

# Study design




| | |
|---|---|
| **Purpose** | To demonstrate superiority of adaptive versus conventional CRT in HF patients with intact AV conduction and LBBB. |
| **Primary endpoint** | Death from any cause or intervention for HF decompensation. |
| **Sample size** | ~3500 patients for 90% power for an expected reduction of 18% |
| **Design** | Prospective, single-blind, parallel, randomized trial with blinded endpoint adjudication. |
| **Population** | • Sinus rhythm<br>• PR interval ≤200 ms<br>• LVEF ≤35%<br>• NYHA Class II-IV HF symptoms despite medical therapy<br>• LBBB according to Strauss criteria (QRS ≥140 ms in men, ≥130 ms in women) |
| **Secondary endpoints** | • Components of primary endpoint<br>• CCS at 6 months<br>• AF (first occurrence of ≥ 6 hours on a single day)<br>• KCCQ<br>• EQ-5D<br>• 30-day readmissions after discharge from a HF admission |

Filippatos G, et al. *Eur J Heart Fail*. 2017;19:950-957.

# Study recruitment

**3617**
randomized*

**227**
sites

**27**
countries

**59**
months median follow-up

*3797 patients recruited between August 2014 and January 2019

1.6% exited due to unsuccessful implant

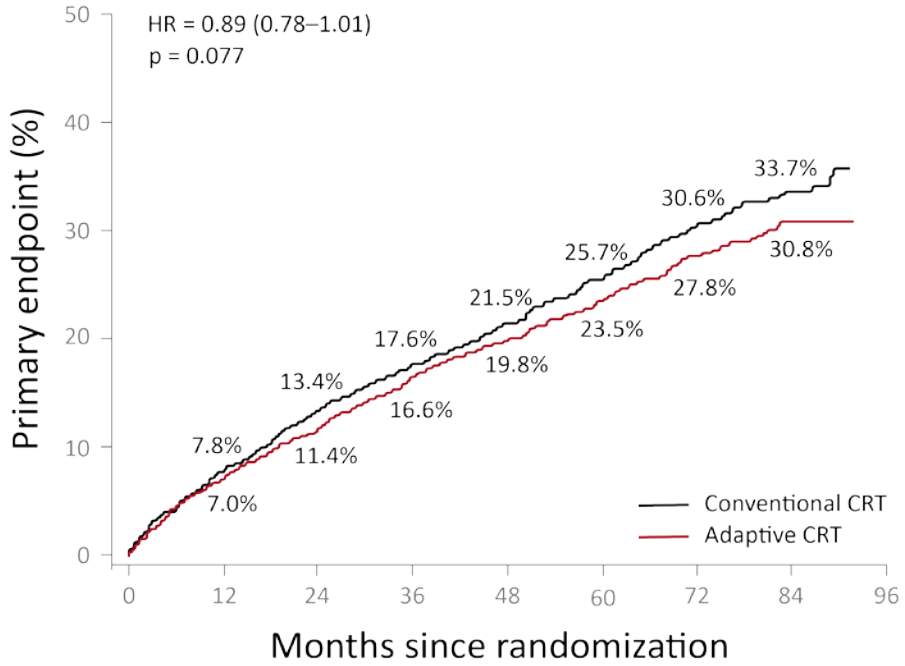
# Baseline characteristics

| Characteristic | AdaptivCRT (n=1810) | Conventional CRT (n=1807) |
|---|---|---|
| Age | 64.6 ± 11.1 | 65.2 ± 11.0 |
| Female | 43.2% | 43.5% |
| LVEF - % | 25.6 ± 6.3 | 25.4 ± 6.3 |
| LBBB* | 96.6% | 95.4% |
| QRS - ms | 162.6 ± 17.1 | 162.7 ± 16.2 |
| PR interval – ms | 171.5 ± 20.9 | 172.1 ± 21.1 |
| AF | 13.0% | 13.2% |
| NYHA Class II<br>NYHA Class III/IV | 48.7%<br>51.4% | 48.0%<br>52.0% |
| Nonischemic | 68.2% | 67.9% |
| CRT-D | 95.1% | 95.5% |
| Beta-blocker<br>RAAS inhibitor<br>ARNI<br>MRA<br>SGLT2 inhibitor<br>Diuretic | 89.8%<br>84.3%<br>10.9%<br>47.9%<br>0.8%<br>65.4% | 90.5%<br>85.1%<br>11.7%<br>48.4%<br>0.3%<br>64.9% |

*Strauss criteria core lab confirmed

Baseline characteristics and medication usage were similar between groups.

# Primary endpoint: All-cause mortality or HF event




N at Risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Conventional CRT | 1807 | 1588 | 1438 | 1317 | 1108 | 772 | 415 | 160 |
| Adaptive CRT | 1810 | 1620 | 1490 | 1361 | 1164 | 801 | 411 | 163 |

- The trial was stopped after the 3rd interim analysis for futility.
- The strategy of adaptive CRT compared with conventional CRT did not significantly reduce the incidence of all-cause mortality or HF events; therefore, the primary endpoint was not met.

Results are reflective of the final study database and include 5 additional months of follow-up after the 3rd interim analysis.

900 total primary endpoint events
(430 adaptive CRT, 470 conventional CRT)

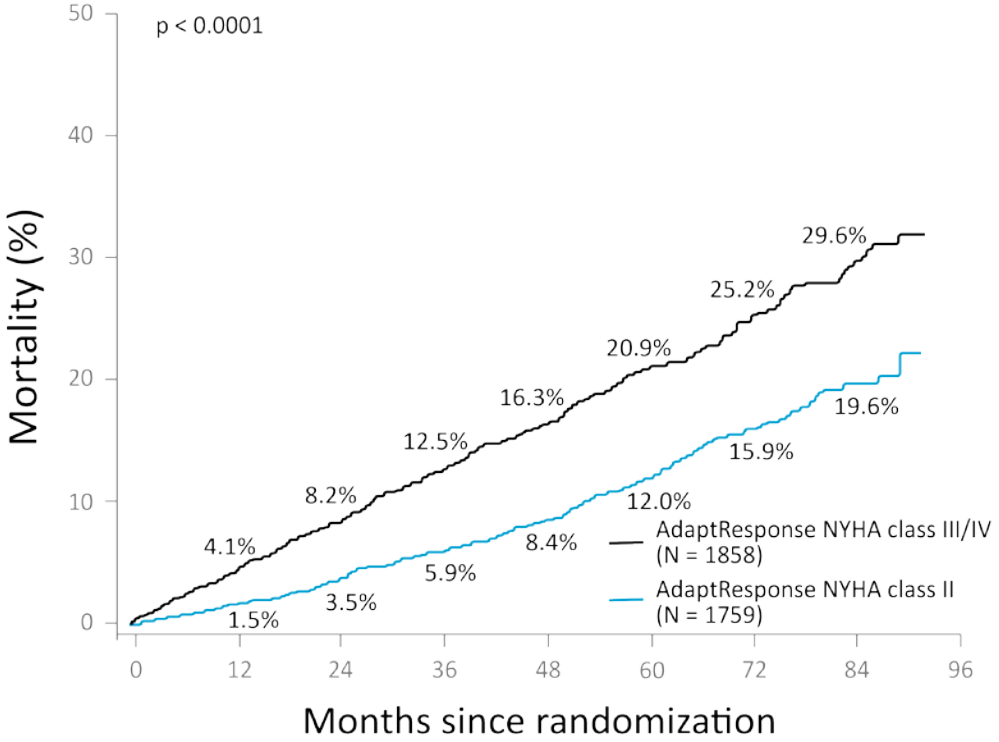
# Secondary endpoints

| Secondary endpoint | Adaptive CRT (n=1810) | Conventional CRT (n=1807) | Treatment effect | P-value |
|---|---|---|---|---|
| | Occurrence rate at 5 years | | HR (95% CI) | |
| All-cause mortality | 15.6% | 17.7% | 0.88 (0.75-1.03) | 0.12 |
| HF event | 13.2% | 14.5% | 0.91 (0.76-1.8) | 0.28 |
| AF (≥ 6 hours) | 18.8% | 19.8% | 0.99 (0.85-1.16) | 0.89 |
| | Percent of patients | | OR (95% CI) | |
| Clinical Composite Score<br>Improved<br>Stabilized<br>Worsened | 69.1%<br>23.3%<br>7.6% | 71.4%<br>21.4%<br>7.1% | 0.89 (0.77-1.03) | 0.11 |
| | Rate per 100 patient-years | | RR (95% CI) | |
| 30-day readmission after HFH | 1.07 | 0.93 | 1.15 (0.75-1.75) | 0.52 |
| | Mean (SD) change baseline to 2 yrs | | Difference (95% CI) | |
| KCCQ | 16.8 (21.2) | 16.5 (20.4) | -0.1 (-1.0-0.9) | 0.88 |
| EQ-5D Utility index* | 54 (190) | 48 (180) | 1.3 (-6.8-9.4) | 0.75 |

*EQ-5D utility index values reported as x 0.001

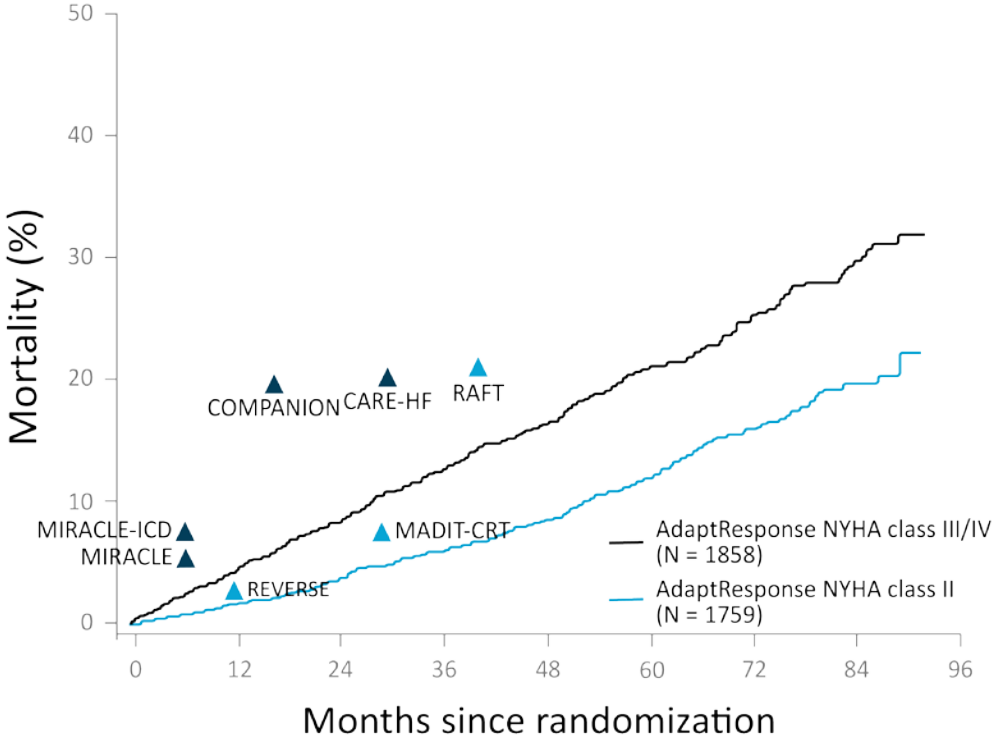
- No significant differences between groups for secondary endpoints.
- Overall rates of all-cause mortality, HF events, and AF were very low.
- CRT response rates were very high.

# Mortality by NYHA class




Overall mortality across all randomized patients in AdaptResponse was low (16.5% at 5 years) and differed by NYHA class.

# Mortality across CRT trials



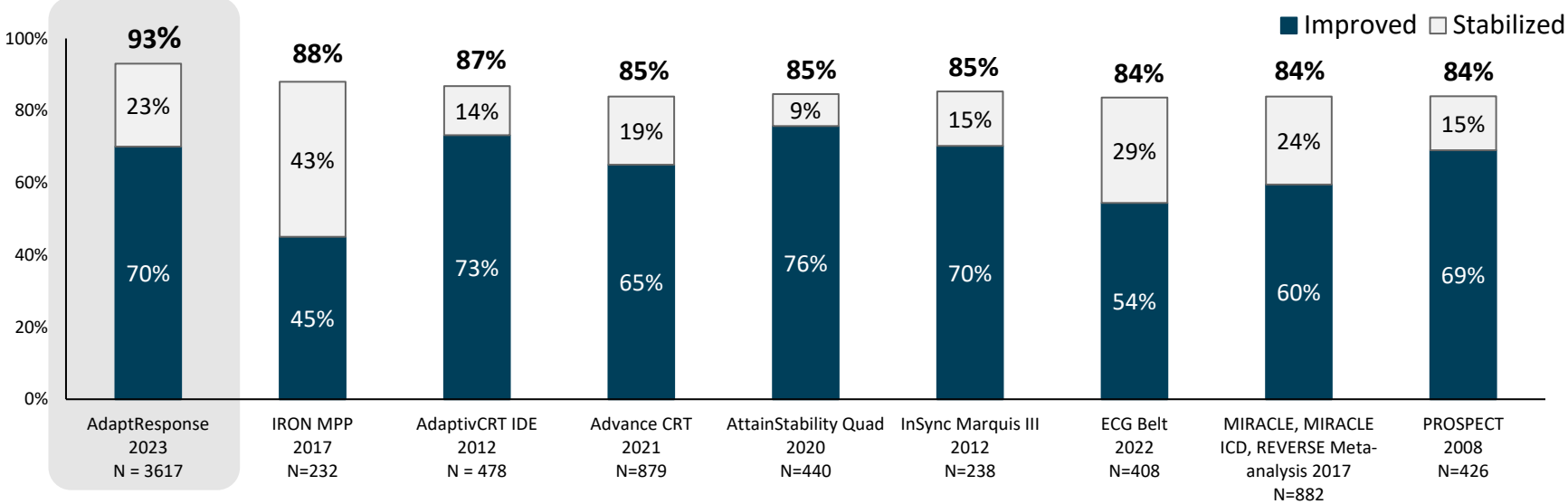

Accounting for NYHA class, AdaptResponse reports the lowest mortality of randomized CRT trials to-date.

MIRACLE 2002; NYHA III/IV (N=228)
MIRACLE ICD 2003; NYHA III/IV (N=187)
COMPANION 2004; NYHA III/IV (N=595)
CARE-HF 2005; NYHA III/IV (N=409)
REVERSE 2008; NYHA I/II (N=419)
MADIT CRT 2009; NYHA I/II (N=1089)
RAFT 2010; NYHA II/III (N=894)

Abraham, et al. N Engl J Med. 2002;346(24):1845-53. Young, et al. *JAMA*. 2003;289(20):2685-94. Bristow, et al. N Engl J Med. 2004; 350(21): 2140-50. Cleland, et al. N *Engl J Med*. 2005;352(15):1539-49. Linde, et al. *J Am Coll Cardiol*. 2008;52(23):1834-43. Moss, et al. *N Engl J Med*. 2009;361(14):1329-38. Tang, et al. *N Engl J Med*. 2010;363(25):2385-95.

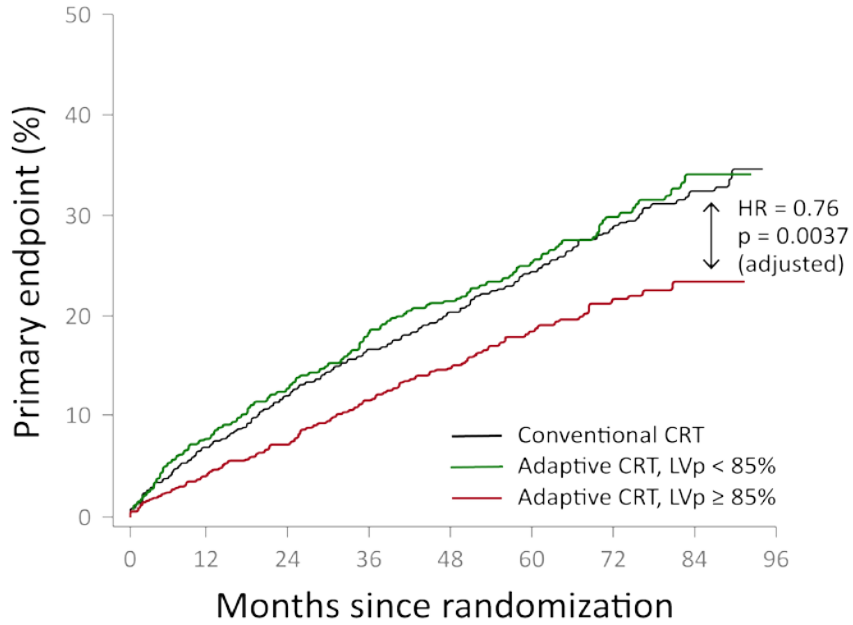
# Clinical composite score across CRT trials

AdaptResponse had the highest response rate among CRT trials reporting clinical composite score at 6 months.




Forleo, et al. *Europace*. 217;19(7):1170-77. Martin, et al. *Heart Rhythm*. 2012;9(11):1807-14. Varma, et al. *Europace*. 2021;23(10):1586-95. Jackson, et al. *J Cardiovasc Electorphysiol*. 2020;31(5):1147-54. Abraham, et al. *Am Heart J*. 2012;164(5):735-41. Rickard, et al. *Heart Rhythm*. 2022 Nov 5. Epub ahead of print. Linde, et al. *Eur J Heart Fail*. 2017;19(8):1056-63; Chung, et al. *Circulation*. 2008;117(20):2608-16.

# Primary endpoint by synchronized LV pacing




| N at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Conventional CRT | 1651 | 1476 | 1347 | 1238 | 1048 | 731 | 397 | 156 |
| Adaptive CRT, LVp < 85% | 783 | 699 | 635 | 580 | 503 | 366 | 197 | 80 |
| Adaptive CRT, LVp ≥ 85% | 874 | 809 | 760 | 700 | 595 | 394 | 198 | 75 |

- To understand the effects of synchronized LV pacing, a post-hoc analysis was performed.
- Patients with ≥85% synchronized LV pacing had a significantly (24%) lower mortality/HF rate.

% synchronized LV pacing subgroups chosen based upon the median synchronized LV pacing for the adaptive CRT group (median=84.7%).

# Limitations

- The long duration of the trial (8 years) and COVID-19 contributed to delays in reporting primary endpoints.
  - There was a delay in reporting 43 primary endpoints prior to the 3rd interim analysis; had these additional endpoints been reported in a timely fashion, the stopping boundary for futility would not have been crossed.

- A subset of highly responsive CRT-indicated patients (LBBB only) were included, and therefore results may not be applicable to broader CRT populations.

# Conclusions

- **In the largest randomized clinical trial of CRT, in patients with HF, LBBB, and intact AV conduction:**
  - A strategy of adaptive CRT did not significantly reduce the combined endpoint of all-cause mortality or intervention for heart failure decompensation.
  - Overall, patients in this trial experienced the lowest long-term mortality and the highest response rate across randomized trials of CRT.
  - Among patients with ≥85% synchronized LV pacing, there was a significant reduction in the primary endpoint that remained after covariate adjustment.

- **These results suggest a greater overall benefit of CRT in this population than previously reported.**

# Thank you participating centers and patients!

## Investigators

*AUSTRALIA* **Darlinghurst:** C. Hayward; **Heidelberg:** D. O'Donnell (former), A. Teh (Current); **Murdoch:** T. Gattorna; **New Lambton:** M. Barlow *AUSTRIA* **Innsbruck:** W. Dichtl; **Linz:** C. Steinwender *BELGIUM* **Brugge:** Y. Vandekerckhove (former), R. Tavernier (current); **Genk:** W. Mullens *CANADA* **London:** A. Tang; **Montreal:** V. Essebag; **New Westminster:** S. Tung; **Newmarket:** Y. Khaykin; **Ottawa:** D. Birnie; **Quebec:** F. Philippon; **Vancouver:** M. Bennett *DENMARK* **Odense:** J. Brock Johansen *FINLAND* **Jyväskylä:** K. Nyman; **Pori:** P. Karjalainen *FRANCE* **Amiens:** J. Hermida (former), M. Kubala (current); **Ars-Laquenexy:** M. Boursier; **Chambray lès Tours:** B. Pierre; **Clermont Ferrand:** R. Eschalier; **Corbeil-Essonnes:** M. Mahfoud; **Grenoble:** P. Defaye; **La Rochelle:** A. Milhem; **Lille:** L. Guedon-Moreau; **Lomme:** Y. Guyomar; **Marseille:** J. Deharo, A. Mechulan; **Massy:** F. Salerno; **Montpellier:** J-M. Davy (former), J-L. Pasquié (current); **Nantes:** J. Cebron; **Rennes:** C. Leclercq; **Toulouse:** P. Mondoly *GERMANY* **Bad Oeynhausen:** K. Gutleben (former). P. Sommer (current); **Bernau:** C. Butter; **Bochum:** A. Kloppe (former), A. Aweimer (current); **Chemnitz:** K. Kleinertz (former), J. Ernstberger (current); **Coburg:** J. Brachmann (former), S. Busch (current); **Dresden:** S. Spitzer; **Düsseldorf:** D-I. Shin (former), J. Schmidt (current); **Heidelberg:** E. Zitron; **Homburg-Saar:** C. Ukena; **Jena:** R. Surber; **Lübeck:** F. Bode (former), R. Tilz (current); **Lüdenscheid:** B. Lemke (former), M. Zarse (current); **Magdeburg:** R. Braun-Dullaeus; **Mönchengladbach:** I. Szendey; **München:** S. Fichtner; **Riesa:** H-H. Ebert; **Ulm:** D. Walcher (former), T. Dahme (current) *HUNGARY* **Budapest:** G.Z. Duray, B.P. Merkely *INDIA* **Delhi:** A. Saxena; **Gurgaon:** B. Singh (former), S. Mittal (current) *ITALY* **Bologna:** I. Diemberger; **Brescia:** A. Curnis; **Mantova:** A. Reggiani (former), D. Nicolis (current); **Parma:** M. Zardini (former); M.F. Notarangelo (current); **Sottomarina di Chioggia:** R. Valle; **Verona:** G. Morani (former), L. Tomasi (current) *JAPAN* **Chiba:** M. Ueda (former), Y. Kondo (current); **Yoshida-gun:** H. Tada; **Hirosaki:** S. Sasaki; **Kitakyushu:** K. Ando; **Nagoya:** Y. Inden; **Osaka:** K. Kusano; **Sendai:** K. Fukuda (former), M. Nakano (current); **Saitama:** T. Mitsuhashi (former), H. Wada (current); **Tokyo:** K. Soejima; **Toyoake:** E. Watanabe *REPUBLIC OF KOREA* **Daegu:** Y. Kim (former), H. Park (current); D. Shin; **Gyeonggi-do:** Y. Cho (former),I-Y. Oh (current),; **Seoul:** J-M. Lee (former), J-B. Kim (current); S-I. Oh; Y-K. On (former), S-J. Park (current) *MEXICO* **Leon:** S. Lara Vaca *NETHERLANDS* **Amsterdam:** J. de Groot; **Breda:** A. Alings; **Leeuwarden:** M. Feenema-Aardema; **Nijmegen:** E. Zegers; **Rotterdam:** B. Dijkman, T. Szili-Torok; **Utrecht:** M. Meine; **Zwolle:** P. Delnoy *NORWAY* **Bergen:** S. Faerestrand (former), H. Keilegavlen (current) *POLAND* **Kalisz:** M. Zielinski; **Katowice:** M. Gibinski; **Kielce:** W. Gutkowski; **Lublin:** T. Chromiński; **Rzeszow:** J. Romanek; **Zabrze:** Z. Kalarus *PORTUGAL* **Beja:** L. Duarte; **Coimbra:** L.D.V. Elvas; **Évora:** P. Dionísio *RUSSIAN FEDERATION* **Moscow:** A. Revishvili; **Novosibirsk:** A. Romanov; **St. Petersburg:** D. Lebedev *SAUDI ARABIA* **Jeddah:** N. Al Shoaibi; R. Sweidan (former), F. Bokhari (current); **Riyadh:** A. Hersi; A. Shafquat (former), B. Al Ghamdi (current) *SLOVAKIA* **Banska Bystrica:** G. Kaliska; **Bratislava:** P. Margitfalvi *SPAIN* **Badajoz:** J. García Guerrero, J. Fernández de la Concha-Castañeda; **Burgos:** J. Garcia Fernandez; **El Palmar Murcia:** A. García Alberola; **Granada:** L. Tercedor; **Salamanca:** J. Jiménez Candil; **Santa Cruz de Tenerife:** R. Romero Garrido (former), J.S. Hernández Afonso (current); **Sevilla:** A. 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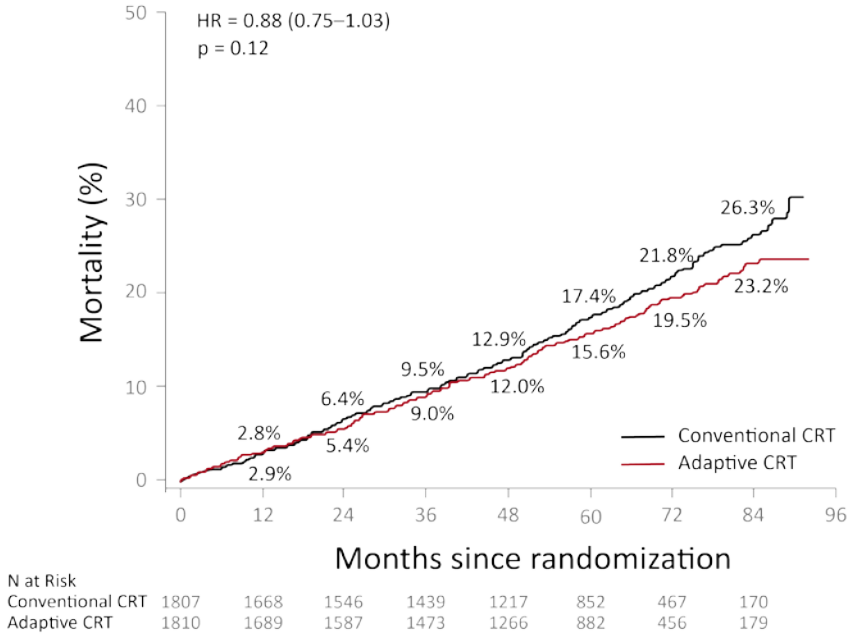
# Thank you study committees!

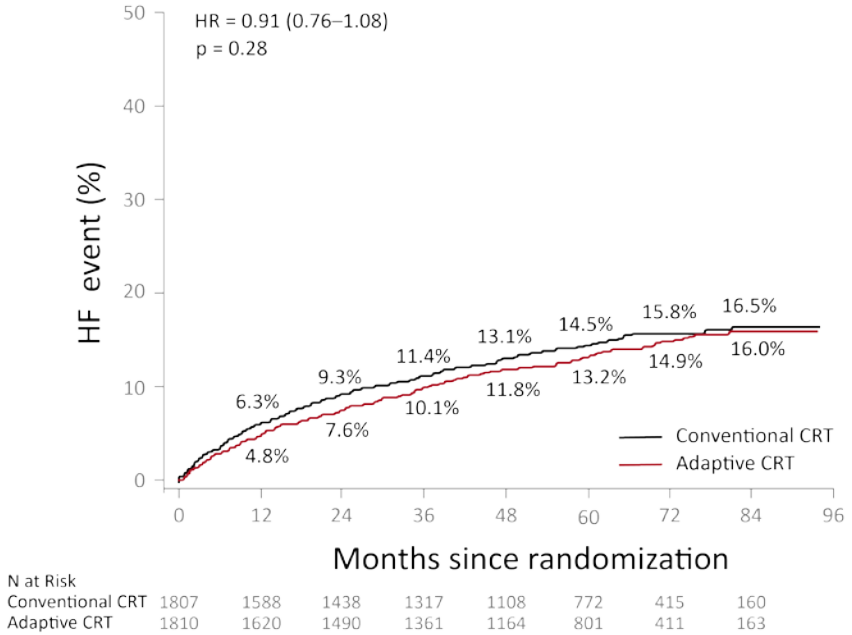
| Committee | Members |
|---|---|
| **Steering Committee** | Bruce L. Wilkoff, MD, Chair, Cleveland Clinic, Cleveland, OH, USA; Gerasimos Filippatos, MD, Co-chair, National and Kapodistrian University of Athens, Athens, Greece; David Birnie, MD, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; Michael R. Gold, MD, Medical University of South Carolina, Charleston, SC, USA; Ahmad Hersi, MD, King Saud University, College of Medicine, Department of Cardiac Sciences, Riyadh, Saudi Arabia; Kengo Kusano, MD, National Cerebral and Cardiovascular Center, Osaka, Japan; Christophe Leclercq, MD, University Hospital Rennes, University of Rennes, Rennes, France;William Little, MD†, University of Mississippi, Jackson, MS, USA, †deceased 9 July 2015; Wilfried Mullens, MD, Ziekenhuis Oost-Limburg, Genk, Belgium. |
| **Data Monitoring Committee** | John Cleland, MD, Chair, University of Glasgow, Glasgow, UK; Kenneth Dickstein, MD, Stavanger Universitetssykehus, Stavanger, Norway; Kerry Lee, PhD, Professor of Biostatistics, Duke Clinical Research Institute, Durham, NC, USA; Jonathan Steinberg, MD, Summit Medical Group Arrhythmia Institute, University of Rochester School of Medicine, Short Hills, NJ, USA. |
| **Endpoint Adjudication Committee** | Michael Felker, MD, Chair, Duke University School of Medicine, Duke University West Campus, Durham, NC, USA; Piotr Ponikowski, MD, Medical University, Military Hospital, Department of Cardiology, Wroclaw, Poland; Frieder Braunschweig, MD, Karolinska University Hospital, Department of Cardiology, Stockholm, Sweden; Daniel Lustgarten, MD, Cardiovascular Medicine, University of Vermont Medical Center, Burlington, VT, USA; John Teerlink, MD, San Francisco VA Medical Center Cardiology, San Francisco, CA, USA; John Lekakis, MD, Cardiology, Athens University Medical School, University Hospital Attikon, Athens, Greece; Harold Schaefer, MD, Department of Cardiology, Catholic Clinic Essen, Essen, Germany |
| **ECG Core Lab** | Christophe Leclercq, MD, Clinical Investigation Centre for Innovative Technology Network, University of Rennes, Rennes, France. |

# Primary endpoint components

No significant differences observed between groups for mortality or intervention for HF decompensation.

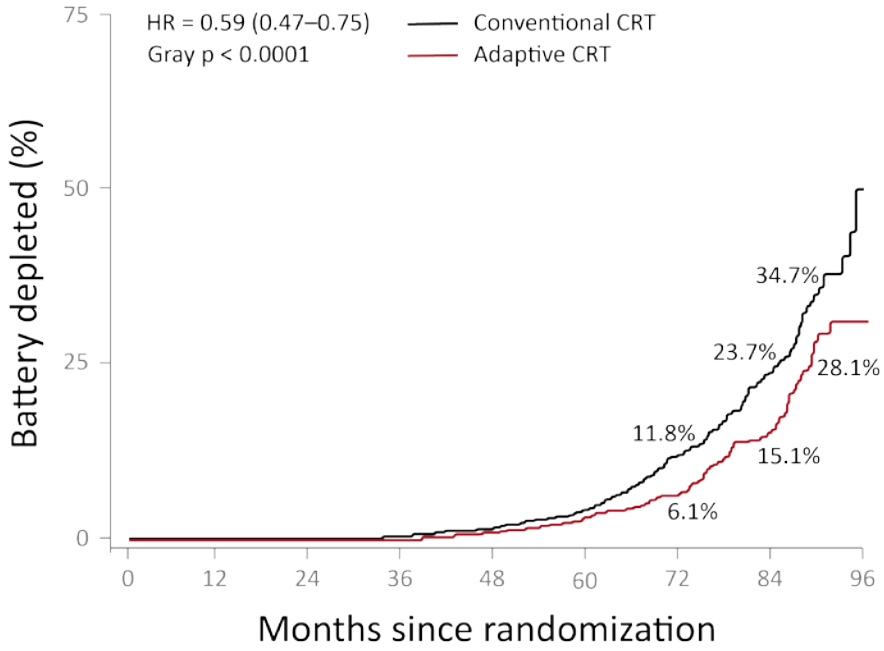



Overall mortality rate across both arms 16.5% through 5 years.




Overall HF event rate across both arms 13.8% through 5 years.

# Device battery longevity




The adaptive CRT group experienced a 41% lower rate of device replacements for battery depletion through over 8 years follow-up.