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The 3rd Conference on
Clinical Studies with Medical Devices and IVDs

Investigator-Sponsored Studies supporting Market Access

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Who am I?

- ✓ MSc in Experimental Psychology
- ✓ PhD in Health Sciences
- ✓ University of Maastricht:
  - ✓ 9 years research for pharmaceutical and governments to assess the adverse effects of drugs on cognition, motor behavior and actual car driving
- ✓ Medtronic:
  - ✓ 14 years in clinical research with increasing managerial responsibilities
- ✓ St Jude Medical, later acquired by Abbott:
  - ✓ 8 years leading the clinical in-house and field organization
  - ✓ 5 years Medical Affairs Director for Heart Failure, Cardiac Arrhythmias and Electrophysiology
- ✓ Present: Independent Consultant, Medical and Clinical Affairs

Disclaimer

This presentation was prepared by Hindrik Robbe in his personal capacity. The opinions expressed are the author's own and do not necessarily reflect the view of his previous employers.

Essential Pillars of Market Access

To gain Market Access for a Medical Device, Clinical Evidence is crucial for demonstrating the safety, efficacy, and performance of the product c.q. therapy

NB Regulatory approval does not imply market access!

High rating in International Guidelines facilitate market access

I	Evidence from at least one large randomized controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity
II	Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts' opinions

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

Not every new device provides a new therapy

In medical devices there are many re-iterations of devices, often with only small incremental enhancements

Enhancements usually come at a higher price

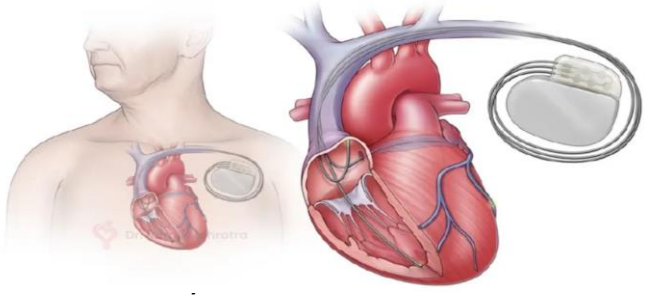
- ✓ **After a new device has received regulatory approval, companies like to charge higher prices for the incremental feature(s) c.q. benefit**

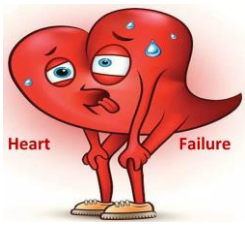
- ✓ **To support the higher price, evidence is needed to demonstrate that the higher price comes with clinically relevant improvements and/or cost savings**
- ✓ **Typically, reimbursement and clinical groups are then requested to provide the evidence for the incremental benefit and similar or better cost-effectiveness**

Example of our Approach

New, quadripolar, pacing lead for cardiac resynchronization (CRT) in Heart Failure (HF)

What is Heart Failure?

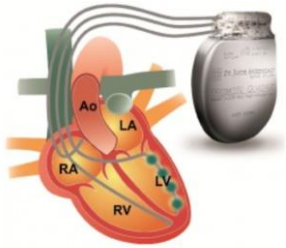




- ✓ **A large proportion of patients have so-called cardiac dissynchronization, i.e. the left and right heart do not pace in synchrony**
- ✓ **Triple-chamber pacing is applied for Cardiac Resynchronization (CRT)**
- ✓ **Whereas the RA and RV leads are placed inside the heart, the LV lead is placed in a cardiac vein on the outside of the left ventricle**

Cardiac Resynchronization in Heart Failure

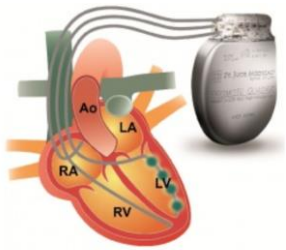
- ✓ **CRT has been proven to improve symptoms and survival in HF patients with dissynchrony.**
- ✓ **The standard at that time was a bipolar LV lead, but there were a few drawbacks:**
  - ✓ **Sometimes the lead dislodged soon after implantation**
  - ✓ **Sometimes it was not possible to place the lead at the optimal location due to anatomy of the cardiac veins or existing scar**
  - ✓ **Sometimes pacing on the left side led to phrenic nerve stimulation**
- ✓ **The quadripolar lead had the potential for better fixation in the cardiac vein with more options to choose the optimal pacing location (due to the four electrodes)**
- ✓ **The lead received CE mark in October 2009**
- ✓ **Multipoint Pacing (MPP) received CE mark in June 2013**



Placing of CRT electrodes -- one in right atrium (RA), one in right Ventricle (RV). The third electrode gives off its pulse energy to the left ventricle (LV) muscles via four poles (Ao = Aorta, LA – Left Atrium). Courtesy of St Jude Medical.

Marketing intended Claims

- ✓ **Quartet™ lead**
  - ✓ **is easier to implant, i.e. fewer repositions**
  - ✓ **has better chance of being able to pace at the optimal site (as a result of more electrode choices)**
  - ✓ **lowers adverse events (reinterventions, phrenic nerve stim)**
  - ✓ **results in better hemodynamics**
  - ✓ **results in higher CRT responder rate**
  - ✓ **Improves survival**
- ✓ **Thus, basically the value message is more successful implantation and better patient outcomes**



Placing of CRT electrodes -- one in right atrium (RA), one in right Ventricle (RV). The third electrode gives off its pulse energy to the left ventricle (LV) muscles via four poles (Ao = Aorta, LA – Left Atrium). Courtesy of St Jude Medical.

Marketing was asking for clinical evidence to support the value proposition for the lead

The problem was that demonstrating small, but clinically relevant, incremental improvements, usually require very large (randomized) clinical studies

This will take many years for completion

(preparation, enrolment, follow-up, analyses, publication, reimbursement dossier)

Yet some physicians always like to try new technologies and/or wish to be amongst the first to publish about the new device c.q. therapy

Opportunity: 2-track clinical evidence generation pathway

Short Term:
Investigator-sponsored

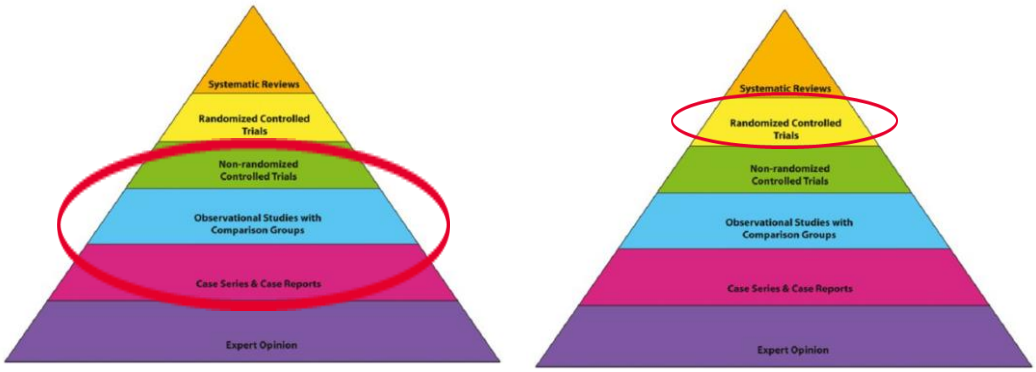
- Small observational studies, little burden for company, relatively low costs
- Focusing on earlier endpoints (e.g. implant success, avoidance of reinterventions, contractility)
- Results available in shorter time frame

Long-Term:
Company-sponsored

- RCT focusing on patient outcomes (e.g. QoL, hospitalizations, mortality)
- Large sample size, labor-intensive, expensive
- Results available after many years

Both types will be complimentary in the Hierarchy of Clinical Evidence

Investigator-Sponsored *vs* **Company-Sponsored**



Thus, while the large RCT is ongoing, the Investigator-Sponsored Studies can already create enthusiasm for the new therapy and create traction in the market

Investigator-Sponsored Studies (terminology)

Terms I have seen:

- Physician-Initiated Trials (PIT)
- External Research Programs (ERP)
- Investigator-Initiated Studies (IIS)
- Investigator-Sponsored Studies (ISS)

Yet "initiated" is not the same as "sponsored"

And "funding" is not the same as "sponsoring"

ISS – Criteria for Review

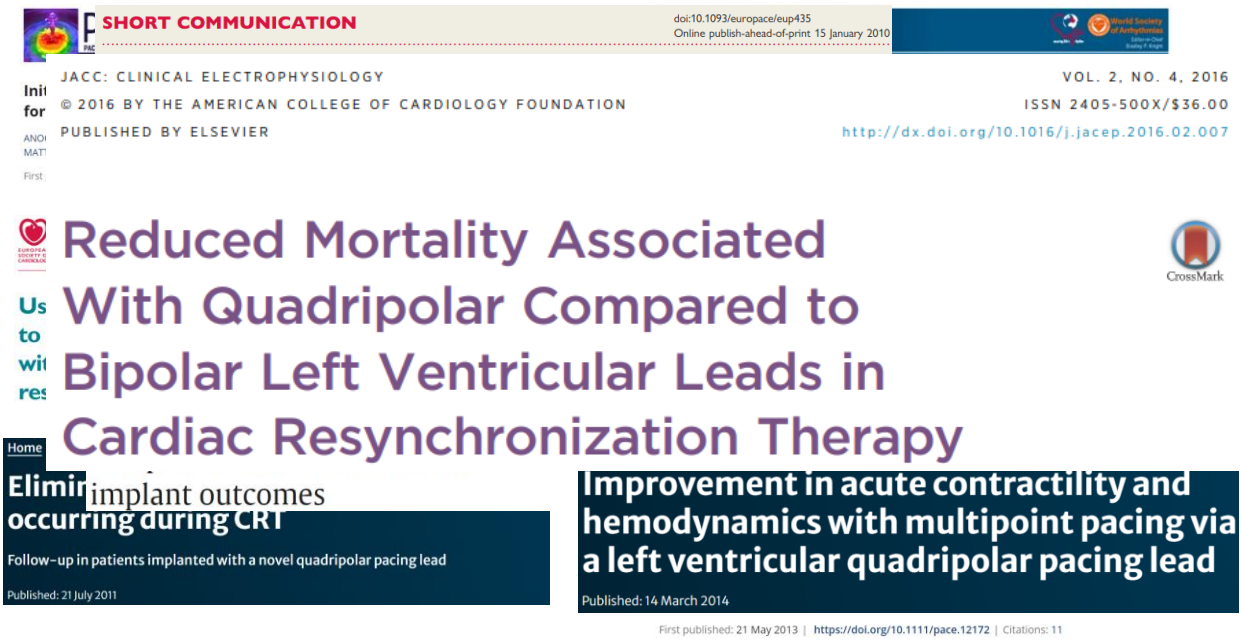
- ✓ **Scientific merit**
- ✓ **Originality of proposal**
- ✓ **Study design (sample size, endpoints)**
- ✓ **Study feasibility (resources, patient pool)**
- ✓ **Strategic fit**
- ✓ **Risk/benefit**
- ✓ **Applicant's qualification/reputation**
- ✓ **Budget**

ISS Execution

- ✓ Investigator:
  - ✓ Study documents
  - ✓ Ethics approval
  - ✓ Study conduct
  - ✓ Analyses and reporting
- ✓ Company:
  - ✓ Agreement
  - ✓ Funding
  - ✓ Monitoring progress against predefined milestones

What happened?

- ✓ Many ISS were initiated shortly after CE approval for the lead, starting in 2010, mainly focusing on short-term benefits, such as ease of implant, better acute hemodynamics
- ✓ Two large company-sponsored RCTs were conducted between 2011 and 2022



SHORT COMMUNICATION

doi:10.1093/europace/eup435
Online publish-ahead-of-print 15 January 2010

JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. 2, NO. 4, 2016

PUBLISHED BY ELSEVIER
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http://dx.doi.org/10.1016/j.jacep.2016.02.007

Reduced Mortality Associated With Quadripolar Compared to Bipolar Left Ventricular Leads in Cardiac Resynchronization Therapy

Home

Elimi implant outcomes occurring during CRT

Follow-up in patients implanted with a novel quadripolar pacing lead

Published: 21 July 2011

Improvement in acute contractility and hemodynamics with multipoint pacing via a left ventricular quadripolar pacing lead

Published: 14 March 2014

First published: 21 May 2013 | https://doi.org/10.1111/pace.12172 | Citations: 11

Results from the Investigator-Sponsored Studies

- ✓ **Studies demonstrated that using the quadripolar lead:**
  - ✓ **Led to successful implantations in patients in whom bipolar leads failed to be implanted**
  - ✓ **Provided intra-operative options to avoid phrenic nerve stimulation**
  - ✓ **Provided more pacing options in case lead could not be placed at optimal site**
  - ✓ **Led to better cardiac contractility and hemodynamic response**
- ✓ **One study (based on nationwide data from implant registration records) even demonstrated improved survival with the quadripolar lead !!**

Company-sponsored Studies

- ✓ **MORE-CRT** — Published 2016
  - ✓ **N=1,078 randomized study of quadripolar lead vs other companies' bipolar leads**
  - ✓ **Endpoint: lead-related events during and after implantation up to 6 months**
- ✓ **MORE-CRT MPP (Phase I)** MPP=multipoint pacing (programming at physician's discretion) — Published 2019
  - ✓ **N=1,921 implanted and all stimulated in conventional bipolar mode**
  - ✓ **N=544 non-responders @6 months were randomized to continued bipolar vs quadripolar pacing therapy for the next 6 months.**
  - ✓ **Endpoint: conversion rate from non-responder to responder**
- ✓ **MORE-CRT MPP (Phase II) with prescribed MPP programming** — Published 2023
  - ✓ **N=3,929 + 1,921 from Phase I (1,111 randomized)**
  - ✓ **Endpoint: conversion rate from non-responder to responder**

MORE-CRT

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Cardiac Resynchronization Therapy With a Quadripolar Electrode Lead Decreases Complications at 6 Months

Results of the MORE-CRT Randomized Trial

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ABSTRACT

OBJECTIVES The aim of this study was to test the hypothesis that a quadripolar left ventricular (LV) lead results in fewer LV lead-related events than a bipolar cardiac resynchronization therapy (CRT) system in a prospective randomized trial.

BACKGROUND Bipolar LV leads cannot be implanted at the optimal site in up to 10% of patients who need CRT, because of anatomic or technical challenges (pacing threshold, phrenic stimulation, or mechanical instability).

METHODS The MORE-CRT (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges) trial enrolled 1,078 patients. Patients with indications for CRT defibrillator therapy were randomized into 2 groups in a 1:2 ratio: a group with a bipolar CRT lead system (the BiP group; any manufacturer) and a group with a quadripolar CRT system (the Quad group; Quartet LV lead). The primary endpoint was freedom from a composite endpoint of intraoperative and post-operative LV lead-related events at 6 months.

RESULTS A total of 1,074 of 1,078 patients (99%) were randomized and contributed to the primary endpoint. Freedom from the composite endpoint was significantly greater in the Quad than the BiP group (83.0% vs. 74.4%, p = 0.0002). The intraoperative component of the endpoint was met less frequently by Quad group patients (6.26% Quad vs. 12.1% BiP), whereas there was no difference for the post-operative component (7.1% Quad vs. 7.6% BiP).

CONCLUSIONS The Quartet LV system significantly reduced total LV lead-related events at 6 months after implantation compared with a bipolar CRT system. The reduction in events demonstrates the superiority of this quadripolar technology to effectively manage CRT patients. (More Options Available With a Quadripolar LV Lead Provide In-Clinic Solutions to CRT Challenges [MORE-CRT]; NCT01510652) (J Am Coll Cardiol EP 2016;2:212-20)

MORE-CRT MPP (Phase I)

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 2979–2987
doi:10.1093/eurheartj/ehz109

CLINICAL RESEARCH
Arrhythmia/electrophysiology

Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I

Christophe Leclercq[1]*, Haran Burri[2], Antonio Curnis[3], Peter Paul Delnoy[4], Christopher A. Rinaldi[5], Johannes Sperzel[6], Kwangdeok Lee[7], Leonardo Calò[8], Alfredo Vicentini[9], Joaquin Fernandez Concha[10], and Bernard Thibault[11]; on behalf of the MORE-CRT MPP Investigators

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Aims	To assess the impact of MultiPoint™ Pacing (MPP)—programmed according to the physician's discretion—in non-responders to standard biventricular pacing after 6 months.
Methods and results	The study enrolled 1921 patients receiving a quadripolar cardiac resynchronization therapy (CRT) system capable of MPP™ therapy. A core laboratory assessed echocardiography at baseline and 6 months and defined volumetric non-response to biventricular pacing as <15% reduction in left ventricular end-systolic volume (LVESV). Clinical sites randomized patients classified as non-responders in a 1:1 ratio to receive MPP (236 patients) or continued biventricular pacing (231 patients) for an additional 6 months and evaluated rate of conversion to echocardiographic response. Baseline characteristics of both groups were comparable. No difference was observed in non-responder to responder conversion rate between MPP and biventricular pacing (31.8% and 33.8%, $P = 0.72$). In the MPP arm, 68 (29%) patients received MPP programmed with a wide LV electrode anatomical separation (≥30 mm) and shortest LV1–LV2 and LV2–RV timing delays (MPP-AS); 168 (71%) patients received MPP programmed with other settings (MPP-Other). MPP-AS elicited a significantly higher non-responder conversion rate compared to MPP-Other (45.6% vs. 26.2%, $P = 0.006$) and a trend in a higher conversion rate compared to biventricular pacing (45.6% vs. 33.8%, $P = 0.10$).
Conclusions	After 6 months, investigator-discretionary MPP programming did not significantly increase echocardiographic response compared to biventricular pacing in CRT non-responders.
Keywords	MultiPoint Pacing • MPP • Heart failure • Biventricular pacing • Cardiac resynchronization • Randomized controlled study • Quadripolar left ventricular pacing

MORE-CRT MPP (Phase II)

ESC European Society of Cardiology
Europace (2023) **25**, 1–11
https://doi.org/10.1093/europace/euad294

CLINICAL RESEARCH

Cardiac resynchronization therapy non-responder to responder conversion rate in the MORE-CRT MPP trial

Christophe Leclercq [1]*, Haran Burri [2], Peter Paul Delnoy[3], Christopher A. Rinaldi [4], Johannes Sperzel[5], Leonardo Calò [6], Joaquin Fernandez Concha [7], Antonio Fusco[8], Faisal Al Samadi[9], Kwangdeok Lee[10], and Bernard Thibault[11] on behalf of the MORE-CRT MPP Investigators

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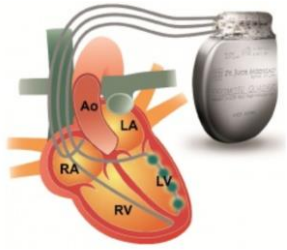
Received 9 May 2023; editorial decision 26 July 2023; accepted after revision 26 July 2023; online publish-ahead-of-print 30 September 2023

Aims	To assess the impact of MultiPoint™ Pacing (MPP) in cardiac resynchronization therapy (CRT) non-responders after 6 months of standard biventricular pacing (BiVP).
Methods and results	The trial enrolled 5850 patients who planned to receive a CRT device. The echocardiography core laboratory assessed CRT response before implant and after 6 months of BiVP; non-response to BiVP was defined as <15% relative reduction in left ventricular end-systolic volume (LVESV). Echocardiographic non-responders were randomized in a 1:1 ratio to receive MPP (541 patients) or continued BiVP (570 patients) for an additional 6 months and evaluated the conversion rate to the echocardiographic response. The characteristics of both groups at randomization were comparable. The percentage of non-responder patients who became responders to CRT therapy was 29.4% in the MPP arm and 30.4% in the BiVP arm ($P = 0.743$). In patients with ≥30 mm spacing between the two left ventricular pacing sites (MPP-AS), identified during the first phase as a potential beneficial subgroup, no significant difference in the conversion rate was observed.
Conclusion	Our trial shows that ~30% of patients, who do not respond to CRT in the first 6 months, experience significant reverse remodelling in the following 6 months. This finding suggests that CRT benefit may be delayed or slowly incremental in a relevant proportion of patients and that the percentage of CRT responders may be higher than what has been described in short-/middle-term studies. MultiPoint™ Pacing does not improve CRT response in non-responders to BiVP, even with MPP-AS.

What happened with the Marketing Claims?

- ✓ Quartet™ lead
  - ✓ is easier to implant, i.e. fewer repositions
  - ✓ has better chance of being able to pace at the optimal site (as a result of more electrode choices)
  - ✓ lowers adverse events (reinterventions, phrenic nerve stim)
  - ✓ results in better hemodynamics
  - ✓ results in higher CRT responder rate
  - ✓ Improves survival
- ✓ Thus, basically the value message is now more successful implantation, fewer adverse events and providing more alternatives if patient symptoms do not improve



Placing of CRT electrodes -- one in right atrium (RA), one in right Ventricle (RV). The third electrode gives off its pulse energy to the left ventricle (LV) muscles via four poles (Ao = Aorta, LA – Left Atrium). Courtesy of St Jude Medical.

Conclusions

- ✓ Clinical Evidence is key for supporting Market Access
- ✓ In case large, long-lasting, RCTs are required, Investigator-Sponsored Studies can 'pave the way' for the device
- ✓ In this example, the ISS demonstrated many short-term advantages of the quadripolar lead, but the RCTs failed to prove benefit on hard endpoints such as all-cause mortality
- ✓ Despite 'failure' of the RCTs, the strategy of ISS and RCTs has been successful: the quadripolar lead is widely used in CRT