Cardiac resynchronization therapy

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Stockholm

Sweden

11 mill inhabitants
Public health care
7 university hospitals

Disclosure Cecilia Linde

Research grants to institution from Astra Zeneca, Roche Diagnostics, Swedish Heart-Lung foundation, Swedish Academy of Science and Stockholm County Council

Speaker honoraria from Medtronic, Abbot, Novartis, Vifor, Impulse-Dynamics, Bayer, Astra Zeneca, Boehringer-Ingelheim

Cardiac resynchronisation therapy in patients with HF and QRS prolongation/LBBB

Disease modifying and life-saving

- Improves survival
- Reduces heart failure hospitalisations
- Through reverse remodelling

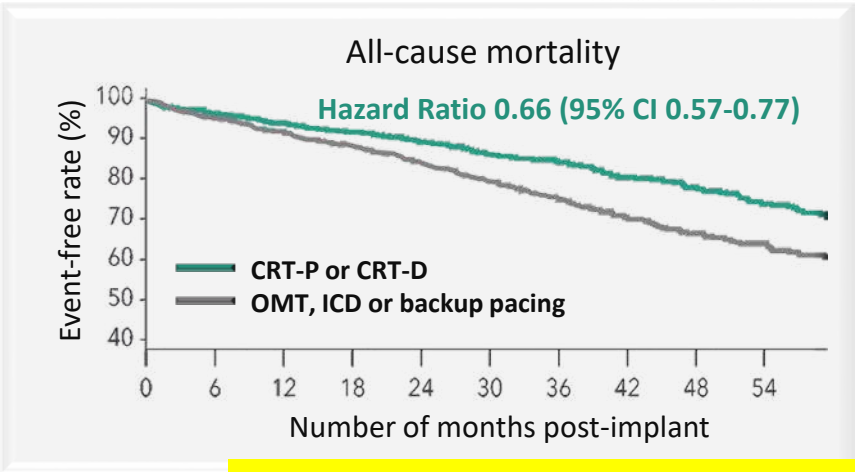
Improves symptoms

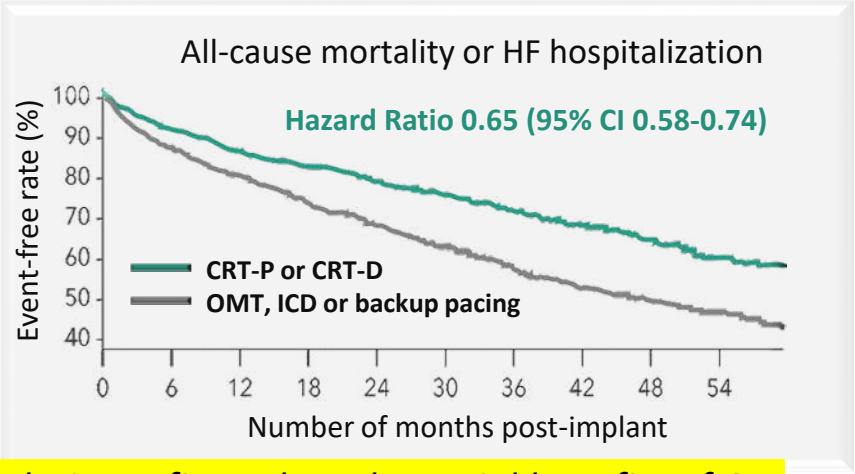
- And improves exercise tolerance, quality of life

Applicable in 20% of HFrEF-patients in NYHA II-IV
but only about 1 in 5 gets therapy

CRT reduces total mortality and HF hospitalizations *in all randomised trials*

Meta-analysis of 3872 patients in 5 RCT:NYHA II-IV HF in *sinus rhythm randomized to CRT vs control*

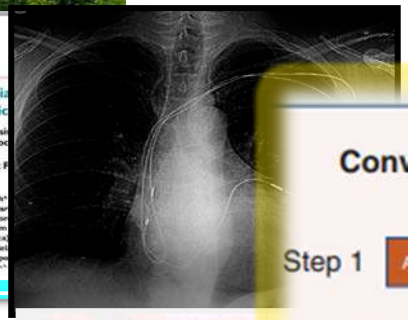




*"This **individual patient data** meta-analysis confirms the substantial benefits of CRT on morbidity and mortality in patients with mild, moderate, or severe HF symptoms who have left ventricular systolic dysfunction, **are in sinus rhythm, and have a prolonged QRS**."*

Cleland JG et al. *Eur Heart J.* 2013;34:3547-56

What do the 2021 ESC HF guidelines say?



Management of patients with HFrEF

- ACE-I/ARNI
- Beta-blocker
- MRA
- Dapagliflozin/Empagliflozin

Conventional Sequencing

Step 1 — ACE inhibitor or angiotensin receptor blocker

Step 2 — Beta-blocker

Step 3 — Mineralocorticoid receptor antagonist

Step 4 — Angiotensin receptor neprilysin inhibitor

Step 5 — SGLT2 inhibitor

Uptitration to target doses at each step
Typically requires 6 months or more

Rapid Sequencing

Step 1 — Beta-blocker + SGLT2 inhibitor

Step 2 — Angiotensin receptor neprilysin inhibitor

Step 3 — Mineralocorticoid receptor antagonist

All 3 steps achieved within 4 weeks
Uptitration to target doses thereafter

SR and LVEF ≤35% and QRS ≥130 ms

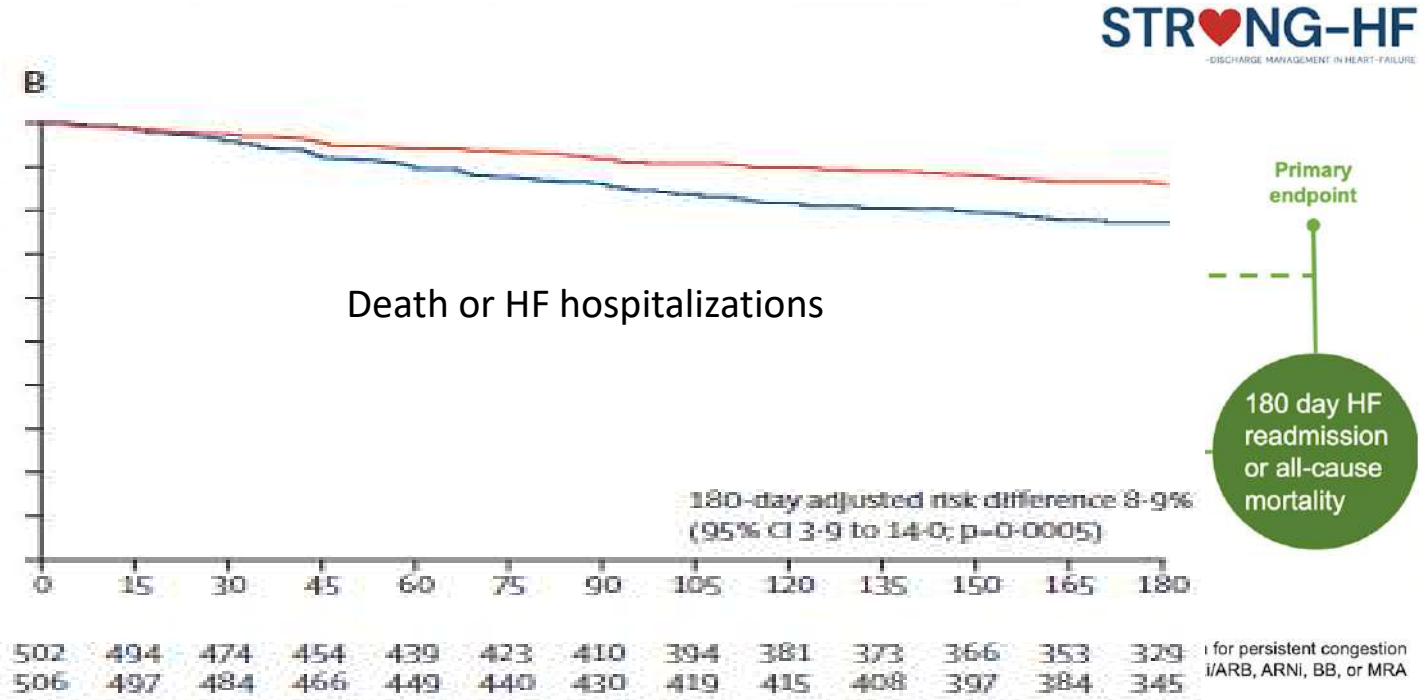
CRT-D[b]/-P

130-149 ms (Class IIa) QRS ≥150 ms (Class I)

ESC

EHRA 2024

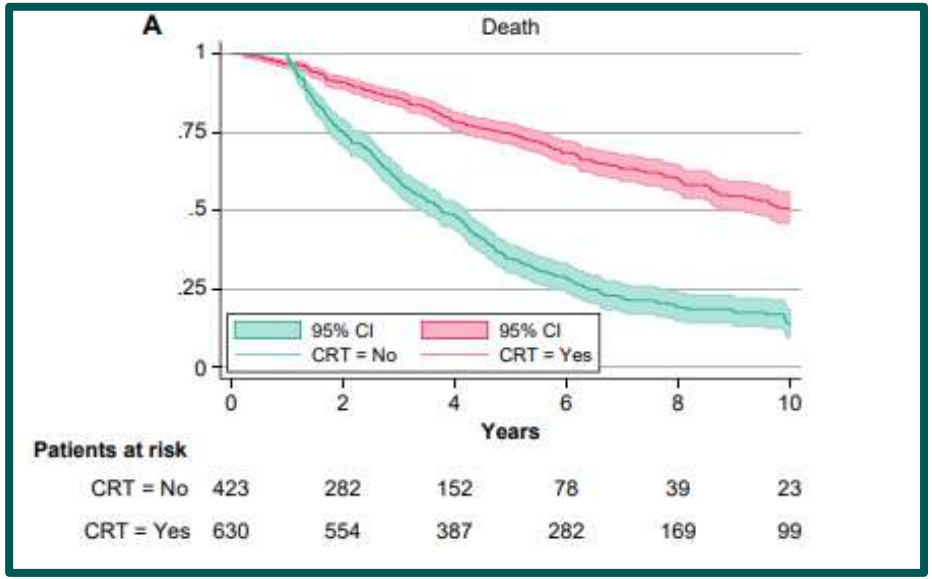
Heart failure medication need to be introduced rapidly

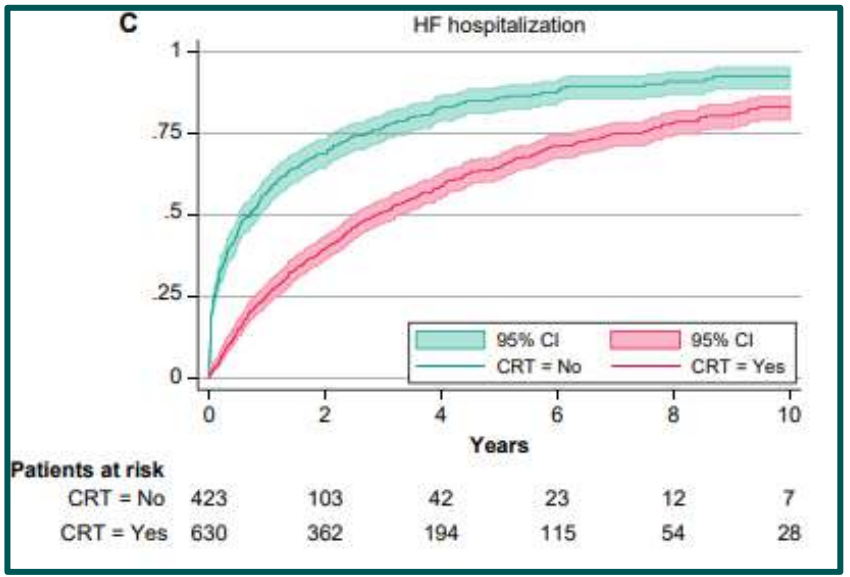


https://www.cfrjournal.com/video-index/aha-22-late-breaker-discussion-strong-hf-trial

CRT needs to be introduced rapidly to obtain the best results and modify heart failure

The outcome of LBBB patients with HF in Stockholm who received CRT vs those who did not





Delay time ***from CRT*** *implantation from indication* (**LBBB on ECG)** was 137 (35–378) days or **4.5 months**.

Delay was associated with higher mortality and more HF hospitalizations

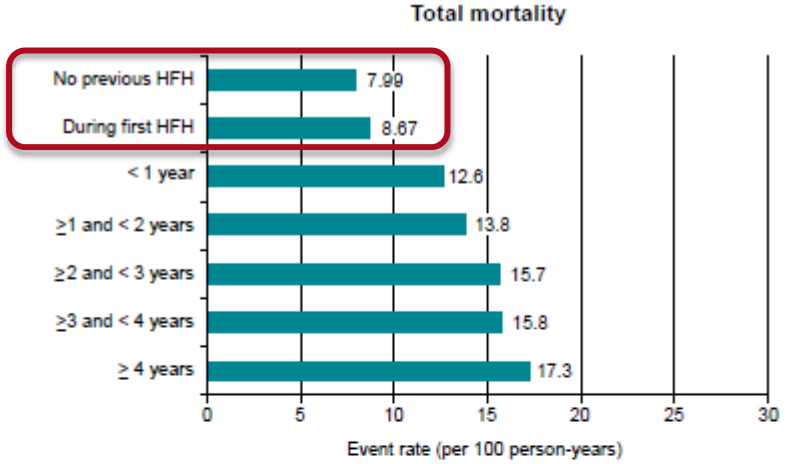
Gatti P et al Europace (2023) 25, 1–12

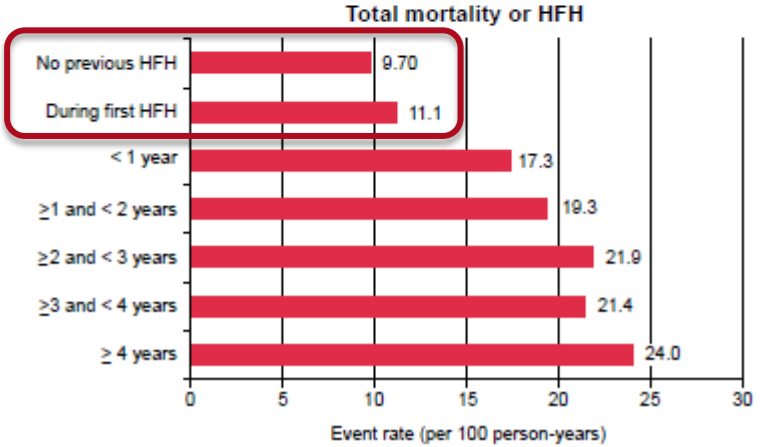
Timing of CRT implantation in UK

ESC European Society of Cardiology
Europace (2023) 00, 1–10
https://doi.org/10.1093/europace/euad059
CLINICAL RESEARCH

Timing of cardiac resynchronization therapy implantation

Francisco Leyva [1]*, Abbasin Zegard [1,2], Peysh Patel [2], Berthold Stegemann [1,2], Howard Marshall [2], Peter Ludman [2], Jamie Walton [2], Joseph de Bono [2], Giuseppe Boriani [3], and Tian Qiu [2]





Best outcome if CRT was implanted early in a British nationwide registry

Recommendations for cardiac resynchronization therapy in patients in sinus rhythm (1)

And left bundle branch block LBBB

Recommendations	Class	Level
LBBB QRS morphology		
CRT is recommended for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality.	I	A
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration 130–149 ms and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality.	IIa	B

CRT = cardiac resynchronization therapy; HF = heart failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; SR = sinus rhythm.

2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab364)

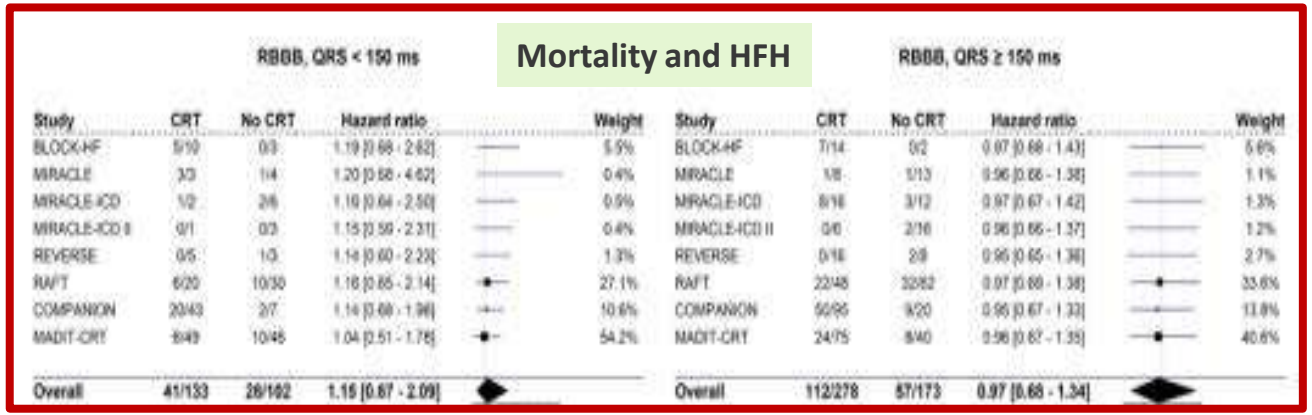
QRS Width and Bundle branch block morphology

- QRS width was the inclusion criteria in RCT
- 65% in RCT had LBBB
- 10% had RBBB meaning there is little evidence in each RCT
- 25% intraventricular conduction disturbance

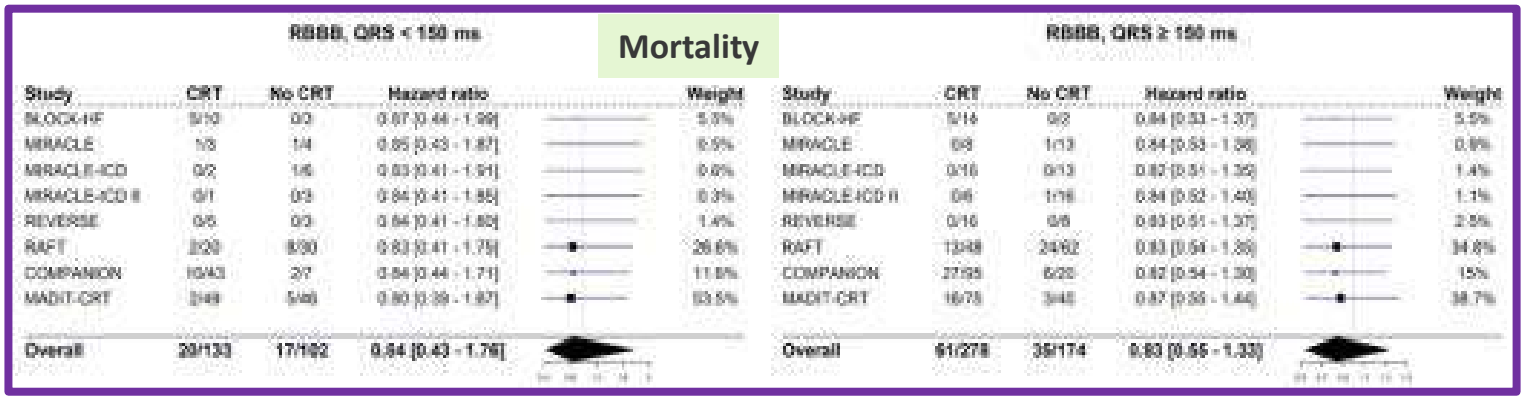
Individual patient based meta-analysis of 8 randomized trials

no benefit of CRT in RBBB

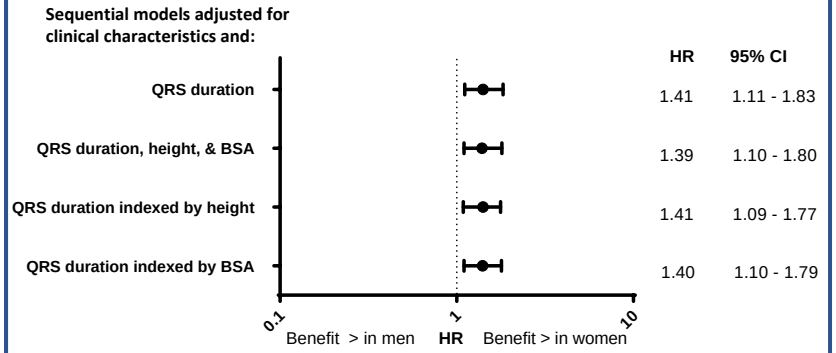
Friedman D et al Circulation. 2023;147:812–823.



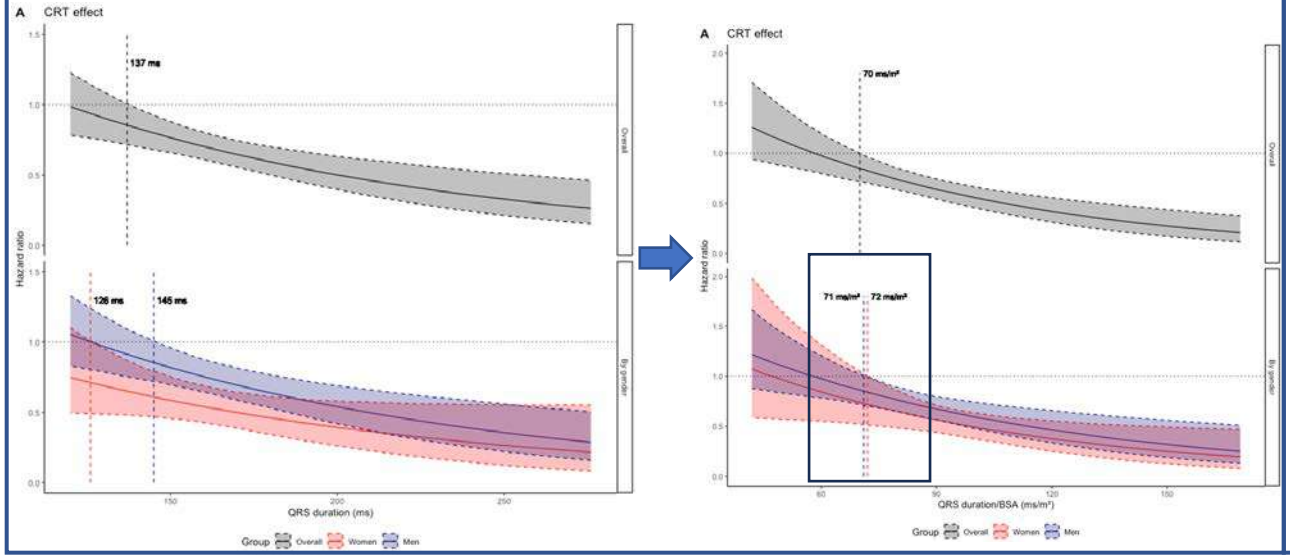
LBBB n=4549
IVCD n=1024
RBBB n=691



	Women (N=1,439)	Men (N=4,189)
QRS, ms	160 (146, 172)	160 (140, 175)
BSA, m^2	1.76 (1.62, 1.90)	2.02 (1.89, 2.16)
Height, m	1.62 (1.57, 1.65)	1.75 (1.70, 1.80)



QRS Duration Threshold for CRT Benefit Before (**left**) & After (**right**) Accounting for Body Size



Summary

- Women have similar QRS durations compared with men despite smaller bodies (**upper left**)
- Women have greater magnitude of CRT benefit compared with men, independent of body size (**upper right**)
- Differences in body size may partially explain sex-specific QRS duration thresholds for CRT benefit (**left**)
- Indexing QRS duration for body size may improve patient selection for CRT, particularly among patients with "borderline" QRS duration

Graphical Abstract

Friedman DJ et al Heart Rhythm 2024

1 million PMs or ICDs are implanted/ year worldwide.

Nearly 30% develop LV systolic dysfunction due to RV pacing

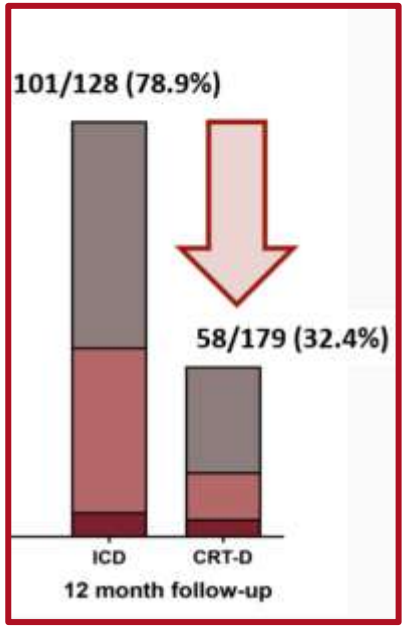
which may lead to heart failure and hospitalisations

But upgrading to CRT or CSP had little scientific evidence

Results of BUDAPEST-CRT Upgrade study

Patients witnh Pacing induced cardiomyopathy randomised to upgrade to ICD or CRTD

Primary endpoint

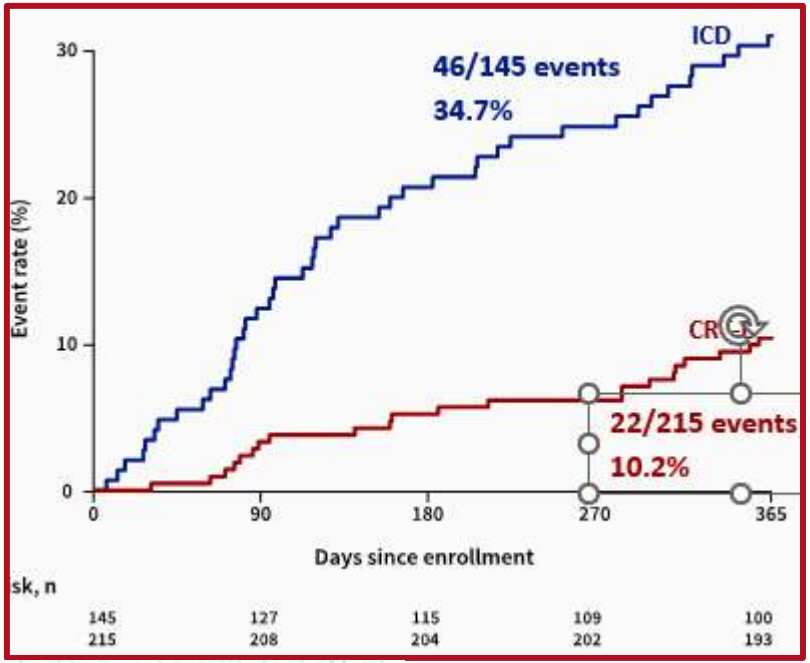


*OR 0.13
(95% CI 0.08-0.22);
p<0.001

Adjusted OR 0.11
(95% CI 0.06-0.19);
p<0.001

NNT= 2.2

Secondary of HFH/total mortality



HR 0.28, 95%CI
0.17-0.46; p<0.001

Adjusted HR 0.27,
95%CI 0.16-0.47;
p<0.001

NNT= 4.7

All-cause mortality HF hospitalization <15% reduction of LVESV

Merkely B et al Eur Heart J. 2023 Oct 21;44(40):4259-4269

Response rates


ESC European Society of Cardiology

European Journal of Heart Failure (2020)

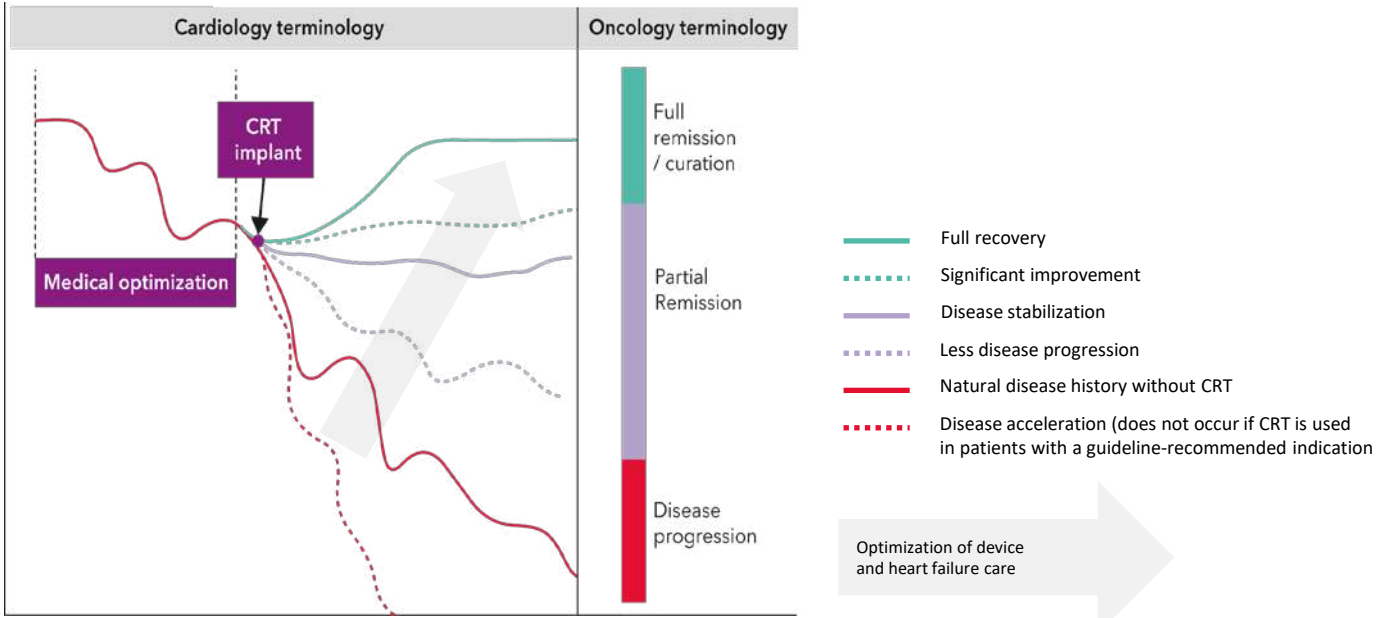
POSITION PAPER

Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care

A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology

Wilfried Mullens[1,2]*, Angelo Auricchio[3], Pieter Martens[1,2], Klaus Witte[4], Martin R. Cowie[5], Victoria Delgado[6], Kenneth Dickstein[7], Cecilia Linde[8], Kevin Vernooy[9,10], Francisco Leyva[11], Johann Bauersachs[12], Carsten W. Israel[13], Lars H. Lund[14], Erwan Donal[15], Giuseppe Boriani[16], Tiny Jaarsma[17,18], Antonio Berruezo[19], Vassil Traykov[20], Zaheer Yousef[21], Zbigniew Kalarus[22], Jens Cosedis Nielsen[23], Jan Steffel[24], Panos Vardas[25], Andrew Coats[26], Petar Seferovic[27], Thor Edvardsen[28], Hein Heidbuchel[29], Frank Ruschitzka[30], and Christophe Leclercq[15]

Role of cardiac resynchronization therapy in modifying the heart failure disease trajectory



CRT should be classified as a treatment for 'disease modification'.

A slowing of a progressive disease is a positive outcome.

Mullens W et al. *Eur J Heart Fail.* 2020;22:2349-69; Mullens W et al. *Europace.* 2021;23:1324-42

5-year analysis of the REVERSE trial

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. ■, NO. ■, 2021

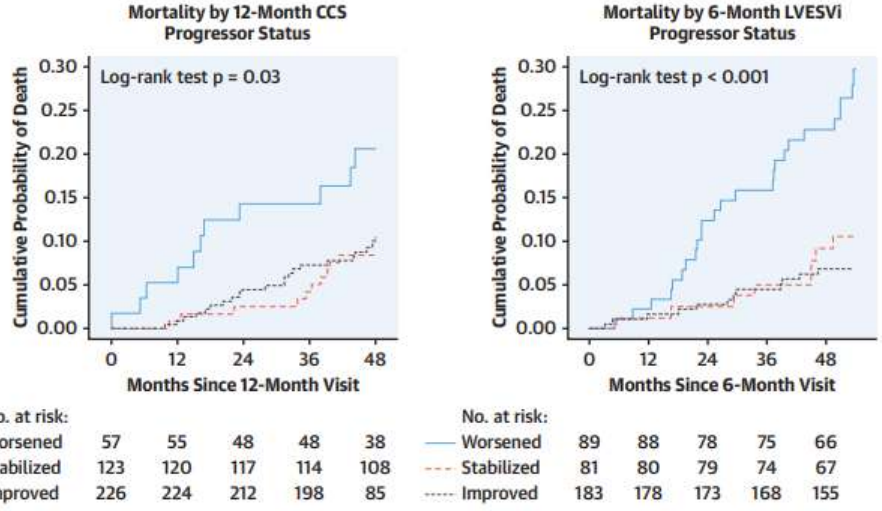
Redefining the Classifications of Response to Cardiac Resynchronization Therapy

Results From the REVERSE Study

Michael R. Gold, MD, PhD,[a] John Rickard, MD, MPH,[b] J. Claude Daubert, MD,[c] Patrick Zimmerman, PhD,[d] Cecilia Linde, MD, PhD[e]

CENTRAL ILLUSTRATION Responder Classification and Mortality by Progressor Status

12-Month CCS Responder Classification	6-Month LVESVi Responder Classification
56% Improved	*52% Improved*
30% Stabilized	*23% Stabilized*
14% Worsened	*25% Worsened*



Gold, M.R. et al. J Am Coll Cardiol EP. 2021;■(■):■-■.

Patients who worsened within 1st year of CRT had high mortality
Those stabilized (unchanged) had comparable 5-year survival as those who improved
Indicating that "non-responder" classification should be modified

CRT is life-saving, but implementation is poor

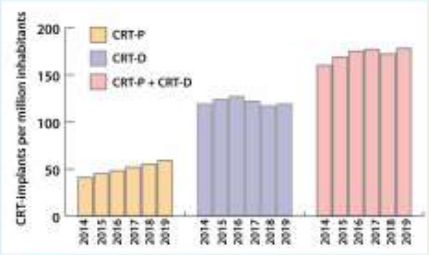


Figure 1 Cardiac resynchronization therapy pacemake (CRT-P) and cardiac resynchronization therapy defibrillato (CRT-D) implants in Europe between 2014 and 2019. Sourc https://www.medtecheurope.org/.

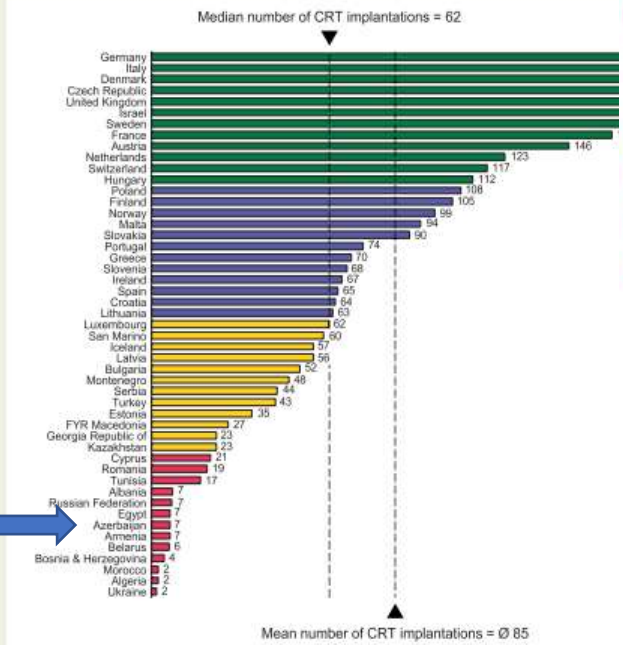
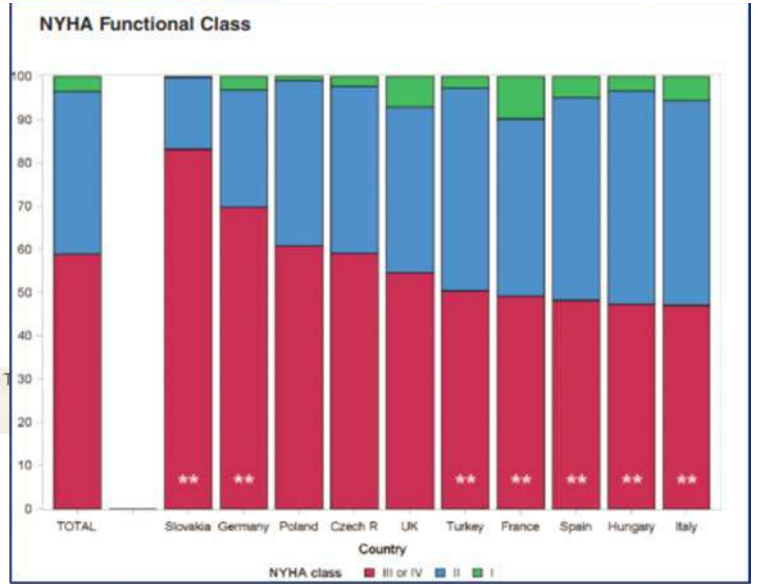


Figure 49 Cardiac resynchronization therapy device implantations per million inhabitants 2016. T weighted by population.

European Journal of Heart Failure (2018) **20**, 1039–1051
doi:10.1002/ejhf.1142

RESEARCH ARTICLE

CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients—who is doing what to whom and how?



From EHRA White book 2017 and CRT Survey II in 11 088 patients

Implantation success rate

European Journal of Heart Failure (2018) 20, 1039–1051
doi:10.1002/ejhf.1142

RESEARCH ARTICLE

CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients—who is doing what to whom and how?

Kenneth Dickstein[1,2]*, Camilla Normand[1,2], Angelo Auricchio[3], Nigussie Bogale[1], John G. Cleland[4], Anselm K. Gitt[5,6,7], Christoph Stellbrink[8], Stefan D. Anker[9,10], Gerasimos Filippatos[11], Maurizio Gasparini[12], Gerhard Hindricks[13], Carina Blomström Lundqvist[14], Piotr Ponikowski[15], Frank Ruschitzka[16], Giovanni Luca Botto[17], Alan Bulava[18,19,20], Gabor Duray[21], Carsten Israel[22], Christophe Leclercq[23], Peter Margitfalvi[24], Óscar Cano[25], Chris Plummer[26], Nedim Umutay Sarigul[27,28], Maciej Sterlinski[29], and Cecilia Linde[30]

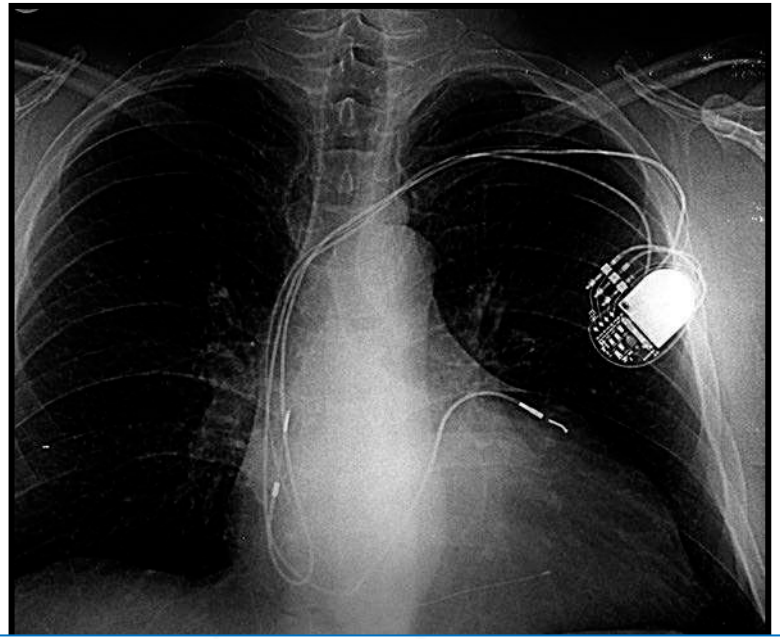
Successful implantation of biventricular pacemaker in 97% in 288 centres across 42 ESC countries

Reasons for unsuccessful implantation of LV lead in CRT Survey II

	Men		Women		
	CRT-P (n = 2,220)	CRT-D (n = 5,857)	CRT-P (n = 998)	CRT-D (n = 1,588)	p Value
LV lead placement					
Successful LV placement	99.8 (2,204/2,208)	99.4 (5,766/5,800)	99.3 (980/987)	99.0 (1,558/1,574)	0.009
Epicardial approach	9.3 (205/2,204)	9.0 (517/5,766)	8.5 (83/980)	10.3 (161/1,558)	
Reason for LV lead placement failure					0.992
CS not identified	25.0 (1/4)	17.6 (6/34)	14.3 (1/7)	18.8 (3/16)	
Extracardiac stimulation	0.0 (0/4)	0.0 (0/34)	0.0 (0/7)	0.0 (0/16)	
No suitable coronary vein	50.0 (2/4)	55.9 (19/34)	57.1 (4/7)	50.0 (8/16)	
Complication	0.0 (0/4)	5.9 (2/34)	14.3 (1/7)	6.3 (1/16)	
Other	25.0 (1/4)	20.6 (7,734)	14.3 (1/7)	25.0 (4/16)	

Auricchio A et al JACC EP 2019

Biventricular or left bundle LBB area pacing

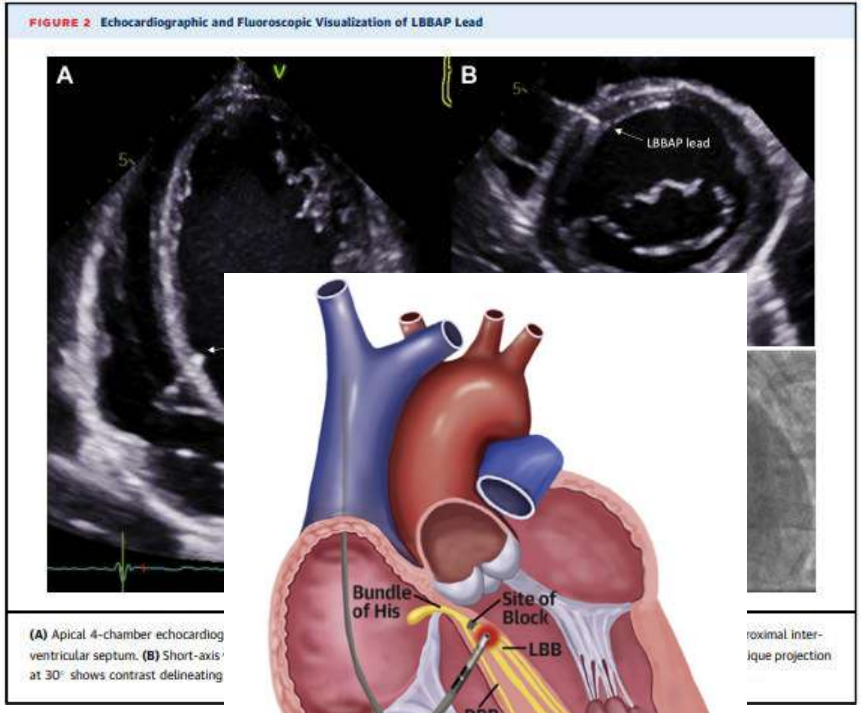


Permanent Left Ventricular Pacing With Transvenous Leads Inserted Into The Coronary Veins

J. CLAUDE DAUBERT[1], PHILIPPE RITTER[2], HERVÉ LE BRETON[1], DANIEL GRAS[1,2], CHRISTOPHE LECLERCQ[1], ARNAUD LAZARUS[2], JACQUES MUGICA[2], PHILIPPE MABO[1] and SERGE CAZEAU[2]

From the [1]Service de Cardiologie A, Hotel Dieu/CHRU 35033 Rennes Cedex, [2]Département de Stimulation Cardiaque, Centre Chirurgical du Val d'Or, Saint-Cloud France

PACE 1998;21:239-245



ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–14
https://doi.org/10.1093/eurheartj/ehac445

CLINICAL RESEARCH
Arrhythmias

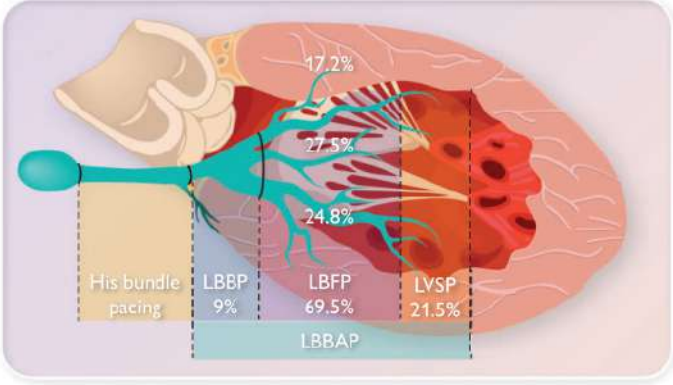
Left bundle branch area pacing outcomes: the multicentre European MELOS study

Marek Jastrzębski[1]*, Grzegorz Kiełbasa[1], Oscar Cano[2,3], Karol Curila[4], Luuk Heckman[5], Jan De Pooter[6], Milan Chovanec[7], Leonard Rademakers[8], Wim Huybrechts[9], Domenico Grieco[10], Zachary I. Whinnett[11], Stefan A.J. Timmer[12], Arif Elvan[13], Petr Stros[4], Paweł Moskal[1], Haran Burri[14], Francesco Zanon[15], and Kevin Vernooy[4,16]

Prospective, multicenter, registry-based observational study

2533 Participants

14 European centres



LBBAP implantation success

Bradycardia indication success	**92.4%**
Heart failure indication success	**82.2%**

LBBAP lead complications **8.3%**

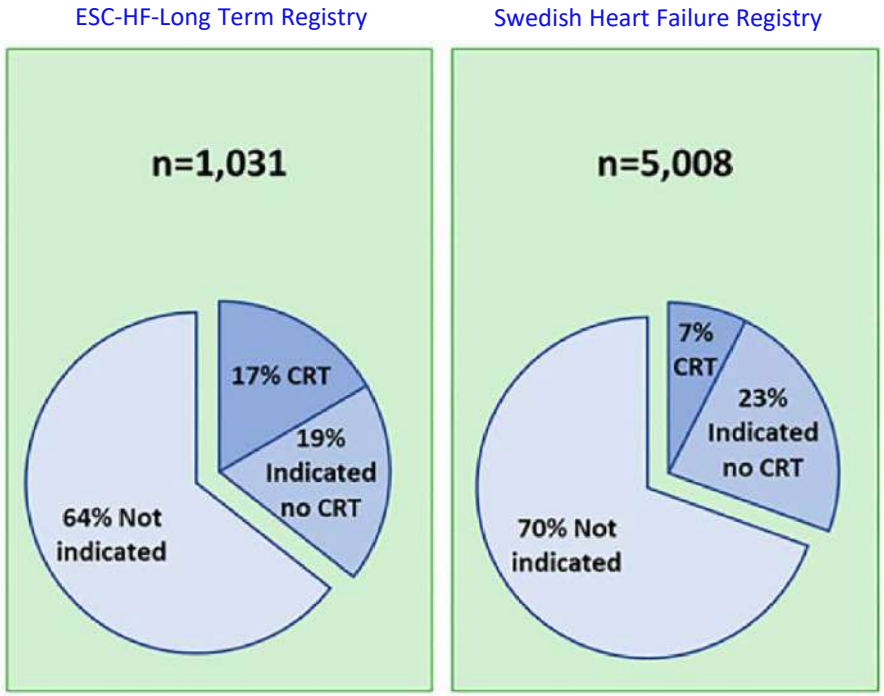
• Acute perforation to LV	3.7%
• Lead dislodgement	1.5%
• Acute chest pain	1.0%
• Capture threshold rise	0.7%
• Acute coronary syndrome	0.4%
• Trapped/damaged helix	0.4%
• Delayed perforation to LV	0.1%
• Other	0.7%

Independent predictors of LBBAP lead implantation failure

Heart failure indication	**OR 1.49**, 95% CI 1.01–2.21
Baseline QRS duration, per 10 ms	**OR 1.08**, 95% CI 1.03–1.14
LVEDD, per 10 mm increase	**OR 1.53**, 95% CI 1.26–1.86

CRT is used in a minority of eligible patients

HFrEF patients in the ESC-HF-Long Term Registry (n = 1031) and the Swedish Heart Failure Registry (n = 5008)



In **ESC-HF-LT,**
36% had a CRT indication,
of which **47%** had CRT.

In SwedeHF,
30% had a CRT indication,
of which **25%** had CRT.

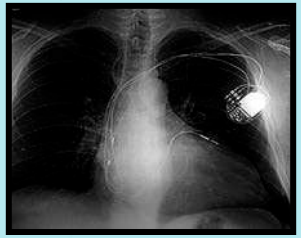
Independent predictors of CRT use included AF, milder HF (NYHA I-II), and greater use of GDMT.

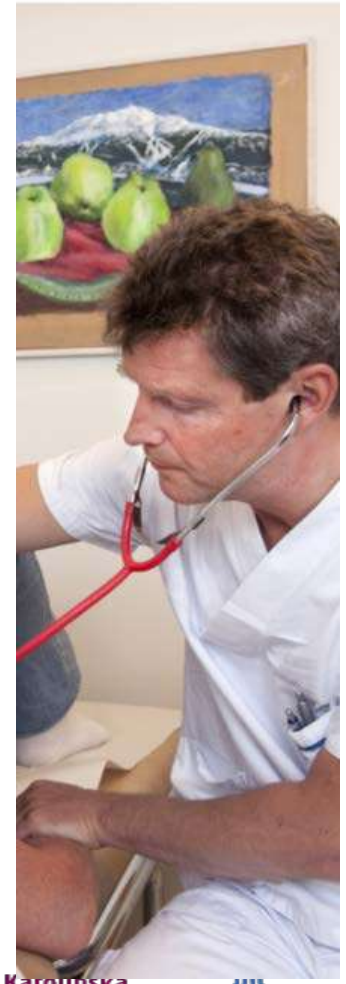
Results suggest suboptimal in-house and external referral patterns as well as lack of awareness of CRT therapy.

Gatti P et al. *Eur Heart J Qual Care Clin Outcomes.* 2023; Apr 19 [Online ahead of print]

The Heart failure clinics are the sources of knowledge
What is done at all Stockholm hospital based HF clinics?

- Establish correct diagnosis and HF etiology
- Optimize drug treatment
- Assess indication for biventricular pacemaker-CRT /ICD
- Provide Patient-education
- Physiotherapy
- Individual care plan for patient and primary care
- Interact with primary care and private care





Uniform care process over Stockholm

Karolinska Institutet

Stockholms läns landsting

Take home message

- CRT saves lives and reduced HF hospitalisations
- In Sinus rhythm and wide QRS *but not RBBB*
- *Upgrade to CRT if paced patients develop HF*
- Women respond well to CRT
- Body size should be considered in decision making
- Responder term should be replaced by stabilization/improvement
- Worsening during CRT calls for other therapies

Take home message

- CRT Implantation success rate is high
- Lack of appropriate CS branch or accessibility is a limitation
  - LBBAP may help when scientific evidence is ready
- CRT is under-implemented
  - organisation of HF care,
  - education and
  - simplified guidelines may help

The Pacemaker- a Swedish invention

The engineer	The Surgeon	The Patient
Rune Elmqvist 1906 - 1997	Åke Senning 1915 - 2000	Arne Larsson 1915 - **2001**

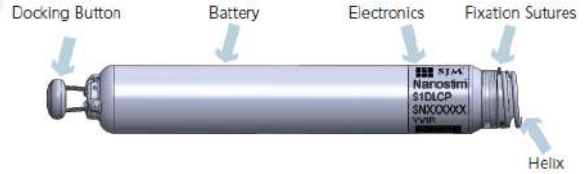
1958

Thick, simple, short life

Now

Leadless pacemaker small

Figure 2: Design of the Leadless Pacemaker



Thank you!

Cecilia Linde Karolinska Institutet Karolinska University Hospital