

Kardiyak Resenkronizasyon Tedavisinden Beklentiler ve Yeni Tedavi Alanları

Dr. Ömer Akyürek
AÜTF

- Bir tedaviye OLUMLU yanıt verilmesi (ya da tedaviden BEKLENEN şey):
 - Verilen tedavi ile hastanın kendisini, tedavinin olmadığı duruma göre daha iyi hissetmesi (SEMPTOMATİK iyileşme hali)
 - Yaşamın uzatılması (azalan MORTALİTE)

- GemiŖte ğrendiėimiz –ve daima aklımızda tutmamız gereken gerek-:

“ semptomatik iyileŖme ile prognoz arasında doėrusal bir iliŖki olmayabilir”.

- Kalp yetmezliėi zelinde bu bazen ok daha belirgindir (diüretik tedavi, pozitif inotrop tedavi...vs semptomatik iyileŖmeye karŖın prognozu ktleŖtirdi ya da deėiŖtirmede)

- Kalp yetmezliđi hastalarında bir ***beklenti*** geliřtirmemiz ve bunun gerekleřmesini takip etmemiz (yani YANIT veren –***responder-***) ok g olabilir:
 - semptom ve hemodinamide hem anlık dalgalanmalar hem uzun vadeli deđiřkenlikler olabilir:
 - Hastalar arasında hatta aynı hastada hastalıđın progresyon hızı deđiřkenlik gsterir
 - Hemodinamik ve ekokardiyografik parametreler ile semptomlar arası iliřki son derece zayıftır

Harika bir örnek:

Persistent Hemodynamic Benefits of Cardiac Resynchronization Therapy With Disease Progression in Advanced Heart Failure

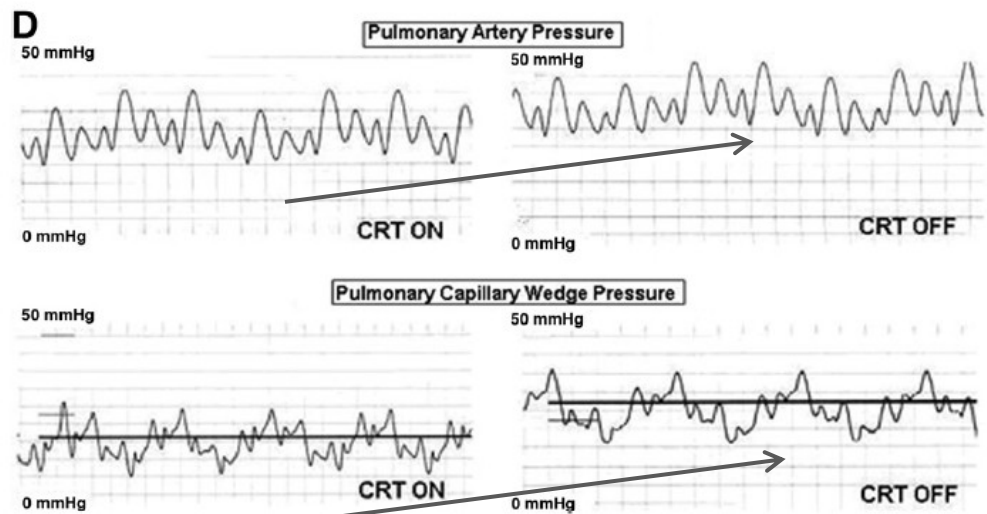
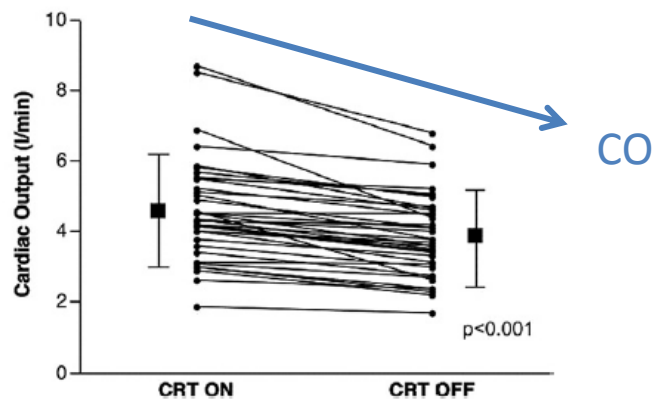
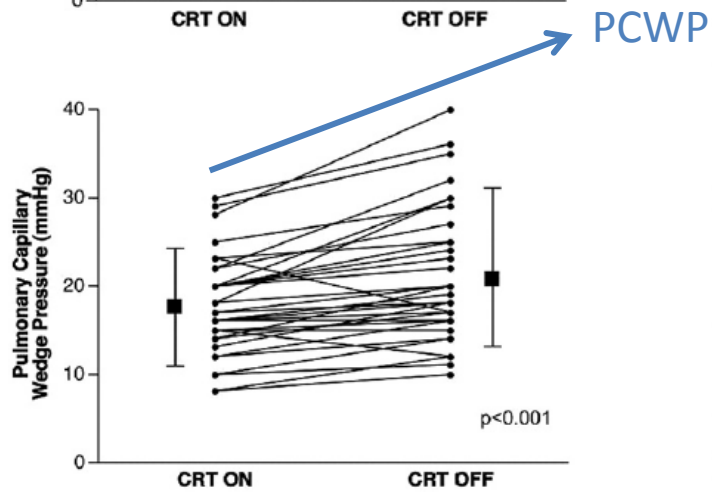
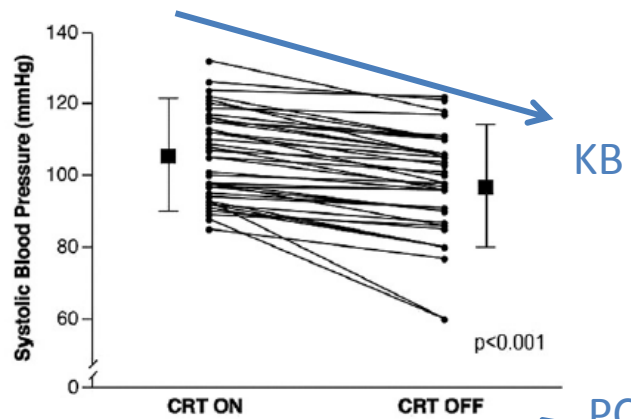
Wilfried Mullens, MD, Tanya Verga, RN, Richard A. Grimm, DO, FACC,
Randall C. Starling, MD, MPH, FACC, Bruce L. Wilkoff, MD, FACC,
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Objectives	Our aim was to determine the potential hemodynamic contributions of cardiac resynchronization therapy (CRT) in patients admitted for advanced decompensated heart failure.
Background	CRT restores synchrony of the heart resulting in hemodynamic support that can facilitate the reversal of left ventricular (LV) remodeling in some patients.
Methods	A total of 40 consecutive patients with advanced decompensated heart failure and CRT implanted >3 months, admitted due to hemodynamic derangements, underwent simultaneous comprehensive echocardiographic and invasive hemodynamic evaluation under different CRT settings.
Results	All patients (mean LV ejection fraction $22 \pm 7\%$, LV end-diastolic volume 323 ± 140 ml, 40% ischemic) had experienced progressive cardiac remodeling despite adequate LV lead positions and continuous biventricular pacing. A significant worsening of hemodynamics was observed immediately when CRT was programmed OFF in the majority (88%) of patients (systolic blood pressure: 105 ± 12 mm Hg to 98 ± 13 mm Hg; pulmonary capillary wedge pressure: 17 ± 6 mm Hg to 21 ± 7 mm Hg; cardiac output: 4.6 ± 1.4 l/min-m ² to 4.0 ± 1.1 l/min-m ² ; all $p < 0.001$). Worsening of hemodynamics coincided with reappearance of significant electrical (QRS width 161 ± 29 ms to 202 ± 39 ms, $p < 0.001$) and intraventricular mechanical dyssynchrony (15 ± 26 ms to 57 ± 41 ms, $p < 0.001$), together with a significant reduction in diastolic filling time (377 ± 138 ms to 300 ± 118 ms, $p < 0.001$).
Conclusions	Despite progressive cardiac remodeling and decompensation, chronic CRT continues to provide hemodynamic augmentation in the failing heart in most patients. Our data suggest that disease progression may not be explained by diminished beneficial hemodynamic contributions of successful resynchronization. (J Am Coll Cardiol 2009;53:600-7) © 2009 by the American College of Cardiology Foundation

- CRT tedavisinin zamanla beklentileri karşılamadığı düşünülen 40 hasta:
 - NHYA'da kötüleşme, hastaneye yatışlarda artış
 - LVESV ve LVEDV'da artış

CRT halen hemodinamik desteğe devam ediyor



- Bu hastalar CRT'ye yanıt vermemiş midir...
- Yoksa BEKLENTİLER deđiştirilmeli midir ?

- Tüm kalp yetmezliđi hastalarında aynı beklentiler mi olmalıdır..
- Yoksa hastalar kategorize edilerek mi beklentiler oluşturulmalıdır?
- Ya da HER HASTA için ÖZEL bir beklenti seti mi olmalıdır ?

Tedaviye yanıt aslında bir beklenti sorunsalıdır.

- **NHYA I-II** olan bir hasta ile CRT-D tedavisi tartışırken ölüm olasılığı hasta için çok uzak bir ihtimaldir.
- Diğer tarafta **ileri kalp yetmezliği** hastaları vardır. Bu hastalar birkaç iyi gün geçirebilmek için yaşamlarından ayları feda etmeye hazırdır (hastanın BEKLENTİSİ)
- CRT ile daha iyi hissetmeye başlayan hastalar bu kez dikkatlerini daha az hastaneye yatmaya, spor ve sosyal aktivitelere katılmaya yöneltir (BEKLENTİ yine değişmiştir)
- Devamlı değişen hedefler sonuçta tedaviye yanıtın da sürekli güncellenmesi gerekliliğini doğurmaktadır

PATH-CHF

MUSTIC

MIRACLE

COMPANION

CARE HF

NHYA Sınıf III-IV

CONTAK CD

MIRACLE II

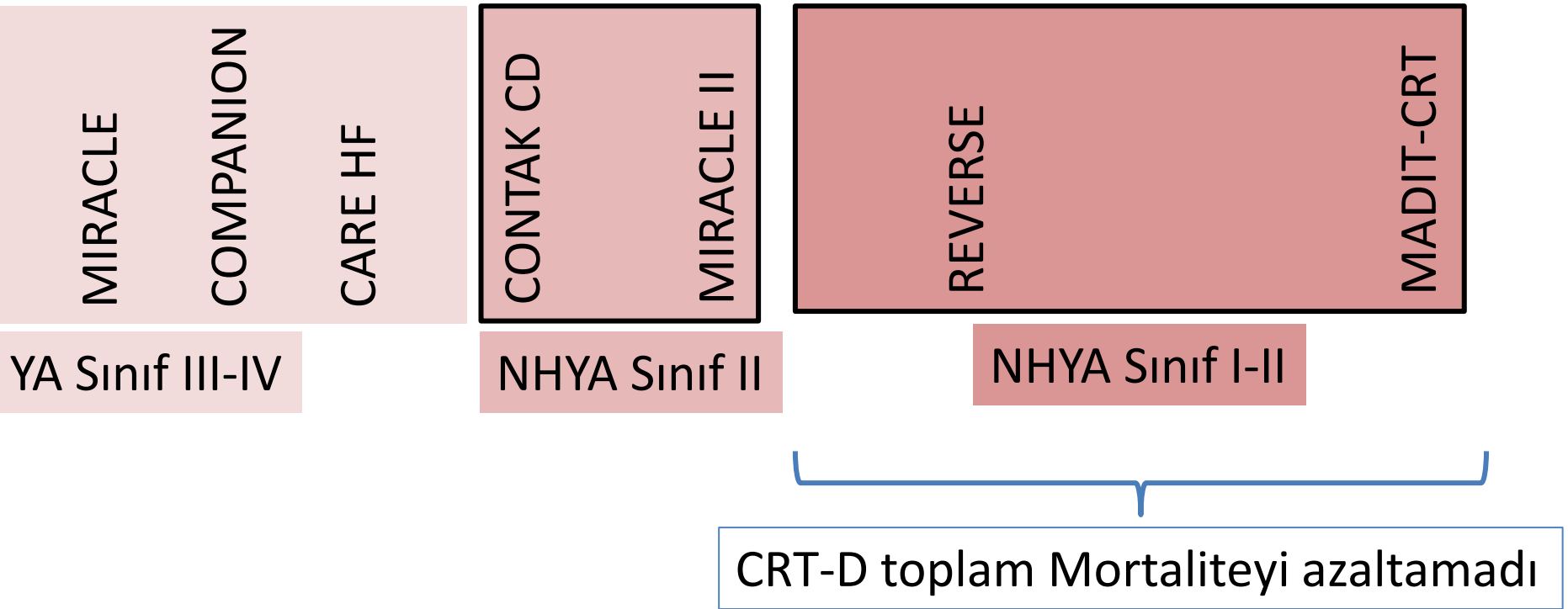
NHYA Sınıf II

REVERSE

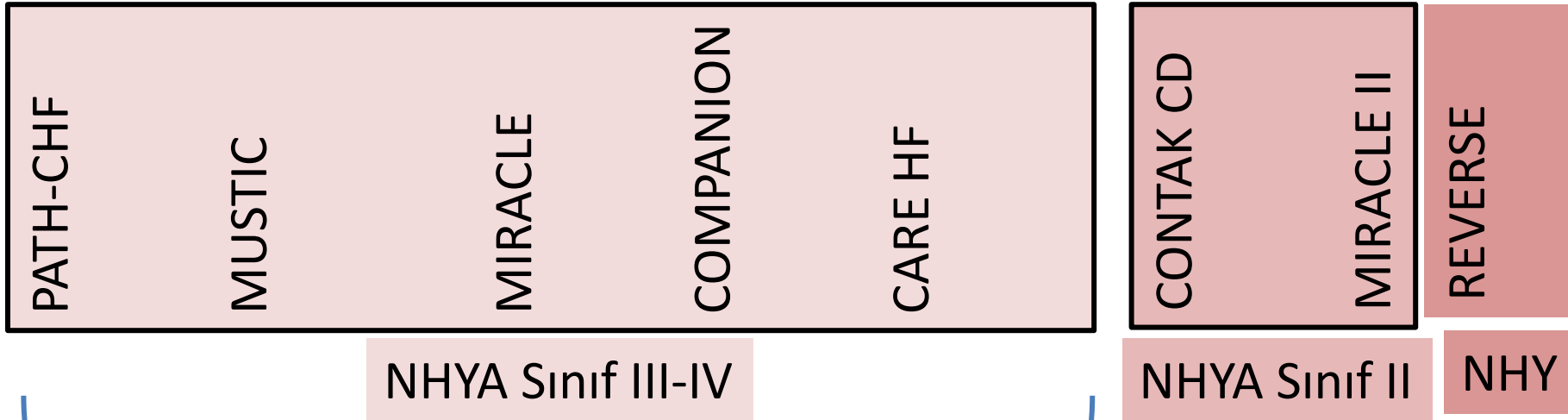
MADIT-CRT

NHYA Sınıf I-II

- Major Beklenti:
 - Mortalitenin azaltılması



- Major Beklenti:
 - Mortalitenin azaltılması

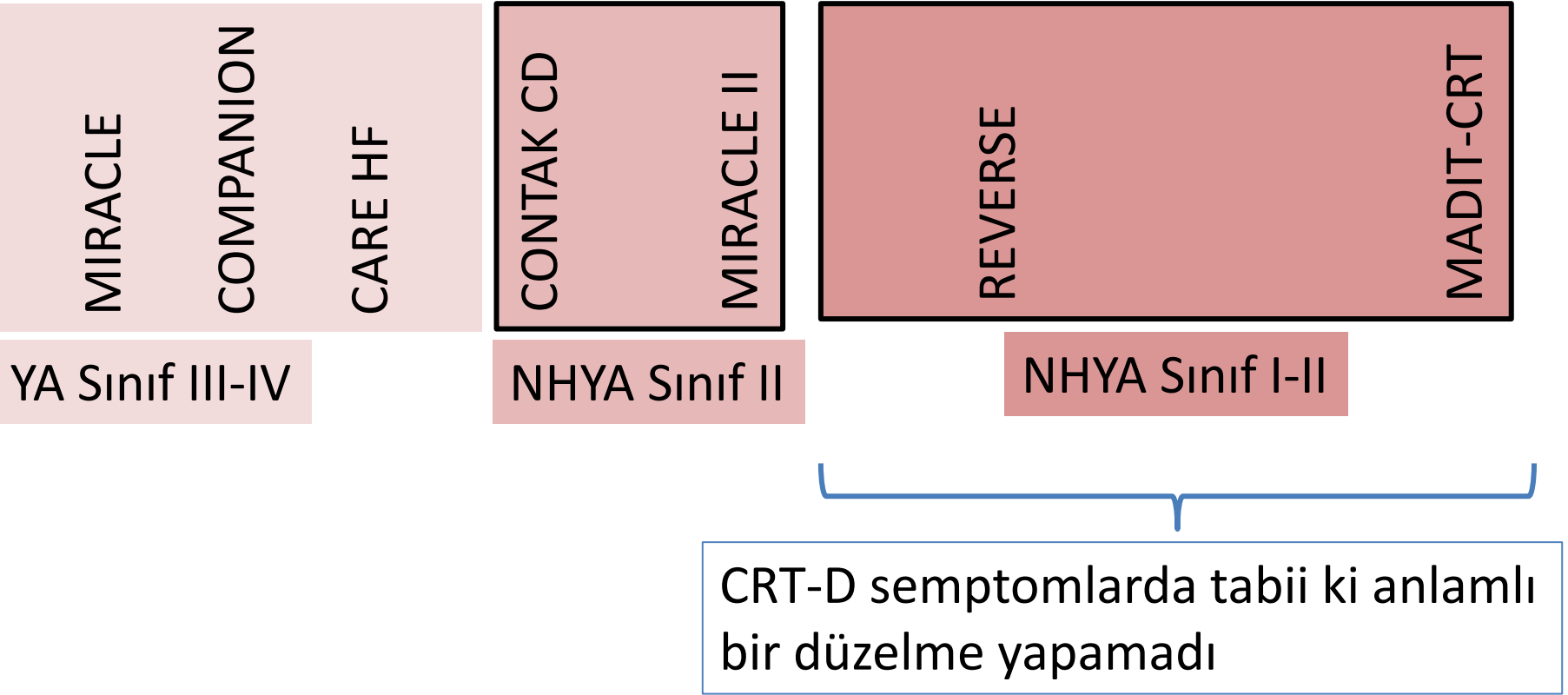


Toplam mortalitede azalma hiçbir tedavide olmadığı kadar belirgin

- Soru: CRT, temel beklentimiz olan mortaliteyi azaltmada başarısız mıdır?
(Söz konusu olan NHYA I-II hastalar ise yanıt %100 evet)

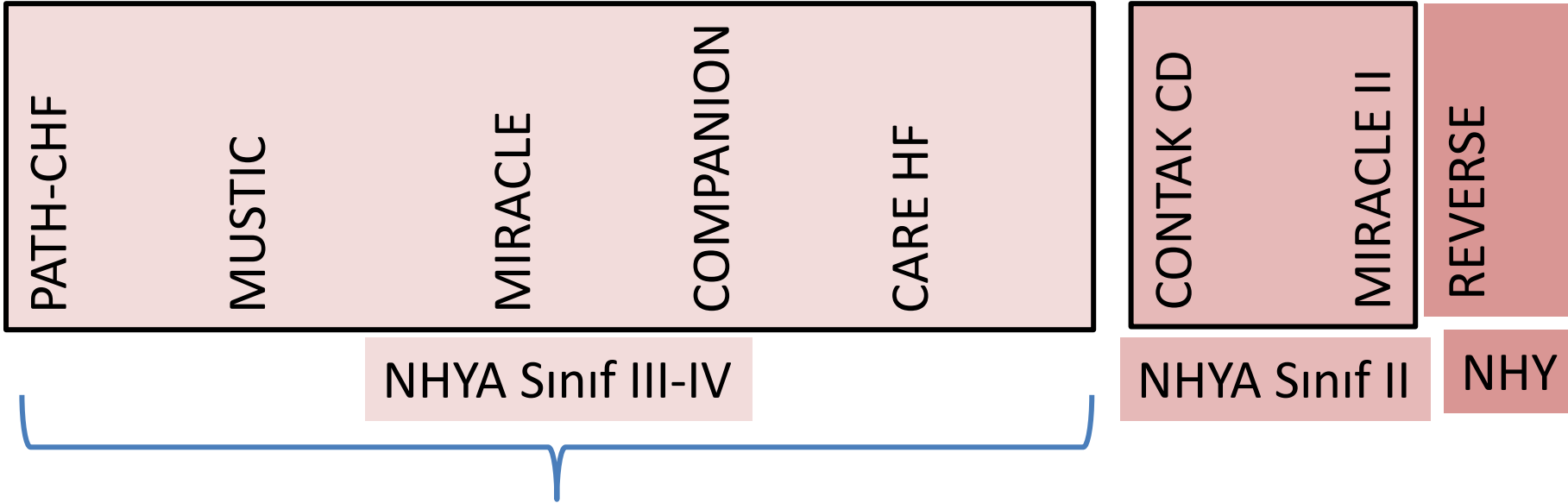
- Major Beklenti:

- Semptomların azalması (dispnenin) azalması, fonksiyonel grupta iyileşme, ..vs



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- Semptomların azalması (dispnenin) azalması, fonksiyonel grupta iyileşme, ..vs



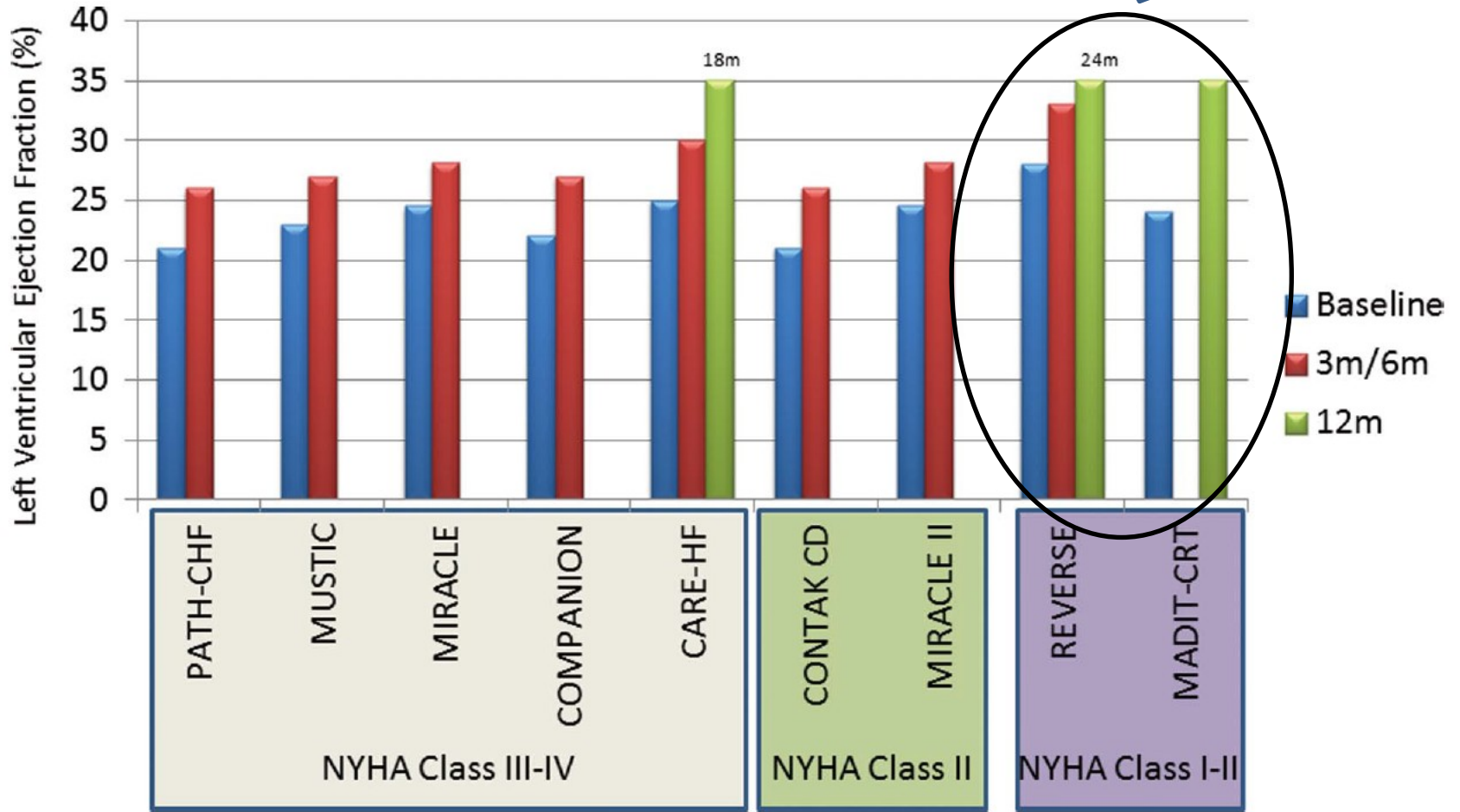
Ortalamada son derece anlamlı semptom düzelmesi, hastane yatışlarında azalma, yürüme mesafelerinde uzama, yaşam kalitesinde artış
Bazı hastalarda semptomlarda olağanüstü düzelme (süperresponder)

- Soru: CRT, semptomatik iyileşme beklentisini karşılayamamakta mıdır?
 - NHYA III-IV hastalarında bu oran %30 civarında iken söz konusu NHYA Sınıf I-II %100 dür !

- Major Beklenti: Mortalitenin dolaylı belirteçlerinde iyileşme:
 - Ventriküler reverse remodelling: Daha ölçümlenebilir bir parametre (?) CRT icadından bu yana yararlı etkinin gösterilmesinde temel bir element olageldi
 - Hastane yatışlarında azalma: çok yönlü bir değişken. Tek bir tedavinin değil multidisipliner yaklaşımın bir ölçütü

Reverse Remodelling

Nihayet bu grupta bir beklenti karşılandı (rahatlama)



- Ventriküler reverse remodelling:
 - LVESV
 - LVESVI
 - LVEDV
 - LVEDVI
 -

Left Ventricular Reverse Remodeling but Not Clinical Improvement Predicts Long-Term Survival After Cardiac Resynchronization Therapy

Cheuk-Man Yu, MD, FRCP; Gabe B. Bleeker, MD; Jeffrey Wing-Hong Fung, MRCP, FHKAM;
Martin J. Schalij, MD, PhD; Qing Zhang, BM, MM; Ernst E. van der Wall, MD, PhD;
Yat-Sun Chan, MRCP, FHKAM; Shun-Ling Kong, BN, MN; Jeroen J. Bax, MD, PhD

Background—In patients with severe heart failure and dilated cardiomyopathy, cardiac resynchronization therapy (CRT) improves left ventricular (LV) systolic function associated with LV reverse remodeling and favorable 1-year survival. However, it is unknown whether LV reverse remodeling translates into a better long-term prognosis and what extent of reverse remodeling is clinically relevant, which were investigated in this study.

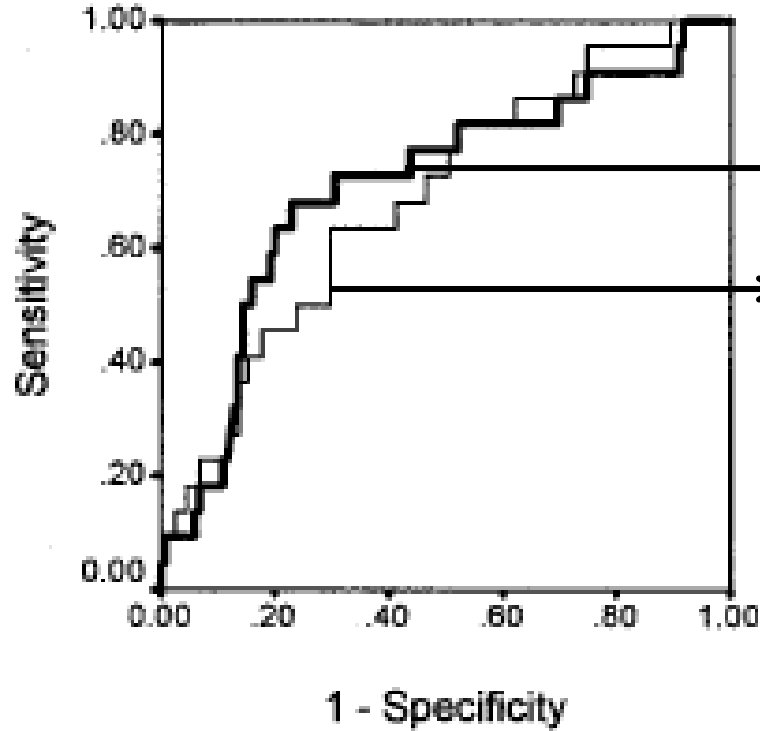
Methods and Results—Patients (n=141) with advanced heart failure (mean±SD age, 64±11 years; 73% men) who received CRT were followed up for a mean (±SD) of 695±491 days. The extent of reduction in LV end-systolic volume (LVESV) at 3 to 6 months relative to baseline was examined for its predictive value on long-term clinical outcome. The cutoff value for LV reverse remodeling in predicting mortality was derived from the receiver operating characteristic curve. Then the relation between potential predictors of mortality and heart failure hospitalizations were compared by Kaplan-Meier survival analysis, followed by Cox regression analysis. There were 22 (15.6%) deaths, mostly due to heart failure or sudden cardiac death. The receiver operating characteristic curve found that a reduction in LVESV of ≥9.5% had a sensitivity of 70% and specificity of 70% in predicting all-cause mortality and of 87% and 69%, respectively, for cardiovascular mortality. With this cutoff value, there were 87 (61.7%) responders to reverse remodeling. In Kaplan-Meier survival analysis, responders had significantly lower all-cause mortality (6.9% versus 30.6%, log-rank $\chi^2=13.26$, $P=0.0003$), cardiovascular mortality (2.3% versus 24.1%, log-rank $\chi^2=17.1$, $P<0.0001$), and heart failure events (11.5% versus 33.3%, log-rank $\chi^2=8.71$, $P=0.0032$) than nonresponders. In the Cox regression analysis model, the change in LVESV was the single most important predictor of all-cause ($\beta=1.048$, 95% confidence interval=1.019 to 1.078, $P=0.001$) and cardiovascular ($\beta=1.072$, 95% confidence interval=1.033 to 1.112, $P<0.001$) mortality. Clinical parameters were unable to predict any outcome event.

Conclusions—A reduction in LVESV of 10% signifies clinically relevant reverse remodeling, which is a strong predictor of lower long-term mortality and heart failure events. This study suggests that assessing volumetric changes after an intervention in patients with heart failure provides information predictive of natural history outcomes. (*Circulation*. 2005;112:1580-1586.)

Key Words: pacing ■ prognosis ■ heart failure ■ echocardiography ■ mortality

LVESV ve LVEDV azalmanın mortalite üzerine etkisine ait ROC eğrisi

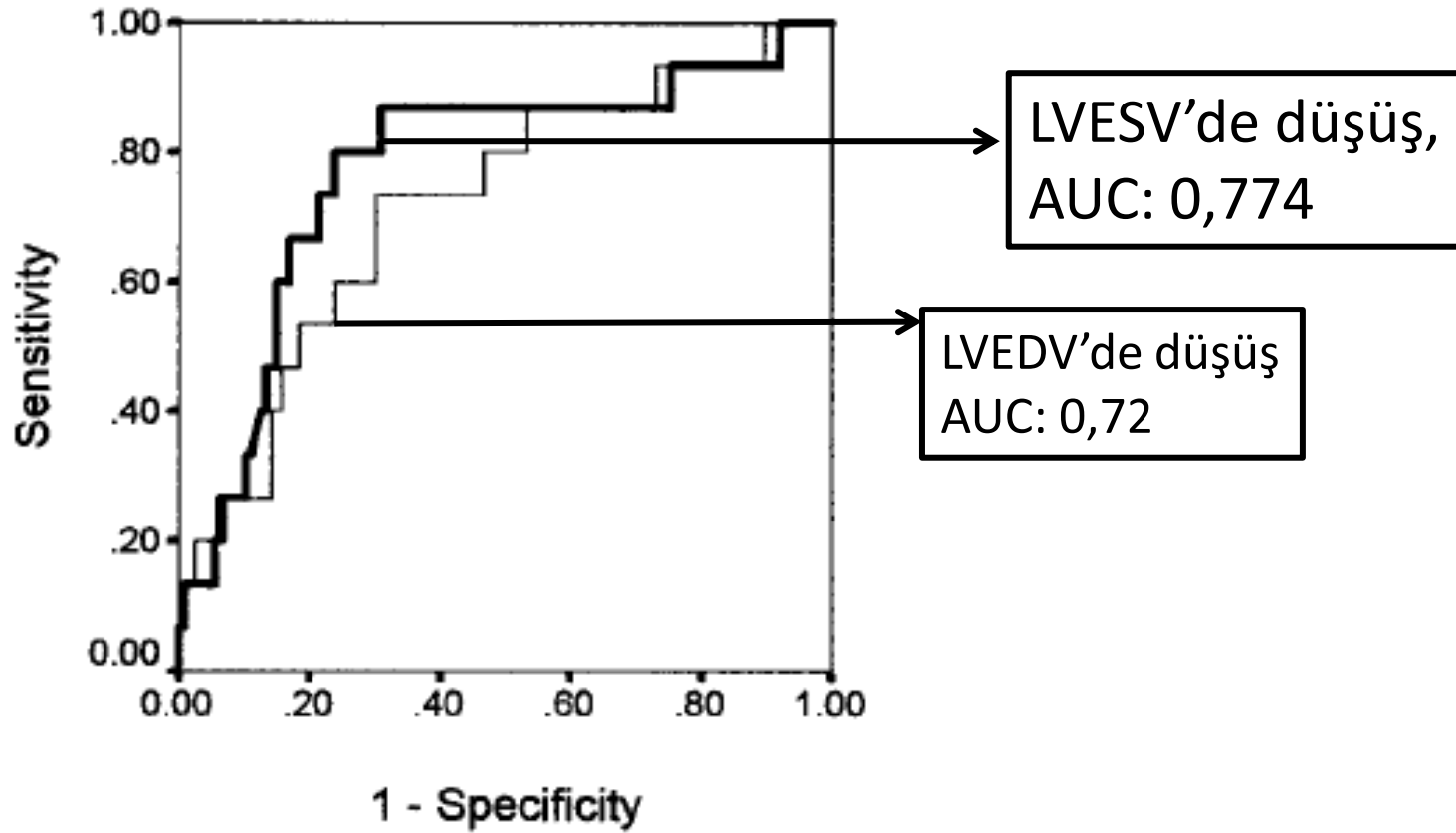
A All-cause mortality



LVESV'de düşüş daha belirleyici
-AUC: 0,71
Cut off: LVESV'de %9.5'luk azalma

B

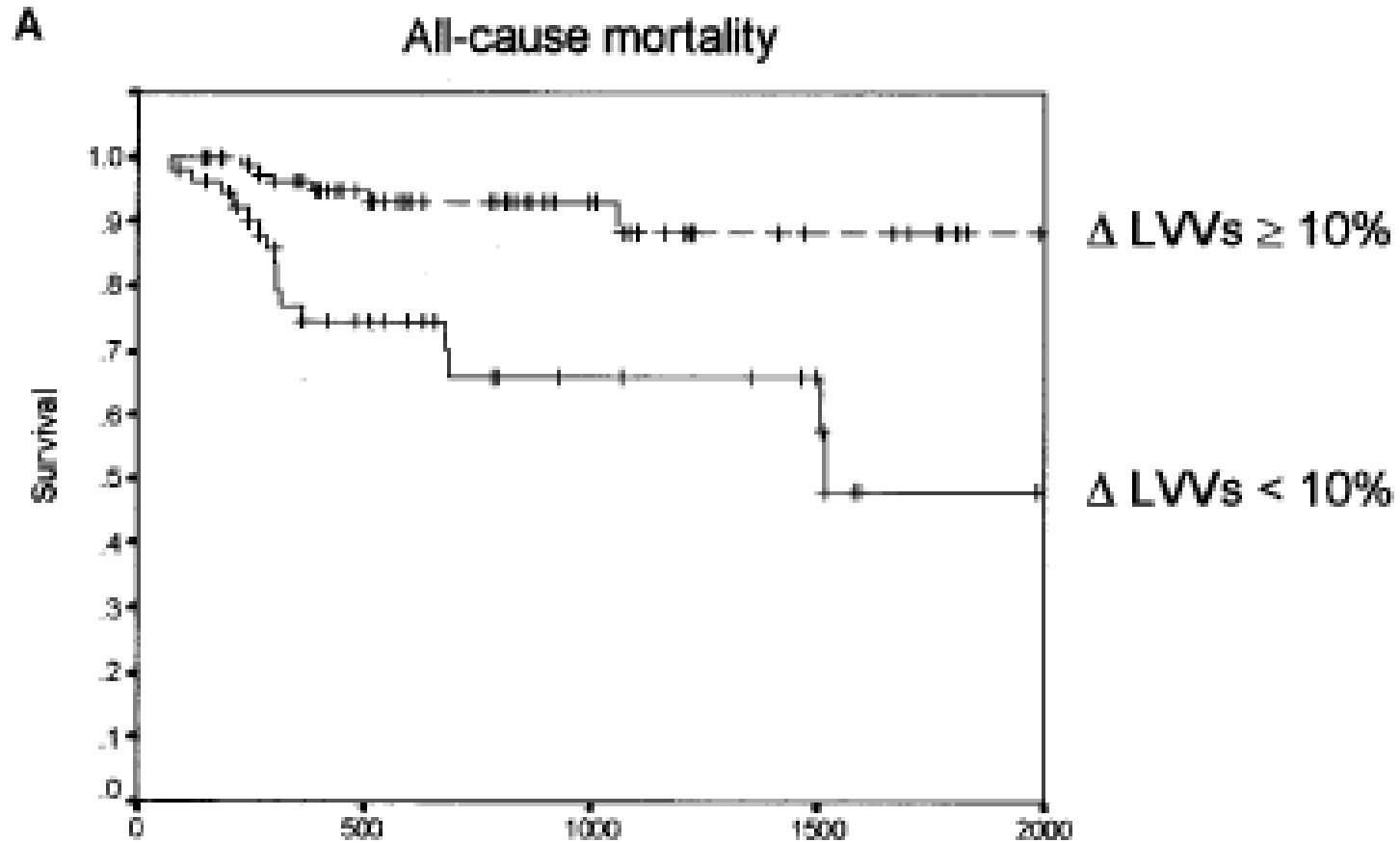
CVS mortality



LVESV'de düşüş,
AUC: 0,774

LVEDV'de düşüş
AUC: 0,72

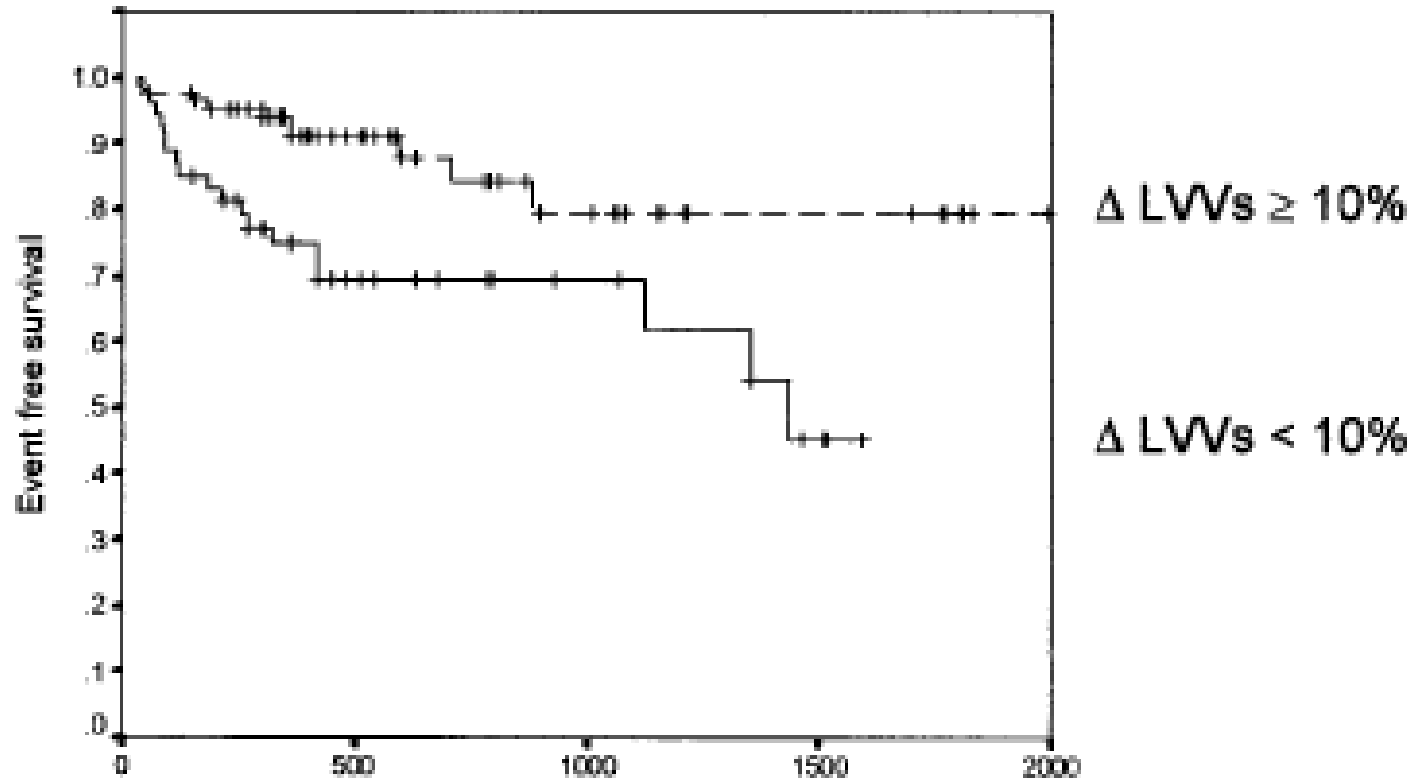
CRT'de reverse remodelling için *beklenti*: LVESV >%10 düşüş



CRT'de reverse remodelling için *beklenti*: LVESV'de $> \%10$ düşüş

B

Fatal and non-fatal CHF

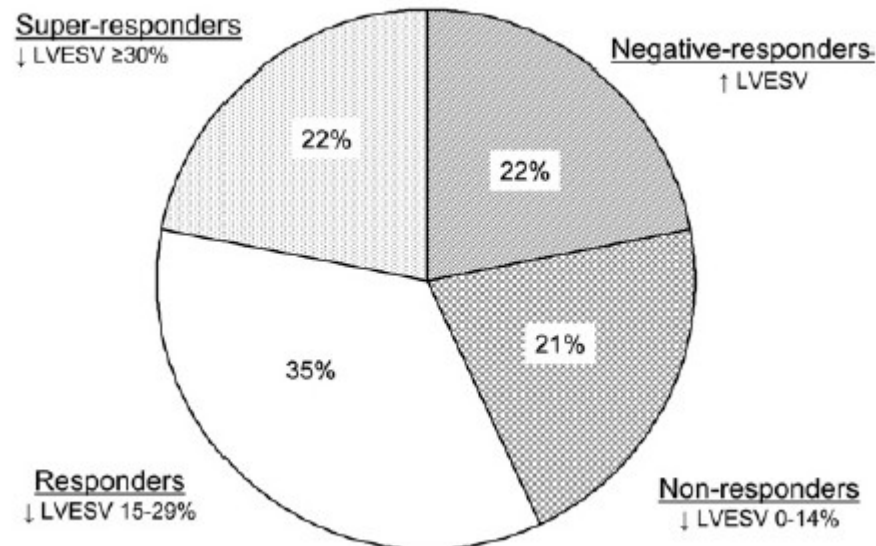


Beklenti: LVESV düşüş sınırı >%15 olarak alınırsa

Long-Term Prognosis After Cardiac Resynchronization Therapy Is Related to the Extent of Left Ventricular Reverse Remodeling at Midterm Follow-Up

Claudia Ypenburg, MD,* Rutger J. van Bommel, MD,* C. Jan Willem Borleffs, MD,* Gabe B. Bleeker, MD, PHD,* Eric Boersma, PHD,† Martin J. Schalij, MD, PHD,* Jeroen J. Bax, MD, PHD*

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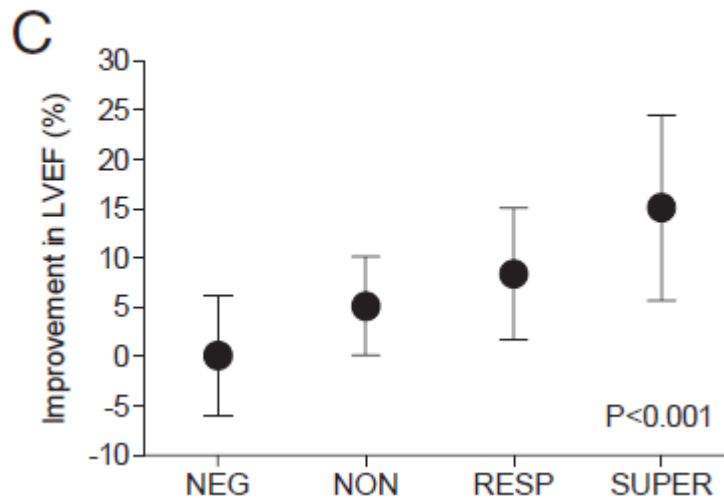


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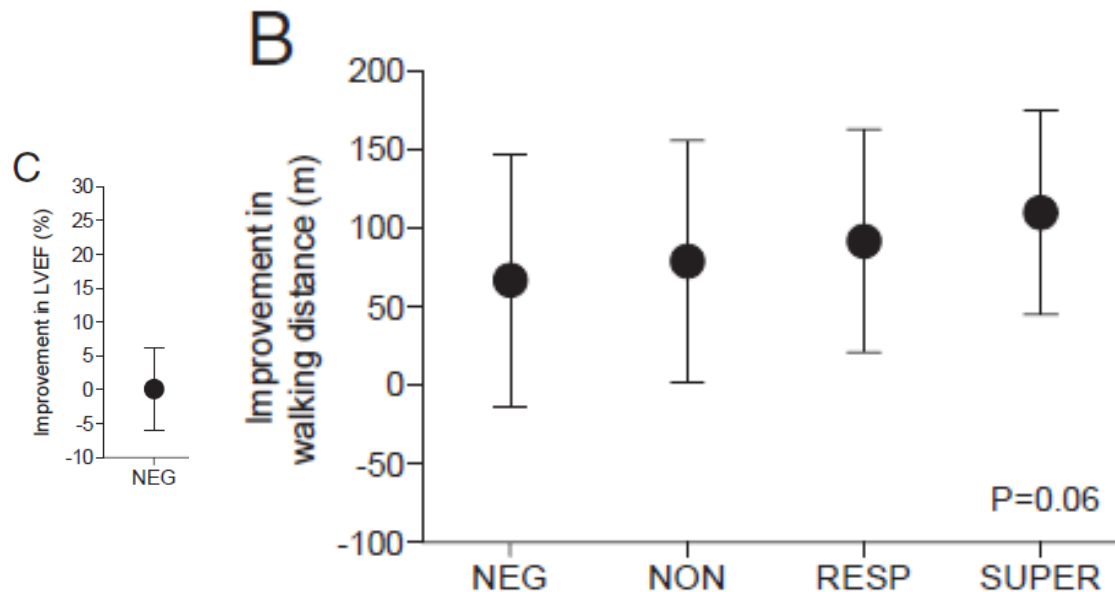


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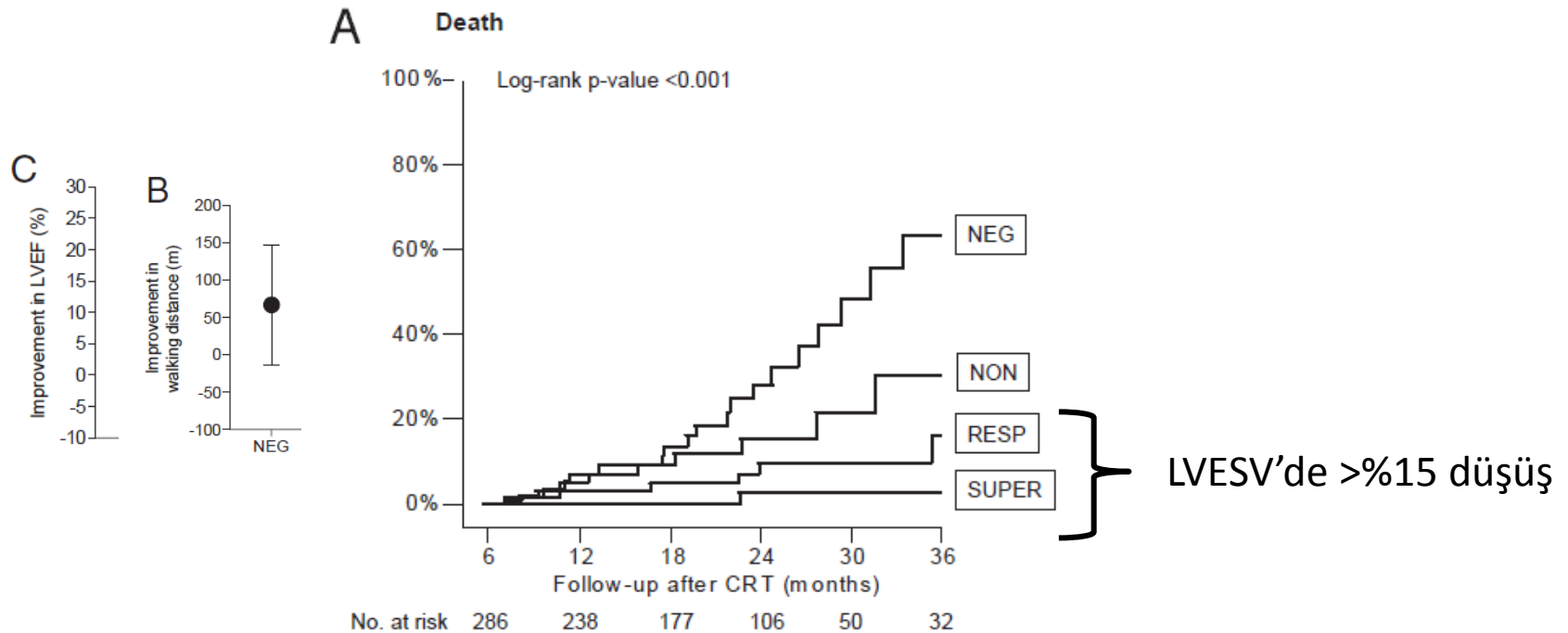


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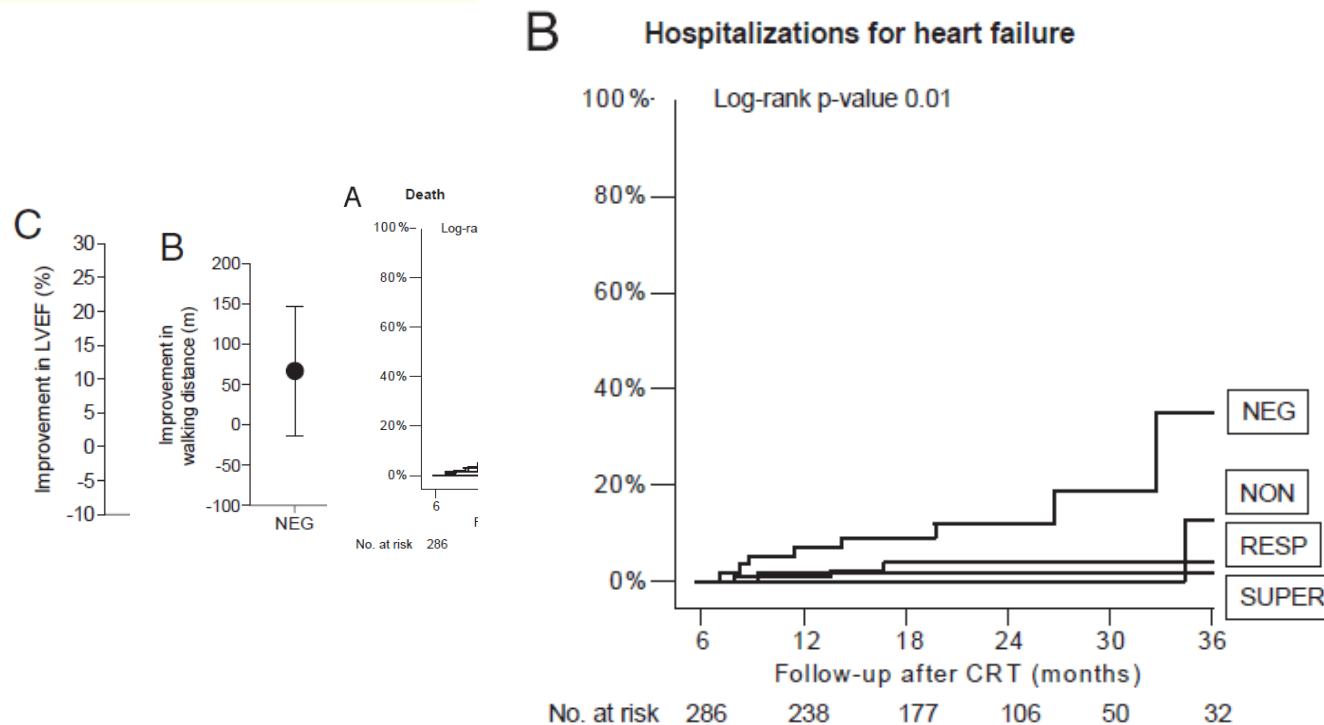


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Leiden and Rotterdam, the Netherlands



LVEDV'de azalma bir reverse remodelling göstergesi olabilir mi

Effect of Cardiac Resynchronization Therapy on Reverse Remodeling and Relation to Outcome Multicenter Automatic Defibrillator Implantation Trial: Cardiac Resynchronization Therapy

Scott D. Solomon, MD; Elyse Foster, MD; Mikhail Bourgoun, MD; Amil Shah, MD; Esperanza Vilorio, BS; Mary W. Brown, MS; W. Jackson Hall, PhD; Marc A. Pfeffer, MD, PhD; Arthur J. Moss, MD; for the MADIT-CRT Investigators

Background—Cardiac resynchronization therapy (CRT) plus implantation of an implantable cardioverter defibrillator (ICD) reduced the risk of death or heart failure event in patients with mildly symptomatic heart failure, left ventricular dysfunction, and wide QRS complex compared with an ICD only. We assessed echocardiographic changes in patients enrolled in the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial: Cardiac Resynchronization Therapy) to evaluate whether the improvement in outcomes with CRT plus an ICD was associated with favorable alterations in cardiac size and function.

Methods and Results—A total of 1820 patients were randomly assigned to CRT plus an ICD or to an ICD only in a 3:2 ratio. Echocardiographic studies were obtained at baseline and 12 months later in 1372 patients. We compared changes in cardiac size and performance between treatment groups and assessed the relationship between these changes over the first year, as well as subsequent outcomes. Compared with the ICD-only group, the CRT-plus-ICD group had greater improvement in left ventricular end-diastolic volume index (-26.2 versus -7.4 mL/m²), left ventricular end-systolic volume index (-28.7 versus -9.1 mL/m²), left ventricular ejection fraction (11% versus 3%), left atrial volume index (-11.9 versus -4.7 mL/m²), and right ventricular fractional area change (8% versus 5%; $P < 0.001$ for all). Improvement in end-diastolic volume at 1 year was predictive of subsequent death or heart failure, with adjustment for baseline covariates and treatment group; each 10% decrease in end-diastolic volume was associated with a 40% reduction in risk ($P < 0.001$).

Conclusions—CRT resulted in significant improvement in cardiac size and performance compared with an ICD-only strategy in patients with mildly symptomatic heart failure. Improvement in these measures accounted for the outcomes benefit.

Clinical Trial Registration Information—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00180271. (*Circulation*. 2010;122:985-992.)

Key Words: pacemakers ■ cardiac ■ resynchronization ■ therapy ■ echocardiography ■ remodeling

LVEDV'de azalma bir reverse remodelling göstergesi olabilir mi

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Multicenter Automatic Defibrillator Implantation Trial: Cardiac Resynchronization Therapy

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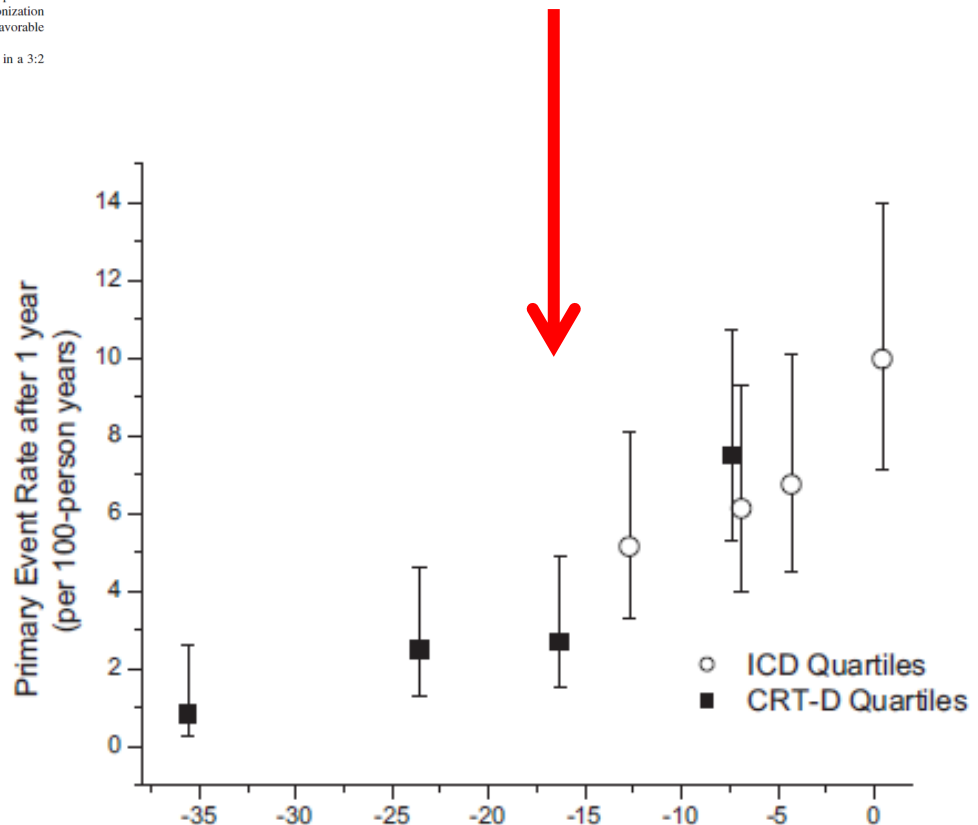
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Conclusions—CRT resulted in significant improvement in cardiac size and performance compared with an ICD-only strategy in patients with mildly symptomatic heart failure. Improvement in these measures accounted for the reduction in risk.

Clinical Trial Registration Information—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00108122.

Key Words: pacemakers ■ cardiac ■ resynchronization ■ therapy ■ echocardiography ■ reverse remodeling



Beklentilerimizi Seçimlerimiz Belirler

Table. Outcomes of CRT in the Various NYHA Classes

Parameters	Patient's functional class at implantation			
	NYHA I	NYHA II	NYHA III	NYHA IV
Change in functional class	-	+/-	+	+
Reverse LV remodeling	+	+	+	+/-
HF hospitalization	-*	+	+	+
Mortality	-*	+	+	+

- *Yeni tedavileri* beklentilerimizi karřılamak için buluruz

Kalp
yetmezliđi



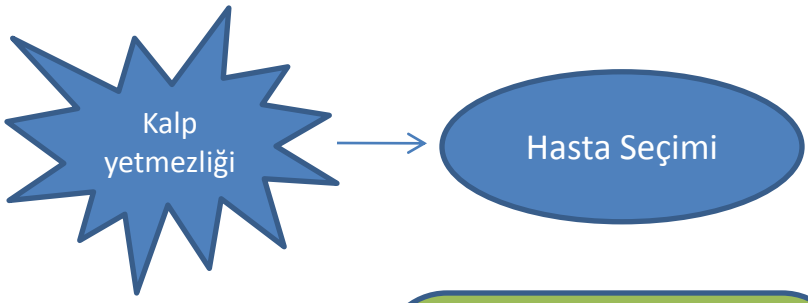
Hasta Seęimi

Beklenti ve yanıt
optimizasyonu

- Düşük EF
- Tipik Sol dal Blođu
- QRS >150 msn
- Semptomatik hasta (NHYA >I)
- Sürekli pace ihtiyacı vs...

Gelecek

Hastaya Özel Yaklaşım



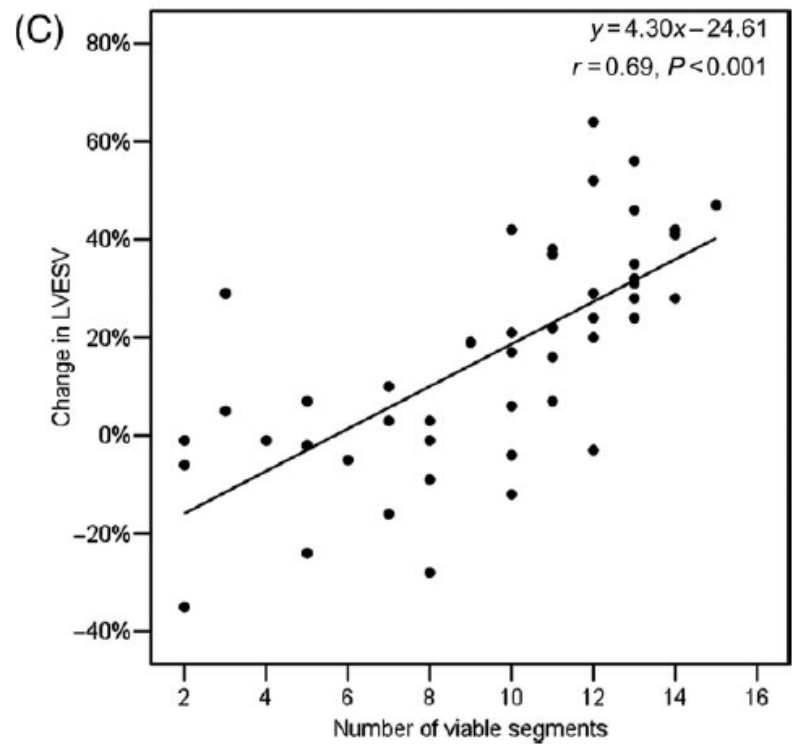
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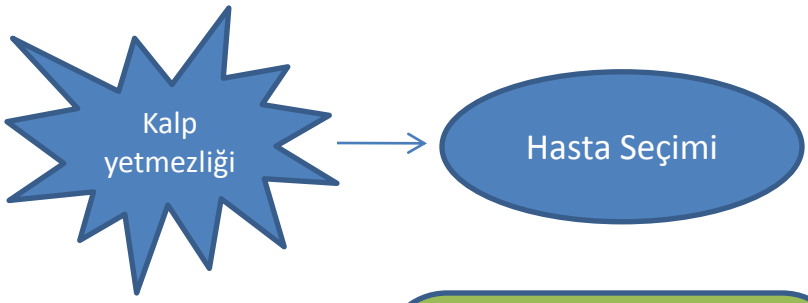
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- Tipik Sol dal Bloğu
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- Semptomatik hasta (NHYA >I)
- Sürekli pace ihtiyacı vs...

Gelecek

Hastaya Özel Yaklaşım

Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients
Claudia Ypenburg¹, Martin J. Schalij¹, Gabe B. Bleeker¹, Paul Steendijk¹, Eric Boersma², Petra Dibbets-Schneider³, Marcel P.M. Stokkel³, Ernst E. van der Wall¹, and Jeroen J. Bax^{1*}



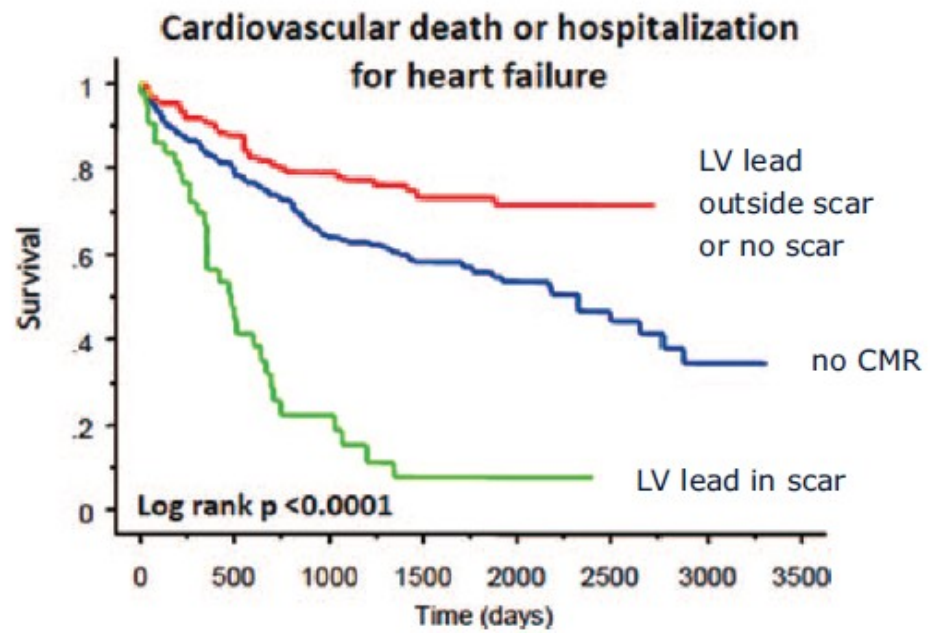


Beklenti ve yanıt optimizasyonu

- Düşük EF
- Tipik Sol dal Bloğu
- QRS >150 msn
- Semptomatik hasta (NHYA >I)
- Sürekli pace ihtiyacı vs...

Gelecek

Hastaya Özel Yaklaşım



Kalp yetmezliği

Hasta Seçimi

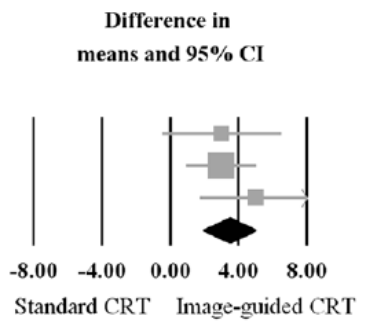
Beklenti ve yanıt optimizasyonu

- Düşük E
- Tipik So
- QRS >1
- Semptom
- >I)
- Sürekli

A

LVEF

Study name	Statistics for each study						Z-Value	p-Value	Relative weight	Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit					
Saba (2013)	3.000	1.761	3.102	-0.452	6.452	1.703	0.088	20.09		
Khan (2012)	3.000	1.045	1.093	0.951	5.049	2.870	0.004	57.04		
Bai (2011)	5.000	1.651	2.724	1.765	8.235	3.029	0.002	22.87		
Pooled estimate (fixed)	3.457	0.789	0.623	1.910	5.005	4.380	0.000			



Q = 1.132 (df = 2) with p=0.568, I-square = 0.0

Gelecek

Hastaya Özel Yaklaşım

Kalp yetmezliği

Hasta Seçimi

- Düşük EF
- Tipik Sol dal Bloğu

Beklenen optimizasyon

A LVEF

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LVESV'de düşüş

Study name	Statistics for each study						Z-Value	p-Value	Relative weight	Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit					
Khan (2012)	-20.000	3.951	15.607	-27.743	-12.257	-5.063	0.000	92.79		
Bai (2011)	-25.000	14.173	200.886	-52.779	2.779	-1.764	0.078	7.21		
Pooled estimate (fixed)	-20.360	3.805	14.482	-27.819	-12.902	-5.350	0.000			

-60.00 -30.00 0.00 30.00 60.00
Image-guided CRT Standard CRT

Q = 0.115 (df= 1) with p=0.734, I-square = 0.0

Gelecek

Hastaya Özel Yaklaşım

Kalp
yetmezliđi

Hasta Seęimi

CRT
implantasyonu

Beklenti ve yanıt
optimizasyonu

- Düşük EF
- Tipik Sol dal Blođu
- QRS >150 msn
- Semptomatik hasta (NHYA >I)
- Sürekli pace ihtiyacı vs...

- Uygun Lead pozisyonu:
 - Posterior/lateral
 - LV bazalı
 - En uzun QLV

Gelecek

Hastaya Özel Yaklaşım

- Uygun implantasyon: %
30 !!!!

Kalp
yetmezliđi

Hasta Seęimi

Beklenti ve yanıt
optimizasyonu

- Düşük EF
- Tipik Sol dal Blođu
- QRS >150 msn
- Semptomatik hasta (NHYA >I)
- Sürekli pace ihtiyacı vs...

Gelecek

Hastaya Özel Yaklaşım

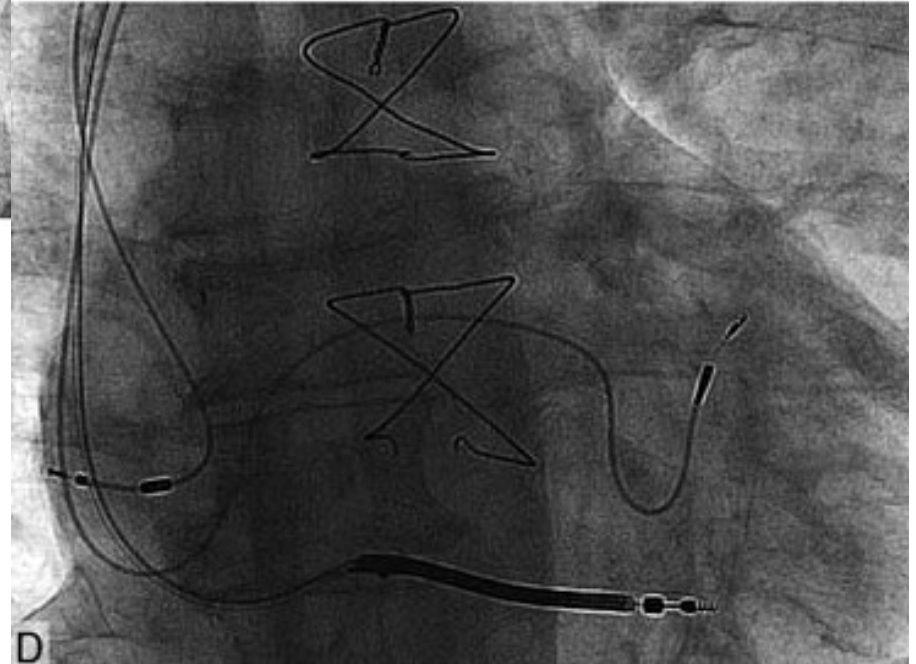
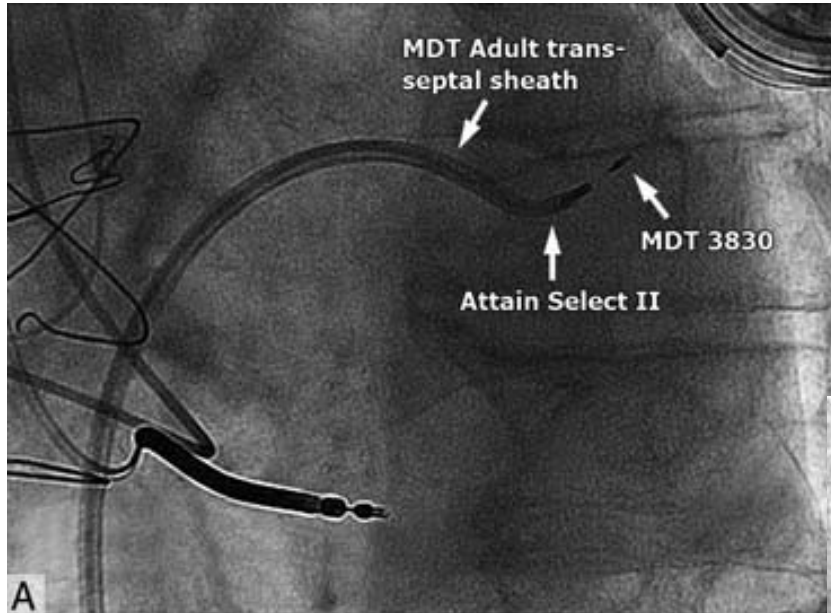
Multisite Pacing
Multipole Pacing
Endocardial LV pacing

- Multisite pacing: Birden çok CS elektrodu ile LV pacing

First author, year	n*	Study population	Lead configuration	Benefits of multisite pacing
Pappone, 2000 (67)	14	NYHA III/IV, sinus rhythm, LBBB, QRS >150 ms	Two coronary sinus leads (posterior base & lateral wall)	Increased peak dP/dt, higher aortic pulse pressure, shorter QRS duration
Leclercq, 2008 (71)	40	NYHA III/IV, permanent AF, LVEF ≤35%	Two coronary sinus leads (widest distance)	Higher LVEF
Padeletti, 2008 (68)	12	NYHA III/IV, LVEF ≤35%, QRS ≥120 ms	Two coronary sinus leads (lateral/posterolateral & anterior/anterolateral)	None
Lenarczyk, 2009 (72)	27	NYHA III/IV, LVEF ≤35%, QRS ≥120 ms	Two coronary sinus leads (widest distance)	Lower NYHA, increased VO2max & 6MWD, higher LVEF, less dyssynchrony, more responders
Ginks, 2012 (69)	22	Conventional CRT criteria	Two coronary sinus leads (widest distance)	Increased peak dP/dt
Rogers, 2012 (64)	43	NYHA II/III/IV, LVEF ≤35%, QRS ≥150 ms	Two coronary sinus leads (widest distance)	Increased 6MWD, MLWHF score and LVEF
Lenarczyk, 2012 (73)	48	NYHA III/IV, sinus rhythm, LVEF ≤35%, dyssynchrony on echocardiography	Two coronary sinus leads (widest distance)	Lower NYHA
Ogano, 2013 (75)	22	NYHA III/IV, LVEF ≤35%, QRS ≥120 ms	Two coronary sinus leads (best hemodynamic response)	Less ventricular arrhythmia

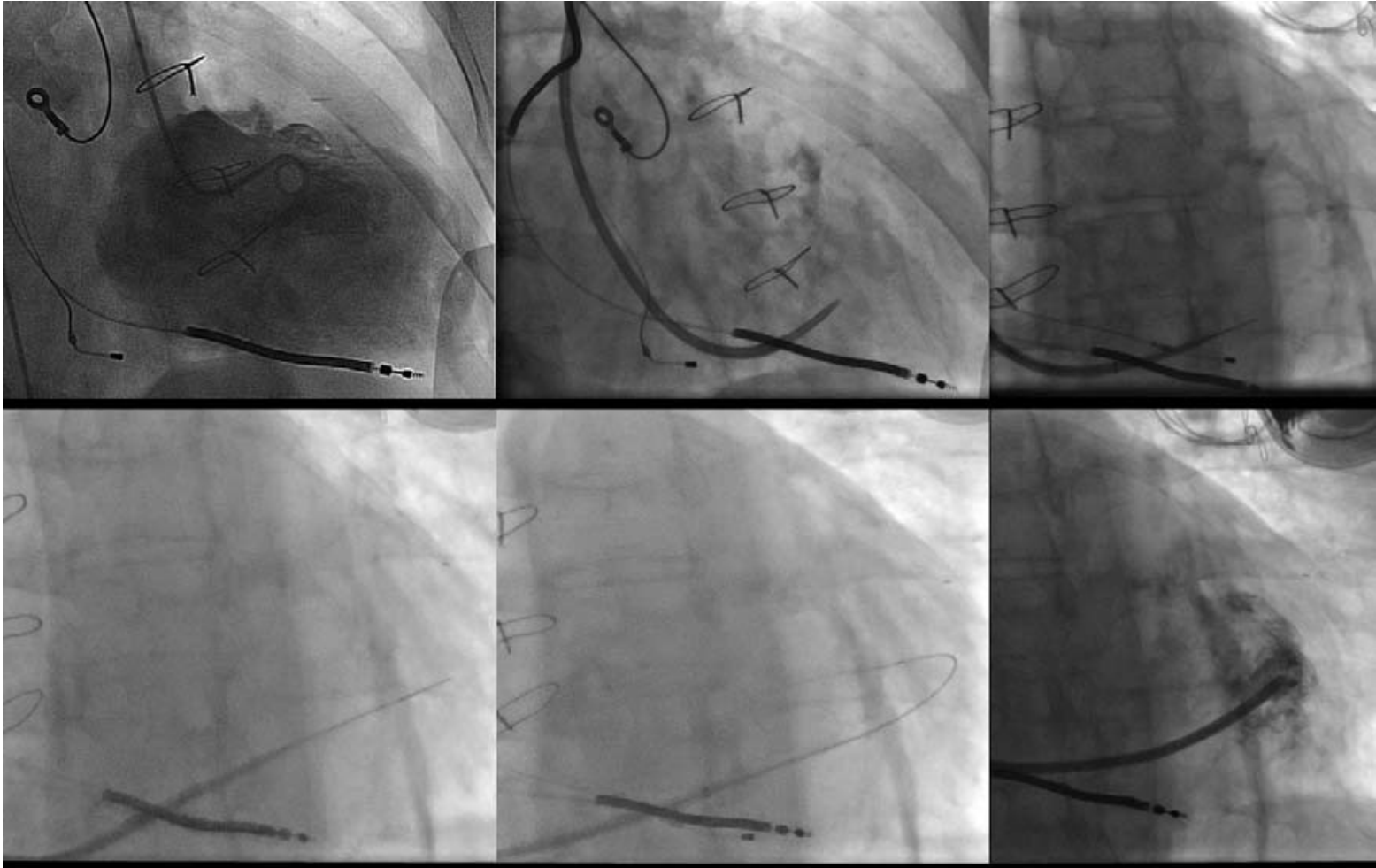
LV Endokardial Pacing

- Trans Atrial Septal



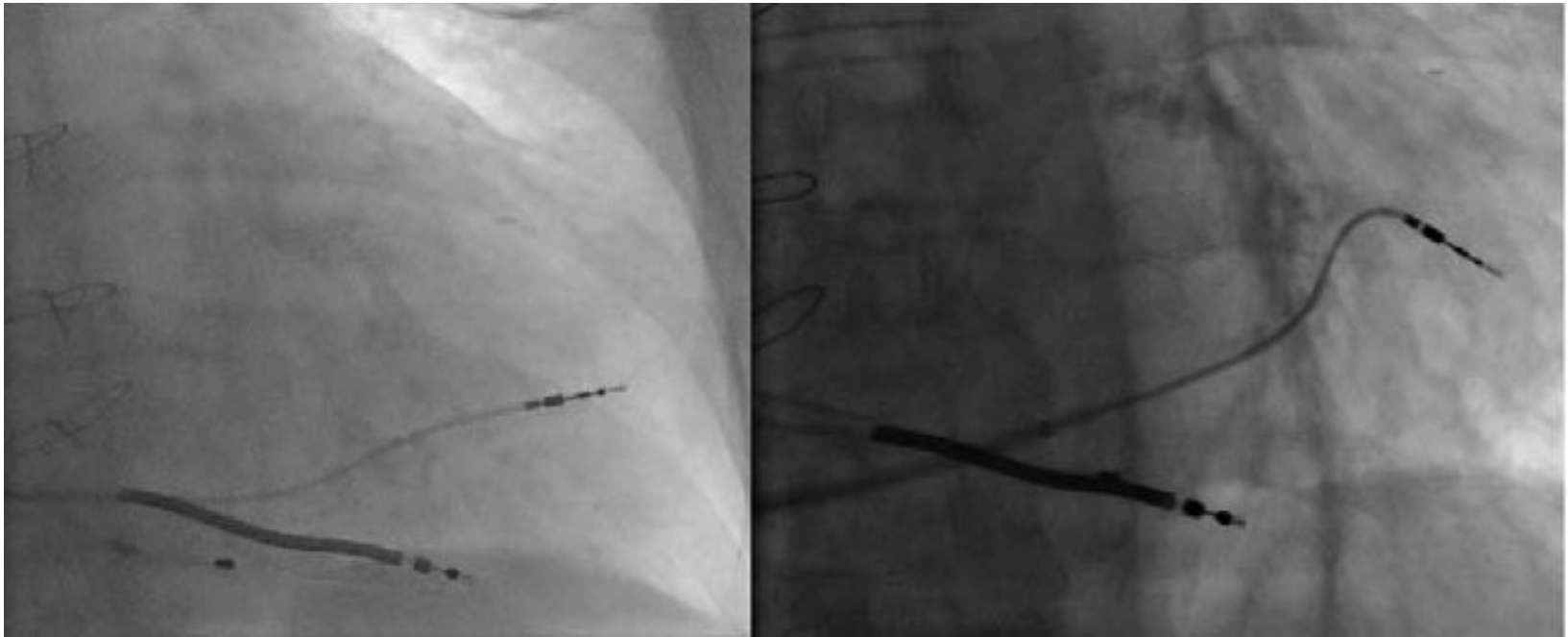
LV Endokardial Pacing

- Trans Ventriküler Septal

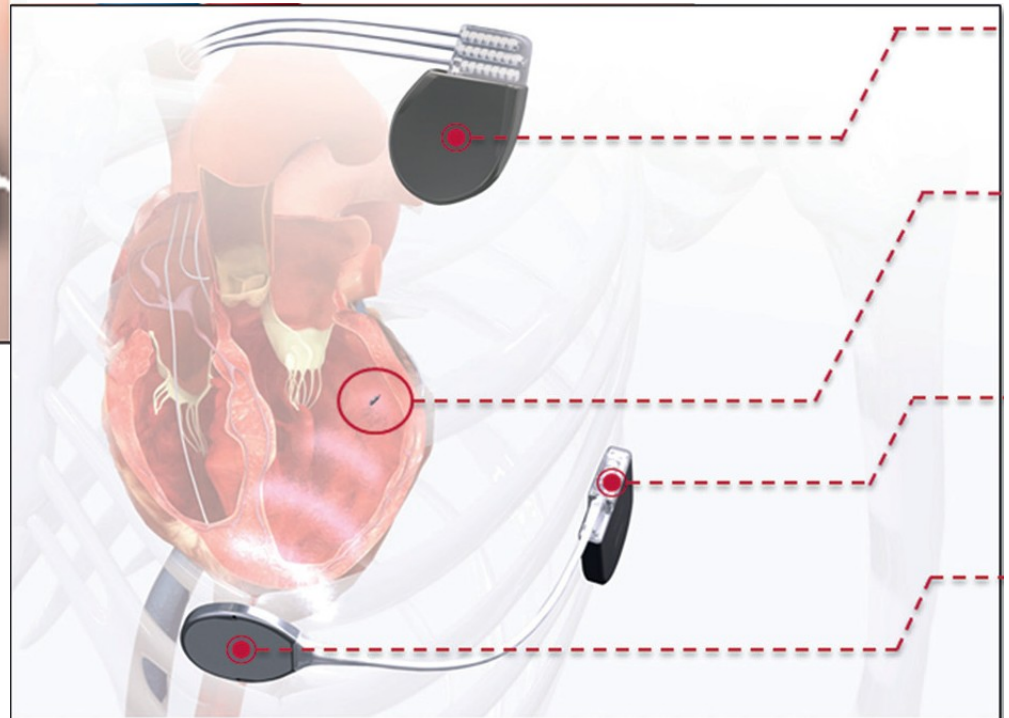
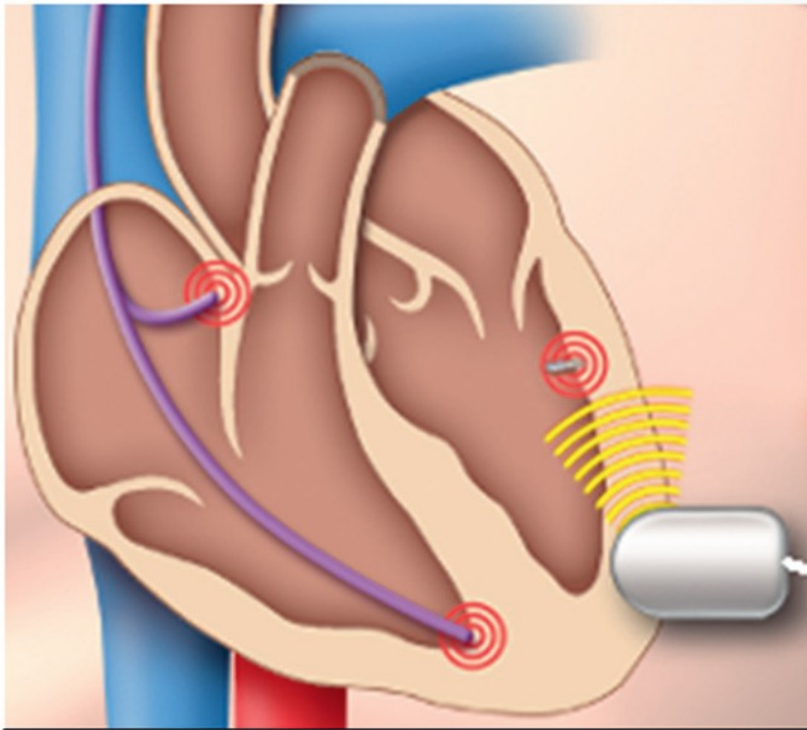


LV Endokardial Pacing

- Trans Ventriküler Septal



Multicomponent Leadless Pacing System



Feasibility, safety, and short-term outcome of leadless ultrasound-based endocardial left ventricular resynchronization in heart failure patients: results of the Wireless Stimulation Endocardially for CRT (WiSE-CRT) study

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Aims

Left ventricular (LV) endocardial pacing may address the limitations in the selection of an LV pacing site and provide improvements in cardiac resynchronization therapy (CRT) effectiveness. We report on the feasibility, the safety, and the short-term outcome of a leadless ultrasound-based technology for LV endocardial resynchronization in heart failure (HF) patients enrolled into the Wireless Stimulation Endocardially for CRT (WiSE-CRT) study.

Methods and results

Seventeen HF patients were enrolled and categorized as: (i) patients in whom attempted coronary sinus lead implantation for CRT had failed ($n = 7$); (ii) patients with a previously implanted CRT device, not responding to CRT ($n = 2$); and (iii) patients with previously implanted pacemakers or implantable cardioverter-defibrillator and meeting the standard indications for CRT ($n = 8$). System implantation was achieved in 13 patients (76.5%); mean R-wave amplitude was 5.6 ± 3.2 mV and the mean pacing threshold was 1.6 ± 1.0 V, respectively. In one patient, no sufficient pacing thresholds were found; in three patients pericardial effusion occurred. Biventricular pacing was recorded in 83% and 92% of the patients at 1 month and 6 months, respectively. QRS duration was shorter during biventricular pacing compared with right ventricular pacing at 1 month (-41 ms; $P = 0.0002$) and 6 months (-42 ms; $P = 0.0011$), respectively. At the 6-month follow-up, two-thirds of the patients had at least one functional class change. Left ventricular ejection fraction significantly increased ($P < 0.01$) by 6 points at the 6-month follow-up.

Conclusion

The feasibility of providing an endocardial stimulation for CRT with a leadless technology was successfully demonstrated. Despite the promising results for a novel technology, further study is required to definitively conclude the safety and the performance of the system.

Clinical Trial Registration Information

NCT01294527.

Keywords

Cardiac resynchronization therapy • Outcome • Heart failure • Cardiac pacing