Kardiyojenik şokta Farmakolojik yönetimdeki değişiklikler

Dr. Zerrin Sungur

AKIŞ

- Geleneksel inotroplar
- Kalsiyum mobilizasyonu
- Levosimendan
- Omekamtiv
- İstaroksim

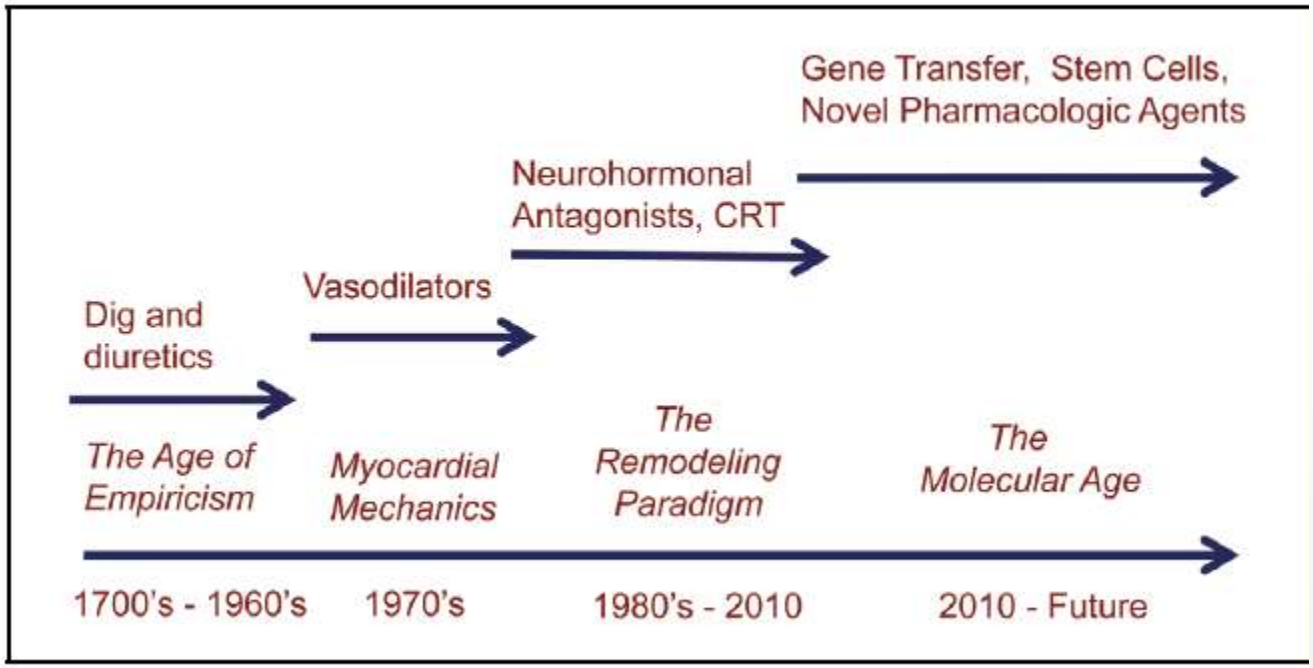
Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

REVIEW

Novel Therapies for Heart Failure

– Where Do They Stand? –

Barry Greenberg, MD



inotroplar ve prognoz

- **AKY inotroplar (Dob ve Mil) vazodialtatörlere (NG ve Nes) mortalite X2**

ADHERE 2005

- **KŞ Adr ile Dob+NA göre laktik asidoz, disritmi ↑, gastrik perfüzyon ↓**

Levy B, CC Med 2011

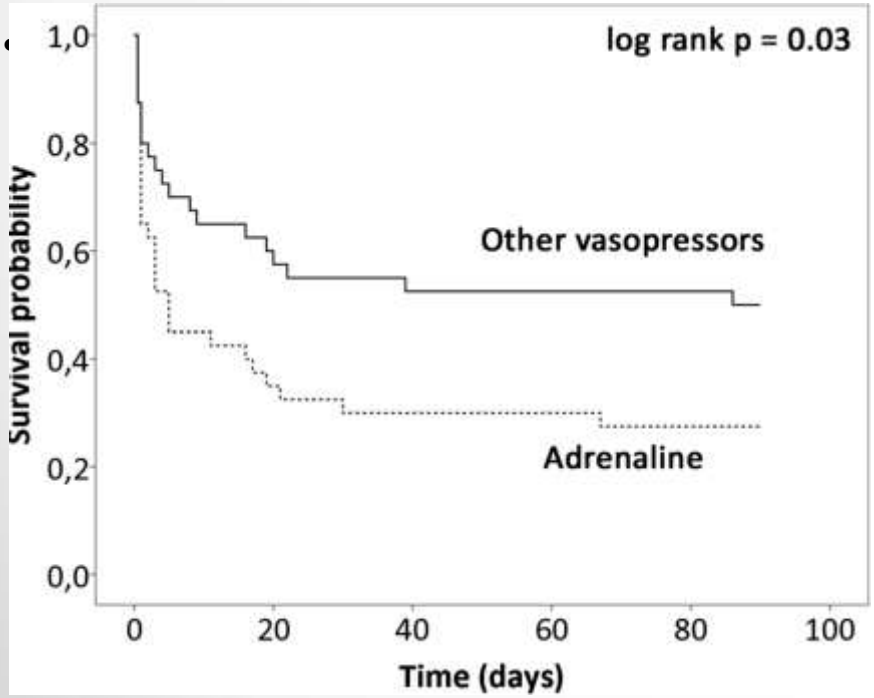
Tarvasmäki et al. Critical Care (2016) 20:208
DOI 10.1186/s13054-016-1387-1

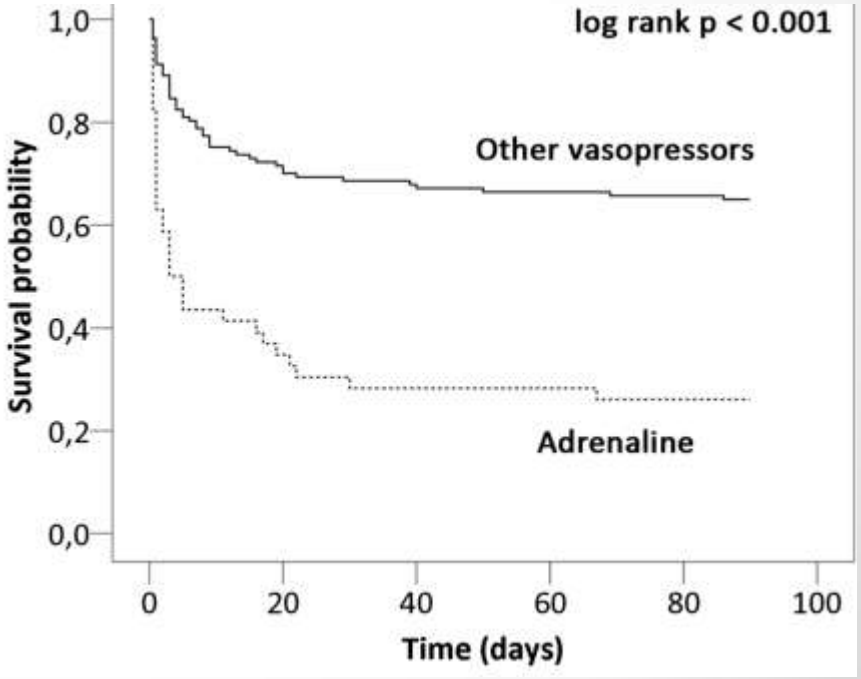
Critical Care

RESEARCH Open Access

Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality

Tuukka Tarvasmäki[1*], Johan Lassus[2], Marjut Varpula[2], Alessandro Sionis[3], Reijo Sund[4], Lars Køber[5], Jindrich Spinar[6], John Parissis[7], Marek Banaszewski[8], Jose Silva Cardoso[9], Valentina Carubelli[10], Salvatore Di Somma[11], Alexandre Mebazaa[12], Veli-Pekka Harjola[1] and for the CardShock study investigators





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doi:10.1016/S0735-1097(02)02968-6

Heart Failure

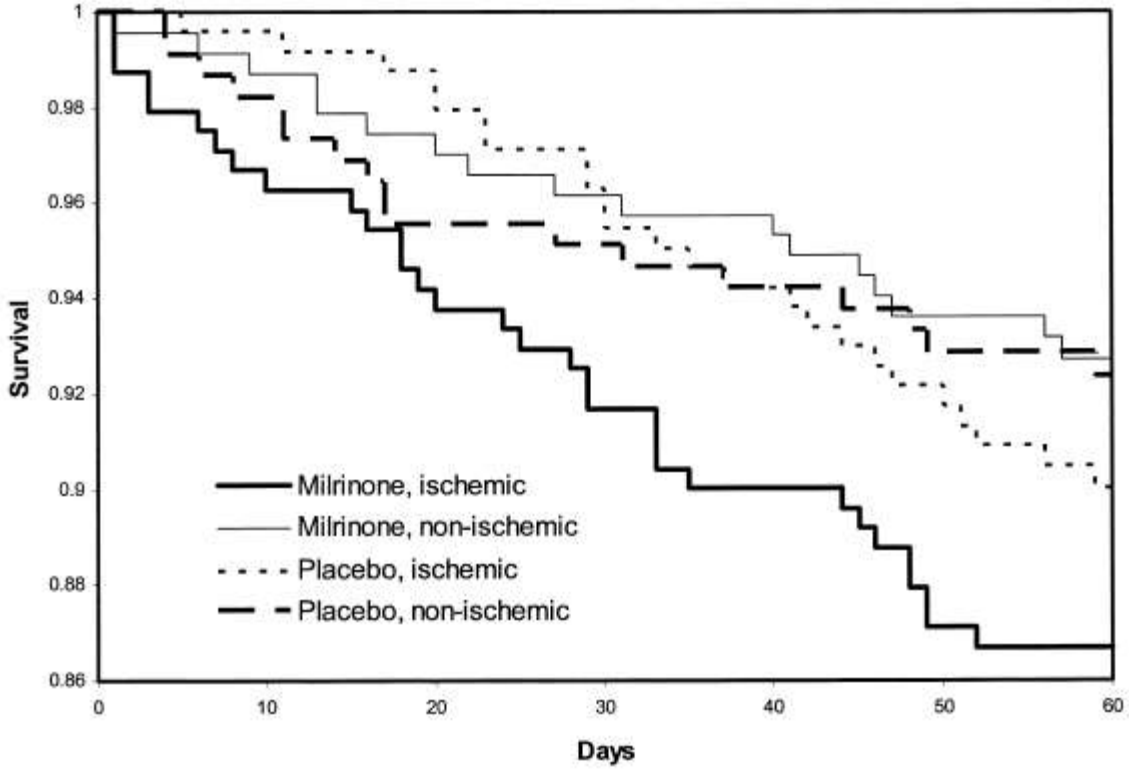
Heart Failure Etiology and Response to Milrinone in Decompensated Heart Failure

Results From the OPTIME-CHF Study

G. Michael Felker, MD,* Raymond L. Benza, MD,† A. Bleakley Chandler, MD,‡
Jeffrey D. Leimberger, PHD,* Michael S. Cuffe, MD,* Robert M. Califf, MD,* Mihai Gheorghiade, MD,§
Christopher M. O'Connor, MD,* for the OPTIME-CHF Investigators

Durham, North Carolina; Birmingham, Alabama; Augusta, Georgia; and Chicago, Illinois

- **OPTIME-HF n=950**
- **Mil vs plasebo**
- **Kardiyak yatış süresi**



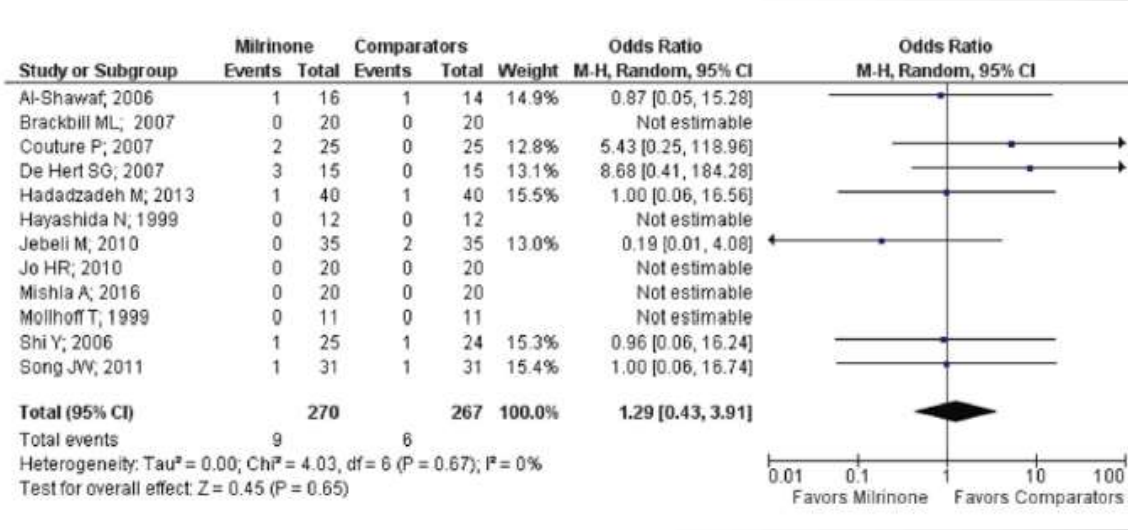
Impact of Milrinone Administration in Adult Cardiac Surgery Patients: Updated Meta-Analysis

Masahiro Ushio, MD,* Moritoki Egi, MD, PhD,† Junji Wakabayashi, MD,† Taichi Nishimura, MD,† Yuji Miyatake, CE,‡ Norihiko Obata, MD, PhD,† and Satoshi Mizobuchi, MD, PhD†

- **13 çalışma, >500 hasta**
- **Farklı inotroplar ve plasebo**
- **KABG (↓ EF, LCOS)**
- **Kapak cerrahisi**

⇒heterojen

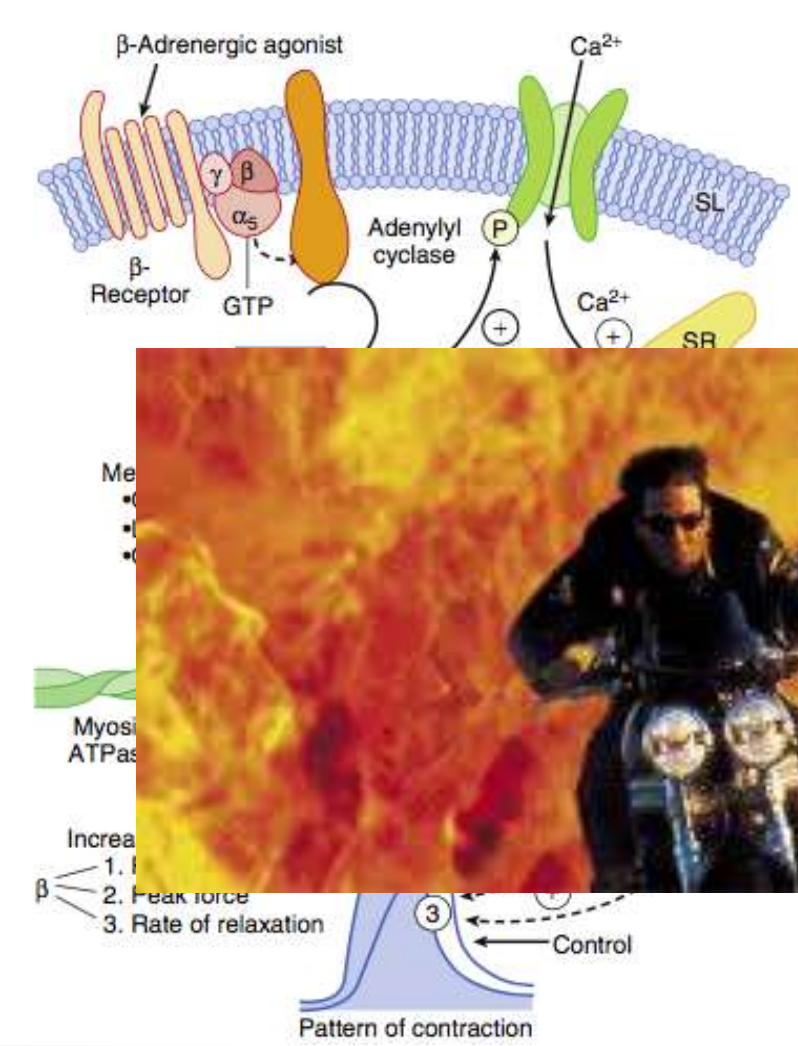
⇒ventriküler disritmi



Study or Subgroup	Milrinone Events	Total	Comparators Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Shawaf; 2006	1	16	1	14	14.9%	0.87 [0.05, 15.28]
Brackbill ML; 2007	0	20	0	20		Not estimable
Couture P; 2007	2	25	0	25	12.8%	5.43 [0.25, 118.96]
De Hert SG; 2007	3	15	0	15	13.1%	8.68 [0.41, 184.28]
Hadadzadeh M; 2013	1	40	1	40	15.5%	1.00 [0.06, 16.56]
Hayashida N; 1999	0	12	0	12		Not estimable
Jebeli M; 2010	0	35	2	35	13.0%	0.19 [0.01, 4.08]
Jo HR; 2010	0	20	0	20		Not estimable
Mishla A; 2016	0	20	0	20		Not estimable
Mollhoff T; 1999	0	11	0	11		Not estimable
Shi Y; 2006	1	25	1	24	15.3%	0.96 [0.06, 16.24]
Song JW; 2011	1	31	1	31	15.4%	1.00 [0.06, 16.74]
Total (95% CI)		**270**		**267**	**100.0%**	**1.29 [0.43, 3.91]**
Total events	9		6			

Heterogeneity: Tau² = 0.00; Chi² = 4.03, df = 6 (P = 0.67); I² = 0%

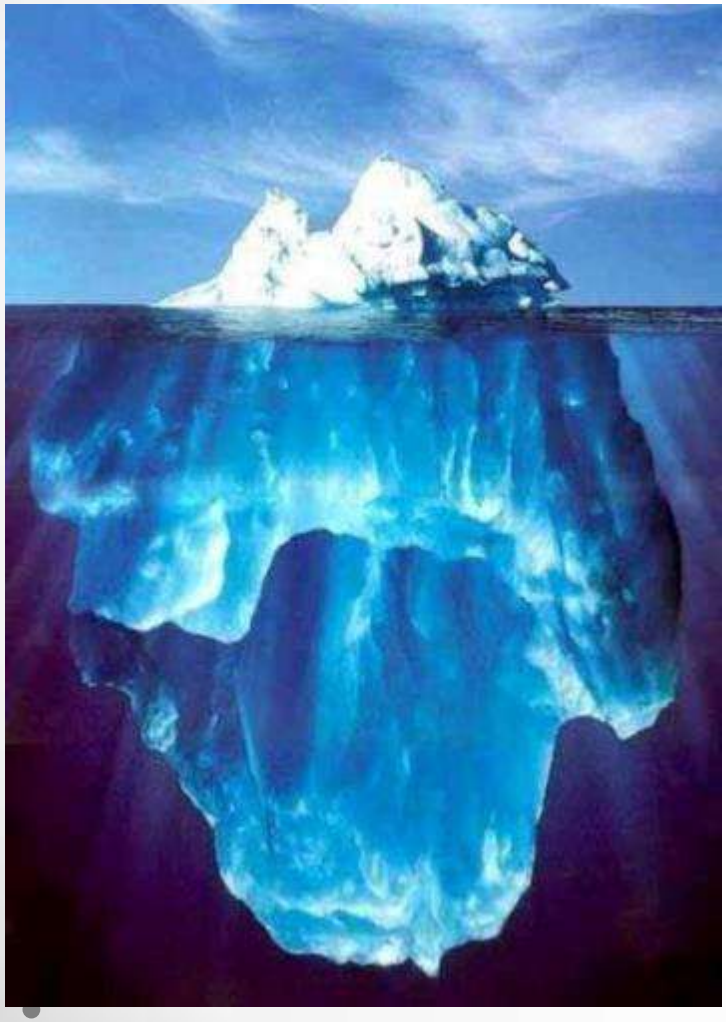
Test for overall effect: Z = 0.45 (P = 0.65)



✓ O2 tüketiminde ↑

a++
mobilizasyonu

Kalsiyum mobilizasyonu



- **Diastolde Ca'un SR'a girmesi ATP gereksinimi**
- **Diastolik disfonksiyon**
- **cAMPbağımlı ilaçlar:**

*** (+) kronotropik: iskemi**

*** Troponin I fosfatlanır ⇒ Ca'a duyarsızlık**

- **Hücre içi Ca ↑:**

***erken/ gecikmiş depolarizasyon VEV, disritmiler**

***miyokardial remodeling**

***miyosit apoptoz**

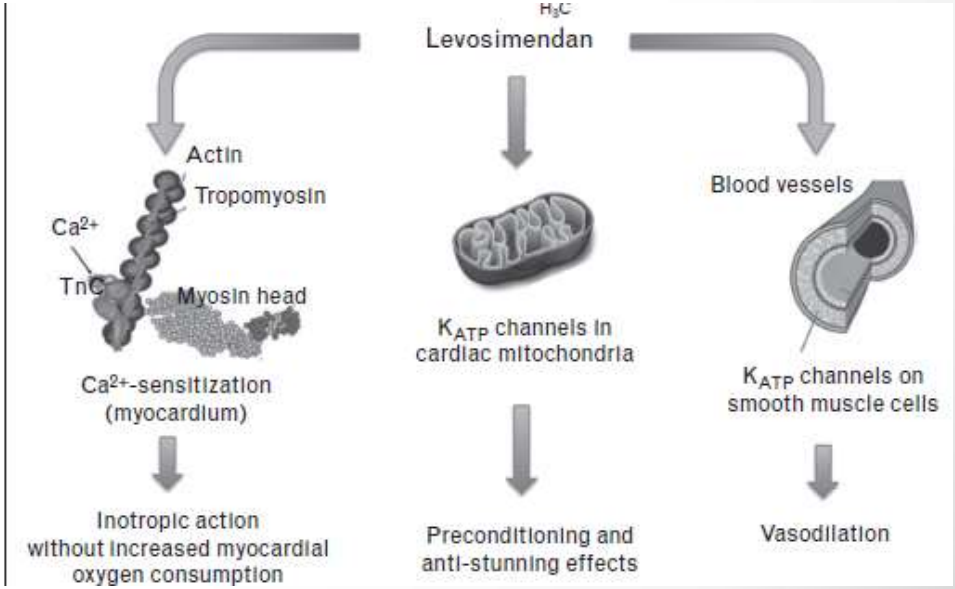
Nasıl bir inotropi???

Ca++ mobilizasyonu mu?

Mevcut Ca++ etkin kullanmak ?
Ca++ duyarlılaşma veya etkin kullanma

Levosimendan

- **Hücre içi Ca'a Troponin C duyarlılığında ↑⇒ (+) inotropi ve lusitropi**
- **ATP duyarlı K kanalları ⇒ vazodilatasyon**
- **PDE3 inhibisyonu**



International Journal of Cardiology 222 (2016) 303–312

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

Review

Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper

Dimitrios Farmakis [a,*], Julian Alvarez [b], Tuvia Ben Gal [c], Dulce Brito [d], Francesco Fedele [e], Candida Fonseca [f], Anthony C. Gordon [g], Israel Gotsman [h], Elena Grossini [i], Fabio Guarracino [j], Veli-Pekka Harjola [k],

- ✓ **Lusitropi**
- ✓ **İskemi –reperfüzyon, *antistunning***
- ✓ **Remodeling'de ↓**
- ✓ **Ventrikülo-arteriyel eşleşme**
- ✓ **Endotel işlevi, enflamasyon**
- ✓ **Diğer organlar (böbrek!)**

Levosimendan

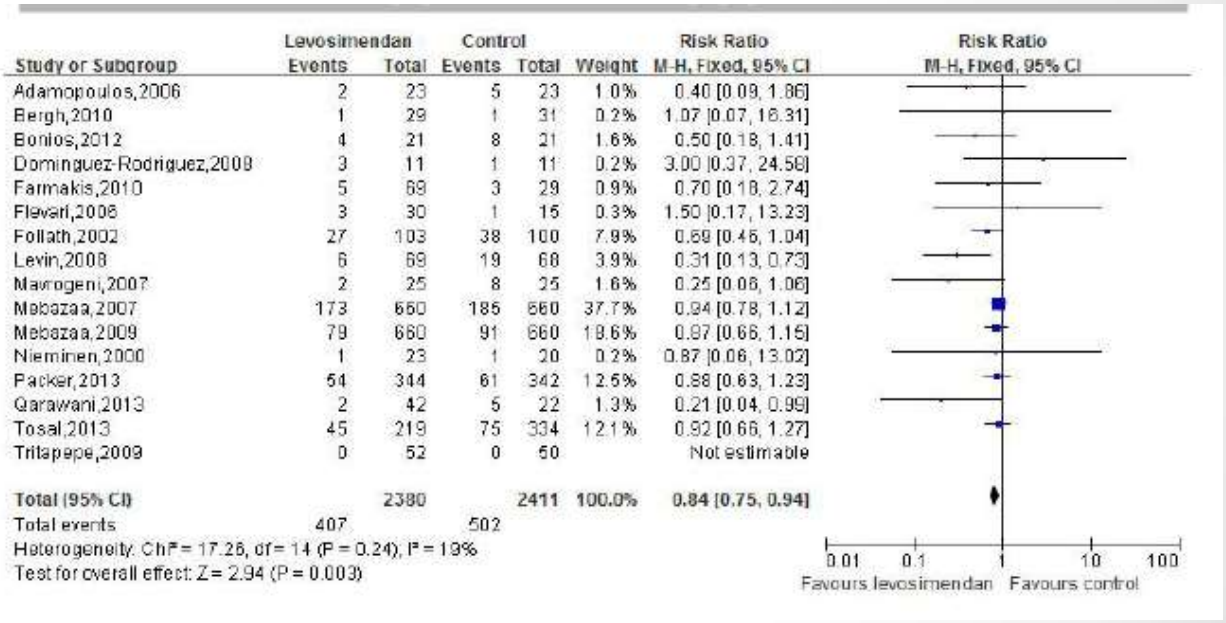
- **LIDO (2002) Levo vs Dob** *ağır KY hemodinami, mortalite*
- **RUSSLAN (2002)** *MI sonrası KY ve mortalite*
- **SURVİVE (2007)** *AKY'de*
- **REVİVE-II (2013)** *AKY'de*

Levosimendan Treatment for Heart failure: A Systematic Review and Meta-Analysis

Bojun Gong, Zicheng Li, Philip Ching Yat Wong,

- **25 çalışma 5300 hasta**
- **Levo vs Dob/plasebo**
- **Mortalite**
- **AKY,** KABG

Dob göre mortaliteyi azaltmakta daha iyi



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

- **Periop KV disfonksiyon (↓EF, IABP, ↑↑ inotrop)**
- **Levo vs plasebo**
- **30gün mortalite**
- **≅500 hastada kesildi(!)**

- ✓ **DOZ**
- ✓ **Hasta seçimi KABG vs mitral**
- ✓ **Zamanlama**

Outcome	Levosimendan (N=248)	Placebo (N=258)	Difference (95% CI)†	P Valu
Primary outcome				
30-Day mortality — no. (%)	32 (12.9)	33 (12.8)	0.1 (−5.7 to 5.9)	0.97
Secondary outcomes				
Acute kidney injury, according to RIFLE criteria — no./total no. (%)‡				
Risk	41/247 (16.6)	55/258 (21.3)	−4.7 (−11.5 to 2.1)	0.18
Injury	26/247 (10.5)	27/258 (10.5)	0.1 (−5.3 to 5.4)	0.98
Failure	17/247 (6.9)	22/258 (8.5)	−1.6 (−6.3 to 3.0)	0.49
Renal-replacement therapy — no. (%)	24 (9.7)	33 (12.8)	−3.1 (−8.6 to 2.4)	0.27
Death or renal-replacement therapy — no. (%)	42 (16.9)	49 (19.0)	−2.1 (−8.7 to 4.6)	0.55
Duration of mechanical ventilation — hr				
Median	19	21	−2 (−5 to 1)	0.48
Interquartile range	14 to 40	14 to 41		
Duration of ICU stay — hr				
Median	72	84	−12 (−21 to 2)	0.08
Interquartile range	46 to 114	48 to 139		
Duration of hospital stay — days				
Median	14	14	0 (−1 to 2)	0.39
Interquartile range	8 to 21	9 to 21		
Need for open-label levosimendan — no. (%)	2 (0.8)	8 (3.1)	−2.3 (−4.7 to 0.1)	0.11
Interruption of infusion due to adverse events — no./total no. (%)	9/236 (3.8)	4/246 (1.6)	2.2 (−0.7 to 5.1)	0.17

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

- **EF<%35 Levo vs plasebo**
- **Operasyonda**
- **30günlük mortalite, kardiyak ve renal prognoz**
- **≅900 hasta**

End Point	Levosimendan (N=428)	Placebo (N=421)	Odds Ratio (95% CI)†	P Value
Primary end points — no. (%)				
Four-component end point‡	105 (24.5)	103 (24.5)	1.00 (0.66–1.54)	0.98
Two-component end point§	56 (13.1)	48 (11.4)	1.18 (0.76–1.82)	0.45
Components of primary end points — no. (%)				
Death at 30 days	15 (3.5)	19 (4.5)	0.77 (0.38–1.53)	0.45
Renal-replacement therapy at 30 days	9 (2.1)	16 (3.8)	0.54 (0.24–1.24)	0.15
Myocardial infarction at 5 days	67 (15.7)	63 (15.0)	1.06 (0.73–1.53)	0.78
Use of mechanical cardiac assist device at 5 days	47 (11.0)	38 (9.0)	1.24 (0.79–1.95)	0.34
Secondary end points¶				
Duration of stay in ICU — days‖				
Median	2.8	2.9	—	0.25
Interquartile range	1.6–4.8	1.8–4.9		
Low cardiac output syndrome — no. (%)‖	78 (18.2)	108 (25.7)	0.62 (0.44–0.88)	0.007
Use of inotrope at or beyond 24 hr after infusion initiation — no. (%)‖	235 (54.9)	264 (62.7)	0.71 (0.53–0.94)	0.02

- ✓ **Mortalitede fark ∅, LCOS (+)**
- ✓ **Sayı?**

Omekamtiv

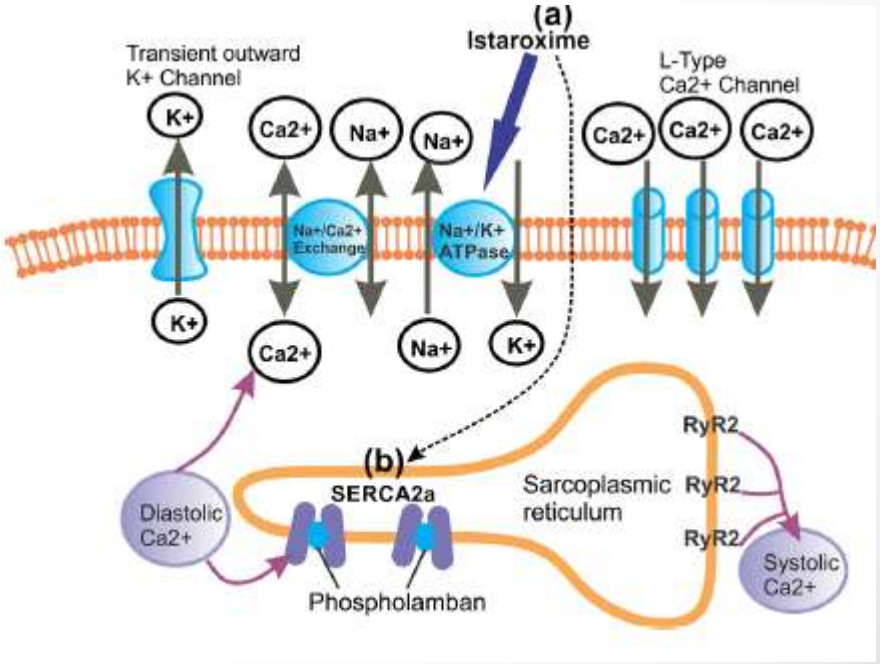
- **İlk selektif miyozin aktivatörü miyokarda spesifik**
- **ATPaz aktivasyonu ⇒ miyofilaman etkileşimi ↑ ⇒ etkin kasılma**
- **Sistolik performans ↑ diastol**
- **Ca mobilizasyonu YOK!**

Omekamtiv

- **İskemik hastada**
- **ATOMIC-HF** *faz 2*
- **COSMIC-HF** *faz 2*
- **GALACTIC –HF** *faz 3; 8000 hasta*

Istaroksim

- **Na-K ATPaz inhibisyonu ve SR'da Ca ATPaz uyarılması**
- **Ca döngüsünde düzelme**
- **Lusitropik**



HORIZON ***istaroksim vs plasebo***

- ✓ **↑ dozla CI ↑**
- ✓ **PCWP ↓ (tüm dozlarda)**
- ✓ **Troponin N**
- ✓ **Böbrek işlevi korunmuş**

kısa vade çalışması (6 saat)

Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome (Protocol)

Unverzagt S, Hirsch K, Buerke M, Thiele H, Haerting J, Werdan K, Prondzinsky R

THE COCHRANE COLLABORATION®

- **≅4000 kaynaktan 3 çalışma ve 63 hasta**
- **Makrodolaşım genellikle toparlanmış; mikro dolaşım???**
- **Bu grupta RKÇ zor ve pahalı**

European Journal of Heart Failure (2015) 17, 544–558
doi:10.1002/ejhf.289

REVIEW

Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine

- Dobutamine may be used to increase cardiac output; levosimendan may be considered, especially in CHF patients on oral beta-blockade
- Vasopressors should only be used if there is a strict need to maintain systolic BP in the presence of persistent hypoperfusion; if needed, norepinephrine is recommended over dopamine

GELECEK…

- **Ularatid**
- **Seralaksin**
- **Guanilat siklaz uyaranları**
- **Gen tedavisi**

İdeal inotrop

1. Kasılmayı seçici bir yolla arttırmalı
2. Lusitropik etkisi olmalı
3. Ritim düzensizliklerine yol açmamalı
4. Koroner akımı düşük olan yerde arttırmalı

Son söz

- **Doğru «hedef noktalar»; makro değişkenlerden fazlası**
- **Kasılmada Ca'un etkin kullanılması**
- **Diyastolik işlevin gözetilmesi**