

KRONİK KALP YETERSİZLİĞİNİN KANITA DAYALI TEDAVİSİ

Editör

Mehmet Timur SELÇUK

Yazar

Hatice SELÇUK

© Copyright 2019

Bu kitabın, basım, yayın ve satış hakları Akademisyen Kitabevi A.Ş.'ne aittir. Anılan kuruluşun izni alınmadan kitabın tümü ya da bölümleri mekanik, elektronik, fotokopi, manyetik kağıt ve/veya başka yöntemlerle çoğaltılamaz, basılamaz, dağıtılamaz. Tablo, şekil ve grafikler izin alınmadan, ticari amaçlı kullanılamaz. Bu kitap T.C. Kültür Bakanlığının bandrolü ile satılmaktadır.

ISBN

978-605-258-694-5

Kitap Adı

Kronik Kalp Yetersizliğinin Kanıtı Dayalı Tedavisi

Editör

Mehmet Timur SELÇUK

Yayın Koordinatörü

Yasin Dilmen

Sayfa ve Kapak Tasarımı

Akademisyen Dizgi Ünitesi

Yayıncı Sertifika No

25465

Baskı ve Cilt

Sonçağ Matbaacılık

Bisac Code

MED010000

DOI

10.37609/akya.1369

GENEL DAĞITIM

Akademisyen Kitabevi A.Ş.

Halk Sokak 5 / A

Yenişehir / Ankara

Tel: 0312 431 16 33

siparis@akademisyen.com

www.akademisyen.com

ÖNSÖZ

1980 öncesinde kalp yetersizliği tedavisinin temeli yatak istirahati, hareketsizlik, sıvı kısıtlaması, yaşam tarzı değişiklikleri, dijitaller ve diüretikler üzerine kuruluydu. 1980' lerde yapılan çalışmalar sonucunda kalp yetersizliği tedavisinde fizyopatolojik mekanizmalar üzerine etkili farmakolojik ajanların kullanıldığı bir dönem başlamıştır. Bu döneme kadar sadece dijital ve diüretiklerle yapılan farmakolojik tedaviye vazodilatör ilaçlar da eklenmiştir. 1990' lı yıllarda kalp yetersizliğinde sağ kalımı arttıran, prognozda ve yaşam kalitesinde artış sağlayan nörohormonal ilaçların ve beta blokerlerin tedavide kullanılması ile daha önceki yıllara göre kalp yetersizliği tedavisinde tatmin edici sonuçlara ulaşılmaya başlanmıştır. Kalp yetersizliği tedavisinde 2000' li yıllara kadar olan dönem sadece farmakolojik ajanların kullanıldığı bir dönemken; 2000' li yıllar, kalp yetersizliği tedavisinde farmakolojik ajanlara ek olarak cihazların da kullanılmaya başlandığı bir dönemi oluşturmaktadır. 2010 ve sonrası kalp yetersizliği tedavisinde gen terapileri, hücre implantasyonu, hücre rejenerasyonu ve ksenotransplantasyon gibi hücrenel ve genetik tedavilerin araştırıldığı bir dönemdir. Günümüzde gelişmiş tedavi şekillerinin rutin kullanıma girebilmesi için, daha çok çalışmaya ihtiyaç vardır. Bu kitap güncel kalp yetersizliği kılavuzlarının tedavi önerileri dikkate alınarak hazırlanmış, kronik kalp yetersizliği tedavisinde yer alan her bir ilaç grubunun kalp yetersizliği tedavisinde kullanılmasına temel oluşturan bilimsel kanıtlar kısaca sunulmuş ve bu ilaç gruplarının kalp yetersizliği tedavisinde kullanıma nasıl girdiğine ışık tutulmaya çalışılmıştır. Günlük pratikte kronik kalp yetersizliği tedavisinde karşılaşılan sorunların daha kolay aşılabilmesi için, tedavide kullanılan ilaçların farmakolojik özelliklerini bilmek önemlidir. Bu amaçla, aynı yapısal grupta olmasına

rağmen etkinliđi ve farmakokinetiđi farklı bazı ilaçların özellikleri ayrıntılı olarak ele alınmıştır. Farmakolojik tedavi dışında, kronik kalp yetersizliđi tedavisinde önemli bir yeri olan yaşam tarzı deđişikleri ve egzersiz gibi diđer destekleyici tedavilere de yer verilmiştir. Ayrıca bu kitap, kronik kalp yetersizliđi ile birlikte bulunabilen hastalıkların yönetimi konusunda da bilgiler içermektedir. Teknolojinin ilerlemesi ile birlikte kronik kalp yetersizliđi tedavisinde önemli bir yer tutan cihaz tedavisi, farklı bir bölüm olarak kitapta yer bulmuş, bu konuda yapılmış çalışmalar detaylı olarak incelenmiş, cihaz tedavisinin kronik kalp yetersizliđindeki kullanım önerileri güncel kılavuzların ışığında ortaya konmuş ve böylelikle kronik kalp yetersizliđi tedavi yönetiminde yer alan cihaz dışı tedavi ve cihaz tedavisi, bir bütün olarak aynı kitapta sunulmuştur.

İÇİNDEKİLER

BÖLÜM I

Kronik Kalp Yetersizliğinde Cihaz Dışı Tedavi	1
1. Giriş.....	1
2. Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Tedavi.....	6
3. Kalp Yetersizliğinde Kullanılan İlaçlar	9
3.1. Anjiyotensin Dönüştürücü Enzim İnhibitörleri (ADEİ).....	9
3.1.1. Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde ADEİ Çalışmaları.....	10
3.2. Anjiyotensin Reseptör Blokerleri (ARB)	17
3.3. Anjiyotensin Reseptör Nephilisin İnhibitörü (ARNİ)	19
3.4. Beta Blokerler	22
3.4.1. Kalp Yetersizliğinde Beta Bloker Çalışmaları	27
3.4.2. Kanıtı Dayalı Olarak Kalp Yetersizliğinde Kullanılan Beta Blokerler	34
3.4.2.1. Metoprolol.....	34
3.4.2.2. Karvedilol.....	37
3.4.2.3. Bisoprolol	41
3.4.2.4. Nebivolol	42
3.5. Mineralokortikoid Reseptör Antagonistleri (MRA)	43
3.5.1. Kalp Yetersizliğinde MRA Çalışmaları	43
3.6. Diüretikler	49
3.7. İvabradin.....	52
3.8. Hidralazin- İsosorbid dinitrat (H- İSDN).....	55
3.8.1. Kalp Yetersizliğinde H- İSDN Çalışmaları	55
3.9. Digoksin.....	58
3.9.1. Kalp Yetersizliğinde Digoksin Çalışmaları	58
3.10. Vasopressin Antagonistleri.....	65
3.10.1. Kalp Yetersizliği Tedavisinde Kullanımda Olan Vasopressin Antagonistleri	66

3.10.1.1. Tolvaptan.....	66
3.10.1.2. Konivaptan.....	71
3.11. N- 3 PUFA (Omega 3- Çoklu Doymamış Yağlar).....	73
3.12. Statinler.....	74
3.13. Antikoagülasyon.....	75
3.14. Tip V Fosfodiesteraz İnhibitörü- Sildenafil.....	76
3.15. Hormon Tedavisi ve Besin Takviyeleri.....	77
3.16. Kalp Yetersizliği Olan Gebelerde İlaç Seçimi.....	77
4. Kalp Yetersizliğinde Kullanılmaması Gereken İlaçlar.....	78
5. Kalp Yetersizliğinde Görülen Komorbid Durumlarda Tedavi.....	79
5.1. Koroner Arter Hastalığı.....	79
5.2. Kaşeksi ve Sarkopeni.....	80
5.3. Kanser.....	80
5.4. Merkezi Sinir Sistemi Hastalıkları.....	81
5.5. Diyabetes Mellitus.....	81
5.6. Erektile Disfonksiyon.....	82
5.7. Gut ve Artrit.....	83
5.8. Hipertansiyon.....	83
5.9. Hipokalemi ve Hiperkalemi.....	84
5.10. Anemi.....	85
5.11. Demir Eksikliği.....	86
5.12. Uyku Solunum Bozukluğu.....	86
5.13. Böbrek Fonksiyon Bozukluğu.....	86
5.14. Pulmoner Hastalıklar.....	87
5.15. Kapak Hastalıkları.....	87
6. Son Dönem (Evre- D Refrakter) Kalp Yetersizliği Olan Hastaların Tedavisi.....	88
7. Kalp Yetersizliği Tedavisinde İlaç Dışı Yaklaşım.....	92
7.1. Diyet- Sıvı Kısıtlaması- Yaşam Tarzı Değişikliği.....	92
7.2. Fiziksel Aktivite.....	93
7.3. Kalp Yetersizliği Hastalarının Eğitimi- Bakımı- Aşılama.....	93
8. Korunmuş Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Tedavi.....	94

Liste 1. Kronik DEF- KY' de Kullanılan İlaçların Günlük Dozları	97
Liste 2. Kalp Yetersizliğinde Günlük Diüretik Dozları.....	98
Kaynaklar.....	99

BÖLÜM II

Kalp Yetersizliğinde Cihaz Tedavisi.....	115
1. Giriş.....	115
2. Kardiyak Resenkronizasyon Tedavi.....	115
2.1. Semptomatik Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Kardiyak Resenkronizasyon Tedavi.....	118
2.1.1. NYHA Fonksiyonel Sınıfı I/ II Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Kardiyak Resenkronizasyon Tedavi.....	118
2.1.2. NYHA Fonksiyonel Sınıfı III/ IV Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliğinde Kardiyak Resenkronizasyon Tedavi.....	120
2.1.3. Atriyal Fibrilasyon Bulunan Kalp Yetersizliğinde Kardiyak Resenkronizasyon Tedavi.....	124
2.1.4. Kalp Pili Endikasyonu Bulunan Kalp Yetersizliğinde Kardiyak Resenkronizasyon Tedavi.....	125
2.1.5. Biventriküler Kalp Pili Yerleştirilmesi.....	128
3. Kalp Yetersizliğinde İmplant Edilebilir Kardiyak Defibrilatör Tedavisi	128
3.1. İskemik Kardiyomiyopatide Ani Ölümden Birincil Koruma Çalışmaları	129
3.2. İskemik Olmayan Kardiyomiyopatide Ani Ölümden Birincil Koruma Çalışmaları	131
3.3. Kalp Yetersizliğinde Ani Ölümden İkincil Koruma Çalışmaları.....	132
3.4. Kalp Yetersizliğinde İmplant Edilebilir Kardiyak Defibrilatör Endikasyonları.....	132
3.4.1. Birincil Koruma Endikasyonları.....	132
3.4.2. İkincil Koruma Endikasyonları	133
Kaynaklar.....	135
Kısaltmalar	139

KAYNAKLAR

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200.
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239.
3. Orsborne C, Chaggar PS, Shaw SM, Williams SG. The renin-angiotensin-aldosterone system in heart failure for the non-specialist: the past, the present and the future. *Postgrad Med J*. 2017;93(1095):29-37.
4. Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF. *Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine*. Elsevier Health Sciences; 2018.
5. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70(6):776-803.
6. Maggioni AP, Anker SD, Dahlstrom U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013;15(10):1173-1184.
7. Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316(23):1429-1435.
8. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325(5):293-302.

9. Investigators S, Yusuf S, Pitt B, Davis CE, Hood WB, Jr., Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 1992;327(10):685-691.
10. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE Investigators. *Circulation.* 1994;90(4):1731-1738.
11. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet.* 1993;342(8875):821-828.
12. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N Engl J Med.* 1995;333(25):1670-1676.
13. Garg R, Yusuf S, Bussmann WD, et al. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *Jama.* 1995;273(18):1450-1456.
14. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. 2003;362(9386):772-776.
15. Anand IS, Fisher LD, Chiang Y-T, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). 2003;107(9):1278-1283.
16. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. 2000;355(9215):1582-1587.
17. Velazquez EJ, Pfeffer MA, McMurray JV, et al. VALsartan In Acute myocardial iNfarcTion (VALIANT) trial: baseline characteristics in context. 2003;5(4):537-544.
18. McMurray JJ, Östergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. 2003;362(9386):767-771.

19. Konstam MA, Neaton JD, Dickstein K, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *2009;374(9704):1840-1848.*
20. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SRJAoim. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. *2004;141(9):693-704.*
21. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation.* 2002;106(8):920-926.
22. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens.* 2004;17(2):103-111.
23. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail.* 2014;2(6):663-670.
24. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014;371(11):993-1004.
25. Novartis. Entresto (sacubitril and valsartan) tablets prescribing information. East Hanover, NJ; 2015 Jul.
26. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation.* 2005;112(16):2426-2435.
27. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet.* 1993;342(8885):1441-1446.
28. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. *Circulation.* 1994;90(4):1765-1773.
29. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353(9169):2001-2007.
30. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart fa-

- ilure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med.* 1996;334(21):1349-1355.
31. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet.* 1999;353(9146):9-13.
 32. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001;344(22):1651-1658.
 33. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J.* 2005;26(3):215-225.
 34. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiane MJ, JotACoC. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. 2004;43(9):1534-1541.
 35. Gattis WA, O'Connor CM, Gallup DS, et al. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol.* 2004;43(9):1534-1541.
 36. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol.* 2009;53(2):184-192.
 37. Binanay C, Califf RM, Hasselblad V, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA.* 2005;294(13):1625-1633.
 38. Jondeau G, Neuder Y, Eicher JC, et al. B-CONVINCED: Beta-blocker CONTinuation Vs. INTerruption in patients with Congestive heart failure hospitalized for a decompensation episode. *Eur Heart J.* 2009;30(18):2186-2192.
 39. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. *J Heart Lung Transplant.* 2002;21(12):1290-1295.
 40. Deedwania PC, Giles TD, Klibaner M, et al. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J.* 2005;149(1):159-167.

41. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004;292(18):2227-2236.
42. Celik T, Iyisoy A, Kursaklioglu H, et al. Comparative effects of nebivolol and metoprolol on oxidative stress, insulin resistance, plasma adiponectin and soluble P-selectin levels in hypertensive patients. *Journal of hypertension*. 2006;24(3):591-596.
43. Toprol-XL (metoprolol succinate) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014 May.
44. Duramed Pharmaceuticals, Inc. Ziac (bisoprolol fumarate and hydrochlorothiazide) tablets prescribing information. Pomona, NY; 2011 Mar.
45. Coreg (carvedilol) package insert. Research Triangle Park, NC: GlaxoSmithKline; 2017 Sept.
46. Forest Laboratories, Inc. Bystolic (nebivolol) tablets prescribing information. St. Louis, MO; 2008 Aug.
47. Lopressor (metoprolol tartrate) tablets and injection. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012 Dec.
48. Waagstein F, Hjalmarson A, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. 1993;342(8885):1441-1446.
49. Lechat P. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation*. 1994;90:1765-1773.
50. Precise Study G. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The Precise Trial. *Circulation*. 1996;94:2793-2799.
51. Briwtow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE. for the MOCH Investigators: Carvedilol produces dose-related improvements in left Ventricular Function and survival in subjects with chronic heart failure. *Circulation*. 1996;94:2807-2816.
52. Colluci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart failure Study Group. *Circulation*. 1996;94(11):2800-2806.
53. Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V. The US Carvedilol Heart Failure Group. Safety and efficacy of carvedilol in severe heart failure. *J Card Fail*. 1997;3:173-179.

54. MacMahon S, Sharpe NJTL. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to. 1997;349(9049):375-380.
55. Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. *Circulation*. 1995;92(2):212-218.
56. Lancet M-HSGJT. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in-congestive heart failure (MERIT-HF). 1999;353(9169):2001-2007.
57. Beta-Blocker Evaluation of Survival Trial I, Eichhorn EJ, Domanski MJ, Krause-Steinrauf H, Bristow MR, Lavori PW. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344(22):1659-1667.
58. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357(9266):1385-1390.
59. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. 2003;362(9377):7-13.
60. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). 2005;26(3):215-225.
61. Willenheimer R, van Veldhuisen DJ, Silke B, et al. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. 2005;112(16):2426-2435.
62. Opie LH. B-blocking agents. *Drugs for the Heart*. 2019:11.
63. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. 1996;94(11):2807-2816.
64. Reeves RA, Boer WH, DeLeve L, Leenen FHH. β -Blockade disappearance rate predicts β -adrenergic hypersensitivity. *Clinical Pharmacology & Therapeutics*. 1989;46(3):279-290.
65. McDevitt DG. Comparison of pharmacokinetic properties of beta-adrenoceptor blocking drugs. *European heart journal*. 1987;8(suppl_M):9-14.

66. Morselli PL, Boutroy MJ, Bianchetti G, Thénot JP. Pharmacokinetics of antihypertensive drugs in the neonatal period. *Developmental pharmacology and therapeutics*. 1989;13:190-198.
67. Kapsargo sprinkle (metoprolol succinate) capsules extended-release package insert. Cranbury, NJ: Sun Pharmaceuticals Industries, Inc.; 2018 May.
68. Aronson JK. *Meyler's side effects of drugs: the international encyclopedia of adverse drug reactions and interactions*. Elsevier; 2015.
69. Morgan T. Clinical pharmacokinetics and pharmacodynamics of carvedilol. *Clinical pharmacokinetics*. 1994;26(5):335-346.
70. Wilson Tang WH, Fowler MB. Clinical Trials of Carvedilol in Heart Failure. *Heart Failure Reviews*. 1999;4(1):79-88.
71. Frishman WH. Carvedilol. *N Engl J Med*. 1998;339(24):1759-1765.
72. Macdonald PS, Keogh AM, Aboyoun C, Lund M, Amor R, McCaffrey D. Impact of concurrent amiodarone treatment on the tolerability and efficacy of carvedilol in patients with chronic heart failure. *Heart*. 1999;82(5):589-593.
73. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007;298(10):1171-1179.
74. Nul D, Zambrano C, Diaz A, et al. Impact of a standardized titration protocol with carvedilol in heart failure: safety, tolerability, and efficacy—a report from the GESICA registry. *Cardiovascular drugs and therapy*. 2005;19(2):125-134.
75. Krum H, Conway EL, Broadbear JH, Howes LG, Louis WJ. Postural hypotension in elderly patients given carvedilol. *BMJ*. 1994;309(6957):775-776.
76. Markou N, Antzoulatos N, Haniotou A, Kanakaki M, Parissis J, Damianos A. A case of drug-induced pneumonitis caused by carvedilol. *Respiration*. 2004;71(6):650-652.
77. Kobayakawa N, Sawaki D, Otani Y, et al. A case of severe diabetes mellitus occurred during management of heart failure with carvedilol and furosemide. *Cardiovasc Drugs Ther*. 2003;17(3):295.
78. Hauf-Zachariou U, Widmann L, Zulsdorf B, Hennig M, Lang PD. A double-blind comparison of the effects of carvedilol and captopril on serum lipid concentrations in patients with mild to moderate essential hypertension and dyslipidaemia. *Eur J Clin Pharmacol*. 1993;45(2):95-100.
79. Lancaster SG, Sorkin EM. Bisoprolol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and the-

- rapeutic efficacy in hypertension and angina pectoris. *Drugs*. 1988;36(3):256-285.
80. Vizzardi E, Regazzoni V, Caretta G, et al. Mineralocorticoid receptor antagonist in heart failure: Past, present and future perspectives. *Int J Cardiol Heart Vessel*. 2014;3:6-14.
 81. Cittadini A, Monti MG, Isgaard J, et al. Aldosterone receptor blockade improves left ventricular remodeling and increases ventricular fibrillation threshold in experimental heart failure. *Cardiovasc Res*. 2003;58(3):555-564.
 82. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709-717.
 83. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321.
 84. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11-21.
 85. de Gasparo M, Joss U, Ramjoue HP, et al. Three new epoxy-spirolactone derivatives: characterization in vivo and in vitro. *J Pharmacol Exp Ther*. 1987;240(2):650-656.
 86. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents eplerenone and spironolactone. *Clin Cardiol*. 2008;31(4):153-158.
 87. Pfizer. Aldactone (spironolactone) tablets prescribing information. New York, NY; 2014 Oct.
 88. Paterna S, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail*. 2000;2(3):305-313.
 89. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J*. 2003;145(3):459-466.
 90. Parrinello G, Paterna S, Di Pasquale P, et al. Changes in estimating echocardiography pulmonary capillary wedge pressure after hyper-saline plus furosemide versus furosemide alone in decompensated heart failure. *J Card Fail*. 2011;17(4):331-339.

91. Paterna S, Fasullo S, Parrinello G, et al. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (Class C) (SMAC-HF Study). *Am J Med Sci*. 2011;342(1):27-37.
92. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797-805.
93. Cacciapuoti F. Ranolazine and Ivabradine: two different modalities to act against ischemic heart disease. *Ther Adv Cardiovasc Dis*. 2016;10(2):98-102.
94. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875-885.
95. Bohm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. *Clin Res Cardiol*. 2013;102(1):11-22.
96. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314(24):1547-1552.
97. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325(5):303-310.
98. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004;351(20):2049-2057.
99. Carson P, Ziesche S, Johnson G, Cohn JN. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. *J Card Fail*. 1999;5(3):178-187.
100. Farag M, Mabote T, Shoaib A, et al. Hydralazine and nitrates alone or combined for the management of chronic heart failure: A systematic review. *Int J Cardiol*. 2015;196:61-69.
101. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. *J Am Coll Cardiol*. 1993;22(4):955-962.

102. Packer M, Gheorghiu M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med.* 1993;329(1):1-7.
103. Digitalis Investigation G. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med.* 1997;336(8):525-533.
104. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J.* 2006;27(2):178-186.
105. Ouyang AJ, Lv YN, Zhong HL, et al. Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation. *Am J Cardiol.* 2015;115(7):901-906.
106. Whitbeck MG, Charnigo RJ, Shah J, et al. QRS duration predicts death and hospitalization among patients with atrial fibrillation irrespective of heart failure: evidence from the AFFIRM study. *Europace.* 2014;16(6):803-811.
107. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347(23):1825-1833.
108. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *J Am Coll Cardiol.* 2014;64(7):660-668.
109. Allen LA, Fonarow GC, Simon DN, et al. Digoxin Use and Subsequent Outcomes Among Patients in a Contemporary Atrial Fibrillation Cohort. *J Am Coll Cardiol.* 2015;65(25):2691-2698.
110. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol.* 1999;33(2):304-310.
111. Jelliffe RW, Brooker G. A nomogram for digoxin therapy. *Am J Med.* 1974;57(1):63-68.
112. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA.* 2003;289(7):871-878.
113. Adams KF, Jr., Patterson JH, Gattis WA, et al. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. *J Am Coll Cardiol.* 2005;46(3):497-504.

114. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA*. 2003;289(13):1652-1658.
115. Hager WD, Fenster P, Mayersohn M, et al. Digoxin-quinidine interaction Pharmacokinetic evaluation. *N Engl J Med*. 1979;300(22):1238-1241.
116. Bizjak ED, Mauro VF. Digoxin-macrolide drug interaction. *Ann Pharmacother*. 1997;31(9):1077-1079.
117. Messerli FH, Nussberger J. Vasoepitidase inhibition and angio-oedema. *Lancet*. 2000;356(9230):608-609.
118. Gheorghide M, Konstam MA, Burnett JC, Jr., et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA*. 2007;297(12):1332-1343.
119. Hauptman PJ, Burnett J, Gheorghide M, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. *J Card Fail*. 2013;19(6):390-397.
120. Otsuka America Pharmaceutical, Inc. Samsca (tolvaptan) tablets prescribing information. Rockville, MD; 2013 Apr.
121. Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation*. 2001;104(20):2417-2423.
122. Yatsu T, Tomura Y, Tahara A, et al. Cardiovascular and renal effects of conivaptan hydrochloride (YM087), a vasopressin V1A and V2 receptor antagonist, in dogs with pacing-induced congestive heart failure. *Eur J Pharmacol*. 1999;376(3):239-246.
123. Tahara A, Tomura Y, Wada KI, et al. Pharmacological profile of YM087, a novel potent nonpeptide vasopressin V1A and V2 receptor antagonist, in vitro and in vivo. *J Pharmacol Exp Ther*. 1997;282(1):301-308.
124. Fukuzawa J, Haneda T, Kikuchi K. Arginine vasopressin increases the rate of protein synthesis in isolated perfused adult rat heart via the V1 receptor. *Mol Cell Biochem*. 1999;195(1-2):93-98.
125. Nakamura Y, Haneda T, Osaki J, Miyata S, Kikuchi K. Hypertrophic growth of cultured neonatal rat heart cells mediated by vasopressin V1A receptor. *European journal of pharmacology*. 2000;391(1-2):39-48.
126. Tahara A, Saito M, Sugimoto T, et al. Pharmacological characterization of YM087, a potent, nonpeptide human vasopressin V1A and

- V2 receptor antagonist. *Naunyn-Schmiedeberg's archives of pharmacology*. 1997;357(1):63-69.
127. Goldsmith SR. Current treatments and novel pharmacologic treatments for hyponatremia in congestive heart failure. *Am J Cardiol*. 2005;95(9A):14B-23B.
 128. Chatterjee K. Neurohormonal activation in congestive heart failure and the role of vasopressin. *Am J Cardiol*. 2005;95(9A):8B-13B.
 129. Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. *Am Heart J*. 2003;146(1):9-18.
 130. Burnier M, Fricker AF, Hayoz D, Nussberger J, Brunner HR. Pharmacokinetic and pharmacodynamic effects of YM087, a combined V1/V2 vasopressin receptor antagonist in normal subjects. *Eur J Clin Pharmacol*. 1999;55(9):633-637.
 131. Astellas Pharma US. Vaprisol (conivaptan hydrochloride) injection prescribing information. Deerfield, IL; 2010 May.
 132. Kimmig LM, Karalis DG. Do omega-3 polyunsaturated Fatty acids prevent cardiovascular disease? A review of the randomized clinical trials. *Lipid Insights*. 2013;6:13-20.
 133. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9645):1223-1230.
 134. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9645):1231-1239.
 135. Rogers JK, Jhund PS, Perez AC, et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). *JACC Heart Fail*. 2014;2(3):289-297.
 136. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. *Circ Heart Fail*. 2011;4(1):8-17.
 137. Zhuang XD, Long M, Li F, Hu X, Liao XX, Du ZM. PDE5 inhibitor sildenafil in the treatment of heart failure: a meta-analysis of randomized controlled trials. *Int J Cardiol*. 2014;172(3):581-587.
 138. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart

- failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309(12):1268-1277.
139. Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care*. 2003;26(11):2983-2989.
 140. Dargie HJ, Hildebrandt PR, Riegger GA, et al. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association Functional Class I or II Heart Failure. *J Am Coll Cardiol*. 2007;49(16):1696-1704.
 141. Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J*. 2010;31(7):824-831.
 142. Pratt CM, Camm AJ, Cooper W, et al. Mortality in the Survival With ORal D-sotalol (SWORD) trial: why did patients die? *The American journal of cardiology*. 1998;81(7):869-876.
 143. Hohnloser SH, Crijns HJGM, Van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *New England Journal of Medicine*. 2009;360(7):668-678.
 144. Hohnloser SH, Crijns HJGM, van Eickels M, et al. Dronedarone in patients with congestive heart failure: insights from ATHENA. *European heart journal*. 2010;31(14):1717-1721.
 145. Køber L, Torp-Pedersen C, McMurray JJV, et al. Increased mortality after dronedarone therapy for severe heart failure. *New England Journal of Medicine*. 2008;358(25):2678-2687.
 146. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. *New England Journal of Medicine*. 2011;365(24):2268-2276.
 147. Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). *Lancet*. 1994;344(8921):493-498.
 148. Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med*. 1995;333(2):77-82.
 149. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish Investigations of Arrhythmia and Mortality on Dofetilide Study Group. *N Engl J Med*. 1999;341(12):857-865.

150. Kober L, Bloch Thomsen PE, Moller M, et al. Effect of dofetilide in patients with recent myocardial infarction and left-ventricular dysfunction: a randomised trial. *Lancet*. 2000;356(9247):2052-2058.
151. De Vecchis R, Cantatrione C, Mazzei D, Baldi C, Di Maio M. Non-ergot dopamine agonists do not increase the risk of heart failure in Parkinson's disease patients: a meta-analysis of randomized controlled trials. *Journal of clinical medicine research*. 2016;8(6):449.
152. Hsieh PH, Hsiao FY. Risk of heart failure associated with dopamine agonists: a nested case-control study. *Drugs & aging*. 2013;30(9):739-745.
153. Food US, Drug A. FDA drug safety communication: ongoing safety review of Parkinson's drug Mirapex (Pramipexole) and possible risk of heart failure. *US Food and Drug Administration*. 2013.
154. Page RL, 2nd, O'Bryant CL, Cheng D, et al. Drugs That May Cause or Exacerbate Heart Failure: A Scientific Statement From the American Heart Association. *Circulation*. 2016;134(6):e32-69.
155. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clinical nutrition*. 2008;27(6):793-799.
156. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326.
157. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA*. 2000;283(15):1967-1975.
158. Cohn JN, Pfeffer MA, Rouleau J, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail*. 2003;5(5):659-667.
159. Swedberg K, Young JB, Anand IS, et al. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med*. 2013;368(13):1210-1219.
160. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361(25):2436-2448.
161. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J*. 2015;36(11):657-668.
162. Allen LA, Fonarow GC, Grau-Sepulveda MV, et al. Hospital variation in intravenous inotrope use for patients hospitalized with he-

- art failure: insights from Get With The Guidelines. *Circ Heart Fail.* 2014;7(2):251-260.
163. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362(9):779-789.
 164. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA.* 2009;301(14):1439-1450.
 165. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet.* 2012;380(9851):1387-1395.
 166. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med.* 2014;370(15):1383-1392.
 167. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. *Eur J Prev Cardiol.* 2016;23(1):78-85.
 168. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev.* 2012(2):CD003838.
 169. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol.* 2002;82(2):149-158.
 170. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol.* 2009;53(23):2150-2158.

KAYNAKLAR

1. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MULTIsite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol.* 2002;40(1):111-118.
2. Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CARDiac RESynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J.* 2006;27(16):1928-1932.
3. Gervais R, Leclercq C, Shankar A, et al. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail.* 2009;11(7):699-705.
4. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation.* 2004;110(18):2864-2868.
5. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* 2009;361(14):1329-1338.
6. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol.* 2008;52(23):1834-1843.
7. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med.* 2010;363(25):2385-2395.
8. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005;352(15):1539-1549.
9. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350(21):2140-2150.
10. Lindenfeld J, Feldman AM, Saxon L, et al. Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. *Circulation.* 2007;115(2):204-212.

11. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129-2200.
12. Sohaib SM, Finegold JA, Nijjer SS, et al. Opportunity to increase life span in narrow QRS cardiac resynchronization therapy recipients by deactivating ventricular pacing: evidence from randomized controlled trials. *JACC Heart Fail*. 2015;3(4):327-336.
13. Cleland JG, Mareev Y, Linde C. Reflections on EchoCRT: sound guidance on QRS duration and morphology for CRT? *Eur Heart J*. 2015;36(30):1948-1951.
14. Woods B, Hawkins N, Mealing S, et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart*. 2015;101(22):1800-1806.
15. Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med*. 2014;174(8):1340-1348.
16. Linde C, Stahlberg M, Benson L, et al. Gender, underutilization of cardiac resynchronization therapy, and prognostic impact of QRS prolongation and left bundle branch block in heart failure. *Europace*. 2015;17(3):424-431.
17. Fukunaga M, Ando K. Should We Include a Defibrillator for All Cardiac Resynchronization Therapy?- Comparison of Cardiac Resynchronization Therapy Without and With Defibrillation. *Circ J*. 2017;81(12):1768-1769.
18. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med*. 2013;368(17):1585-1593.
19. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J*. 2011;32(19):2420-2429.
20. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. *Europace*. 2012;14(10):1490-1497.
21. Doshi RN, Daoud EG, Fellows C, et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol*. 2005;16(11):1160-1165.

22. van Rees JB, de Bie MK, Thijssen J, Borleffs CJ, Schalij MJ, van Erven L. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. *J Am Coll Cardiol*. 2011;58(10):995-1000.
23. Dewland TA, Pellegrini CN, Wang Y, Marcus GM, Keung E, Varosy PD. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR implantable cardioverter-defibrillator registry. *J Am Coll Cardiol*. 2011;58(10):1007-1013.
24. Slotwiner D, Varma N, Akar JG, et al. HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. *Heart Rhythm*. 2015;12(7):e69-100.
25. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med*. 1996;335(26):1933-1940.
26. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346(12):877-883.
27. Bigger JT, Jr. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. *N Engl J Med*. 1997;337(22):1569-1575.
28. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med*. 1999;341(25):1882-1890.
29. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352(3):225-237.
30. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med*. 2004;351(24):2481-2488.
31. Steinbeck G, Andresen D, Seidl K, et al. Defibrillator implantation early after myocardial infarction. *N Engl J Med*. 2009;361(15):1427-1436.
32. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients

- with nonischemic dilated cardiomyopathy and asymptomatic non-sustained ventricular tachycardia--AMIOVIRT. *J Am Coll Cardiol.* 2003;41(10):1707-1712.
33. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation.* 2002;105(12):1453-1458.
 34. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med.* 2004;350(21):2151-2158.
 35. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med.* 1997;337(22):1576-1583.
 36. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation.* 2000;101(11):1297-1302.
 37. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). *Circulation.* 2000;102(7):748-754.