# KARDİYOVASKÜLER İLAÇLAR

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## UYARI

*Bu üründe yer alan bilgiler sadece lisanslı tıbbi çalışanlar için kaynak olarak sunulmuştur. Herhangi bir konuda profesyonel tıbbi danışmanlık veya tıbbi tanı amacıyla kullanılmamalıdır. Akademisyen Kitabevi ve alıcı arasında herhangi bir şekilde doktor-hasta, terapist-hasta ve/veya başka bir sağlık sunum hizmeti ilişkisi oluşturmaz. Bu ürün profesyonel tıbbi kararların eşleniği veya yedeği değildir. Akademisyen Kitabevi ve bağlı şirketleri, yazarları, katılımcıları, partnerleri ve sponsorları ürün bilgilerine dayalı olarak yapılan bütün uygulamalardan doğan, insanlarda ve ihazlarda yaralanma ve/veya hasarlardan sorumlu değildir.*

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*Akademisyen Kitabevi, üçüncü bir taraf tarafından yapılan ürüne dair değişiklikler, tekrar paketlemeler ve özelleştirmelerden sorumlu değildir.*

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# ÖNSÖZ

*Değerli meslektaşlarım,*

Son 10 yılda kardiyovasküler alanında baş döndürücü bir hızla birçok yeni ilaç çalışmaları yapılmış olup bu ilaçlarda bazıları rutin tedavimize girmiştir. Yenilenen kardiyoloji kılavuzları her ne kadar bize yol gösterse de tüm kardiyovasküler ilaçları bir ara anlatan ve elimizin altında olacak güncel bir kitaba ihtiyaç duyulduğunu düşünmekteyiz. Kitabımız temel tıp ve kardiyoloji asistanlık eğitiminde, hatta uzmanlığın ilk dönemlerinde bile meslektaşlarımızın yararlanılabileceği kardiyovasküler ilaçlar alanında güncel kılavuz bilgileri içermektedir.

Kardiyovasküler ilaçlar temel düzeyden başlayarak anlatılmış, güncel akademik bilgilerle ve kılavuzlarla desteklenmiştir. Güncel çalışmalar ve kılavuzlar eşliğinde kardiyovasküler ilaçlar özetlenmiş olup şekil ve tablolarla daha kolay anlaşılır düzeyde olması sağlanmaya çalışılmıştır.

Kitabın her bir bölüm yazarına yoğun emekleriyle hazırladıkları güncel bilgiler, görseller ve tablolar için ayrı ayrı teşekkür ederim. Akademisyen Yayınevi ve ekibine kitabın basımında yaptıkları titiz çalışmadan ötürü teşekkür ederim. Yine kitabın basımı sırasında çok emeği geçen sevgili çalışma arkadaşım, Uzm Dr Caner Topaloğlu'na ayrıca teşekkür ederim.

Bu kitabı bana her daim destek olan sevgili annem, babam, kardeşim, eşim Seda ve biricik kızımız Pera'ya armağan etmek istiyorum.

Sevgi ve Saygılarımla…

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*Değerli meslektaşlarım,*

Kardiyovasküler sistem hastalıklara bağlı tedaviler hızla gelişmekte ve değişime uğramaktadır. Güncel tanı ve tedavi klavuzları ışığımız olup tüm kardiyovasküler sistem ilaçları bütüncül anlatan güncel kaynaklar sınırlıdır. Kitabımız ile klavuzların önderliğinde kardiyovasküler sistem ilaçlarını toparlamaya çalıştık. Kitabımız sadece tıp fakültesi ve asistan eğitimi için değil aynı zamanda tüm meslektaşlarımıza da yararlı olacaktır.

Kitabın hazırlanmasında katkıları olan tüm yazarlara teşekkürlerimi sunarım. Ayrıca büyük katkıları olan çalışma arkadaşım İzmir Ekonomi Üniversitesi Kardiyoloji AD Başkanı Doç. Dr. Cihan Altın'a da teşekkürlerimi sunarım.

Bu kitabı her zaman bana destek olup koşulsuz seven sevgili annem, babam ve *'babasının en değerli kıymetlisi'* kızım ZEYNEP ADA'ma armağan etmek istiyorum.

*'Bilgi, paylaştıkça çoğalan bir hazinedir'*

Sevgi ve saygılarımla…

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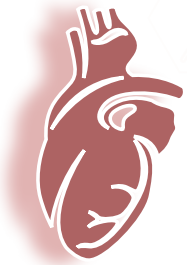

# BÖLÜM 1

# Kalp Yetmezliğinde Kullanılan İlaçlar

*Emre ERTÜRK* [1]

## GİRİŞ

Kalp yetmezliği (KY), kalbin etkin kan akımını sağlayamaması nedeni ile oluşan, periferik doku ve organlara yetersiz kan akımı ve oksijen sunumu ile sonuçlanan, kompleks bir klinik sendromdur. Kalbin yapısal ve/veya fonksiyonel bozukluklarına bağlı olarak, kardiyak output azalması ve kalp içi basınçların artması sonucunda kalp yetmezliğine özgü semptom ve bulgular ortaya çıkmaktadır. Son yayınlanan kalp yetmezliği kılavuzunda kalp yetmezliği, HFrEF (düşük ejeksiyon fraksiyonlu kalp yetmezliği), HFimpEF (düzelmiş EF'li KY), HFmrEF(hafif azalmış EF'li KY), HFpEF (korunmuş EF'li KY) olarak sınıflandırılmış ve güncel literatür ışığında, KY'nin alt türlerine uygun tedavi önerilerinde bulunulmuştur. (1)

Tedavi hedefleri, kalp yetmezliğinin patogenezi ışığında belirlenerek, belirli yolakların aktivasyonu/deaktivasyonu yoluyla uygun tedavi sağlanmaktadır. İlaçların etki mekanizmalarının anlaşılması için kalp yetmezliğinde hangi sistemlerin, peptidlerin ve yapısal değişikliklerin rol oynadığını göz önünde bulundurmak gerekmektedir. Temel olarak şu yolaklar kalp yetmezliği patogenezinde aktif rol oynamaktadır:

» Renin-anjiyotensin-aldosteron sistemi (RAAS)
» Sempatik sinir sistemi

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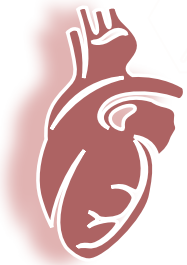
## KAYNAKLAR


1. Theresa A McDonagh, Marco Metra,et al, ESC Scientific Document Group, 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 42, Issue 36, 21 September 2021, Pages 3599–3726, https://doi.org/10.1093/eurheartj/ehab368
2. Pathophysiology of Heart Failure, Gerd Hasenfuss and Douglas L. Mann, Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Twelfth Edition, 47, 913-932
3. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273:14501456.
4. Heart Failure, Chapter 3, Jefferson L. Vieira, Mandeep R. Mehra, Opie's Cardiovascular Drugs: A Companion to Braunwald's Heart Disease, 9th Edition - October 20, 2020
5. Kayaalp O. Akılcıl Tedavi Yönünden Tıbbi Farmakoloji, 12. Basım, İstanbul, Pelikan Yayınevi, 2012, 459-476
6. Velazquez EJ, Morrow DA, DeVore AD, et al. PIONEER-HF Investigators. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2019 Feb 7;380(6):539-548. doi: 10.1056/NEJMoa1812851. Epub 2018 Nov 11. Erratum in: N Engl J Med. 2019 Mar 14;380(11):1090. PMID: 30415601.
7. Nişancı Y. Kardiyovasküler İlaçlar. Adalet K (Ed.), Klinik Kardiyoloji – Tanı ve Tedavi. İstanbul, İstanbul Tıp Kitabevi; 2013. 209-261
8. Mann DL, Felker GM. Mechanisms and Models in Heart Failure: A Translational Approach. Circ Res. 2021 May 14;128(10):1435-1450. doi: 10.1161/CIRCRESAHA.121.318158. Epub 2021 May 13. PMID: 33983832; PMCID: PMC8130816.
9. Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018 Oct 9;72(15):1845-1855. doi: 10.1016/j.jacc.2018.06.040. Epub 2018 Jul 31. PMID: 30075873.
10. Lytvyn Y, Bjornstad P, Udell JA, et al. Sodium Glucose Cotransporter-2 Inhibition in Heart Failure: Potential Mechanisms, Clinical Applications, and Summary of Clinical Trials. Circulation. 2017 Oct 24;136(17):1643-1658.
11. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. Circulation. 2020 Apr 14;141(15):1227-1234. doi: 10.1161/CIRCULATIONAHA.119.044183. Epub 2020 Jan 27. PMID: 31983236.
12. Braunwald's Heart Disease, 12th Edition,Peter Libby, MD, PhD, Robert O. Bonow, MD, MS, Douglas L. Mann, MD, Gordon F. Tomaselli, MD, Deepak Bhatt, MD, MPH, FACC, FAHA, FSCAI, FESC, Scott D. Solomon, MD and Eugene Braunwald, MD, MD(Hon), ScD(Hon), FRCP, ISBN: 9780323722193, Copyright: 2022, Publication Date: 11-15-2021, Imprint: Elsevier
13. Katzung G. B. (ed), Temel ve Klinik Farmakoloji, 14. Baskı, İstanbul, Nobel Tıp Kitabevleri; 2021; 214-229
14. Dandan R. H. Brunton Laurence; Goodman ve Gilman'ın Farmakoloji ve Tedavi El Kitabı, 2. Baskı, Ankara, Güneş Tıp Kitabevi, 2017, 477-493



# BÖLÜM 2

# Beta-Blokerler

*Kadir OCAK* [1]

## GİRİŞ

β-adrenerjik antagonistler (β-blokerler), β-adrenoseptörlere seçici olarak bağlanarak, yarışmacı ve geri dönüşümlü olarak β-adrenerjik uyaranların çeşitli organlardaki etkilerini antagonize ederler. Bu şekilde oluşan anti iskemik, antiaritmik ve antihipertansif özellikleri nedeniyle kardiyovasküler hastalıkların tedavisinde önemli rol alırlar. Ancak son 20 yıldaki gelişmelerle özellikle kalp yetmezliği tedavisinde de önemli bir yere sahip olmuşlardır.

### 1. β-blokerlerin Sınıflandırılması

β-blokerler genel olarak bloke ettikleri reseptöre göre sınıflandırılır. a) Non-selektif (kardiyoselektif olmayan); hem β1 hem β2 reseptörlerinde yarışmacı blokaj yapanlar. b) β1 selektif (kardiyoselektif olan); β1 reseptörlerine, β2 reseptörlerine göre çok daha yüksek afinitede bağlananlar.

Selektivite, doza bağımlı olup doz arttıkça azalabilir hatta kaybolabilir. Paradoksik olarak bazı β-blokerler hafif agonist aktivite gösterebilir (intrinsik sempatomimetik aktivite (ISA)). Bazı β-blokerler α1-adrenoseptör blokajı aracılığıyla (karvedilol, labetalol), β2-adrenerjik reseptör agonizmi (celiprolol) veya adrenoseptör blokajından bağımsız mekanizmalar yoluyla (busindolol, nebivolol) periferik vazodilatör aktiviteye sahiptir (Tablo 1).

Ek olarak, β-blokerler lipofilik veya hidrofilik olarak sınıflandırılabilir.

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## KAYNAKLAR


1. Cruickshank JM, Prichard BNC. Beta-adrenoceptors. In: Cruickshank JM, Prichard BNC, editors. Beta-blockers in clinical practice. London: Churchill Livingstone; 1996. p. 9–86.
1. Tamargo JL, Delpon E. Optimisation of b-blockers pharmacology. *J Cardiovasc Pharmacol* 1990;16(Suppl. 5):S8–S10.
2. Frishman WH, Lazar EJ, Gorodokin G. Pharmacokinetic optimisation of therapy with beta-adrenergic-blocking agents. *Clin Pharmacokinet.* 1991;20:311–8.
3. Frishman WH. Carvedilol. *N Engl J Med.* 1998;339:1759–65.
4. Benfield P, Sorkin EM. Esmolol. A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1987;33:392–412.
5. Bristow MR. Pathophysiologic and pharmacologic rationale for clinical management of chronic hart failure with beta-blocking agents. *Am J Cardiol.* 1993;71:12C–22C.
6. Bouzamondo A, Hulot JS, Sanchez P et al. Beta-blocker treatment in heart failure. *Fundam Clin Pharmacol*. 2001;15:95–109.
7. Waagstein F. Beta-blockers in congestive heart failure: the evolution of a new treatment concept-mechanism of action and clinical implications. *J Clin Basic Cardiol.* 2002;5:215–23.
8. Man in't Veld AJ, van der Meiracker A, Schalekamp MA. The effect of beta-adrenoceptor antagonists on total peripheral resistance. *J Cardiovasc Pharmacol.* 1986;8(Suppl. 4):S49–60.
9. Frishman WH. Multifactorial actions of beta-adrenergic-blocking drugs in ischemic heart disease: current concepts. *Circulation.* 1983;67(Suppl. I):I-11-8.
10. Opie LH. Effect of beta-adrenergic blockade on biochemical and metabolic response to exercise. *Am J Cardiol.* 1985;55:95D.
11. Kukin ML, Kalman J, Charney R et al. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. *Circulation.* 1999;102:2646–51.
12. Cleland JG, Dargie HJ. Arrhythmias, catecholamines and electrolytes. *Am J Coll Cardiol.* 1988;62:55–9.
13. Shizukuda Y, Buttrick PM, Geenen D et al. Beta-adrenergic stimulation causes cardiocyte apoptosis: influence of tachycardia and hypertrophy. *Am J Physiol.* 1998;275:961–8.
14. Lowes BD, Gilbert EM, Abraham WT et al. Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. *N Engl J Med.* 2002;346:1357–65.
15. Hjalmarson A, Elmfeldt D, Herlitz J et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet.* 1981;ii:823–87.
16. Hjalmarson A, Goldstein S, Fagerberg B et al. for the MERIT-HF Study Group: Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure. The metoprolol CR/Xl randomized intervention trial in congestive heart failure (MERIT-HF). *JAMA*. 2000;283:1293–302.
17. Thadani U, Whitsett TL. Beta-adrenergic-blockers and intermittent claudication: time for reappraisal. *Arch Int Med.* 1991;151: 1705–7.
18. Radack K, Deck C. b-Adrenergic blocker therapy does not worsen intermitent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. *Arch Int Med* 1991;151:1769–76.
19. Kjekshus J, Gilpin E, Gali G et al. Diabetic patients and beta blockers after acute myocardial infarction. *Eur Heart J* 1990;11:43–50.
20. Gottlieb S, McCarter R, Vogel R. Effect of beta-blockade on mortality among high risk patients after myocardial infarction. *N Engl J Med.* 1998;338:489–97.
21. Poole-Wilson P. COMET study. European Congress of Cardiology. Vienna, September 2003.

22. Chen J, Radford MJ, Wang Y et al. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol.* 2001;37:1950–6.
23. Salem S, McDevitt D. Central effects of beta-adrenoceptor antagonists. Clin Pharmacol Ther 1983;33:52–7. 25. Houston MC, Hodge R. Beta-adrenergic blocker withdrawal syndromes in hypertension and other cardiovascular diseases. *Am Heart J.* 1988;116:515–23.
24. Psaty BM, Koepsell TD, Wagner EH et al. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. *JAMA.* 1990;263:1653–7.
25. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate control management. *Postgrad Med J.* 2009;85:303-312.
26. Van Gelder IC, Rienstra M, Crijns HJ et al. Rate control in atrial fibrillation. *Lancet.* 2016;388:818-828.
27. Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet.* 2014;384(9961):2235-2243. doi:10.1016/S0140-6736(14)61373-8
28. Ulimoen SR, Enger S, Carlson J, et al. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. *Am J Cardiol.* 2013;111:225-230.
29. Ziff OJ, Lane DA, Samra M, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015;351:h4451.
30. Scheuermeyer FX, Grafstein E, Stenstrom R, et al. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med.* 2013;20:222-230
31. Tisdale JE, Padhi ID, Goldberg AD, et al. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary artery bypass surgery. *Am Heart J.* 1998;135:739-747.
32. Darby AE, Dimarco JP. Management of atrial fibrillation in patients with structural heart disease. *Circulation.* 2012;125:945-957.
33. Farshi R, Kistner D, Sarma JS, et al. 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;33:304-310.
34. Khand AU, Rankin AC, Martin W,et al. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol.* 2003;42:1944-1951.
35. Capucci A, Botto G, Molon G, et al; DAPHNE Study Investigators. The Drug And Pace Health cliNical Evaluation (DAPHNE) study: a randomized trial comparing sotalol versus beta-blockers to treat symptomatic atrial fibrillation in patients with brady-tachycardia syndrome implanted with an antitachycardia pacemaker. *Am Heart J.* 2008;156:373.e1-8.
36. Kuhlkamp V, Schirdewan A, Stangl K, et al. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol.* 2000;36:139-146
37. Nergardh AK, Rosenqvist M, Nordlander R, et al. Maintenance of sinus rhythm with metoprolol CR initiated before cardioversion and repeated cardioversion of atrial fibrillation: a randomized double-blind placebo-controlled study. *Eur Heart J.* 2007;28:1351-1357.
38. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:913.
39. Fowler MB. Effects of beta blockers on symptoms and functional capacity in heart failure. *Am J Cardiol.* 1997;80:55L58L.

40. Willenheimer R, van Veldhuisen DJ, Silke B, et al; CIBIS III Investigators. 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;112:2426-2435.
41. Cleland JGF, Bunting KV, Flather MD, et al; Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of doubleblind randomized trials. *Eur Heart J.* 2018;39:26-35.
42. Flather MD, Shibata MC, Coats AJ, et al; SENIORS Investigators. 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;26:215-225.
43. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al; SENIORS Investigators. 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;53:2150-2158
44. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol.* 2010;55:213-220.
45. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation.* 2015;131:1981-1988.
46. Chen ZM, Pan HC, Chen YP, et al; COMMIT Collaborative Group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005;366(9497):1622–1632.
47. Pfisterer M, Cox JL, Granger CB, et al. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: the GUSTO-I experience. Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries. *J Am Coll Cardiol.* 1998;32(3):634–640.
48. Chatterjee S, Chaudhuri D, Vedanthan R, et al. Early intravenous beta-blockers in patients with acute coronary syndrome—a meta-analysis of randomized trials. *Int J Cardiol.* 2013;168(2):915–921.
49. Ibanez B, Macaya C, Sanchez-Brunete V, et al. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. *Circulation.* 2013;128(14):1495–1503.
50. Pizarro G, Fernandez-Friera L, Fuster V, et al. Long-term benefit of early pre-reperfusion metoprolol administration in patients with acute myocardial infarction: results from the METOCARD-CNIC trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). J Am Coll Cardiol 2014;63(22): 2356–2362.
51. Garcia-Prieto J, Villena-Gutierrez R, Gomez M, et al. Neutrophil stunning by metoprolol reduces infarct size. Nat Commun 2017;8:147-80
52. Roolvink V, Ibanez B, Ottervanger JP, et al; EARLY-BAMI Investigators. Early intravenous beta-blockers in patients with ST-segment elevation myocardial infarction before primary percutaneous coronary intervention. J Am Coll Cardiol 2016;67(23):2705–2715
53. Halkin A, Grines CL, Cox DA, et al. Impact of intravenous beta-blockade before primary angioplasty on survival in patients undergoing mechanical reperfusion therapy for acute myocardial infarction. J Am Coll Cardiol 2004;43(10):1780–1787.
54. Harjai KJ, Stone GW, Boura J, et al. Effects of prior beta-blocker therapy on clinical outcomes after primary coronary angioplasty for acute myocardial infarction. Am J Cardiol 2003;91(6):655–660.

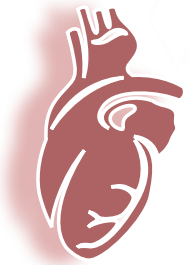
55. Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318(7200):1730–1737.
56. Goldberger JJ, Bonow RO, Cuffe M, et al; OBTAIN Investigators. Effect of beta-blocker dose on survival after acute myocardial infarction. J Am Coll Cardiol 2015;66(13):1431–1441.
57. Andersson C, Shilane D, Go AS, et al. Beta-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. J Am Coll Cardiol 2014;64(3):247–252.
58. Bangalore S, Steg G, Deedwania P, et al; REACH Registry Investigators. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012;308(13):1340–1349.
59. 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.
60. Packer M, Coats AJ, Fowler MB, et al; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651–1658.
61. Bugiardini R, Cenko E, Ricci B, et al. Comparison of early versus delayed oral beta blockers in acute coronary syndromes and effect on outcomes. Am J Cardiol 2016;117(5):760–767
62. Diaz A, Bourassa MG, Guertin MC, et al. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005;26:967-974.
63. Jouven X, Empana JP, Schwartz PJ, et al. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;352:1951-1958.
64. Shu de F, Dong BR, Lin XF, et al. Long-term beta blockers for stable angina: systematic review and meta-analysis. Eur J Prev Cardiol 2012;19:330-341.
65. Fox KM, Mulcahy D, Findlay I, et al. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. Eur Heart J 1996;17:96-103
66. Wallace WA, Wellington KL, Chess MA, et al. Comparison of nifedipine gastrointestinal therapeutic system and atenolol on antianginal efficacies and exercise hemodynamic responses in stable angina pectoris. Am J Cardiol 1994;73:23-28.
67. Kawanishi DT, Reid CL, Morrison EC, et al. Response of angina and ischemia to long-term treatment in patients with chronic stable angina: a double-blind randomized individualized dosing trial of nifedipine, propranolol and their combination. J Am Coll Cardiol 1992;19:409-417.
68. Bangalore S, Bhatt DL, Steg PG, et al. beta-blockers and cardiovascular events in patients with and without myocardial infarction: post hoc analysis from the CHARISMA trial. Circ Cardiovasc Qual Outcomes 2014;7:872-881.
69. 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. Lancet. 2003;362(9377):7-13. doi:10.1016/S0140-6736(03)13800-7
70. Leizorovicz A, Lechat P, Cucherat M, et al. Bisoprolol for the treatment of chronic heart failure: a meta-analysis on individual data of two placebocontrolled studies–CIBIS and CIBIS II. Cardiac Insufficiency Bisoprolol Study. Am Heart J 2002;143:301-307.
71. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349-1355.
72. Hwang D, Lee JM, Kim HK, et al; KAMIR Investigators. Prognostic impact of betablocker dose after acute myocardial infarction. Circ J 2019;83:410-417

73. Dahl Aarvik M, Sandven I, Dondo TB, et al. Effect of oral beta-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother 2019;5:12-20.
74. Motivala AA, Parikh V, Roe M, et al. Predictors, trends, and outcomes (among older patients >_65 years of age) associated with beta-blocker use in patients with stable angina undergoing elective percutaneous coronary intervention: insights From the NCDR registry. JACC Cardiovasc Interv 2016;9:1639-1648.
75. Zhang H, Yuan X, Zhang H, et al. Efficacy of long-term beta-blocker therapy for secondary prevention of long-term outcomes after coronary artery bypass grafting surgery. Circulation 2015;131:2194-2201.
76. Puymirat E, Riant E, Aissaoui N, et al. b blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. BMJ 2016;354:i4801.
77. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med 2014;127:939-953.
78. Hong J, Barry AR. Long-term beta-blocker therapy after myocardial infarction in the reperfusion era: a systematic review. Pharmacotherapy 2018;38:546554
79. Tsujimoto T, Kajio H, Shapiro MF, et al. Risk of all-cause mortality in diabetic patients taking beta-blockers. Mayo Clin Proc 2018;93:409-418.
80. Sorbets E, Steg PG, Young R, et al. b-blockers, calcium antagonists, and mortality in stable coronary artery disease: an international cohort study. Eur Heart J 2018:40;1399-1407.
81. Neumann A, Maura G, Weill A, et al. Clinical events after discontinuation of beta-blockers in patients without heart failure optimally treated after acute myocardial infarction: a cohort study on the French healthcare databases. Circ Cardiovasc Qual Outcomes 2018;11:e004356
82. Tanaka K, Tanaka H, Kamiya C, et al. Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. Circ J 2016;80:2221–2226.
83. Lip GY, Beevers M, Churchill D, et al. Effect of atenolol on birth weight. Am J Cardiol 1997;79:1436–1438.
84. Shekhar S, Gupta N, Kirubakaran R, et al. Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: A systematic review and meta-analysis. BJOG 2016;123:40–47
85. Clark SM, Dunn HE, Hankins GD. A review of oral labetalol and nifedipine in mild to moderate hypertension in pregnancy. Semin Perinatol 2015;39:548–555
86. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–615.
87. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–967.
88. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. J Hypertens 2017;35:2150–2160
89. Dondo TB, Hall M, West RM, et al. Beta-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. J Am Coll Cardiol 2017;69:2710–2720.
90. Bakris GL, Fonseca V, Katholi RE, et al; GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 2004;292:2227–2236.
91. Ayers K, Byrne LM, DeMatteo A, et al. Differential effects of nebivolol and metoprolol on insulin sensitivity and plasminogen activator inhibitor in the metabolic syndrome. Hypertension 2012;59:893–898

92. Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. J Hypertens 2008;26:819–824.
93. Buxton AE, Marchlinski FE, Doherty JU, et al. Repetitive, monomorphic ventricular tachycardia: clinical and electrophysiologic characteristics in patients with and patients without organic heart disease. Am J Cardiol 1984;54:997–1002
94. Griffith MJ, Garratt CJ, Rowland E, et al. Effects of intravenous adenosine on verapamil-sensitive 'idiopathic' ventricular tachycardia. Am J Cardiol 1994;73:759–764.
95. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv 2010;3:200–207
96. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevatio
97. Dumas F, Bougouin W, Geri G, et al. Emergency percutaneous coronary intervention in post-cardiac arrest patients without ST-segment elevation pattern: insights from the PROCAT II registry. JACC Cardiovasc Interv 2016;9:1011–1018.
98. Martí-Carvajal AJ, Simancas-Racines D, Anand V, et al. Prophylactic lidocaine for myocardial infarction. Cochrane Database Syst Rev 2015;2015:CD008553
99. Mazzanti A, Maragna R, Vacanti G, et al. Interplay between genetic substrate, QTc duration, and arrhythmia risk in patients with long QT syndrome. J Am Coll Cardiol 2018;71:1663–1671.
100. Chockalingam P, Crotti L, Girardengo G, et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. J Am Coll Cardiol 2012;60:2092–2099.
101. Ahn J, Kim HJ, Choi J-I,et al. Effectiveness of beta-blockers depending on the genotype of congenital long-QT syndrome: a meta-analysis. PLoS One 2017;12:e0185680.
102. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004;292:1341–1344
103. Priori SG, Wilde AA, Horie M, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Europace 2013;15: 1389–1406
104. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation 2009;119:2426–2434.
105. Leren IS, Saberniak J, Majid E,et al. Nadolol decreases the incidence and severity of ventricular arrhythmias during exercise stress testing compared with β1-selective β-blockers in patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2016;13:433–440
106. Peltenburg PJ, Kallas D, Bos JM, et al. An international multicenter cohort study on β-blockers for the treatment of symptomatic children with catecholaminergic polymorphic ventricular tachycardia. Circulation 2022;145:333–344.
107. van der Werf C, Nederend I, Hofman N, et al. Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives. Circ Arrhythm Electrophysiol 2012;5:748–756.
108. Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med 2009;15:380–383
109. Wang G, Zhao N, Zhong S, et al. Safety and efficacy of flecainide for patients with catecholaminergic polymorphic ventricular tachycardia: a systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e16961

110. van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol 2011;57:2244–2254.
111. Padfield GJ, AlAhmari L, Lieve KV, et al. Flecainide monotherapy is an option for selected patients with catecholaminergic polymorphic ventricular tachycardia intolerant of β-blockade. Heart Rhythm. 2016;13(2):609-613. doi:10.1016/j.hrthm.2015.09.027
112. Gupta A, Naik A, Vora A, et al. Comparison of efficacy of intravenous diltiazem and esmolol in terminating supraventricular tachycardia. J Assoc Physicians India 1999;47:969-972.
113. Das G, Tschida V, Gray R,et al. Efficacy of esmolol in the treatment and transfer of patients with supraventricular tachyarrhythmias to alternate oral antiarrhythmic agents. J Clin Pharmacol 1988;28:746-750.
114. Amsterdam EA, Kulcyski J, Ridgeway MG. Efficacy of cardioselective beta-adrenergic blockade with intravenously administered metoprolol in the treatment of supraventricular tachyarrhythmias. J Clin Pharmacol 1991;31:714-718.
115. Brubaker S, Long B, Koyfman A. Alternative treatment options for atrioventricular-nodal-reentry tachycardia: an emergency medicine review. J Emerg Med 2018;54:198-206
116. Ptaszynski P, Kaczmarek K, Ruta J, et al Ivabradine in combination with metoprolol succinate in the treatment of inappropriate sinus tachycardia. J Cardiovasc Pharmacol Ther 2013;18:338-344
117. Raj SR, Black BK, Biaggioni I, et al. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome. Less is more. Circulation 2009;120:725-734
118. Fu Q, VanGundy TB, Shibata S, et al. Exercise training versus propranolol in the treatment of the postural orthostatic tachycardia syndrome. Hypertension 2011;58:167-175.
119. Chen SA, Chiang CE, Yang CJ, et al. Sustained atrial tachycardia in adult patients. Electrophysiological characteristics, pharmacological response, possible mechanisms, and effects of radiofrequency ablation. Circulation 1994;90:1262-1278.
120. Mehta AV, Sanchez GR, Sacks EJ, et al. Ectopic automatic atrial tachycardia in children: clinical characteristics, management and follow-up. J Am Coll Cardiol 1988;11:379-385.
121. Arsura E, Lefkin AS, Scher DL, et al. A randomized, double-blind, placebo-controlled study of verapamil and metoprolol in treatment of multifocal atrial tachycardia. Am J Med 1988;85:519-524.
122. Hamer A, Peter T, Platt M, et al. Effects of verapamil on supraventricular tachycardia in patients with overt and concealed Wolff-Parkinson-White syndrome. Am Heart J 1981;101:600-612.
123. Huycke EC, Sung RJ, Dias VC, et al. Intravenous diltiazem for termination of reentrant supraventricular tachycardia: a placebocontrolled, randomized, double-blind, multicenter study. J Am Coll Cardiol 1989;13:538-544.
124. Fujimura O, Kuo C-S, Smith BA. Pre-excited RR intervals during atrial fibrillation in the Wolff-Parkinson-White syndrome: influence of the atrioventricular node refractory period. J Am Coll Cardiol 1991;18:1722-1726
125. Morady F, DiCarlo LA Jr, Baerman JM, et al. Effect of propranolol on ventricular rate during atrial fibrillation in the Wolff-Parkinson-White syndrome. Pacing Clin Electrophysiol 1987;10:492-496.
126. Sellers TD Jr, Bashore TM, Gallagher JJ. Digitalis in the pre-excitation syndrome. Analysis during atrial fibrillation. Circulation 1977;56:260-267.
127. Grimm RH Jr, Grandits GA, Prineas RJ, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). *Hypertension*. 1997;29(1 Pt 1):8-14. doi:10.1161/01.hyp.29.1.8

128. Bangalore S, Messerli FH, Kostis JB, et al. Cardiovascular protection using beta-blockers: a critical review of the evidence. *J Am Coll Cardiol*. 2007;50(7):563-572. doi:10.1016/j.jacc.2007.04.060
129. Jandeleit-Dahm KA, Tikellis C, Reid CM, et al. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J Hypertens*. 2005;23(3):463-473. doi:10.1097/01.hjh.0000160198.05416.72
130. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359(9311):995-1003. doi:10.1016/S0140-6736(02)08089-3
131. Broeders MA, Doevendans PA, Bekkers BC, et al. Nebivolol: a third-generation beta-blocker that augments vascular nitric oxide release: endothelial beta(2)-adrenergic receptor-mediated nitric oxide production. *Circulation*. 2000;102(6):677-684. doi:10.1161/01.cir.102.6.677
132. Van de Water A, Janssens W, Van Neuten J, et al. Pharmacological and hemodynamic profile of nebivolol, a chemically novel, potent, and selective beta 1-adrenergic antagonist. *J Cardiovasc Pharmacol*. 1988;11(5):552-563. doi:10.1097/00005344-198805000-00007
133. 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. *J Hypertens*. 2006;24(3):591-596. doi:10.1097/01.hjh.0000209993.26057.de
134. Hohnloser SH, Meinertz T, Klingenheben T, et al. Usefulness of esmolol in unstable angina pectoris. European Esmolol Study Group. *Am J Cardiol*. 1991;67(16):1319-1323. doi:10.1016/0002-9149(91)90458-w
135. Koutouzis M, Nikolidakis S, Grigoriadis A, et al. Intravenous esmolol is well tolerated in elderly patients with heart failure in the early phase of non-ST elevation myocardial infarction. *Drugs Aging*. 2006;23(8):673-680. doi:10.2165/00002512-200623080-00004
136. Lam SK, Owen A. Incident diabetes in clinical trials of antihypertensive drugs. *Lancet*. 2007;369(9572):1513-1514. doi:10.1016/S0140-6736(07)60697-7
137. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). *Circulation*. 1994;90(2):762-768. doi:10.1161/01.cir.90.2.762
138. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003;290(21):2805-2816. doi:10.1001/jama.290.21.2805
139. Engelhardt S. Alternative signaling: cardiomyocyte beta1-adrenergic receptors signal through EGFRs. *J Clin Invest*. 2007;117(9):2396-2398. doi:10.1172/JCI33135
140. Lithell H, Andersson PE. Metabolic effects of carvedilol in hypertensive patients. *Eur J Clin Pharmacol*. 1997;52(1):13-17. doi:10.1007/s002280050242



# BÖLÜM 3

# Anjıyotensın Convertıng Enzim İnhibitörleri (ACEİ)

*Caner TOPALOĞLU* [1]

## GİRİŞ

Anjiyotensin dönüştürücü enzim inhibitörleri (ACEİ), koroner arter hastalığı (KAH), kalp yetmezliğinin (KY) tüm evrelerinde, nefropati, inme, kardiyovasküler koruma ve diğer birçok kardiyovasküler durum için önemli bir risk faktörü olan hipertansiyonu tedavi etmek ve yönetmek için kullanılan ilaç gruplarındandır. Çoğu hastalıkta tedavide ilk seçenek ilaç gruplarındandır.

### ACEİ Kullanım Alanları

ACEİ'leri; kalp yetmezliği, akut koroner sendromlar (AKS) dahil koroner kalp hastalığı, nefrotik sendrom (NS), diyabetes mellitüs (DM) ve hipertansiyon (HT) olmak üzere tedavisinde en sık kullanılan ilaç grubundandır (1). Hem hipertansif hem de normotansiflerde sistolik-diyastolik ve ortalama arteriyel kan basıncını etkili bir şekilde düşürür (2,3). Çok sayıda randomize kontrollü çalışmada antihipertansif ilaçlar olarak değerlendirilmiştir (4). Sekizinci Ortak Ulusal Komisyon (JNC8-2014) kılavuzunda, ACEİ'lerinin yüksek tansiyonu olan yetişkinler için başlangıç tedavisinde dört ilaç sınıfından biri olması önerilmiştir. Diğer üç ilaç sınıfı ise siyah olmayan genel popülasyon için kalsiyum kanal blokerleri (KKB), tiyazid diüretikler ve anjiyotensin reseptör blokerleridir (ARB) (5). Yüksek kan basıncına sahip siyah hasta popülasyon için başlangıç tedavisi olarak

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## KAYNAKLAR

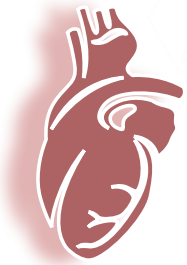

1. Nasution SA. The use of ACE inhibitor in cardiovascular disease. Acta Med Indones. 2006 Jan-Mar;38(1):60-4.
2. Vidt DG, Bravo EL, Fouad FM. Medical intelligence drug therapy: captopril. N Engl J Med. 1982 Jan 28;306(4):214-9.
3. Todd PA, Heel RC. Enalapril A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. Drugs. 1986 Mar;31(3):198-248.
4. Messerli FH, Bangalore S, Bavishi C, et al. Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? J Am Coll Cardiol. 2018 Apr 03;71(13):1474-1482.
5. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 05;311(5):507-20.
6. Page MR. The JNC 8 hypertension guidelines: an in-depth guide. Am J Manag Care. 2014 Jan;20(1 Spec No.):E8.
7. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018 May 15;71(19):e127-e248.
8. Williams B, Mancia G, Spiering W, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 01;39(33):3021-3104.
9. Veterans Administration Co-Operative Study Group on Antihypertensive Agents. Racial differences in response to low-dose captopril are abolished by the addition of hydrochlorothiazide. Br J Clin Pharmacol. 1982;14 Suppl 2(Suppl 2):97S-101S.
10. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):e13-e115.
11. Gavras H, Faxon DP, Berkoben J, et al. Angiotensin converting enzyme inhibition in patients with congestive heart failure. Circulation. 1978 Nov;58(5):770-6.
12. Dzau VJ, Colucci WS, Williams GH, et al. Sustained effectiveness of converting-enzyme inhibition in patients with severe congestive heart failure. N Engl J Med. 1980 Jun 19;302(25):1373-9.
13. CONSENSUS Trial Study Group. 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 Jun 04;316(23):1429-35.
14. Yusuf S, Pitt B, Davis CE, et al. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991 Aug 01;325(5):293-302.
15. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet. 1993 Oct 02;342(8875):821-8.
16. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med. 1992 Sep 03;327(10):669-77.

17. 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. Circulation. 2017 Aug 08;136(6):e137-e161.
18. Ponikowski P, Voors AA, Anker SD, ESC Scientific Document Group. 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 Jul 14;37(27):2129-2200.
19. Swedberg K, Held P, Kjekshus J, et al. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med. 1992 Sep 03;327(10):678-84.
20. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med. 1995 Jan 12;332(2):80-5.
21. Pfeffer MA. Left ventricular remodeling after acute myocardial infarction. Annu Rev Med. 1995;46:455-66.
22. O'Gara PT, Kushner FG, Ascheim DD, American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Jan 29;127(4):e362-425.
23. Knežević T, Gellineo L, Jelaković A, et al. Treatment of Hypertension Induced Albuminuria. Curr Pharm Des. 2018;24(37):4404-4412.
24. Hradec J. Pharmacological therapy for chronic heart failure. Vnitr Lek. 2018 Fall;64(9):853-859.
25. Leru PM, Anton VF, Bumbea H. Nine year follow-up of a rare case of angioedema due to acquired C1-inhibitor deficiency with late onset and good response to attenuated androgen. Allergy Asthma Clin Immunol. 2018;14:69.
26. Ichikawa I, Brenner BM. Glomerular actions of angiotensin II. Am J Med. 1984 May 31;76(5B):43-9.
27. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993 Nov 11;329(20):1456-62.
28. Zhang Y, Ding X, Hua B, et al. Real-world use of ACEI/ARB in diabetic hypertensive patients before the initial diagnosis of obstructive coronary artery disease: patient characteristics and long-term follow-up outcome. J Transl Med. 2020 Apr 01;18(1):150.
29- Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. J Clin Invest. 1986 Jun;77(6):1993-2000.
30. Ravid M, Lang R, Rachmani R, et al. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med. 1996 Feb 12;156(3):286-9.
31. Silvariño R, Rios P, Baldovinos G, et al. Is Chronic Kidney Disease Progression Influenced by the Type of Renin-Angiotensin-System Blocker Used? Nephron. 2019;143(2):100-107.
32. Rigat B, Hubert C, Alhenc-Gelas F, et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990 Oct;86(4):1343-6.

33. Pazik J, Ostrowska J, Lewandowski Z, et al. Renin-Angiotensin-Aldosterone system inhibitors and statins prolong graft survival in post-transplant glomerulonephritis. Ann Transplant. 2008;13(4):41-5.
34. Krečak I, Morić Perić M, Zekanović I, et al. Beneficial effect of ACE inhibitors on kidney function in polycythemia vera. Wien Klin Wochenschr. 2021 Aug;133(15-16):808-815.
35. Yao J, Fan S, Shi X, et al. Angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers on insulin sensitivity in hypertensive patients: A meta-analysis of randomized controlled trials. PLoS One. 2021;16(7):e0253492.
36. Salmenkari H, Korpela R, Vapaatalo H. Renin-angiotensin system in intestinal inflammation-Angiotensin inhibitors to treat inflammatory bowel diseases? Basic Clin Pharmacol Toxicol. 2021 Sep;129(3):161-172.
37. Patel S, Rauf A, Khan H, et al. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother. 2017 Oct;94:317-325.
38. Silva P, Brown RS, Epstein FH. Adaptation to potassium. Kidney Int. 1977 Jun;11(6):466-75.
39. Yee AH, Burns JD, Wijdicks EF. Cerebral salt wasting: pathophysiology, diagnosis, and treatment. Neurosurg Clin N Am. 2010 Apr;21(2):339-52.
40. Folkoww B, Johansson B, Mellander S. The comparative effects of angiotensin and noradrenaline on consecutive vascular sections. Acta Physiol Scand. 1961 Oct;53:99-104.
41. Bell L, Madri JA. Influence of the angiotensin system on endothelial and smooth muscle cell migration. Am J Pathol. 1990 Jul;137(1):7-12.
42. Timmermans PB, Wong PC, Chiu AT, et al. Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol Rev. 1993 Jun;45(2):205-51.
43. Cascieri MA, Bull HG, Mumford RA, et al. Carboxyl-terminal tripeptidyl hydrolysis of substance P by purified rabbit lung angiotensin-converting enzyme and the potentiation of substance P activity in vivo by captopril and MK-422. Mol Pharmacol. 1984 Mar;25(2):287-93.
44. Spyroulias GA, Galanis AS, Pairas G, et al. Structural features of angiotensin-I converting enzyme catalytic sites: conformational studies in solution, homology models and comparison with other zinc metallopeptidases. Curr Top Med Chem. 2004;4(4):403-29.
45. Regulski M, Regulska K, Stanisz BJ, et al. Chemistry and pharmacology of Angiotensin-converting enzyme inhibitors. Curr Pharm Des. 2015;21(13):1764-75.
46. Donnini S, et al. Sulfhydryl angiotensin-converting enzyme inhibitor promotes endothelial cell survival through nitric-oxide synthase, fibroblast growth factor-2, and telomerase crosstalk. J Pharmacol Exp Ther 2010;332:776–784.
47. Williams B. Drug discovery in renin-angiotensin system intervention: past and future. Ther Adv Cardiovasc Dis. 2016 Jun;10(3):118-25.
48. Pinargote P, Guillen D, Guarderas JC. ACE inhibitors: upper respiratory symptoms. BMJ Case Rep. 2014 Jul 17;2014
49. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med. 1992 Aug 01;117(3):234-42.
50. Tenenbaum A, Grossman E, Shemesh J, et al. Intermediate but not low doses of aspirin can suppress angiotensin-converting enzyme inhibitor-induced cough. Am J Hypertens. 2000 Jul;13(7):776-82.
51. Os I, Bratland B, Dahlöf B, et al. Female sex as an important determinant of lisinopril-induced cough. Lancet. 1992 Feb 08;339(8789):372.
52. Yeo WW, Chadwick IG, Kraskiewicz M, et al. Resolution of ACE inhibitor cough: changes in subjective cough and responses to inhaled capsaicin, intradermal bradykinin and substance-P. Br J Clin Pharmacol. 1995 Nov;40(5):423-9.

53. Lunde H, Hedner T, Samuelsson O, et al. Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. BMJ. 1994 Jan 01;308(6920):18-21.
54. Malini PL, Strocchi E, Zanardi M, et al. Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. Lancet. 1997 Jul 05;350(9070):15-8.
55. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med. 2008 Jan 01;148(1):16-29.
56. Slater EE, Merrill DD, Guess HA, et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. JAMA. 1988 Aug 19;260(7):967-70.
57. Korzeniowska K, Cielewiczi A, Pawlaczyk M, et al. Angıoedema after angiotensin-converting enzyme inhibitors. Acta Pol Pharm. 2017 May;74(3):983-986.
58. Ghouse J, Ahlberg G, Andreasen L, et al. Association of Variants Near the Bradykinin Receptor $B_2$ Gene With Angioedema in Patients Taking ACE Inhibitors. J Am Coll Cardiol. 2021 Aug 17;78(7):696-709.
59. Murphy BF, Whitworth JA, Kincaid-Smith P. Renal insufficiency with combinations of angiotensin converting enzyme inhibitors and diuretics. Br Med J (Clin Res Ed). 1984 Mar 17;288(6420):844-5.
60. Khosla S, Ahmed A, Siddiqui M, et al. Safety of angiotensin-converting enzyme inhibitors in patients with bilateral renal artery stenosis following successful renal artery stent revascularization. Am J Ther. 2006 Jul-Aug;13(4):306-8.
61. Rosano GMC, Tamargo J, Kjeldsen KP, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2018 Jul 01;4(3):180-188.
62. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med. 2000 Mar 13;160(5):685-93.
63. Kostis JB, Shelton B, Gosselin G, et al. Adverse effects of enalapril in the Studies of Left Ventricular Dysfunction (SOLVD). SOLVD Investigators. Am Heart J. 1996 Feb;131(2):350-5.
64. Hodsman GP, Isles CG, Murray GD, et al. Factors related to first dose hypotensive effect of captopril: prediction and treatment. Br Med J (Clin Res Ed). 1983 Mar 12;286(6368):832-4.
65. Kifor I, Moore TJ, Fallo F, et al. Potassium-stimulated angiotensin release from superfused adrenal capsules and enzymatically dispersed cells of the zona glomerulosa. Endocrinology. 1991 Aug;129(2):823-31.
66. Perazella MA. Hyperkalemia and trimethoprim-sulfamethoxazole: a new problem emerges 25 years later. Conn Med. 1997 Aug;61(8):451-8.
67. Sachs B, Meier T, Nöthen MM, et al. Drug-induced angioedema: Focus on bradykinin. Hautarzt. 2018 Apr;69(4):298-305.
68. Khera R, Clark C, Lu Y, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers With the Risk of Hospitalization and Death in Hypertensive Patients With COVID-19. J Am Heart Assoc. 2021 Jul 06;10(13):e018086.
69. Rahmat J, Gelfand RL, Gelfand MC, et al. Captopril-associated cholestatic jaundice. Ann Intern Med. 1985 Jan;102(1):56-8.
70. Brown NJ, Ray WA, Snowden M, et al. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther. 1996 Jul;60(1):8-13.
71. Wilkins B, Hullikunte S, Simmonds M, et al. Improving the Prescribing Gap For Guideline Recommended Medications Post Myocardial Infarction. Heart Lung Circ. 2019 Feb;28(2):257-262.

72. Shaikh A. A Practical Approach to Hypertension Management in Diabetes. Diabetes Ther. 2017 Oct;8(5):981-989.
73. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. Early Hum Dev. 2006 Jan;82(1):23-8.
74. Gubler MC, Antignac C. Renin-angiotensin system in kidney development: renal tubular dysgenesis. Kidney Int. 2010 Mar;77(5):400-6.
75. Kuenzli A, Bucher HC, Anand I, et al. Meta-analysis of combined therapy with angiotensin receptor antagonists versus ACE inhibitors alone in patients with heart failure. PLoS One. 2010 Apr 01;5(4):e9946.
76. Lucas C, Christie GA, Waring WS. Rapid onset of haemodynamic effects after angiotensin converting enzyme-inhibitor overdose: implications for initial patient triage. Emerg Med J. 2006 Nov;23(11):854-7.
77. Raebel MA, McClure DL, Simon SR, et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Pharmacoepidemiol Drug Saf. 2007 Jan;16(1):55-64.
78. DiBianco R. Adverse reactions with angiotensin converting enzyme (ACE) inhibitors. Med Toxicol. 1986 Mar-Apr;1(2):122-41.
79. Lip GY, Ferner RE. Poisoning with anti-hypertensive drugs: angiotensin converting enzyme inhibitors. J Hum Hypertens. 1995 Sep;9(9):711-5.
80. Sorodoc V, Sorodoc L, Lionte C, et al. Intentional poisoning with ACE inhibitors. Emergency Hospital. Rev Med Chir Soc Med Nat Iasi. 2010 Apr-Jun;114(2):359-62.
81. Varughese A, Taylor AA, Nelson EB. Consequences of angiotensin-converting enzyme inhibitor overdose. Am J Hypertens. 1989 May;2(5 Pt 1):355-7.
82. Jackson T, Corke C, Agar J. Enalapril overdose treated with angiotensin infusion. Lancet. 1993 Mar 13;341(8846):703.
83. Lip GY, Ferner RE. Poisoning with anti-hypertensive drugs: angiotensin converting enzyme inhibitors. J Hum Hypertens. 1995 Sep;9(9):711-5.



# BÖLÜM 4

# Anjiotensin-II Tip I Reseptör Blokerleri

*Umut UYAN* [1]

## GİRİŞ

Renin-anjiyotensin-aldosteron sistemi (RAAS), kan hacminin ve sistemik vasküler direncin önemli bir düzenleyicisidir. Baroreseptör refleksi azalan arter basıncına kısa süreli yanıt verirken, RAAS daha kronik değişikliklerden sorumludur. Üç ana bileşikten oluşur: renin, anjiyotensin II ve aldosteron. Bu bileşenler, azalan renal kan basıncına, distal kıvrık tübüle azalan tuz iletimine ve beta-agonizme cevap olarak arteriyel basıncı arttırmak üzere hareket eder. Tüm bunların sayesinde kan basıncını uzun süreli olarak yükseltebilir (1). Renin-anjiyotensin-aldosteron sistemi öncelikle kan hacmini, sodyum geri emilimini, potasyum salgısını, su geri emilimini ve damar tonusunu modüle ederek kan basıncı düzenlemesi ile ilişkilidir. RAAS'ın açıklanan diğer işlevleri arasında enflamasyon, apoptoz ve fibroz yer alır (2).

Böbreğin afferent arteriyollerinde, jukstaglomerüler (JG) hücreler yapısal olarak inaktif prorenin içerir. JG hücrelerinin aktivasyonu, prorenin'in renin'e dönüşmesine aracılık eder. Bu hücrelerin aktivasyonu, azalan kan basıncına, beta aktivasyonuna veya distal kıvrık tübüldeki sodyum yükünün azalmasına yanıt olarak makula densa hücrelerinin aktivasyonuna yanıt olarak gerçekleşir (3).

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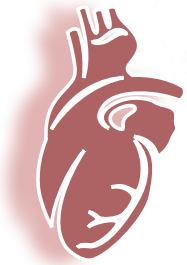
## KAYNAKLAR


1. Liu J, Zhou Y, Liu Y, et al. (Pro)renin receptor regulates lung development via the Wnt/β-catenin signaling pathway. Am J Physiol Lung Cell Mol Physiol. 2019 Aug 01;317(2):L202-L211.
2. Laghlam D, Jozwiak M, Nguyen LS. Renin-Angiotensin-Aldosterone System and Immunomodulation: A State-of-the-Art Review. Cells. 2021 Jul 13;10(7)
3. Ren L, Lu X, Danser AHJ. Revisiting the Brain Renin-Angiotensin System-Focus on Novel Therapies. Curr Hypertens Rep. 2019 Apr 04;21(4):28.
4. Bernstein KE, Khan Z, Giani JF, et al. Angiotensin-converting enzyme in innate and adaptive immunity. Nat Rev Nephrol. 2018 May;14(5):325-336.
5. Arroyo JP, Ronzaud C, Lagnaz D, et al. Aldosterone paradox: differential regulation of ion transport in distal nephron. Physiology (Bethesda). 2011 Apr;26(2):115-23.
6. Wagner CA. Effect of mineralocorticoids on acid-base balance. Nephron Physiol. 2014;128(1-2):26-34.
7. Shibata S, Arroyo JP, Castañeda-Bueno M, et al. Angiotensin II signaling via protein kinase C phosphorylates Kelch-like 3, preventing WNK4 degradation. Proc Natl Acad Sci U S A. 2014 Oct 28;111(43):15556-61.
8. Tham YK, Bernardo BC, Ooi JYY, et al. Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets. Arch Toxicol 2015;89:1401-38.
9. Sadoshima J, Izumo S. Molecular characterization of angiotensin II--induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. Circ Res 1993;73:413-23. https://doi.org/10.1161/01.RES.73.3.413
10. Clavell A, Stingo A, Margulies K, et al. Physiological significance of endothelin: Its role in congestive heart failure. Circulation 1993;87:V45-50
11. Holubarsch C, Hasenfuss G, Schmidt-Schweda et al. Angiotensin I and II exert inotropic effects in atrial but not in ventricular human myocardium. An in vitro study under physiological experimental conditions. Circulation 1993;88:1228-37.
12. Lopez JJ, Lorell BH, Ingelfinger JR, et al. Distribution and function of cardiac angiotensin AT1- and AT2-receptor subtypes in hypertrophied rat hearts. Am J Physiol Circ Physiol 1994;267:H844-52.
13. Burrell LM, Risvanis J, Kubota E, et al. Myocardial infarction increases ACE2 expression in rat and humans. Eur Heart J 2005;26:369-75.
14. Der Sarkissian S, Grobe JL, Yuan L, et al. Cardiac Overexpression of Angiotensin Converting Enzyme 2 Protects the Heart From Ischemia-Induced Pathophysiology. Hypertension 2008;51:712-8.
15. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin Receptors and Their Antagonists. N Engl J Med 1996;334:1649-55.
16. Batchu SN, Hughson A, Wadosky KM, et al. Role of Axl in T-Lymphocyte Survival in Salt-Dependent Hypertension. Arterioscler Thromb Vasc Biol 2016;36:1638-46.
17. Carillo BA, Beutel A, Mirandola DA, et al. Differential sympathetic and angiotensinergic responses in rats submitted to low- or high-salt diet. Regul Pept 2007;140:5-11.
18. Ziegler T, Abdel Rahman F, Jurisch V, et al. Atherosclerosis and the Capillary Network; Pathophysiology and Potential Therapeutic Strategies. Cells 2019;9:50.
19. Piqueras L, Sanz M-J. Angiotensin II and leukocyte trafficking: New insights for an old vascular mediator. Role of redox-signaling pathways. Free Radic Biol Med 2020;157:38-54.
20. Shu S, Zhang Y, Li W, et al. The role of monocyte chemotactic protein-induced protein 1 (MCPIP1) in angiotensin II-induced macrophage apoptosis and vulnerable plaque formation. Biochem Biophys Res Commun 2019;515:378-85.

21. Ding Y, Chen J, Cui G, et al. Pathophysiological role of osteopontin and angiotensin II in atherosclerosis. Biochem Biophys Res Commun 2016;471:5-9.
22. Lubrano V, Balzan S. Roles of LOX-1 in microvascular dysfunction. Microvasc Res 2016;105:132-40.
23. Kattoor AJ, Kanuri SH, Mehta JL. Role of Ox-LDL and LOX-1 in Atherogenesis. Curr Med Chem 2019;26:1693-700.
24. Muller J, Flesch G, Odeqosparo M, et al. Pharmakokinetic and Pharmakodynamic Effects of The Angiotensin II Antagonist Valsartan at Steady State in Healthy, Normotensive Subjects. Eart Clin Pharmacol 1997; 52: 441-9.
25. Nishikawa K, Naka T, Chantani, F, et al. Candesartan Cliexetil. A Review of Its Preclinical Pharmacology. J Hum Hypertens 1997; 11: 9-17.
26. O'NEIL, M.J. (Senior Ed.) (2001), The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 13th Ed., Merck&Co., Inc., New Jersey.
27. WARNER, G.T., Jarvis, B. Olmesartan Medoxomil. Drugs 2002; 62:1345-53.
28. CHENG, A. Eprosartan: An Angiotensin II Receptor Antagonists For The Management of Hypertension. Heart Dis 2002; 4: 54-9.
29. Martindale The Complete Drug Reference
30. BRUNNER, H.R. A New Angiotensin II Receptor Antagonists Irbesartan. Pharmakokinetic and Pharmakodynamic Considerations. Am J Hypertens 1997; 10: 311-7.
31. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effective- ness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med. 2008;148(1):16–29.
32. Klingbeil AU, Schneider M, et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med. 2003 Jul;115(1):41-6.
33. Burnett H, Earley A, Voors AA, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection frac- tion: a network meta-analysis. Circ Heart Fail.2017;10(1).
34. Cheng J, Zhang W, Zhang X, et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin II recep- tor blockers on all-cause mortality, cardiovascular deaths, and car- diovascular events in patients with diabetes mellitus: a meta-analy- sis. JAMA Intern Med. 2014;174(5):773– 85.
35. Bangalore S, Fakheri R, Toklu B, et al. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? Insights from 254,301 patients from randomized trials. Mayo Clin Proc. 2016;91(1):51–60.
36. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non- diabetic nephropathies with non-nephrotic proteinuria. Lancet. 1999;354(9176):359–64.
37. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme in- hibition in type 2 diabetes and nephropathy. N Engl J Med. 2004;351(19):1952–61.
38. Bosch J, Yusuf S, Pogue J, et al. Use of ramipril in preventing stroke: double blind randomised trial. BMJ. 2002;324(7339):699–702.



# BÖLÜM 5

# Mineralokortikoid Blokörleri ve Direkt Renin İnhibitörleri

*Ali ÇONER* [1]

## GİRİŞ

Aldosteron Renin-Anjiotensin-Aldosteron sisteminin son basamağını oluşturmaktadır ve kalp yetersizliği hastalarında hem sistemik hem de kalp dokusu düzeyinde yükselmektedir. Aldosteron'un en önemli patolojik etkileri kalp kasında fibrozis artışını hızlandırması ve renal tübüllerden sodyum tutulumunu arttırmasıdır. Standart kalp yetersizliği tedavisine eklenecek mineralokortikoid blokörlerinin (aldosteron blokörleri olan spironolakton ve eplerenon) klinik iyileşmeye ek katkı sağlamaktadır. Terazinin diğer ucunda hiperkalemi gelişim riski bulunmaktadır.

Aliskiren yeni geliştirilmiş bir renin blokörüdür ve klinik çalışmaları devam etmektedir. Elde edilen ilk sonuçlar özellikle hipertansiyon tedavisinde umut vermektedir. Aliskiren kullanımıyla ilgili dikkat edilmesi gereken temel husus böbrek fonksiyonlarının yakın takibidir.

Bu bölümde mineralokortikoid inhibitörleri olan spironolakton ve eplerenon ile birlikte direkt renin inhibitörü olan aliskiren hakkında bilgi vermeyi ve sonuçlanan/devam etmekte olan klinik çalışmaların verilerini tartışmayı amaçladık.

### Aldosteron, Spironolakton ve Eplerenon

RALES ve EPHESUS çalışmalarında kalp yetmezliğinde mortalitenin önemli bir noktası olan aktive olmuş Renin-Anjiotensin-Aldosteron sisteminin (RAAS)

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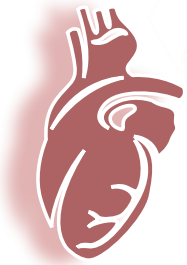
## KAYNAKLAR


1. Doggrell SA, Brown L. The spironolactone renaissance. *Expert Opin Investig Drugs.* 2001;10(5):943-54.
2. Pitt B, Zannad F, Remme WJ ve ark. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med.* 1999;341:709-17.
3. Pitt B, Williams G, Remme W ve ark. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. *Cardiovasc Drugs Ther.* 2001;15(1):79-87.
4. Barrera-Chimal J, Bonnard B, Jaisser F. Roles of mineralocorticoid receptors in cardiovascular and cardiorenal diseases. *Annu Rev Physiol.* 2022; 84:585-610.
5. Buffolo F, Tetti M, Mulatero P ve ark. Aldosterone as a mediator of cardiovascular damage. *Hypertension.* 2022;79(9):1899-911.
6. Dahal K, Hendrani A, Sharma SP ve ark. aldosterone antagonist therapy and mortality in patients with ST-segment elevation myocardial infarction without heart failure: A systematic review and meta-analysis. *JAMA Intern Med.* 2018;178(7):913-20.
7. Mihailidou AS. Aldosterone in heart disease. *Curr Hypertens Rep.* 2012;14(2):125-9.
8. Pitt B, Reichek N, Willenbrock R ve ark. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation.* 2003;108(15):1831-8.
9. Iqbal J, Fay R, Adlam D ve ark. Effect of eplerenone in percutaneous coronary intervention-treated post-myocardial infarction patients with left ventricular systolic dysfunction: a subanalysis of the EPHESUS trial. *Eur J Heart Fail.* 2014;16(6):685-91.
10. Zannad F, McMurray JJ, Krum H ve ark. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med.* 2011;364(1):11-21.
11. Anand IS, Claggett B, Liu J ve ark. Interaction between spironolactone and natriuretic peptides in patients with heart failure and preserved ejection fraction: From the TOPCAT trial. *JACC Heart Fail.* 2017;5(4):241-52.
12. Ravassa S, Trippel T, Bach D ve ark. Biomarker-based phenotyping of myocardial fibrosis identifies patients with heart failure with preserved ejection fraction resistant to the beneficial effects of spironolactone: results from the Aldo-DHF trial. *Eur J Heart Fail.* 2018;20(9):1290-9.
13. Oparil S, Yarows SA, Patel S ve ark. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. *Lancet.* 2007;370(9583):221-9.
14. Oparil S, Yarows SA, Patel S, Zhang J, Satlin A. Dual inhibition of the renin system by aliskiren and valsartan. *Lancet.* 2007;370(9593):1126-7.
15. Heerspink HJL, Persson F, Brenner BM ve ark. Renal outcomes with aliskiren in patients with type 2 diabetes: a prespecified secondary analysis of the ALTITUDE randomised controlled trial. *Lancet Diabetes Endocrinol.* 2016;4(4):309-17.
16. Kristensen SL, Mogensen UM, Tarnesby G ve ark. Aliskiren alone or in combination with enalapril vs. enalapril among patients with chronic heart failure with and without diabetes: a subgroup analysis from the ATMOSPHERE trial. *Eur J Heart Fail.* 2018;20(1):136-47.
17. Brown MJ, McInnes GT, Papst CC, Zhang J, MacDonald TM. Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial. *Lancet.* 2011;377(9762):312-20.
18. Maggioni AP, Greene SJ, Fonarow GC ve ark. Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure: insights from the ASTRONAUT trial. *Eur Heart J.* 2013;34(40):3117-27.



# BÖLÜM 6

# Sodyum Glukoz Ko-Transporter – 2 İnhibitörleri

*Umut KOCABAŞ* [1]

## GİRİŞ

Diyabet prevalansı giderek artan ve yüksek mortalite gelişimi ile ilişkili kronik bir hastalıktır. Diyabet seyrinde mortaliteyi artıran en önemli komplikasyonlar, diyabetin yol açtığı kardiyovasküler komplikasyonlardır. Tip 2 diyabet (T2DM) tedavisinde kullanılan çeşitli oral antidiyabetik ajanlar, diyabetin neden kardiyovasküler komplikasyonları azaltarak mortalite gelişiminin önlenmesini amaçlamaktadır. Böbrek sodyum glukoz ko-transporter – 2 (SGLT-2) inhibitörleri, T2DM tedavisinde yakın zamanda kullanılmaya başlanan bir antidiyabetik ilaç sınıfıdır. Bu sınıf içerisinde empaglifozin, dapaglifozin, canaglifozin, ertuglifozin ve sotaglifozin yer almaktadır.

Nissen ve Wolski tarafından 2007 yılında New England Journal of Medicine dergisinde yayınlanan bir meta-analiz (1), bir antidiyabetik ilaç olan rosiglitazonun artmış miyokard infarktüsü ve kardiyovasküler ölümler ile ilişkili olduğunu ortaya koymuştur. Bu meta-analizin yayınlanmasından bir yıl sonra, 2008 yılında, Amerikan İlaç Dairesi endüstriye yönelik yayınladığı bir kılavuzda, yeni geliştirilen tüm antidiyabetik ilaçlar için ruhsat onayı öncesi kardiyovasküler sonlanım çalışmaları yapılmasını ve kardiyovasküler ölüm, ölümcül olmayan miyokard infarktüsü ve ölümcül olmayan inme sonlanım noktaları açısından risk artışı ile ilişkili olmadığını kanıtlaması zorunlu kılınmıştır (2). SGLT-2 inhibitörleri ile yapılan kardiyovasküler sonlanım çalışmalarında, aterosklerotik

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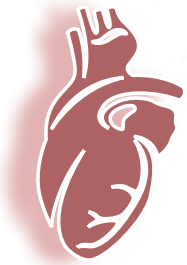
talarda kıvrım diüretiği dozunun azaltılabileceği önerilmektedir. Bir başka altı çizilen husus, SGLT-2 inhibitörü tedavisi seyrinde artmış ürogenital enfeksiyon riskidir. SGLT-2 inhibitörü tedavisi sonrası genital mikotik enfeskiyonlar, ürosepsis, piyelonefrit ve nadir olarak nekrotizan fasiyit gelişebileceği, bu sebeple tedavi başlanan olgulara ürogenital sistem hijyeninin önemi konusunda bilgilendirme yapılması ve mevcut riskler hakkında bilgi verilmesi önerilmektedir. SGLT-2 inhibitörleri hipoglisemi riski açısından düşük riskli ilaçlardır. T2DM varlığından bağımsız olarak, kalp yetersizliği hastalarında kullanılan SGLT-2 inhibitörü tedavisi seyrinde hipoglisemi beklenen bir komplikasyon değildir. Ancak hipoglisemi riski olan sülfonilüre ve/veya insülin tedavisi altındaki T2DM hastalarında, SGLT-2 inhibitörü başlanmasını takiben hipoglisemi gelişim riski artış göstermektedir. Bu nedenle, SGLT-2 inhibitörü başlanan hastalarda eğer sülfonilüre ya da insülin tedavisi kullanıyorlar ise bu tedavilerde doz azaltımı yapılması gerektiği vurgulanmaktadır (22,23).

Sonuç olarak, SGLT-2 inhibitörleri olan empaglifozin ve dapaglifozin tedavileri T2DM varlığından bapımsız olarak tüm kalp yetersizliği hastalarında kalp yetersizliğine bağlı hastane yatış ve ölüm riskini azaltmak amacıyla kullanımı önerilmektedir.

## KAYNAKLAR


1. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356: 2457–2471.
2. Food and Drug Administration. Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 mellitus. 2008.
3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015;373: 2117–2128.
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2019;380: 347–357.
5. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med.* 2020;383: 1413–1424.
6. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med.* 2019;381: 1995–2008.
7. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med.* 2021;385: 1451–1461.
8. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med.* 2022;387: 1089–1098.
9. Garla VV, Butler J, Lien LF. SGLT-2 Inhibitors in Heart Failure: Guide for Prescribing and Future Perspectives. *Curr Cardiol Rep.* 2021;23: 59.
10. Scheen AJ. Sodium-glucose cotransporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol.* 2020;16: 556–577.

11. Bertero E, Prates Roma L, et al. Cardiac effects of SGLT2 inhibitors: the sodium hypothesis. *Cardiovasc Res.* 2018;114: 12–18.
12. Katsiki N, Triposkiadis F. Resistance to diuretics in heart failure: any role for empagliflozin? *Curr Vasc Pharmacol.* 2019;17: 421–424.
13. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPAREG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care.* 2016;39: 1108–1114.
14. Butler J, Hamo CE, Filippatos G, et al. The potential role and rationale for treatment of heart failure with sodium-glucose cotransporter 2 inhibitors. *Eur J Heart Fail.* 2017;19: 1390–1400.
15. Kang S, Verma S, Teng G, et al. Direct effects of empagliflozin on extracellular matrix remodeling in human cardiac fibroblasts: novel translational clues to EMPA-REG Outcome. *Can J Cardiol.* 2017;33: S169.
16. Packer M. Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis. *Diabetes Obes Metab.* 2018;20: 1361–1366.
17. Figtree GA, Rådholm K, Barrett TD, et al. Effects of Canagliflozin on Heart Failure Outcomes AssociatedWith Preserved and Reduced Ejection Fraction in Type 2 Diabetes Mellitus: Results From the CANVAS Program. *Circulation.* 2019;139: 2591–2593.
18. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2019;380: 2295–2306.
19. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med.* 2020;383: 1425–1435.
20. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med.* 2021;384: 129–139.
21. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med.* 2021;384: 117–128.
22. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42: 3599–3726.
23. Maddox TM, Januzzi JL, Allen LA, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;77: 772–810.
24. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79: e263–e421.



# BÖLÜM 7

# Digoksin, Kolşisin

*Mehmet KIŞ* [1]

## GİRİŞ

Digoksin, kardiyolojide kullanılan en eski ilaçlardan biridir. Digoksinin birleşik inotropik-bradikardik etkileri, taşikardiye neden olma eğiliminde olan birçok sempatomimetik inotrop ilaçlarla karşılaştırıldığında benzersizdir. Zayıf pozitif inotropik etkisinin yanı sıra ventrikül hızını yavaşlatır, bu da özellikle atriyal fibrilasyonlu (AF) kronik kalp yetmezliğinde (KKY) ventriküler dolumun daha iyi olmasını sağlar. Digoksinin, ek olarak sinüs ritminde (SR) olan KKY' li hastalarda kullanılmasına bir gerekçede sempatik aktivasyonu azaltmasıdır. Bununla birlikte, yapılan çalışmalarda β-blokerler, aldosteron antagonistleri ve cihazlarla tedaviye digoksin eklenmesi herhangi bir mortalite yararı gösteremediği için digoxin kullanımı artık tartışmalıdır (1). Digoksinin optimal kullanımı, çok sayıda ilaç etkileşimlerinin, digoksinin etkinliğini ve toksisitesini etkileyen faktörlerin kapsamlı bir şekilde bilinmesini gerektirir. Hipoksi ve elektrolit bozukluğu olan hastalarda digoksinin etkilerinin tahmin edilmesi genellikle zor olduğundan ve etkinliğine dair kanıt bulunmadığından, digoksin artık akut kalp yetmezliğinde (KY) çok nadiren kullanılmaktadır.

Kolşisin, Colchicum fallale'den elde edilen eski bir bitkisel ilaçtır. İlk olarak ailevi akdeniz ateşi ve gut tedavisinde kullanılmıştır. Bir anti-inflamatuar ajan olarak benzersiz etkinliğine dayanara kolşisin, koroner arter hastalığı (KAH),

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Kolşisinin, atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil ve fenofibrik asit veya siklosporinin birlikte kullanımı miyopati gelişimini artırabilir. Kolşisin gebelik kategorisi C olarak sınıflandırır. Hamilelik sırasında kolşisin, yalnızca anneye olan potansiyel yararın fetüs üzerindeki olası riske ağır basması durumunda kullanılmalıdır (25).

## Toksisite ve Tedavisi

Önemli toksisite ile sonuçlanan kesin kolşisin dozu bilinmemektedir Kolşisin serum konsantrasyonunu belirlemek için herhangi bir kan testi mevcut değildir. Karaciğer veya böbrek yetmezliği veya hastalığı olan hastalarda ya da P-glikoprotein veya CYP3A4 inhibitörü alan hastalarda tam kan sayımı, renal ve hepatik fonksiyon test takipleri yapılabilir.

Akut kolşisin toksisitesi genellikle alımdan sonraki 24 saat içinde başlar ve gastrointestinal semptomları içerir, sonunda önemli sıvı ve hacim kaybına yol açar. Başlangıç aşamasında, periferik lökositoz da mevcut olabilir. Hayatı tehdit eden komplikasyonlar genellikle ilaç uygulamasından 24 ila 72 saat sonra ortaya çıkar ve genellikle çoklu organ yetmezliğine atfedilir (25). Ölüm tipik olarak solunum depresyonu ve kardiyovasküler kollapsın bir sonucudur.

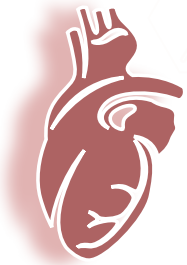
Kolşisin zehirlenmesinin tedavisi, gastrik lavaj ve şoku önleyici önlemlerle başlamalıdır. Aksi takdirde tedavi semptomatik ve destekleyicidir. Bilinen spesifik bir panzehir yoktur ve kolşisin diyaliz ile etkili bir şekilde uzaklaştırılmaz. Herhangi bir hastaya kolşisin uygulamadan önce, mevcut doz önerileri ve hastanın yaşı, böbrek ve karaciğer fonksiyonu bilinmelidir. Kolşisinle ilgili tüm ilaç hatalarının en az %30'u yanlış doz rejimleriyle ilgilidir (25).

## KAYNAKLAR


1. Abdul-Rahim AH, MacIsaac RL, Jhund PS, Petrie MC, Lees KR, McMurray JJ; On behalf the VICCTA-Heart Failure Collaborators. Efficacy and safety of digoxin in patients with heart failure and reduced ejection fraction according to diabetes status: An analysis of the Digitalis Investigation Group (DIG) trial. Int J Cardiol. 2016;209:310-6. doi: 10.1016/j.ijcard.2016.02.074.
2. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP,et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med. 2019;381(26):2497-2505. doi: 10.1056/NEJMoa1912388.
3. Opstal TSJ, Fiolet ATL, van Broekhoven A, Mosterd A, Eikelboom JW, Nidorf SM, et al; LoDoCo2 Trial Investigators. Colchicine in Patients With Chronic Coronary Disease in Relation to Prior Acute Coronary Syndrome. J Am Coll Cardiol. 2021;78(9):859-866. doi: 10.1016/j.jacc.2021.06.037.

4. Patocka J, Nepovimova E, Wu W, Kuca K. Digoxin: Pharmacology and toxicology-A review. Environ Toxicol Pharmacol. 2020;79:103400. doi: 10.1016/j.etap.2020.103400.
5. Saunders NR, Dziegielewska KM, Møllgård K, Habgood MD. Recent Developments in Understanding Barrier Mechanisms in the Developing Brain: Drugs and Drug Transporters in Pregnancy, Susceptibility or Protection in the Fetal Brain? Annu Rev Pharmacol Toxicol. 2019;59:487-505. doi: 10.1146/annurev-pharmtox-010818-021430.
6. Albert CL, Kamdar F, Hanna M. Contemporary Controversies in Digoxin Use in Systolic Heart Failure. Curr Heart Fail Rep. 2016;13(5):197-206. doi: 10.1007/s11897-016-0302-z. PMID: 27696142.
7. Konstantinou DM, Karvounis H, Giannakoulas G. Digoxin in Heart Failure with a Reduced Ejection Fraction: A Risk Factor or a Risk Marker. Cardiology. 2016;134(3):311-9. doi: 10.1159/000444078.
8. Sukoyan GV, Berberashvili TM, Karsanov NV. Submolecular mechanisms underlying in vitro and in vivo effect of cardiac glycosides on contractile activity of myocardial myofibrils during heart failure. Bull Exp Biol Med. 2006;141(4):424-6. doi: 10.1007/s10517-006-0189-x.
9. Opie, Lionel H., and Bernard J. Gersh. Drugs for the Heart. Elsevier Health Sciences, 2012.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. Eur Heart J. 2021;42(5):373-498. doi: 10.1093/eurheartj/ehaa612.
11. Ferrari F, Santander IRMF, Stein R. Digoxin in Atrial Fibrillation: An Old Topic Revisited. Curr Cardiol Rev. 2020;16(2):141-146. doi: 10.2174/1573403X15666190618110941.
12. Kotecha D, Bunting KV, Gill SK, Mehta S, Stanbury M, Jones JC, et al. Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) Team. Effect of Digoxin vs Bisoprolol for Heart Rate Control in Atrial Fibrillation on Patient-Reported Quality of Life. JAMA. 2020;324(24):2497-2508. doi: 10.1001/jama.2020.23138.
13. Singh S, Moore H, Karasik PE, Lam PH, Wopperer S, Arundel C, et al. Digoxin Initiation and Outcomes in Patients with Heart Failure (HFrEF and HFpEF) and Atrial Fibrillation. Am J Med. 2020;133(12):1460-1470. doi: 10.1016/j.amjmed.2020.05.030.
14. Georgiopoulou VV, Kalogeropoulos AP, Giamouzis G, Agha SA, Rashad MA, Waheed S, et al. Digoxin therapy does not improve outcomes in patients with advanced heart failure on contemporary medical therapy. Circ Heart Fail. 2009;2(2):90-7. doi: 10.1161/CIRCHEARTFAILURE.108.807032.
15. Yukawa M, Yukawa E, Suematsu F, Takiguchi T, Ikeda H, Aki H, et al. Determination of digoxin clearance in Japanese elderly patients for optimization of drug therapy: a population pharmacokinetics analysis using nonlinear mixed-effects modelling. Drugs Aging 2011;28:831–841.
16. Shi L, Sun LD, Odel JG.. Colored floaters as a manifestation of digoxin toxicity. Am. J. Ophthalmol. 2018;10: 233–235.
17. Broeren MA, Geerdink EA, Vader HL, van den Wall Bake AW. Hypomagnesemia induced by several proton-pump inhibitors. Ann Intern Med. 2009;151(10):755-6. doi: 10.7326/0003-4819-151-10-200911170-00016.
18. Archer J, Dargan P.Cardiovascular poisoning. Medicine. 2020; 48 (3): 199–202.
19. Ren Y, Ribas HT, Heath K, Wu S, Ren J, Shriwas P, et al. Na+/K+-ATPase-Targeted Cytotoxicity of (+)-Digoxin and Several Semisynthetic Derivatives. J Nat Prod. 2020;83(3):638-648. doi: 10.1021/acs.jnatprod.9b01060.
20. Pita-Fernández S, Lombardía-Cortiña M, Orozco-Veltran D, Gil-Guillén V. Clinical manifestations of elderly patients with digitalis intoxication in the emergency department. Arch Gerontol Geriatr. 2011;53(2):e106-10. doi: 10.1016/j.archger.2010.07.003.

21. Deftereos SG, Beerkens FJ, Shah B, Giannopoulos G, Vrachatis DA, Giotaki SG, et al. Colchicine in Cardiovascular Disease: In-Depth Review. Circulation. 2022;145(1):61-78. doi: 10.1161/CIRCULATIONAHA.121.056171.
22. Shah B, Pillinger M, Zhong H, Cronstein B, Xia Y, Lorin JD, et al. Effects of Acute Colchicine Administration Prior to Percutaneous Coronary Intervention: COLCHICINE-PCI Randomized Trial. Circ Cardiovasc Interv. 2020 Apr;13(4):e008717. doi: 10.1161/CIRCINTERVENTIONS.119.008717.
23. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al;ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. Eur Heart J. 2015;36(42):2921-2964. doi: 10.1093/eurheartj/ehv318.
24. Lee JZ, Singh N, Howe CL, Low SW, Huang JJ, Ortega G, et al. Colchicine for Prevention of Post-Operative Atrial Fibrillation: A Meta-Analysis. JACC Clin Electrophysiol. 2016;2(1):78-85. doi: 10.1016/j.jacep.2015.09.016.
25. Sadiq NM, Robinson KJ, Terrell JM. Colchicine. In: StatPearls [Internet]. Treasure Island (FL). 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431102/.



# BÖLÜM 8

# Pozitif İnotrop Ajanlar

*Ahmet Anıl BAŞKURT* [1]

## GİRİŞ

Hipotansiyon birçok neden sonucu oluşabilen acil müdahale gerektiren bir durumdur. Doku perfüzyonu bozulduğundan hedef doku hasarını önlemek için hipotansiyon hızlı bir şekilde düzeltilmelidir. Uygun hidrasyon tedavisine rağmen hipotansiyonun devam ettiği durumlarda inotrop ve vazopresör ajanlar kullanılmaktadır. Bu ajanların kardiyoloji pratiğinde en sık kullanıldığı durum ise akut kalp yetersizliği tablosudur.

Akut kalp yetersizliği, kalp yetersizliği semptomlarının ani olarak başladığı veya var olan semptomların ani olarak kötüleştiği ve acil tıbbi müdahale gerektiren bir durumdur. Özellikle 65 yaş üzerindeki hastalarda mortalite ve tekrar hastaneye başvuru oranları yüksektir.(1–4)Akut kalp yetersizliği hastaları klinik pratiğimizde sık karşılaştığımız, acil serviste ya da koroner yoğun bakımda acil tedavi ihtiyacı olan hastalardır. Özellikle düşük kardiyak outputu olan, sistolik kan basıncı 90 mm Hg altında olup hipoperfüzyon bulguları olan hastalarda inotrop ve vazopresör ajanlar kullanılmaktadır. Bu bölümde inotrop ve vazopresör ajanların farmakolojik özellikleri, kullanımları, etkileri ve birbirlerinden farklılıkları güncel çalışmalar ve kılavuzlar eşliğinde tartışılacaktır.

Damar tonusuna adrenerjik sistem üzerinden etki ederek vazokonstrüksiyon yapan ve kan basıncı artışına neden olan ajanlara vazopresör ajanlar denilmektedir. Kalp kası kontraktilitesini artırarak kardiyak debi artışına neden olan ajanla-

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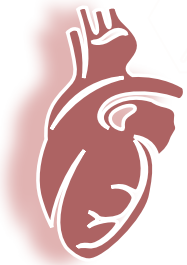
## KAYNAKLAR


1. Nieminen MS, Brutsaert D, Dickstein K et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006 Nis 11;27(22):2725-36. doi: 10.1093/eurheartj/ehl193.
2. Chioncel O, Mebazaa A, Harjola VP et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017 Eki;19(10):1242-54. doi: 10.1002/ejhf.890.
3. Chioncel O, Mebazaa A, Maggioni AP et al. Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry. Eur J Heart Fail. 2019 Kas 24;21(11):1338-52. doi: 10.1002/ejhf.1492.
4. Miró Ò, García Sarasola A, Fuenzalida C et al. Departments involved during the first episode of acute heart failure and subsequent emergency department revisits and rehospitalisations: an outlook through the NOVICA cohort. Eur J Heart Fail. 2019 Eki 7;21(10):1231-44. doi: 10.1002/ejhf.1567.
5. Hollenberg SM, Ahrens TS, Annane D et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med. 2004 Eyl;32(9):1928-48. doi: 10.1097/01.ccm.0000139761.05492.d6.
6. Hoffman BB. Catecholamines and Sympathomimetic Drugs, and Adrenergic Receptor-Antagonist. Içinde: Hardman JG, editör. Goodman and Gilman's, 1996 The Pharmacological Basis of Therapeutics . 1996. s. 199-250.
7. Bistola V, Chioncel O. Inotropes in acute heart failure. Continuing Cardiology Education. 2017 Eyl;3(3):107-16. doi: 10.15420/cfr.2019.11.2
8. Cecconi M, de Backer D, Antonelli M et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2014 Ara 13;40(12):1795-815. doi: 10.1007/s00134-014-3525-z.
9. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. Crit Care Med. 2000 Ağu;28(8):2758-65. doi: 10.1097/00003246-200008000-00012.
10. de Backer D, Biston P, Devriendt J et al. Comparison of Dopamine and Norepinephrine in the Treatment of Shock. New England Journal of Medicine. 2010 Mar 4;362(9):779-89. DOI: 10.1056/NEJMoa0907118
11. Soar J, Deakin CD, Nolan JP et al. European Resuscitation Council Guidelines for Resuscitation 2005. Resuscitation. 2005 Ara;67:S135-70. doi: 10.1016/j.resuscitation.2005.10.009.
12. Nolan JP, Deakin CD, Soar J et al. European Resuscitation Council Guidelines for Resuscitation 2005. Resuscitation. 2005 Ara;67:S39-86. doi: 10.1016/j.resuscitation.2005.10.009.
13. Levy B, Clere-Jehl R, Legras A et al. Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction. J Am Coll Cardiol. 2018 Tem;72(2):173-82. doi: 10.1016/j.jacc.2018.04.051.
14. Marik P. Low-dose dopamine: a systematic review. Intensive Care Med. 2002 Tem 31;28(7):877-83. doi: 10.1007/s00134-002-1346-y.
15. Felker GM, Benza RL, Chandler AB et al. Heart failure etiology and response tomilrinone in decompensated heart failure. J Am Coll Cardiol. 2003 Mar;41(6):997-1003. doi: 10.1016/s0735-1097(02)02968-6.
16. Mathew R, di Santo P, Jung RG et al. Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock. New England Journal of Medicine. 2021 Ağu 5;385(6):516-25. doi: 10.1056/NEJMoa2026845.

17. Szarpak L, Szwed P, Gasecka A et al. Milrinone or dobutamine in patients with heart failure: evidence from meta-analysis. ESC Heart Fail. 2022 Haz 5;9(3):2049-50. doi: 10.1002/ehf2.13812
18. Rauch H, Motsch J, Böttiger BW. Newer approaches to the pharmacological management of heart failure. Curr Opin Anaesthesiol. 2006 Şub;19(1):75-81. doi: 10.1097/01.aco.0000192781.62892.c3.
19. Teerlink JR, Diaz R, Felker GM et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. New England Journal of Medicine. 2021 Oca 14;384(2):105-16. doi: 10.1056/NEJMoa2025797.
20. Adresi Y, Arzu TOPELİ İSKİT Hacettepe Üniversitesi Tıp Fakültesi D, Hastalıkları Anabilim Dalı İ, Bakım Ünitesi Y. Makalenin Kabul Tarihi: 02.12. C. 6, Yoğun Bakım Dergisi. 2006.
21. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Eyl 21;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.



# BÖLÜM 9

# Acil Serviste Hipertansif Acillerden Akut Kalp Yetmezliğine Yaklaşım ve Tedavisi

*Deniz ORAY* [1]

## GİRİŞ VE TANIM

Sistolik kan basıncının (KB) 180 mmHg' nın üzerinde ve/veya diyastolik KB' nın 120 mmHg' nın üzerinde olduğu akut KB yükselmesi hipertansif kriz olarak adlandırılmaktadır. Hipertansif acil (Emergent) ve hipertansif ivedi durum (Urgent) olarak adlandırılan iki formu vardır. Hedef organlarda (Beyin, kalp, aort, böbrek ve göz) hasarın eşlik ettiği hipertansif krizler, hipertansif aciller olarak adlandırılırlar. Hipertansif ivedi durumlarda hedef organ hasarı bulunmamaktadır. Whelton ve ark. yayınladığı kılavuzda belirtilen hipertansiyon (HT) hastalığının ana başlıkları tablo 1' de gösterilmiştir. Tablo 2'de hedef organ hasarının eşlik ettiği hipertansif aciller gösterilmektedir (1).

Günümüzde HT hastalığı olan yetişkin kişilerin sayısı 1,3 milyarı aşmıştır. Amerika Birleşik Devletleri'nde acil servis başvurularının %6'sını şiddetli HT oluşturmaktadır. Bu başvuruların %25-50'sinde hedef organ hasarı bulunmaktadır (2-6). Ülkemizde HT prevalansı %34' ün üzerindedir (7). Akut kalp yetmezliği ile acil servise başvuran hastaların %50-70'ini akut dekompanse kalp yetmezliği oluşturmaktadır (8).

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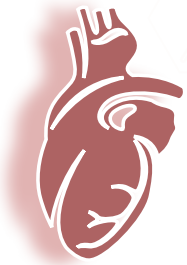
## KAYNAKLAR


1. Whelton PK, Carey RM, Aronow WS, et al: Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 71: e13, 2018.
2. wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Examination& CycleBeginYear=2013 (Centers for Disease Control and Prevention, National Center for Health Statistics: National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [2011-2014]). Accessed June 28, 2018.
3. Janke AT, McNaughton CD, Brody AM, et al: Trends in the incidence of hypertensive emergencies in US emergency departments from 2006 to 2013. J Am Heart Assoc 5: 1, 2016.
4. Karras DJ, Kruus LK, Cienki JJ, et al: Evaluation and treatment of patients with severely elevated blood pressure in academic emergency departments: a multicenter study. Ann Emerg Med 47: 230, 2006.
5. Martin JF, Higashiama E, Garcia E, et al: Hypertensive crisis profile. Prevalence and clinical presentation. Arq Bras Cardiol 83: 131, 2004.
6. Pinna G, Pascale C, Fornengo P, et al: Hospital admissions for hypertensive crisis in the emergency departments: a large multicenter Italian study. PLoS One 9: e93542, 2014.
7. WHO. Hypertension, Erişim: 'https://www.who.int/health-topics/hypertension/#tab=tab_1'. Erişim tarihi: 25 Aralık 2022.
8. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021;42:3599-3726.
9. Smith LM, Mahler SA. Kardiyovasküler hastalık. Tintinalli Acil Tıp, kapsamlı bir çalışma kılavuzu (Eroğlu SE, Özhaseneker A, Çev. Ed.). İstanbul: Nobel Tıp Kitapevleri Tic. Ltd. Şti.; 2021.
10. Heidenreich PA, Albert NM, Allen LA, et al: Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 6: 606, 2013.
11. Ramirez A, Abelmann WH: Cardiac decompensation. N Engl J Med 290: 499, 1974.
12. O'Connor CM, Starling RC, Hernandez AF, et al: Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 365: 32, 2011.
13. Merchant RM, Topjian AA, Panchal AR, et al. Part 1: executive summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142
14. Felker GM, Lee KL, Bull DA, et al: Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 364: 797, 2011.
15. Gardner CJ, Lee K: Hyperperfusion syndromes: insight into the pathophysiology and treatment of hypertensive encephalopathy. CNS Spectr 12: 35, 2007.
16. Sheta MA, Paladugu M, Mendelson J, et al: When should nitroglycerine be avoided in hypertensive encephalopathy? Hypertension 58: e187, 2011.
17. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, et al: Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 43: 1711, 2012.



# BÖLÜM 10

# Kalsiyum Kanal Blokerleri

*Begüm YETİŞ SAYIN* [1]

## GİRİŞ

Kalsiyum kanal blokerleri (KKB) geniş bir kullanım alanına sahiptir. Hücre içinde bulunan kalsiyum iyonları kasılma, salgılama ve nöral etkilerin yer aldığı fizyolojik olaylardan sorumludur. Kalsiyum iyonlarının hücre içine girişi damar düz kası ve kalp kasında kontraksiyona neden olur. Ekstraselüler kalsiyum girişi hücre içinde kalsiyum salınımını tetikler. Hücre depolarizasyonu ve repolarizasyonu sırasında sarkolemma düzeyinde sodyum ($Na^{+}$) ve kalsiyum ($Ca^{+2}$) değiş tokuşu meydana gelir. Sodyum ve kalsiyum her zar depolarizasyon döngüsü sırasında, $Na^{+}$ ve L-tipi(uzun etkili) $Ca^{2+}$ kanalı aracılığı ile sarkoplazmik retikulumdaki (SR) iç depolardan büyük miktarda $Ca^{+2}$ salıverilmesini tetikler. Hücre içinde olan kalsiyum artışı troponin C ile etkileşir. Ayrıca aktin miyozin arasındaki etkileşimi aktive ederek sarkomer kısalmasına yol açar. Ekstraselüler $Ca^{+2}$ girişine voltaj-duyarlı kalsiyum kanalları eşlik eder. Kalsiyum kanal blokerleri voltaj bağımlı kalsiyum ($Ca^{+2}$) iyon kanalları üzerinden etkilerini gösterirler. Transmembran kalsiyum akışının düz kas ve kardiyak kas hücrelerinin kontraksiyonuna etkisi 1800 yılların sonlarına doğru anlaşılmıştı. Sonrasında ise değişik dokularda farklı tiplerde kalsiyum kanalları tanımlanmıştır. Bu grupta etki gösteren ilaçlar hücre dışından hücre içine kalsiyum girişini engeller, vasküler ve diğer düz kas hücrelerinin gevşemesini sağlar. Voltaj bağımlı kalsiyum kanalları nöronlar, kalp, iskelet kası, düz kas, endokrin/adrenokortikal hücreler, retina

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## KAYNAKLAR


1. Dolphin AC. A short history of voltage-gated calcium channels. *Br J Pharmacol*. 2006 Jan;147 Suppl 1(Suppl 1):S56-62. doi: 10.1038/sj.bjp.0706442.
2. Errington AC, Stöhr T, Lees G. Voltage gated ion channels: targets for anticonvulsant drugs. *Curr Top Med Chem*. 2005;5(1):15-30. doi: 10.2174/1568026053386872.
3. Katzung, B.G., Masters, S.B. and Trevor, A.J., Eds. (2012) *Basic and Clinical Pharmacology*. 12th Edition, McGraw-Hill Medical, New York.p:169-193.
4. Kayaalp, S. O *Akılcı Tedavi Yönünden Tıbbi Farmakoloji*, Gözden Geçirilmiş 13. Baskı, Pelikan Kitabevi, Ankara, 2012.
5. Dandan RH,Brunton L.*Goodman and Gilman's Manual of Pharmacology and Therapeutics*. 2nd edition New York: McGraw-Hill;2015:p450-477.
6. Godfraind T. Calcium Channel Blockers in Cardiovascular Pharmacotherapy. *Journal of Cardiovascular Pharmacology and Therapeutics*.2014;19(6):501-515.
7. Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. *Am J Med*. 2004 Jan 1;116(1):35-43. doi: 10.1016/j.amjmed.2003.08.027
8. Opie LH. Calcium channel blockers Eds Opie LH, Gersh BJ. *Drugs for the heart 8th edition*. Saunders, Philadelphia 2013. p:64-92
9. Coca A, Mazon P, Aranda P, et al. Role of dihydropyridinic calcium channel blockers in the management of hypertension. *Expert Rev Cardiovasc Ther* 2013;11:91–105.
10. Canbolat Ş, Nurullahoğlu Atalık KE. Kalsiyum Kanal Blokerlerinin Pleiotropik Etkileri. *Kafkas Journal of Medical Sciences*. 2019; 9(2): 125-131.
11. DeRoos F. Calcium channel blockers. In: *Goldfrank's Toxicologic Emergencies*. 8th ed. New York; 2006
12. Scholz H. Pharmacological aspects of calcium channel blockers. *Cardiovascular drugs and therapy*. 1997;10 Suppl 3:869–72.
13. Lip S, Padmanabhan S. Calcium channel blockers in hypertension. Nadar SK, Lip GYH. *Hypertension*, 3rd edition,Oxford University Press.p:147-157
14. Law MR, et al. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *Br Med J* 2009;338:b16–b65.
15. Pepine CJ, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: the International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;290:2805–2816
16. Black HR, Elliott WJ, Grandits G, et al.Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003 Apr 23-30;289(16):2073-82. doi: 10.1001/jama.289.16.2073.
17. Açıkalın A, Taşkın Ö, Dişel R. Kalsiyum Kanal Blokeri Zehirlenmeleri. *Anatolian J Emerg Med*. 2022; 5(2): 92-98.
18. Jang DH, DeRoos F. Calcium Channel Blockers. In: Hoffman RS, Howland M, Lewin NA, Nelson LS, Goldfrank LR. eds. *Goldfrank's Toxicologic Emergencies, 10e*. McGraw Hill; 2015.
19. St-Onge M, Anseeuw K, Cantrell FL, et al. Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults. *Crit Care Med*. 2017 Mar;45(3):e306-e315. doi: 10.1097/CCM.0000000000002087.
20. Magdalan J, Kochman K, Antończyk A, et al. Successful treatment by 4--aminopyridine of three cases of severe verapamil poisoning. *Przeglad lekarski*. 2003;60(4):271–3.
21. Engebretsen KM, Kaczmarek KM, Morgan J, et al. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clinical toxicology* (Philadelphia, Pa). 2011 Apr;49(4):277–83.

22. Caille G., Boucher S., Spenard J., et al. Diltiazem pharmacokinetics in elderly volunteers after single and multiple doses. *Eur. J. Drug Metab. Pharmacokinet*. 1991;16 (1), 75–80.
23. Abernethy DR, et al. Calcium-antagonist drugs. *New Engl J Med 1999*;341:1447–1455.
24. Göbel EJ, et al. Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris. *Eur Heart J* 1998;19:1208–1213
25. Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *New Engl J Med* 1988;319:385–392.
26. Holzgreve H, et al. Verapamil versus hydrochlorothiazide in the treatment of hypertension: results of long term double blind comparative trial. Verapamil versus Diuretic (VERDI) Trial Research Group. *Brit Med J* 1989;299:881–886
27. Barnes C, Hamilton PG, Lebel M. Effects of monotherapy with sustained-release verapamil on blood pressure, lipid levels, renal function, diabetic control, and patient well-being in patients with mild to moderate hypertension. *CUIT Ther Res* 1993 Aug; 54: 127-41.
28. Hansson L, Hedner T, Lund-Johansen P,et al.Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet*. 2000 Jul 29;356(9227):359-65. doi: 10.1016/s0140-6736(00)02526-5.
29. Gottdiener JS, et al. Effect of single-drug therapy on reduction of left ventricular size in mild to moderate hypertension. Comparison of six antihypertensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Circulation* 1998;98:140–148.
30. Hume JR. Agents Used in Cardiac Arrhythmias Katzung, B.G., Masters, S.B. and Trevor, A.J., Eds. (2012) *Basic and Clinical Pharmacology.* 12th Edition, McGraw-Hill Medical, New York.p:227-251.
31. Edraki N, Mehdipour AR, Khoshneviszadeh M, Min R. Dihydropyridines: evaluation of their current and future pharmacological applications. *Drug Discovery Today* 2009;14(21–22):1058–66.
32. Elliott WJ, Ram CV. Calcium channel blockers. *J Clin Hypertens* (Greenwich)2011 Sep; 13(9):687–9.
33. Coca A, Mazon P, Aranda P, Redón J, Divisón JA, Martínez J et al. Role of dihydropyridinic calcium channel blockers in the management of hypertension. *Expert Rev Cardiovasc* Ther 2013;11:91–105.
34. Triggle DJ. Calcium channel antagonists: clinical uses--past, present and future. *Biochem Pharmacol*. 2007 Jun 30;74(1):1-9. doi: 10.1016/j.bcp.2007.01.016.
35. Wang AL, Iadecola C, Wang G. New generations of dihydropyridines for treatment of hypertension. *J Geriatr Cardiol.* 2017 Jan;14(1):67-72. doi: 10.11909/j.issn.1671-5411.2017.01.006.
36. İsmailoğlu Ö, Albayrak B, Çetinalp NE. Travmatik Subaraknoid Kanamalarda Nimodipinin Etkisi. *Sinir Sistemi Cerrahisi Dergisi*.2(4):200-4.
37. Leenen FH. Clinical relevance of 24 h blood pressure control by 1, 4-dihydropyridines. *Am J Hypertens* 1996;9:97–104.
38. Muller J, et al. Nifedipine and conventional therapy for unstable angina pectoris: a randomized, double-blind comparison. *Circulation* 1984;69:728–733.
39. de Champlain J, et al. Different effects of nifedipine and amlodipine on circulating catecholamine levels in essential hypertensive patients. *J Hypertens* 1998;16:1357–1369
40. Simon A, et al. Differential effects of nifedipine and co-amilozide on the progression of early carotid wall changes. *Circulation* 2001;103:2949–2954.
41. Aydoğdu S,Güler K,Bayram F, et al. 2019 Turkish Hypertension Consensus Report. *Turk Kardiyol Dern Ars*. 2019; 47(6): 535-546.

42. Brown MJ, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: intervention as a goal in hypertension treatment. *Lancet* 2000;356:366–372
43. Poole-Wilson PA, et al. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004; 364:849–857.
44. Nayler WG, et al. The unique binding properties of amlodipine: a long-acting calcium antagonist. *J Human Hypertens* 1991;5(Suppl 1):55–59.
45. Meredith, P.A., Elliott, H.L. Clinical Pharmacokinetics of Amlodipine. *Clin-Pharmacokinet* **22**, 22–31 (1992). https://doi.org/10.2165/00003088-199222010-0000.
46. Rinaldi CA, et al. Randomized, double-blind crossover study to investigate the effects of amlodipine and isosorbide mononitrate on the time course and severity of exercise induced myocardial stunning. *Circulation* 1998;98:749–756.
47. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997.
48. Dalhöf B, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895–906.
49. Julius S, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022–2031.
50. Jamerson K, et al. ACCOMPLISH Trial Investigators Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417–2428.
51. Takka S, Acartürk F. Felodipin. *FABAD, Farm.Bil.Der.* 1992, 17,307-320.
52. Manuelsson H, et al. For the TRAFFIC Study Group. Antianginal efficacy of the combination of felodipine-metoprolol 10/100 mg compared with each drug alone in patients with stable effort-induced angina pectoris: a multicenter parallel group study. *Am Heart J* 1999;137:854–862.
53. Akizuki O, Inayoshi A, Kitayama T, Yao K, Shirakura S, Sasaki K et al. Blockade of T-type voltage-dependent Ca2+ channels by benidipine, a dihydropyridine calcium channel blocker, inhibits aldosterone production in human adrenocortical cell line NCI-H295R. *Eur J Pharmacol* 2008;584(2–3):424–34
54. Ruggenenti P, et al. For the DEMAND Study Investigators. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: the Delapril and Manidipine for Nephroprotection in Diabetes (DEMAND) randomized clinical trial. *Hypertension* 2011;58:776–783.
55. Grassi G, Robles NR, Seravalle G, Fici F. Lercanidipine in the management of hypertension: An Update. *J Pharmacol Pharmacother* 2017;8(4):155–5.
56. Berkels R, Taubert D, Rosenkranz A, Rosen R. Vascular protective effects of dihydropyridine calcium antagonists. Involvement of endothelial nitric oxide. *Pharmacology* 2003;69(4):171–6.
57. Prabhakar HS, Somashekar PK, Mohammed R, Umar D, Basheer B, Baroudi K. Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study. *J Adv Pharm Technol Res* 2015;6(2):81–5.

58. Brener SJ, et al. Antihypertensive therapy and regression of coronary artery disease: insights from the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) and Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation (NORMALISE) trials. *Am Heart J* 2006;152:1059–1063.
59. Pitt B, et al.Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. *Circulation* 2000;102:1503–1510.
60. Zanchetti A, et al. On behalf of the ELSA Investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002;106:2422–2427.
61. Hess EJ, Jen JC, Jinnah HA, Benarroch EE. Neuronal voltagegated calcium channels: brief overview of their function and clinical implications in neurology. *Neurology* 2010;75:937–8.
62. Tsien RW, Lipscombe D, Madison DV, Bley KR, Fox AP. Multiple types of neuronal calcium channels and their selective modulation. *Trends Neurosci* 1988;11:431–8.
63. Ishibashi H, Rhee JS, Akaike N. Regional defference of high voltage-activated $Ca^{2+}$ channels in rat CNS neurones. *NeuroReport* 1995;6:1621–4.
64. De Ciuceis C, Rossini C, Tincani A, et al. Effect of antihypertensive treatment with lercanidipine on endothelial progenitor cells and inflammation in patients with mild to moderate essential hypertension. *Blood Press 2016*;25(6):337–43.
65. Spirou A, Rizos E, Liberopoulos EN, Kolaitis N, Achimastos A, Tselepis AD, et al. Effect of barnidipine on blood pressure and serum metabolic parameters in patients with essential hypertension: a pilot study. *J Cardiovasc Pharmacol Ther 2006*;11(4):256–61.
66. Manabe S, Okura T, Fukuoka T, Higaki J. Antioxidative effects of azelnidipine on mesangial cell proliferation induced by highly concentrated insulin. *Eur J Pharmacol* 2007;567(3):252–7
67. Kojima T, Miyauchi K, Yokoyama T, et al. Azelnidipine and amlodipine anti-coronary atherosclerosis trial in hypertensive patients undergoing coronary intervention by serial volumetric intravascular ultrasound analysis in Juntendo University (ALPS-J). *Circ J* 2011;75(5):1071–9.
68. Aslan A, Gurelik M, Cemek M, et al. Nimodipine can improve cerebral metabolism and outcome in patients with severe head trauma. *Pharmacol Res* 2009;59:120–4.
69. Tomino Y. Renoprotective effects of the L-/T-type calcium channel blocker benidipine in patients with hypertension. *Curr Hypertens* Rev 2013;9(2):108–14.
70. Huby M, Rem K, Moris V, Guillier D, Revol M, Cristofari S. Are prostaglandins or calcium channel blockers efficient for free flap salvage? A review of the literature. *J Stomatol Oral Maxillofac Surg* 2018;1:1–4.
71. Golfam F, Golfam P, Golfam B, Pahlevani P. Comparison of topical nifedipine with oral nifedipine for treatment of anal fissure: a randomized controlled trial. *Iran Red Crescent Med J* 2014;16(8):1–3.
72. Lepcha A, Amalanathan S, Augustine AM, Tyagi AK, Balraj A. Flunarizine in the prophylaxis of migrainous vertigo: a randomized controlled trial. *Eur Arch Otorhinolaryngol* 2014;271(11):2931–8.
73. Tully PJ, Peters R, Pérès K, Anstey KJ, Tzourio C. Effect of SSRI and calcium channel blockers on depression symptoms and cognitive function in elderly persons treated for hypertension: three city cohort study. *Int Psychogeriatr* 2018;21:1–10.
74. Dziegielewska B, Gray LS, Dziegielewski J. T–type calcium channels blockers as new tools in cancer therapies. *Pflugers Arch* 2014;466(4):801–10.

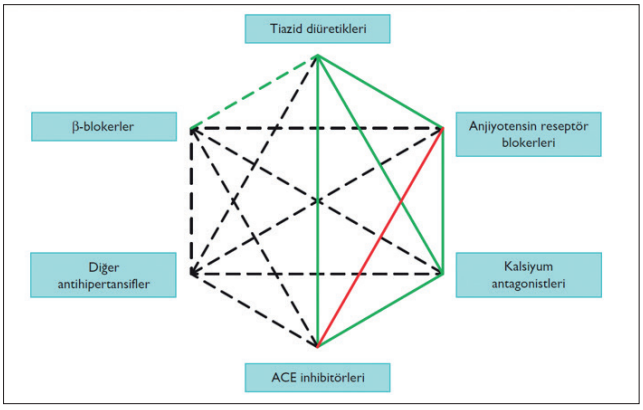
# BÖLÜM 11

# Santral Etkili Antihipertansifler, Alfa Blokerler ve Nitratlar

*Ganbar MAMMADOV* [1]

## GİRİŞ

Güncel kılavuzlarda diüretiklerin (tiazidler, klortalidon ve indapamid), beta-blokerlerin, kalsiyum antagonistlerinin, anjiyotensin-dönüştürücü enzim (ACE) inhibitörlerinin ve anjiyotensin reseptör blokerlerinin tümünün, monoterapi olarak veya bazı kombinasyonlarda antihipertansif tedaviye başlanması veya tedavinin sürdürülmesi için önerilmektedir (şekil 1). *-Diğer bölümlerde ayrıntılı anlatılmıştır.*




**Şekil 1.** Hipertansiyonda tedavi seçenekleri (ESC, HT klavuzu)

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günlük doz genellikle 50 mg'dır, ancak 100 mg'a kadar olan dozlar kullanılmıştır. Bir β-bloker ile ön tedavi, sempatik aktivasyonu sınırlar. Sodyum retansiyonu genellikle diüretik ile kombinasyon gerektirir. Minoksidil anne sütüne geçer ve bu nedenle emziren annelerde kullanımdan kaçınılmalıdır. Gebelikte güvenlik çalışması yoktur (73).

### *Yan etkiler*

İskemik kalp hastalığı olan hastalarda anjinayı şiddetlenebilir. Sıvı tutulmasına ve venöz dilatasyon olmadan arteriolar dilatasyon yapmasına bağlı pulmoner ödeme sebep olabilir. Eş zamanlı olarak bir β-bloker alınmazsa kızarma, çarpıntı ve baş ağrısı ortaya çıkabilir. Yaygın olmayan bir kardiyak yan etki perikardiyal efüzyondur ve nadiren tamponat ile sonuçlanır. Minoxidil'in yaygın bir yan etkisi hirsutizmdir ki bu özellikle kadınlarda rahatsız edici düzeyde oluşur. Hipertrikoz en çok koyu saçlı bireylerde belirgindir ve esas olarak alın ve yüzü etkiler. Aşırı kıllanmanın farmakolojik tedavisi yoktur ve ilaç kesildikten sonra birkaç ay içinde geriler. Minoksidil ile bildirilen diğer yan etkiler burun tıkanıklığı, mide bulantısı, meme hassasiyeti ve cilt reaksiyonlarıdır.

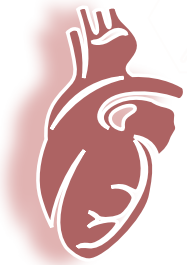
## KAYNAKLAR


1. Rahn KH, Barenbrock M, Hausberg M. The sympathetic nervous system in the pathogenesis of hypertension. J Hypertens Suppl. 1999;17:S11–S14.
2. Frohlich ED. Methyldopa. Mechanisms and treatment 25 years later. Arch Intern Med. 1980;140:954–959.
3. Fenton C, Keating G, Lyseng-Williamson, et al. Moxonidine: a review of its use in essential hypertension. Drugs. 2006;66: 477–496.
4. Reid JL. Rilmenidine: a clinical overview. Am J Hypertens. 2000;13:106S–111S.
5. van Zwieten PA. The renaissance of centrally acting antihypertensive drugs. J Hypertens Suppl. 1999;17:S15–S21.
6. Dollery CT. Advantages and disadvantages of alpha 2-adrenoceptor agonists for systemic hypertension. Am J Cardiol.1988;61:1D–5D.
7. Dorman T, Clarkson K, Rosenfeld BA, et al. Effects of clonidine on prolonged postoperative sympathetic response. Crit Care Med. 1997;25:1147–1152.
8. Khedun S, Maharaj B, Moodley J. Effects of antihypertensive drugs on the unborn child. What is known, and how should this influence prescribing? Paediatr Drugs. 2000;2:419–436.
9. Neerhof MG. Pregnancy in the chronically hypertensive patient. Clin Perinatol. 1997;24:391–406.
10. Houston MC. Treatment of hypertensive emergencies and urgencies with oral clonidine loading and titration. Arch Intern Med. 1986;146:586–589.
11. Hopkins K, Aarons L, Rowland M. Absorption of clonidine from a transdermal therapeutic system when applied to different body sites. In: Weber MA, Mathias CJ, eds. Mild Hypertension. Darmstadt, Germany; Steinkopf Verlag; 1984:143.

12. Meacham RH, Emmett M, Kyriakopoulos AA, et al. Disposition of 14C-guanabenz in patients with essential hypertension. Clin Pharmacol Ther. 1980;27:44–52.
13. Capuzzi DM, Cevallos WH. Inhibition of hepatic cholesterol and triglyceride synthesis by guanabenz acetate. J Cardiovasc Pharmacol. 1984;6(suppl 5):S847–S852.
14. Cornish LA. Guanfacine hydrochloride: a centrally acting antihypertensive agent. Clin Pharm. 1988;7:187–197.
15. Oster JR, Epstein M. Use of centrally acting sympatholytic agents in the management of hypertension. Arch Intern Med. 1991;151:1638–1644.
16. 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;5:659–667.
17. Kirch W, Hutt HJ, Planitz V. The influence of renal function on clinical pharmacokinetics of moxonidine. ClinPharmacokinet. 1988;15:245–253.
18. Zannad F, Aliot E, Florentin J, et al. Hemodynamic and electrophysiologic effects of a new alpha 2-adrenoceptor agonist, rilmenidine, for systemic hypertension. Am J Cardiol. 1988;61:67D–71D.
19. Bravo EL, Tarazi RC, Fouad FM, et al. Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. N Engl J Med. 1981;305:623–626.
20. Carstairs KC, Breckenridge A, Dollery CT, et al. Incidence of a positive direct coombs test in patients on alpha-methyldopa. Lancet. 1966;2:133–135.
21. Hansson L, Hunyor SN, Julius S, et al. Blood pressure crisis following withdrawal of clonidine (Catapres, Catapresan), with special reference to arterial and urinary catecholamine levels, and suggestions for acute management. Am Heart J.1973;85:605–610.
22. Lelkowitz RJ. Pharmacologic principles related to the autonomic nervous system. In: Wyngaarden JB, Smith LH Jr, eds. Cecil textbook of medicine.18th ed. Philadelphia: WB Saunders, 1988;133-40
23. Luther RR New perspectives on selective alpha1 blockade. Am] Hypertens 1989;2(9):729-35
24. Shionoiri H, Yasuda G, Yoshimura H, et al. Antihypertensive effects and pharmacokinetics of single and consecutive administration of doxawsin in patients with mild to moderate essential hypertension. J Cardiovasc Pharmacol1987;10(1):90-5
25. Titmarsh S, MonkJP. Terazosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. 1987;33(5):461-77
26. Brogden RN, Heel RC, Speight TM, et al. Prazosin: a review of its pharmacological properties and therapeutic efficacy in hypertension. Drugs 1977;14(3):163-97
27. Grimm RH Jr. Alpha1-antagonists in the treatment of hypertension. Hypertension 1989; 13(5 Pt2):1-131-6
28. Dauer AD, Abraham PA, Cohen A, et al. Terazosin: an effective once-daily monotherapy for the treatment of hypertension. Am J Med 1986;80 (Suppl 5B):29-34
29. Rosenthal J. A multicenter trial of doxawsin in West Germany. Am J Cardioi1987;59(14):40-45G
30. Jackson EA. Issues with antihypertensive therapy: safety perspectives. Drug lntell Clin Pharm 1988;22(Feb): 115-24
31. Murad F. Discovery of some of the biological effects of nitric oxide and its role in cell signaling. Biosci Rep. 2005;24:452–74.
32. Kukovetz WR, Holzmann S, Braida C, Pöch G. Dual mechanism of the relaxing effect of nicorandil by stimulation of cyclic GMP formation and by hyperpolarization. J Cardiovasc Pharmacol.1991;17:627–33.
33. Horinaka DS. Use of nicorandil in cardiovascular disease and its optimization. Drugs Springer Int Publ. 2011;71:1105–19.

34. Tarkin JM, Kaski JC. Pharmacological treatment of chronic stable angina pectoris. ClinMed Royal Coll Physicians. 2013;13:63–70.
35. Lanza GA, Parrinello R, Figliozzi S. Management of microvascular angina pectoris. Am J Cardiovasc drugs. Springer International Publishing. 2014;14:31–40.
36. Suk-Jae C, Ho-Leung F. Relationship between nitroglycerininduced vascular relaxation and nitric oxide production: probes with inhibitors and tolerance development. Biochem Pharmacol. 1993;45:157–63.
37. Thadani U. Oral nitrates: more than symptomatic therapy in coronary artery disease? Cardiovasc Drugs Ther. 1997;11(Suppl 1): 213–8.
38. Mayer B, Beretta M. The enigma of nitroglycerin bioactivation and nitrate tolerance: news, views and troubles. Br J Pharmacol. 2009;155:170–84.
39. Chen Z, Zhang J, Stamler JS. Identification of the enzymatic mechanism of nitroglycerin bioactivation. Proc. Natl. Acad. Sci.U.S.A. Natl Acad Sci. 2002;99:8306–11.
40. Chen Z, Stamler JS. Bioactivation of nitroglycerin by the mitochondrial aldehyde dehydrogenase. Trends Cardiovasc Med.2006;16:259–65.
41. Torfgård KE, Ahlner J. Mechanisms of action of nitrates.Cardiovasc Drugs Ther. 1994;8:701–17.
42. Horwitz LD, Gorlin R, Taylor WJ, Kemp HG. Effects of nitroglycerin on regional myocardial blood flow in coronary artery disease. J Clin Invest Am Soc Clin Invest. 1971;50:1578–84.
43. Hampton JR, Harrison MJ, Honour AJ, Mitchell JR. Platelet behaviour and drugs used in cardiovascular disease. Cardiovasc Res.1967;1:101–7.
44. Salvemini D, Currie MG, Mollace V. Nitric oxide-mediated cyclooxygenase activation. A key event in the antiplatelet effects of nitrovasodilators. J Clin Investig. 1996;97:2562–8.
45. Diodati J, Theroux P, Latour JG, Lacoste L, Lam JY, Waters D.Effects of nitroglycerin at therapeutic doses on platelet aggregation in unstable angina pectoris and acute myocardial infarction.AJC. 1990;66:683–8.
46. Thadani U. Challenges with nitrate therapy and nitrate tolerance: prevalence, prevention, and clinical relevance. Am J Cardiovasc Drugs. 2014;14:287–301.
47. Thomas GR, DiFabio JM, Gori T, Parker JD. Once daily therapy with isosorbide-5-mononitrate causes endothelial dysfunction in humans: evidence of a free-radical-mediated mechanism. J Am Coll Cardiol. 2007;49:1289–95.
48. Bogaert MG. Pharmacokinetics of organic nitrates in man: an overview. Eur Heart J. The Oxford University Press; 1988;9:33–7.
49. Parker JO. Eccentric dosing with isosorbide-5-mononitrate in angina pectoris. AJC Elsevier. 1993;72:871–6.
50. Thadani U, Lipicky RJ. Short and long-acting oral nitrates for stable angina pectoris. Cardiovasc Drugs Ther. 1994;8:611–23.
51. Parker JO, Fung HL. Transdermal nitroglycerin in angina pectoris.AJC. 1984;54:471–6.
52. ThadaniU, Rodgers T. Side effects of using nitrates to treat angina.Expert Opin Drug Saf. 2006;5:667–74.
53. Cleophas TJM, Niemeyer MG, van der Wall EE. Nitrate-induced headache in patients with stable angina pectoris: beneficial effect of starting on a low dosage. Am J Ther SAGE Publications.1996;3:802–6.

54. Goldschmidt M, Landzberg BR, FrishmanWH. Nicorandil: a potassium channel opening drug for treatment of ischemic heart disease.J Clin Pharmacol. 1996;36:559–72.
55. Taira N. Nicorandil as a hybrid between nitrates and potassium channel activators. AJC. 1989;63:18J–24J.
56. Frydman A. Pharmacokinetic profile of nicorandil in humans: an overview. J Cardiovasc Pharmacol. 1992;20(Suppl 3):S34–44.
57. BrodmannM, Lischnig U, Lueger A, Stark G, Pilger E. The effect of the K+ agonist nicorandil on peripheral vascular resistance. Int J Cardiol. 2006;111:49–52.
58. Knight DC, Purcell H, Fox K. Potassium channel openers: clinical applications in ischemic heart disease—overview of clinical efficacy of nicorandil. Cardiovasc Drugs Ther Kluwer Acad Publishers; 1995;9:229–236.
59. Camm AJ, Maltz MB. A controlled single-dose study of the efficacy, dose response and duration of action of nicorandil in angina pectoris. Am J Cardiol Elsevier. 1989;63:J61–5.
60. Hanai Y,Mita M,Hishinuma S, Shoji M. Systematic review on the short-term efficacy and safety of nicorandil for stable angina pectoris in comparison with those of β-blockers, nitrates and calcium antagonists. Yakugaku Zasshi. 2010;130:1549–63.
61. Wagner G. Selected issues from an overview on nicorandil: tolerance, duration of action, and long-term efficacy. J Cardiovasc Pharmacol. 1992;20:S86.
62. Roland E. Safety profile of an anti-anginal agent with potassium channel opening activity: an overview. Eur Heart J. 1993;14 Suppl B:48–52.
63. Witchitz S, Darmon JY. Nicorandil safety in the long-term treatment of coronary heart disease. Cardiovasc Drugs Ther.1995;9(Suppl 2):237–43.
64. Watson A, Ozairi OA, Fraser A, Loudon M, O'Kelly T. Nicorandil associated anal ulceration. Lancet. 2002;360:546–7.
65. Shepherd AM, Irvine NA. Differential hemodynamic and sympathoadrenal effects of sodium nitroprusside and hydralazine in hypertensive subjects. J Cardiovasc Pharmacol. 1986;8(3):527–533.
66. Shepherd AM, McNay JL, Ludden TM, et al. Plasma concentration and acetylator phenotype determine response to oral hydralazine. Hypertension. 1981;3(5):580–585.
67. O'Malley K, Segal JL, Israili ZH, et al. Duration of hydralazine action in hypertension. Clin Pharmacol Ther. 1975;18(5 Pt 1):581–586.
68. 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.
69. Russell GI, Bing RF, Jones JA, et al. Hydralazine sensitivity: clinical features, autoantibody changes and HLA-DR phenotype. Q J Med.1987;65:845–852.
70. Andersson KE. Clinical pharmacology of potassium channel openers. Pharmacol Toxicol. 1992;70:244–254.
71. Meisheri KD, Cipkus LA, Taylor CJ. Mechanism of action of minoxidil sulphate-induced vasodilatation: a role for increased K+ permeability. J Pharmacol Exp Ther. 1988;245:751–760.
72. Lowenthal DT, Affrime MB. Pharmacology and pharmacokinetics of minoxidil. J Cardiovasc Pharmacol. 1980;2(suppl 2):S93–S106.
73. Swales JD, Bing RF, Heagerty AM, et al. Treatment of refractory hypertension. Lancet. 1982;1:894–896.



# BÖLÜM 12

# Akut Koroner Sendroma Acilde İlk Yaklaşım

*Deniz ORAY* [1]

## GİRİŞ

Tüm dünyada ölümlerin %30'undan kardiyovasküler hastalıklar sorumlu tutulmaktadır. Dünya geneline benzer şekilde koroner arter hastalığı (KAH) ülkemizde de önde gelen ölüm nedenlerindendir. Türkiye'de koroner mortalite, Avrupa ülkeleri arasında erkeklerde 2. sırada, kadınlarda 1. sıradadır ve 50 yaşın altı koroner olay geçirme oranı Avrupa'nın üzerindedir (1-3).

Ana semptomu göğüs ağrısı olan akut koroner sendromlar (AKS), koroner arterlerdeki akımın azalması sonucu miyokard iskemisinin neden olduğu kliniklerin tamamını ifade eder. Amerika Birleşik Devletleri'nde, acil servise yılda 8 milyondan fazla kişi göğüs ağrısı ile başvurmaktadır. Bu hastaların yaklaşık %15'i AKS tanısı almaktadır. Klinik olarak geniş bir spektrumu vardır. Bu geniş spektruma, ani kardiyak arrest, kardiyojenik şok, kalp yetmezliği ve kapak rüptürü, hatta ağrısız iskemi gibi örnekler verilebilir.

Elektrokardiyogram (EKG)'a dayanarak yapılan sınıflamada, ST segment elevasyonlu miyokard enfarktüsü (STEMİ), non–ST-segment elevasyolu miyokard enfarktüsü (NSTEMİ) ve kararsız (anstabil) anjina pektoris (UAP), AKS' lerin ana başlıklarıdır. Neredeyse her zaman, enfarktüsle ilişkili arterdeki aterosklerotik bir plağın yırtılması sonucu arterde oluşan parsiyel ya da total bir trombüs ile ilişkilidir (1). Tanı alan hastaların 1/3'üne yakın oranını STEMİ ve NSTEMİ,

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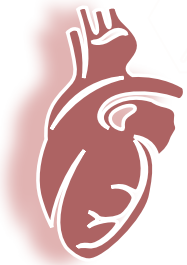
## KAYNAKLAR


1. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289-1367.
2. Onat A, Can G. Erişkinlerimizde Kalp Hastalıkları Prevalansı, Yeni Koroner Olaylar ve Kalpten Ölüm Sıklığı. Onat A, ed. TEKHARF 2017. Tıp Dünyasının Kronik Hastalıklara Yaklaşımına Öncülük. İstanbul: Logos Yayıncılık. 2017; s. 20-28.
3. Tokgozoglu L, et al. (EUROASPIRE III: a comparison between Turkey and Europe). Turk Kardiyol Dern Ars 2010;38(3):164-72.
4. Hollander JE, Diercks DB. Acute Coronary Syndromes Epidemiology PathophysiologyElectrocardography. In: Tintinalli J, Ma OJ, Yealy D et al, editors. Tintinallis Emergency Medicine A Comprehensive Study Guide, 8th. 8th ed. 2016. p. 332–5.
5. Shlomo Stern. Symptoms Other Than Chest Pain May Be Important in the Diagnosis of "Silent Ischemia," or "The Sounds of Silence". 21 Jun 2005 Circulation. 2005;111:e435–e437.
6. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation. 2012 Oct 16. 126(16):2020-35.
7. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
8. Diercks DB, Peacock WF, Hiestand BC, et al. Frequency and consequences of recording an electrocardiogram >10 minutes after arrival in an emergency room in non-ST-segment elevation acute coronary syndromes (from the CRUSADE Initiative). Am J Cardiol 2006;97:437-42.
9. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996 Oct 31. 335(18):1342-9.
10. Heidenreich PA, Alloggiamento T, Melsop K, et al. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. J Am Coll Cardiol. 2001 Aug. 38(2):478-85.
11. Thygesen K, Alpert JS, Jaffe AS, et al. ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237-269.
12. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021 Nov 30;78(22):e187-e285.
13. Dahlslett T, Karlsen S, Grenne B, et al. Early assessment of strain echocardiography can accurately exclude significant coronary artery stenosis in suspected non-ST-segment elevation acute coronary syndrome. J Am Soc Echocardiogr 2014;27:512-519.
14. Grenne B, Eek C, Sjoli B, et al. Acute coronary occlusion in non-ST-elevation acute coronary syndrome: outcome and early identification by strain echocardiography. Heart 2010;96:1550-155.
15. Lancellotti P, Price S, Edvardsen T, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. Eur Heart J Acute Cardiovasc Care 2015;4:3-5.
16. Merchant RM, Topjian AA, Panchal AR, et al. Part 1: executive summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142(suppl 2):In press.

17. Smith LM, Mahler SA. Kardiyovasküler hastalık. Tintinalli Acil Tıp, kapsamlı bir çalışma kılavuzu (Eroğlu SE, Özhaseneker A, Çev. Ed.). İstanbul: Nobel Tıp Kitapevleri Tic. Ltd. Şti.; 2021.
18. Amsterdam EA, Wenger NK, Brindis RG, et al: 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 64: e139, 2014.
19. Ibanez B et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC) European Heart Journal (2018) 39, 119–177.



# BÖLÜM 13

# Antikoagülan İlaçlar

*Özge TURGAY YILDIRIM* [1]

## GİRİŞ

Antitrombotik tedaviler, akut koroner sendrom, akut iskemik inme, venöz tromboembolik hastalık, stent trombozu, kalp içi ve mekanik cihaz trombozu gibi durumların patofizyolojisinin anlaşılmasıyla beraber kardiyovasküler hastalığın önlenmesi ve tedavisi için kullanılmakta olan, faydası ispatlanmış tedavilerdir (1). Antitrombotik ajanlar, pıhtılaşma faktörlerinin sentezini azaltan veya pıhtılaşma kaskadını kesintiye uğratan (antikoagülanlar) ve trombosit fonksiyonunu inhibe eden (antiplatelet ajanlar) ilaçlar olarak ayrılır (2).

Antikoagülanlar, arteriyel trombozlara karşı aktiviteye sahip olmaları dışında, büyük ölçüde venöz trombozların önlenmesi ve tedavisi için kullanılırlar. Başlıca klinik kullanımları, yüksek riskli kişilerde (kalça veya diz protezi ameliyatından sonra veya uzun süreli hareketsiz kalma gibi) derin ven trombozunun önlenmesi ve tedavisi, pulmoner emboli önlenmesi ve tedavisi ve atriyal fibrilasyonu olan hastalarda arteriyel emboli önlenmesidir (2).

Koroner, serebral ve periferik vasküler yatakları tutan aterotrombotik vasküler hastalığın yönetimi, çok çeşitli antitrombotik ajanları içerir. Kardiyoloji alanındaki klinisyenlerin bu yaygın olarak kullanılan ajanları, etki mekanizmalarını, farmakolojilerini, yan etkilerini, ilaç etkileşimlerini ve hasta bakımında kanıta dayalı kullanımlarını bilmeleri önemlidir.

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Bazı bitkiler ve diyet takviyeleri warfarinin veya K vitamininin gastrointestinal sistemden emilimini etkileyerek etkileşebilir. Bazı yiyecekler, şifalı bitkiler veya ek maddeler büyük miktarlarda K vitamini içerebileceğinden, etkinin güçlenmesine neden olabilir. Tersine, bazı şifalı bitkiler ve diyet takviyeleri, warfarin etkilerinin inhibisyonu ile sonuçlanan K vitamini emilimini azaltabilir. Örneğin, ıspanak, brokoli, turp, lahana, karnabahar, suşi ve yeşil çay gibi yiyecekler yüksek düzeyde K vitamini içerir ve aşırı tüketilirse düzensiz INR'ye yol açabilir (36,56–58).

Warfarin etkisinde potansiyalizasyon yapan başka besinler arasında mango, sarımsak, balık yağı, zencefil, greyfurt suyu ve nar suyu sayılabilir (36,57,58).

## SONUÇ

Antitrombotik tedaviler kardiyovasküler hastalıkların tedavisinde temel tedavi basamaklarından biridir. Hem antikoagülan hem de antiplatelet tedaviler konusunda araştırmalar, ilerlemeler ve yeni çıkan ajanlar tedavi seçeneklerimizi arttırmaktadir. Bu hızlı ilerleme ile beraber yeni kılavuzlar ve güncellemeler tedaviye yön vermektedir. Klinisyen tedaviye yön verirken her ilacın farmakolojisini, klinik kullanımını, olası yan etki ve kontrendikasyonlarına mutlaka hakim olmalı, tedaviyi buna göre yönetmelidir. Ve mutlaka yeni gelişmeleri yakından takip etmeli, hastası için en etkili ve en güvenli tedavi seçeneğini aramalıdır.

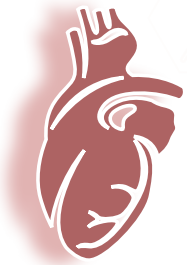
## KAYNAKLAR


1. Becker RC, Vemulapalli S, Cotarlan V, et al. Antithrombotic Drugs. In: Bhatt DL (ed.) Opie's Cardiovascular Drugs: A companion to Braunwald's Heart Disease. 9th ed. Elsevier Inc.; 2021. p. 387-531.
2. Antithrombotic Agents. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2022 Dec 4].
3. Onishi A, St Ange K, Dordick JS, Linhardt RJ. Heparin and anticoagulation. Front Biosci Landmark Ed. 2016 Jun 1;21(7):1372–92.
4. Heparins. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2022 Dec 4].
5. Cohen M, Mahaffey KW, Pieper K, et al. A Subgroup Analysis of the Impact of Prerandomization Antithrombin Therapy on Outcomes in the SYNERGY Trial: Enoxaparin Versus Unfractionated Heparin in Non–ST-Segment Elevation Acute Coronary Syndromes. J Am Coll Cardiol. 2006 Oct 3;48(7):1346–54.
6. Ferguson JJ, Califf RM, Antman EM, et al. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. JAMA. 2004 Jul 7;292(1):45–54.

7. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289–367.
8. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan 7;39(2):119–77.
9. Canadian Cardiovascular Society, American Academy of Family Physicians, American College of Cardiology, American Heart Association, Antman EM, Hand M, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2008 Jan 15;51(2):210–47.
10. Fox KAA, White HD, Gersh BJ, et al. Antithrombotic Agents: Platelet Inhibitors, Acute Anticoagulants, Fibrinolytics, and Chronic Anticoagulants. In: Opie LH and Gersh BJ (eds.) Drugs for the Heart. 8th ed. Elsevier Saunders; 2013. p. 332-397.
11. Solari F, Varacallo M. Low Molecular Weight Heparin (LMWH). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 Dec 4].
12. Hirsh J, O'Donnell M, Eikelboom JW. Beyond unfractionated heparin and warfarin: current and future advances. Circulation. 2007 Jul 31;116(5):552–60.
13. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. Lancet Lond Engl. 2011 Aug 20;378(9792):693–703.
14. Silvain J, Beygui F, Barthélémy O, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ. 2012 Feb 3;344:e553.
15. O'Brien PJ, Mureebe L. Direct thrombin inhibitors. J Cardiovasc Pharmacol Ther. 2012 Mar;17(1):5–11.
16. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008 May 22;358(21):2218–30.
17. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med. 2013 Dec 5;369(23):2207–17.
18. Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J. 2014 Sep 7;35(34):2285–94.
19. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet Lond Engl. 2014 Nov 22;384(9957):1849–58.
20. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA. 2015 Apr 7;313(13):1336–46.
21. Zeymer U, van 't Hof A, Adgey J, Nibbe L, et al. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. Eur Heart J. 2014 Sep 21;35(36):2460–7.
22. Capodanno D, Gargiulo G, Capranzano P, et al. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI: An updated meta-analysis of 10,350 patients from five randomized clinical trials. Eur Heart J Acute Cardiovasc Care. 2016 Jun;5(3):253–62.

23. Valgimigli M, Frigoli E, Leonardi S, et at. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med. 2015 Sep 10;373(11):997–1009.
24. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006 Nov 23;355(21):2203–16.
25. Kastrati A, Neumann FJ, Schulz S, et al. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. N Engl J Med. 2011 Nov 24;365(21):1980–9.
26. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA. 2006 Apr 5;295(13):1519–30.
27. Peters RJG, Joyner C, Bassand JP, et al. The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: a subgroup analysis of the OASIS-6 trial. Eur Heart J. 2008 Feb;29(3):324–31.
28. FUTURA/OASIS-8 Trial Group, Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D, et al. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA/OASIS-8 randomized trial. JAMA. 2010 Sep 22;304(12):1339–49.
29. Fondaparinux. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2022 Dec 9].
30. Patel S, Singh R, Preuss CV, Patel N. Warfarin [Internet]. StatPearls [Internet]. StatPearls Publishing; 2022 [cited 2022 Dec 4].
31. Burnett RS, Voora D, Gatchel S, Tiemeier A, Gage BF. Genetic-based dosing in orthopedic patients beginning warfarin therapy. Blood. 2007 Sep 1;110(5):1511-5. doi: 10.1182/blood-2007-01-069609.
32. Shen AYJ, Yao JF, Brar SS, et al. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol. 2007 Jul 24;50(4):309–15.
33. Loebstein R, Dvoskin I, Halkin H, et al. A coding VKORC1 Asp36Tyr polymorphism predisposes to warfarin resistance. Blood. 2007 Mar 15;109(6):2477–80.
34. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e72–227.
35. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022 Feb 12;43(7):561–632.
36. Gürcü S, Avci E, Kutsal Ö. Varfarin ile Oluşan İlaç ve Besin Etkileşimleri. Eskisehir Med J. 2021 Mar 6;2(1):43–7.
37. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007 Jun 19;146(12):857–67.
38. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021 Feb 1;42(5):373–498.
39. De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013 Dec;110(6):1087–107.
40. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. Circ Cardiovasc Qual Outcomes. 2008 Nov;1(2):84–91.

41. Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263–72.
42. Borre ED, Goode A, Raitz G, et al. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. Thromb Haemost. 2018 Dec;118(12):2171–87.
43. Ruff CT, Giugliano RP, Braunwald E. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet Lond Engl. 2014 Mar 15;383(9921):955–62.
44. Wang KL, Lip GYH, Lin SJ, et al. Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation: Meta-Analysis. Stroke. 2015 Sep;46(9):2555–61.
45. Iung B, Rodés-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. Eur Heart J. 2014 Nov 7;35(42):2942–9.
46. Laffort P, Roudaut R, Roques X, et al.Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. J Am Coll Cardiol. 2000 Mar 1;35(3):739–46.
47. Butchart EG, Gohlke-Bärwolf C, Antunes MJ, et al. Recommendations for the management of patients after heart valve surgery. Eur Heart J. 2005 Nov;26(22):2463–71.
48. Dangas GD, Tijssen JGP, Wöhrle J, et al. A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement. N Engl J Med. 2020 Jan 9;382(2):120–9.
49. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599–726.
50. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020 Jan 21;41(4):543–603.
51. Witt DM, Clark NP, Kaatz S, et al. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016 Jan;41(1):187–205.
52. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ. 2011 May 24;342:d3036.
53. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. Am J Med. 1998 Apr;104(4):332–8.
54. Schulman S, Granqvist S, Holmström M,et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med. 1997 Feb 6;336(6):393–8.
55. Jacobs LG. Warfarin pharmacology, clinical management, and evaluation of hemorrhagic risk for the elderly. Cardiol Clin. 2008 May;26(2):157–67.
56. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005 May 23;165(10):1095–106.
57. Di Minno A, Frigerio B, Spadarella G, et al. Old and new oral anticoagulants: Food, herbal medicines and drug interactions. Blood Rev. 2017 Jul;31(4):193–203.
58. Tan CSS, Lee SWH. Warfarin and food, herbal or dietary supplement interactions: A systematic review. Br J Clin Pharmacol. 2021 Feb;87(2):352–74.



# BÖLÜM 14

# Oral Antiagregan İlaçlar

*Ebru İpek TÜRKOĞLU*[1]

## GİRİŞ

Damar tıkanıklığına neden olan trombüs oluşumu kardiyolojideki zorlu konulardan biridir. Bu nedenle iskemik olayları azaltmak için etkili bir anti-agregasyon elde etmek için büyük çaba sarf edilmiştir. Vasküler trombüs oluşumunda üç aşama esastır. İlk olarak, dolaşımdaki kan damar içinde trombojenik bir nokta ile karşılaşmalıdır. Ardından, çeşitli reseptör uyarımı ve çeşitli substrat salgılanması yoluyla *trombosit adezyon-aktivasyon-agregasyon* süreçleri meydana gelir ve bu da agregasyonun daha da artmasıyla bir kısır döngü oluşturur. Son aşamada ise pıhtılaşma mekanizması devreye girerek trombüs oluşumunu sağlar. Anti-agregasyon etkisi yaratmak için farklı yolları inhibe eden farklı anti-platelet ajanlar vardır. Bu bölümde, oral olarak aktif anti-platelet ajanlar gözden geçirilecektir.

## I. ASPİRİN

Doğal salisilik asit içeren söğüt kabuğu ekstresi yüzyıllardır ağrı ve ateş tedavisinde bir çare olarak tüketilmesine rağmen, sentetik formu olan asetilsalisilik asit veya yaygın olarak bilinen adıyla aspirin, 1900'lü yılların başında Bayer firması tarafından, etki mekanizması hakkında yeterli bilgiye sahip olunmadan ağrı kesici bir ilaç olarak piyasaya verilmiştir.

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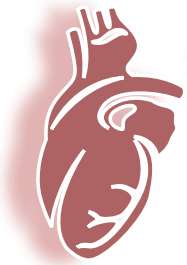
ner arter hastalığı (KAH) veya AKS hastalarında DAPT'nin bir parçası olarak ve yükleme dozuyla başlayıp idame tedavisinde kullanılmak üzere klopidogrel ***sınıf 1A*** düzeyinde önerilmektedir (25).

Koroner arter hastalığında 2017 DAPT ve 2020 akut koroner kılavuzları gibi mevcut farklı Avrupa kılavuzları, AKS yönetiminde tikagrelor ve prasugrele klopidogrelden daha fazla öncelik vermektedir, ancak stabil KAH'da PKG gerektirdiğinde klopidogrel hala ilk seçenek olmaya devam etmektedir. Tüm yeni öneriler DAPT süresinin hastaların iskemik ve kanama risklerini dengeleyecek şekilde bireyselleştirilmesi gerektiği konusunda hem fikirdir. (Hastanın durumuna göre 1 ay kadar kısa veya 2 yıl kadar uzun olabilir) (19,20,25).

## KAYNAKLAR


1. Cadavid AP. Aspirin: The mechanism of action revisited in thecontext of pregnancy complications. Front. Immunol. 2017; 8: 261. doi: 10.3389/fimmu.2017.00261
2. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971; 231(25):232–235. doi:10.1038/ newbio231232a0
3. Smith JB, Willis AL. Aspirin selectively inhibits prostaglandin production in human platelets. Nat New Biol 1971; 231(25):235–237. doi:10.1038/ newbio231235a0
4. Awtry EH, Loscalzo J. Cardiovascular Drugs: Aspirin. Circulation. 2000; 101: 1206-1218.
5. Latini R, Cerletti C, de Gaetano G et al. Comparative bioavailability of aspirin from buffered, enteric-coated and plain preparations. Int J Clin Pharmacol Ther Toxicol. 1986; 24: 313–318.
6. Burch JW, Stanford N, Majerus PW. Inhibition of platelet prostaglandin synthase by oral aspirin. J Clin Invest. 1979; 61: 314-319.
7. Patrono C, Ciabattoni G, Patrignani P, et al. Clinical pharmacology of platelet cyclooxygenase inhibition. Circulation. 1985; 72: 177–184.
8. Loll PJ, Picot D, Garavito RM. The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2synthase. Nat Struct Biol. 1995; 2: 637– 643.
9. McNeil JJ, Wolfe R, Woods RL et al. ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018; 379: 1509 –1518. doi:10.1056/NEJMoa1805819
10. Gaziano JM, Brotons C, Coppolecchia R, et al. ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in pa- tients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018;392:1036–1046. doi: 10.1016/S0140-6736(18)31924-X
11. Bowman L, Mafham M, Wallendszus K, et al. Effects of aspirin for primary pre- vention in persons with diabetes mellitus. N Engl J Med. 2018;379:1529 – 1539. doi: 10.1056/NEJMoa1804988
12. Berger JS. Aspirin for primary prevention- Time to rethink our approach. JAMA Network Open. 2022; 5(4):e2210144. doi:10.1001/jamanetworkopen.2022.10144
13. Arnett DK,Blumenthal RS, Albert MA,et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11): e596-e646. doi:10.1161/CIR.0000000000000678

14. Visseren FLJ, Mach F, Smulders YM, et al. ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227-3337. doi: 10.1093/eurheartj/ehab484
15. Davidson KW, Mangione CM, Barry MJ, etal. Aspirin use to prevent cardiovascular disease: US Preventive Services Task Force recommendation statement. JAMA. Published online April 26, 2022.doi:10.1001/jama. 2022.4983
16. Antiplatelet Trialists' Collaboration. Secondary prevention of vascu- lar disease by prolonged antiplatelet treatment. Br Med J (Clin Res Ed). 1988;296:320–331.
17. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy: I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of pa- tients. BMJ. 1994;308:81–106.
18. Jakobsen AP, Raber I, Blumenthal RS et al. Lifelong aspirin for all in the secondary prevention of chronic coronary syndrome. Circulation. 2020; 142: 1579–1590. Doi:10.1161/CIRCULATIONAHA.120.045695
19. Collet JP, Thiele H, Barbato E et al. 2020 ESC Guidelines fort he management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal (2021) 42, 1289-1367. doi:10.1093/eurheartj/ehaa575
20. Knuuti J, Wijns W, Saraste A et al. 2019 ESC Guidelines fort he diagnosis and management of chronic coronary syndromes. European Heart Journal (2020) 41, 407-477 doi:10.1093/eurheartj/ehz425
21. Wallentin L. P2Y12 inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. European Heart Journal (2009) 30, 1964–1977 doi:10.1093/eurheartj/ehp296
22. Cattaneo M. Update on antithrombotic therapy: New P2Y12 inhibitors. Circulation. 2010; 121: 171-179. Doi:10.1161/CIRCULATIONAHA.109.853069
23. Damman P, Woudstra P, Kuljt W et al. P2Y12 platelet inhibition in clinical practice. J Thromb Thrombolysis (2012) 33:143–153 DOI 10.1007/s11239-011-0667-5
24. Pocock SJ, Mehran R, Clayton TC et al (2010) Prognostic modeling of individual patient risk and mortality impact of ischemic and hemorrhagic complications: assessment from the Acute Catheterization and Urgent Intervention Triage Strategy Trial. Circulation 121(1):43–51
25. Vaglimigli M, Bueno H, Byrne RA et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. European Heart Journal (2018) 39, 213–254 doi:10.1093/eurheartj/ehx419



# BÖLÜM 15

# Fibrinolitik (Trombolitik) İlaçlar

*Ferhat Siyamend YURDAM* [1]

## GİRİŞ

### Tromboz' un Mekanizması

Hemostatik sistem; birbirine karşıt 2 mekanizma, proagregatuar ve antiagregatuar faktörler olarak hassas şekilde çalışmaktadır. Proagregatuar sistem herhangi bir kanama riskine karşı trombüs oluşturmak üzere koruyucu bir görev üstlenmektedir. Trombotik sürecin 3 ana aşaması vardır. İlk olarak, trombosit inhibitörleri arteriyel trombogenez üzerinde etkilidir ve MI ve GİA gibi sonuçların önlenmesine yardımcı olur. İkincisi akut olarak verilen antikoagülanlar (örneğin Heparin) trombüs oluşumu veya kronik olarak verildiğinde (örneğin varfarin) genişlemiş sol atriyumdan veya venöz sistemden kaynaklanan tromboembolizmi önlemeye yardımcı olur. Hem antiplatelet hem de antitrombotik ajanlar revaskülarizasyon ile perkütan koroner girişimin (PCI) trombotik komplikasyonlarını inhibe etmek için gereklidir. Üçüncüsü, fibrinolitik ajanlar ST yükselmeli miyokard enfarktüsü (STEMI) ve periferik arteriyel tromboz gibi akut arteriyel tromboz ve oklüzyon durumlarında, özellikle hızlı mekanik revaskülarizasyon (birincil PKG) mümkün olmadığında en faydalıdır (1-2).

### Klinik Seyri ve Kullanımı

Göğüs ağrısı ile başvuran hastalarda ilk tıbbi temastan 5 dakika içerisinde çekilen elektrokardiyogramda saptanan ST segment elevasyonu ile STEMI (ST ele-

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### Kontrendikasyonlar

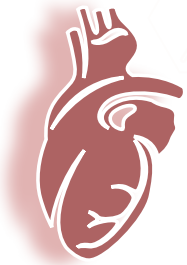
Trombolitik tedavinin mutlak kontrendike olduğu durumlar; aktif gastrointestinal veya iç organlara kanama, aort diseksiyonu, intrakranial tümör, arteriovenöz malformasyon veya anevrizma, hemorajik serebrovasküler olay öyküsü, ST elevasyonlu MI dışı akut koroner sendromlardır. Rölatif kontrendike olduğu durumlar ise uzamış kardiyopulmoner resüsitasyon, gebelik, kanama diyatezi veya antikoagülan kullanımı (INR> 2), trombolitik ajanlara alerjik reaksiyon, kontrolsüz hipertansiyon (kan basıncı>180/110 mmHg), ileri karaciğer veya böbrek yetersizliği, son iki ay içinde kafa travması ve nörovasküler cerrahi öyküsü, aktif peptik ülser ve serebrovasküler olay öyküsüdür (herhangi bir zamanda).

## SONUÇ

Trombolitik ilaçlar STEMI' nde PKG' e alternatif bir tedavi olarak kullanılmakta olup, kanama komplikasyonu açısından dikkat edilmesi gereken hayati öneme haiz ilaçlardır. Son zamanlarda PKG yapılma sıklığı artmış olsa da akut dönemde yaşamı kurtarıcı olarak tedavideki yerini korumaktadır.

## KAYNAKLAR


1. Fay WP, Garg N, Sunkar M, et al. Vascular functions of the plasminogen activation system. *Arteriosclerosis Thrombosis Vascular Biology,* 2007;27(6): 1231–1237.
2. Alessi MC, Poggi M, Irene JV. Plasminogen activator inhibitor-1, adipose tissue and insulin resistance. *Curr Opin Lipidol.* 2007;18(3): 240–245.
3. Neumann, FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Kardiologia Polska (Polish Heart Journal).* 2018;*76*(12): 1585-1664.
4. Steg PG, Bonnefoy E, Chabaud S. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation*, 2003;108(23): 2851-2856. doi: 10.1161/01.
5. Kayaalp O. Antitrombositik ilaçlar. Kayaalp O (Ed), Tıbbi Farmakoloji içinde. Ankara: Hacettepe – Taş Kitapçılık; 2002. p. 608-613.
6. Karaalp A. Trombolitik (Fibrinolitik) ilaçlar. *Türkiye Klinikleri J Int Med Sci*, 2005;1(26): 35-41.



# BÖLÜM 16

# Metabolik Sendrom ve Dislipidemi Tedavisi

*Uğur TAŞKIN* [1]

## GİRİŞ

Metabolik sendrom, kardiyovasküler hastalık riskini doğrudan artıran, tip 2 diabetes mellitus ve mortaliteye neden olan birbirine bağlı fizyolojik, biyokimyasal, klinik ve metabolik faktörlerin bir arada olması durumu olarak tanımlanır. Bu durum insülin direnci, viseral yağlanma, aterojenik dislipidemi, endotel disfonksiyonu, yüksek kan basıncı, hiperkoagüle durum ve kronik stres sendromu oluşturan çeşitli faktörleri içermektedir. Kronik inflamasyonun, tümör nekroz faktörü α, interlökin-1 (IL-1), IL-6, leptin ve adiponektin gibi anormal adipositokinlerin üretimi ile karakterize viseral obezite ve insülin direnci ile ilişkili olduğu bilinmektedir. Metabolik sendromun sistemik etkileri Tablo-1' de özetlenmiştir.

Sendromun klinik fenotipinin bileşenleri ile biyolojik fenotipi (insülin direnci, dislipidemi, vb.) arasındaki etkileşim, proinflamatuar bir durumun gelişmesine ve ayrıca aterosklerotik süreçleri modüle kronik vasküler inflamasyona katkıda bulunur. Yaşam tarzı değişikliği, bu tür popülasyonlar için tercih edilen ilk müdahale olmaya devam etmektedir. Modern yaşam tarzı değişikliği terapisi, diyet ve egzersiz ile ilgili özel önerileri davranışsal stratejilerle birleştirir. Yaşam tarzı değişiklikleri ile risk faktörleri yeterince azalmayanlar için farmakolojik tedavi düşünülmelidir.

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saptanmıştır (94). Fibrat kullanımı esas olarak akut pankreatit riskini azaltmak için şiddetli hipertrigliseritemili hastaların tedavisi için kullanılmaktadır (95). Fibratlar, yüksek ASKVH riski olan hastalarda trigliserit belirgin şekilde yüksekse ek tedavi olarak da düşünülebilir.

## N-3 (Omega-3) Yağ Asitleri

Eikosapentaenoik asit gibi omega-3 yağ asitleri, sterol düzenleyici element bağlayıcı protein genlerinin baskılanması yoluyla de nova lipogenezi inhibe ederek ve peroksizom proliferatör aktive reseptör gen ailesi üyelerinin spesifik olmayan aktivasyonu yoluyla hem yağ asidi oksidasyonunu hem de trigliserit katabolizmasını artırarak trigliserit seviyelerini hafif bir şekilde düşürür (96).

Omega-3 yağ asidi preparatları, ASKVH riskinin azaldığına dair tutarsız kanıtlara sahiptir (97). Bazı çalışmalarda ASKVH olaylarında azalma gösterilmiş olmakla birlikte bazı çalışmalarda faydası gösterilememiştir.

## KAYNAKLAR


1. K. G. M. M. Alberti, R. H. Eckel, S. M. Grundy et al., "Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity," *Circulation*, vol. 120, no. 16, pp. 1640–1645, 2009.
2. Jaspinder Kaur, "A Comprehensive Review on Metabolic Syndrome", *Cardiology Research and Practice*, vol. 2014, Article ID 943162, 21 pages, 2014. https://doi.org/10.1155/2014/943162
3. J. K. Olijhoek, Y. Van Der Graaf, J.-D. Banga, et al. "The Metabolic Syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm," *European Heart Journal*, vol. 25, no. 4, pp. 342–348, 2004.
4. S. Desroches, B. Lamarche, "The evolving definitions and increasing prevalence of the metabolic syndrome," *Applied Physiology, Nutrition and Metabolism*, vol. 32, no. 1, pp. 23–32, 2007.
5. G. D. Kolovou, K. K. Anagnostopoulou, K. D. Salpea, et al. "The prevalence of metabolic syndrome in various populations," *The American Journal of the Medical Sciences*, vol. 333, no. 6, pp. 362–371, 2007.
6. D. Deen, "Metabolic syndrome: time for action," *The American Family Physician*, vol. 69, no. 12, pp. 2875–2887, 2004.
7. F. Locatelli, P. Pozzoni, L. Del Vecchio, "Renal manifestations in the metabolic syndrome," *Journal of the American Society of Nephrology*, vol. 17, no. 4, supplement 2, pp. S81–S85, 2006.
8. K. D. Bruce, C. D. Byrne, "The metabolic syndrome: common origins of a multifactorial disorder," *Postgraduate Medical Journal*, vol. 85, no. 1009, pp. 614–621, 2009.
9. T. Padhi, Garima, "Metabolic syndrome and skin: psoriasis and beyond," *Indian Journal of Dermatology*, vol. 58, no. 3, pp. 299–305, 2013.

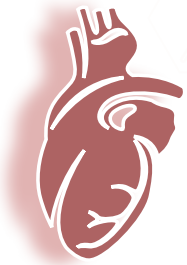
10. R. Chopra, A. Chander, J. J. Jacob, "Ocular associations of metabolic syndrome," *Indian Journal of Endocrinology and Metabolism*, vol. 16, supplement 1, pp. S6–S11, 2012.
11. J. C. M. Lam, S. M. I. Mary, "Sleep & the metabolic syndrome," *Indian Journal of Medical Research*, vol. 131, no. 2, pp. 206–216, 2010.
12. A. Dokras, M. Bochner, E. Hollinrake, et al. "Screening women with polycystic ovary syndrome for metabolic syndrome," *Obstetrics and Gynecology*, vol. 106, no. 1, pp. 131–137, 2005.
13. E. Standl, "Aetiology and consequences of the metabolic syndrome," *European Heart Journal, Supplement*, vol. 7, supplement D, pp. D10–D13, 2005.
14. Y. Handelsman, "Metabolic syndrome pathophysiology and clinical presentation," *Toxicologic Pathology*, vol. 37, no. 1, pp. 18–20, 2009.
15. "National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult treatment panel III) final report," *Circulation*, vol. 106, no. 25, pp. 3143–3421, 2002.
16. S. Bellentani, R. D. Grave, A. Suppini et al., "Behavior therapy for nonalcoholic fatty liver disease: the need for a multidisciplinary approach," *Hepatology*, vol. 47, no. 2, pp. 746–754, 2008.
17. K. A. Donato, "Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults," *Archives of Internal Medicine*, vol. 158, no. 17, pp. 1855–1867, 1998.
18. G. E. Duncan, M. G. Perri, D. W. Theriaque, et al. "Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults," *Diabetes Care*, vol. 26, no. 3, pp. 557–562, 2003.
19. L. F. Van Gaal, M. A. Wauters, I. H. De Leeuw, "The beneficial effects of modest weight loss on cardiovascular risk factors," *International Journal of Obesity*, vol. 21, supplement 1, pp. S5–S9, 1997.
20. P. K. Whelton, L. J. Appel, M. A. Espeland et al., "Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group," *Journal of the American Medical Association*, vol. 279, no. 11, pp. 839–846, 1998.
21. R. R. Wing, R. Koeske, L. H. Epstein, et al. "Long-term effects of modest weight loss in type II diabetic patients," *Archives of Internal Medicine*, vol. 147, no. 10, pp. 1749–1753, 1987.
22. R. Ross, I. Janssen, J. Dawson et al., "Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial," *Obesity Research*, vol. 12, no. 5, pp. 789–798, 2004.
23. J. O. Hill, H. R. Wyatt, "Role of physical activity in preventing and treating obesity," *Journal of Applied Physiology*, vol. 99, no. 2, pp. 765–770, 2005.
24. L. F. Lien, A. J. Brown, J. D. Ard et al. "Effects of PREMIER lifestyle modifications on participants with and without the metabolic syndrome," *Hypertension*, vol. 50, no. 4, pp. 609–616, 2007.
25. A. Garg, J. P. Bantle, R. R. Henry et al. "Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus," *Journal of the American Medical Association*, vol. 271, no. 18, pp. 1421–1428, 1994.
26. W. E. Mitch, "Beneficial responses to modified diets in treating patients with chronic kidney disease," *Kidney International, Supplement*, vol. 67, no. 94, pp. S133–S135, 2005.
27. A. G. Johnson, T. V. Nguyen, D. Davis, "Blood pressure is linked to salt intake and modulated by the angiotensinogen gene in normotensive and hypertensive elderly subjects," *Journal of Hypertension*, vol. 19, no. 6, pp. 1053–1060, 2001.

28. J. He, L. G. Ogden, S. Vupputuri, et al. "Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults," *Journal of the American Medical Association*, vol. 282, no. 21, pp. 2027–2034, 1999.
29. J. He, L. G. Ogden, L. A. Bazzano, et al. "Dietary sodium intake and incidence of congestive heart failure in overweight US men and women: first national health and nutrition examination survey epidemiologic follow-up study," *Archives of Internal Medicine*, vol. 162, no. 14, pp. 1619–1624, 2002.
30. L. J. Appel, M. W. Brands, S. R. Daniels, et al. "Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association," *Hypertension*, vol. 47, no. 2, pp. 296–308, 2006.
31. P. K. Whelton, J. He, J. A. Cutler et al., "Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials," *Journal of the American Medical Association*, vol. 277, no. 20, pp. 1624–1632, 1997.
32. American Diabetes Association, "Evidence based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications," *Diabetes Care*, vol. 25, no. 1, pp. 202–212, 2002.
33. D. J. A. Jenkins, C. W. C. Kendall, L. S. A. Augustin et al., "Glycemic index: overview of implications in health and disease," *The American Journal of Clinical Nutrition*, vol. 76, no. 1, pp. 266S–273S, 2002.
34. N. M. McKeown, J. B. Meigs, S. Liu, et al. "Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort," *Diabetes Care*, vol. 27, no. 2, pp. 538–546, 2004.
35. P. D. Thompson, D. Buchner, I. L. Piña et al., "Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical activity)," *Circulation*, vol. 107, no. 24, pp. 3109–3116, 2003.
36. S. M. Grundy, B. Hansen, S. C. Smith Jr., et al. "American Heart Association; National Heart, Lung, and Blood Institute; American Diabetes Association. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management," *Circulation*, vol. 109, no. 4, pp. 551–556, 2004.
37. M. L. Pollock, B. A. Franklin, G. J. Balady et al., "Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association," *Circulation*, vol. 101, no. 7, pp. 828–833, 2000.
38. The Diabetes Prevention Program Research Group, "The Diabetes Prevention Program (DPP): description of lifestyle intervention," *Diabetes Care*, vol. 25, no. 12, pp. 2165–2171, 2002.
39. B. H. Goodpaster, J. He, S. Watkins, D. E. Kelley, "Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 12, pp. 5755–5761, 2001.
40. J. M. Miles, L. Leiter, P. Hollander et al., "Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin," *Diabetes Care*, vol. 25, no. 7, pp. 1123–1128, 2002.
41. C. K. Haddock, W. S. C. Poston, P. L. Dill, et al. "Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials," *International Journal of Obesity*, vol. 26, no. 2, pp. 262–273, 2002.

42. P. W. F. Wilson, S. M. Grundy, "The metabolic syndrome practical guide to origins and treatment: part I," *Circulation*, vol. 108, no. 12, pp. 1422–1424, 2003.
43. F. Folli, A. E. Pontiroli, W. H. Schwesinger, "Metabolic aspects of bariatric surgery," *Medical Clinics of North America*, vol. 91, no. 3, pp. 393–414, 2007.
44. R. H. Eckel, S. M. Grundy, P. Z. Zimmet, "The metabolic syndrome," *The Lancet*, vol. 365, no. 9468, pp. 1415–1428, 2005.
45. L. Sjöström, A.-K. Lindroos, M. Peltonen et al., "Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery," *The New England Journal of Medicine*, vol. 351, no. 26, pp. 2683–2693, 2004.
46. S. Engeli, J. Böhnke, K. Gorzelniak et al., "Weight loss and the renin-angiotensin-aldosterone system," *Hypertension*, vol. 45, no. 3, pp. 356–362, 2005.
47. P. K. Whelton, J. He, L. J. Appel et al., "Primary prevention of hypertension: clinical and public health advisory from the National High Blood Pressure Education Program," *Journal of the American Medical Association*, vol. 288, no. 15, pp. 1882–1888, 2002.
48. Z. H. Israili, B. Lyoussi, R. Hernández-Hernández, et al. "Metabolic syndrome: treatment of hypertensive patients," *The American Journal of Therapeutics*, vol. 14, no. 4, pp. 386–402, 2007.
49. S. G. Ball, W. B. White, "Debate: angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers—a gap in evidence-based medicine," *The American Journal of Cardiology*, vol. 91, no. 10, pp. 15G–21G, 2003.
50. A. H. Barnett, S. C. Bain, P. Bouter et al., "Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy," *The New England Journal of Medicine*, vol. 351, no. 19, pp. 1952–1961, 2004.
51. A. V. Chobanian, G. L. Bakris, H. R. Black et al., "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report," *Journal of the American Medical Association*, vol. 289, no. 19, pp. 2560–2572, 2003.
52. H. R. Black, B. Davis, J. Barzilay et al., "Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlorthalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT)," *Diabetes Care*, vol. 31, no. 2, pp. 353–360, 2008.
53. "Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *Journal of the American Medical Association*, vol. 288, no. 23, pp. 2981–2997, 2002.
54. W. C. Knowler, E. Barrett-Connor, S. E. Fowler et al., "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin," *The New England Journal of Medicine*, vol. 346, no. 6, pp. 393–403, 2002.
55. W. C. Knowler, R. F. Hamman, S. L. Edelstein et al., "Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program," *Diabetes*, vol. 54, no. 4, pp. 1150–1156, 2005.
56. J.-L. Chiasson, R. G. Josse, R. Gomis, et al. "Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial," *The Lancet*, vol. 359, no. 9323, pp. 2072–2077, 2002.
57. T. J. Orchard, M. Temprosa, R. Goldberg et al., "The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the diabetes prevention program randomized trial," *Annals of Internal Medicine*, vol. 142, no. 8, pp. 611–619, 2005.
58. J.-L. Chiasson, R. G. Josse, R. Gomis, et al. "Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial," *Journal of the American Medical Association*, vol. 290, no. 4, pp. 486–494, 2003.

59. R. Rajagopalan, S. Iyer, M. Khan, "Effect of pioglitazone on metabolic syndrome risk factors: results of double-blind, multicenter, randomized clinical trials," *Current Medical Research and Opinion*, vol. 21, no. 1, pp. 163–172, 2005.
60. Rader DJ, Hoeg JM, Brewer HB. Quantitation of plasma apolipoproteins in the primary and secondary prevention of coronary artery disease. Ann Intern Med. 1994 Jun 15;120(12):1012-25.
61. Mozaffarian D, Benjamin EJ, Go AS, et al. American Heart Association Statistics Committee. Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016 Jan 26;133(4):e38-360.
62. Defesche JC, Gidding SS, Harada-Shiba M, et al. Familial hypercholesterolaemia. Nat Rev Dis Primers. 2017 Dec 07;3:17093.
63. Pappan N, Rehman A. Dyslipidemia. [Updated 2022 Jul 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560891/
64. Lugo-Somolinos A, Sánchez JE. Xanthomas: a marker for hyperlipidemias. Bol Asoc Med P R. 2003 Jul-Aug;95(4):12-6.
65. Kopin L, Lowenstein C. Dyslipidemia. Ann Intern Med. 2017 Dec 05;167(11):ITC81-ITC96.
66. Fredrickson DS. An international classification of hyperlipidemias and hyperlipoproteinemias. Ann Intern Med. 1971 Sep;75(3):471-2.
67. Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. *Expert Opin Drug Metab Toxicol.* 2020;16(9):809-822.
68. Watts GF, Barrett PH, Ji J, et al. Differential regulation of lipoprotein kinetics by atorvastatin and fenofibrate in subjects with the metabolic syndrome. *Diabetes.* 2003;52(3):803-811.
69. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J.* 2020;41(24):2313-2330.
70. Fulcher J, O'Connell R, Voysey M, et al. Cholesterol Treatment Trialists' (CTT) Collaboration . Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet.* 2015;385(9976):1397-1405.
71. Packard CJ. Strategies to alter the trajectory of atherosclerotic cardiovascular disease. *Curr Opin Lipidol.* 2019;30(6):438-445.
72. Mach F, Ray KK, Wiklund O, et al.; European Atherosclerosis Society Consensus Panel . Adverse effects of statin therapy: perception vs. the evidence—focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J.* 2018;39(27):2526-2539.
73. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. *Cardiovasc Drugs Ther.* 2005;19(6):403-414.
74. Zhang H, Plutzky J, Skentzos S, et al.. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med.* 2013;158(7):526-534.
75. Cohen JD, Brinton EA, Ito MK, et al. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10 138 current and former statin users. *J Clin Lipidol.* 2012;6(3):208-215.
76. Berberich AJ, Hegele RA. A Modern Approach to Dyslipidemia. Endocr Rev. 2022 Jul 13;43(4):611-653. doi: 10.1210/endrev/bnab037. PMID: 34676866; PMCID: PMC9277652.
77. Feingold KR. Maximizing the benefits of cholesterol-lowering drugs. *Curr Opin Lipidol.* 2019;30(5):388-394.

78. Rakipovski G, Hovingh GK, Nyberg M. Proprotein convertase subtilisin/kexin type 9 inhibition as the next statin? *Curr Opin Lipidol.* 2020;31(6):340-346.
79. Spolitu S, Dai W, Zadroga JA, et al. Proprotein convertase subtilisin/kexin type 9 and lipid metabolism. *Curr Opin Lipidol.* 2019;30(3):186-191.
80. Kent ST, Rosenson RS, Avery CL, et al. PCSK9 loss-of-function variants, low-density lipoprotein cholesterol, and risk of coronary heart disease and stroke: Data from 9 studies of blacks and whites. *Circ Cardiovasc Genet.* 2017;10(4):e001632.
81. Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol.* 2019;16(3):155-165.
82. Lee S, Cannon CP. Combination lipid-lowering therapies for the prevention of recurrent cardiovascular events. *Curr Cardiol Rep.* 2018;20(7):55.
83. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA.* 2016;316(22):2373-2384.
84. Tiwari V, Khokhar M. Mechanism of action of anti-hypercholesterolemia drugs and their resistance. *Eur J Pharmacol.* 2014;741:156-170.
85. Mazidi M, Rezaie P, Karimi E, et al. The effects of bile acid sequestrants on lipid profile and blood glucose concentrations: a systematic review and meta-analysis of randomized controlled trials. *Int J Cardiol.* 2017;227:850-857.
86. Creider JC, Hegele RA, Joy TR. Niacin: another look at an underutilized lipid-lowering medication. *Nat Rev Endocrinol.* 2012;8(9):517-528.
87. Landray MJ, Haynes R, Hopewell JC, et al.; HPS2-THRIVE Collaborative Group . Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med.* 2014;371(3):203-212.
88. Cuchel M, Meagher EA, du Toit Theron H, et al.; Phase 3 HoFH Lomitapide Study investigators . Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet.* 2013;381(9860):40-46.
89. Berberich AJ, Hegele RA. Lomitapide for the treatment of hypercholesterolemia. *Expert Opin Pharmacother.* 2017;18(12):1261-1268.
90. Brahm AJ, Hegele RA. Lomitapide for the treatment of hypertriglyceridemia. *Expert Opin Investig Drugs.* 2016;25(12):1457-1463.
91. Cuchel M, Rader DJ. Microsomal transfer protein inhibition in humans. *Curr Opin Lipidol.* 2013;24(3):246-250.
92. Blom DJ, Averna MR, Meagher EA, et al. Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia. *Circulation.* 2017;136(3):332-335.
93. Boden WE, Probstfield JL, Anderson T, et al.; AIM-HIGH Investigators . Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med.* 2011;365(24):2255-2267.
94. Ganda OP. When to lower triglycerides? *Curr Opin Lipidol.* 2020;31(4):238-245.
95. Mancini GBJ, Hegele RA, Leiter LA; Diabetes Canada Clinical Practice Guidelines Expert Committee . Dyslipidemia. *Can J Diabetes.* 2018;42 Suppl 1:S178-S185.
96. Liu QK. Triglyceride-lowering and anti-inflammatory mechanisms of omega-3 polyunsaturated fatty acids for atherosclerotic cardiovascular risk reduction. *J Clin Lipidol.* 2021;S1933-2874(21)00108-2.
97. Nicholls SJ, Nelson AJ. The fish-oil paradox. *Cur Opin Lipidol.* 2020;31(6):356-361.



# BÖLÜM 17

# Antiaritmik İlaçlar

*Mustafa DOĞDUŞ* [1]

## GİRİŞ

Kardiyak aritmiler önemsiz ektopik atımlardan hayatı tehdit eden ventriküler fibrilasyona kadar değişir. Bir aritminin müdahale gerektirip gerektirmediği, büyük ölçüde kalp debisi üzerinde önemli bir etki yapma kapasitesine bağlıdır. Miyokardiyal fonksiyonu zaten bozulmuş olan bir hastada (örn. yaygın anterior ST-segment yükselmeli miyokard enfarktüsü), normal sinüs ritminden ventriküler hızı dakikada 140 atım olan atriyal fibrilasyona geçiş kalp yetmezliğine neden olmak için yeterli olabilir. Buna karşılık, normal miyokardiyuma sahip genç bir kişi, herhangi bir kardiyak dekompansasyon kanıtı olmaksızın günlerce aynı hızda supraventriküler taşikardiyi sürdürebilir. Müdahalenin aciliyeti ve müdahalenin doğası, aritminin meydana geldiği durum ve aritminin kendisinin natürü tarafından eşit derecede belirlenir.

**Aritmilerin yaygın ve/veya önemli nedenleri şunlardır:**

- iskemik kalp hastalığı
- kalp kapak hastalığı
- kardiyomiyopati
- hipoksi
- elektrolit bozukluğu – hipokalemi, hiperkalemi, hipokalsemi, hipomagnezemi

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| | | | | |
|---|---|---|---|---|
| Sotalol (sınıf III) | Günde 160-640 mg, bazen ikiye bölünmüş dozlarda daha yüksek. | Yarı ömrü: 12 saat. Metabolize değil. Hidrofilik. Böbrekten atılır. | Miyokard depresyonu, sinüs bradikardisi, AV bloğu. Hipokalemik ise torsades. | IA ajanları veya diüretiklerle torsade riski artar. Böbrek yetmezliğinde dozu azaltın. |
| Amiodaron (sınıf III) | Oral yükleme dozu 1200-1600 mg günlük; idamede günde 200-400 mg, bazen daha az. IV 150 mg 10 dakikada, sonra 360 mg 6 saatte, ardından kalan 24 saatte 540 mg, sonra 0,5 mg/dak | Yarı ömrü: 25-110 gün. Seviye 1-2,5 mcg/mL. Karaciğer metabolizması. Vücutta geniş dağılıma sahip yağda çözünür. Deri, safra yolları, gözyaşı bezleri ile atılım. | Pulmoner fibrozis dahil karmaşık doza bağlı yan etkiler. QT uzaması. Yaygın olmayan Torsades. | Sınıf IA ajanları, torsades eğilimi gösterir. β-blokerler nodal depresyona zemin hazırlar, ancak daha iyi terapötik etkiler sağlar. |

## KAYNAKLAR


1. Parmley W, Nesto RW, Singh BN, et al. Attenuation of the circadian patterns of myocardial ischemia with nifedipine GITS in patients with chronic stable angina. *J Am Coll Cardiol.* 1992; 19: 1380–1389.
2. Sadowski ZP, Alexander JH, Skrabucha B, et al. Multicenter randomized trial and systemic overview of lidocaine in acute myocardial infarction. *Am Heart J.* 1999; 137: 792–798.
3. Ryan TK, Anderson JL, Antman EM,et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: Executive summary. *Circulation.* 1996; 94: 2341–2350.
4. Siebels J, Cappato R, Rüppel R, et al. Preliminary results of the Cardiac Arrest Study Hamburg (CASH). *Am J Cardiol.* 1993; 72: 109–113.
5. Reiffel JA, Blitzer M. The actions of ibutilide and class Ic drugs on the slow sodium channel: new insights regarding individual pharmacologic effects elucidated through combination therapies. *J Cardiovasc Pharmacol Ther.* 2000; 5: 177–181.
6. Cahill SA, Gross GJ. Propafenone and its metabolites preferentially inhibit IKr in rabbit ventricular myocytes. *J Pharmacol Exp Ther.* 2004; 308: 59–65.
7. Hwang HS, Hasdemir C, Laver D, et al. Inhibition of cardiac Ca21 release channels (RyR2) determines efficacy of class I antiarrhythmic drugs in catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol.* 2011; 4: 128–135.
8. Reiffel JA, Hahn E, Hartz V, et al. Sotalol for ventricular tachyarrhythmias; beta blocking and class III contributions, and relative efficacy versus class 1 drugs after prior drug failure. *Am J Cardiol.* 1997; 79: 1048–1053.
9. McNamara RL, Tamariz LJ, Segal JB, et al. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med.* 2003; 139: 1018–1033.

10. CAST Investigators. Preliminary report: effect of encainide and flecainide on mortality in randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med.* 1989; 321: 406–412.
11. UK Propafenone PSVT Study Group. A randomized, placebo-controlled trial of propafenone in the prophylaxis of paroxysmal supraventricular tachycardia and paroxysmal atrial fibrillation. *Circulation*. 1995; 92: 2550–2557.
12. Kochiadakis GE, Igoumenidis NE, Parthenakis FI, et al. Amiodarone versus propafenone for conversion of chronic atrial fibrillation: results of a randomized, controlled study. *J Am Coll Cardiol.* 1999; 33: 966–971.
13. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. *JAMA*. 1993; 270: 1589–1595.
14. Ellison KE, Hafley GE, Hickey K, et al. Effect of beta-blocking therapy on outcome in the Multicenter UnSustained Tachycardia Trial (MUSTT). *Circulation*. 2002; 106: 2694–2699.
15. Dargie HJ. Beta blockers in heart failure. *Lancet*. 2003; 362: 2–3.
16. CIBIS II Study. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999; 353: 9–13.
17. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999; 353: 2001–2007.
18. Exner DV, Reiffel JA, Epstein AE, et al. Beta-blocker use and survival in patients with ventricular fibrillation or symptomatic ventricular tachycardia: The Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. *J Am Coll Cardiol*. 1999; 34: 325–333.
19. Boutitie F, Boissel JP, Connolly SJ, et al. Amiodarone interactions with beta-blockers. Analysis of the merged EMIAT (European Myocardial Infarct Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarct Trial) databases. *Circulation*. 1999; 99: 2268–2275.
20. Nademanee K, Taylor R, Bailey WE, et al. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation*. 2000; 102: 742–747.
21. Wiest D. Esmolol. A review of its therapeutic efficacy and pharmacokinetic characteristics. *Clin Pharmacokinet*. 1995; 28: 190–202.
22. Manz M, Jung W, Lüderitz B. Interactions between drugs and devices: experimental and clinical studies. *Am Heart J.* 1994; 127: 978–984.
23. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med.* 1999; 340: 1855–1862.
24. ESVEM Investigators. Electrophysiologic Study Versus Electrocardiographic Monitoring for selection of antiarrhythmic therapy of ventricular tachycardia. *Circulation.* 1989; 70: 1354–1360.
25. Steinbeck G, Andresen D, Bach P, et al. A comparison of electrophysiologically guided antiarrhythmic drug therapy with beta-blocker therapy in patients with symptomatic, sustained ventricular tachyarrhythmias. *N Engl J Med*. 1992; 327: 987–992.
26. ESVEM Investigators, Mason JW. For the Electrophyisologic Study Versus Electrocardiographic Monitoring Investigators. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. *N Engl J Med*. 1993; 329: 452–458.
27. Julian DG, Camm AJ, Frangin G, et al. Randomized trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction. EMIAT. *Lancet*. 1997; 347: 667–674.
28. Cairns JA, Connolly SJ, Roberts R, et al. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT.

Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet.* 1997; 349: 675–682.
29. Moss AJ, Hall WJ, Cannom DS, et al. For the Multicenter Automatic Defibrillator Implantation Trial (MADITT) Investigators. Improved survival with an implanted defibrillator in patients with coronary artery disease at high risk for ventricular arrhythmia. *N Engl J Med*. 1996; 335: 1933–1940.
30. AVID Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997; 337: 1576–1583.
31. Buxton AE, Lee KL, Fisher JD, et al. For the Multicenter Unsustained Tachycardia Trial (MUSTT) Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med*. 1999; 341: 1882–1890.
32. 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: 877–883.
33. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. *J Am Coll Cardiol*. 2003; 41: 1707–1712.
34. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation*. 1999; 100: 2025–2034.
35. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med*. 2000; 342: 913–920.
36. Sicouri S, Belardinelli L, Carlsson L, et al. Potent antiarrhythmic effects of chronic amiodarone in canine pulmonary vein sleeve preparations. *J Cardiovasc Electrophysiol*. 2009; 20: 803–810.
37. Nattel S. Pharmacodynamic studies of amiodarone and its active N-desethyl metabolite. *J Cardiovasc Pharmacol*. 1986; 8: 771–777.
38. Zimetbaum P. Amiodarone for atrial fibrillation. *N Engl J Med*. 2007; 356: 935–941.
39. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med*. 2005; 352: 1861–1872.
40. Jong GP, Chang MH, Chang TC, et al. Long-term efficacy and safety of very-low-dose amiodarone treatment for the maintenance of sinus rhythm in patients with chronic atrial fibrillation after successful direct-current cardioversion. *Chin Med J (Engl)*. 2006; 119: 2030–2035.
41. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med*. 2002; 346: 884–890.
42. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA*. 2007; 298: 1312–1322.
43. Kato R, Ikeda N, Yabek SM, et al. Electrophysiologic effects of the levo- and dextrorotatory isomers of sotalol in isolated cardiac muscle and their in vivo pharmacokinetics. *JACC.* 1986; 7: 116–125.
44. Waldo AL, Camm AJ, deRuyter H, et al. Prevention of sudden death in patients with LV dysfunction after myocardial infarction. The SWORD trial. *Lancet.* 1996; 348: 7–12.
45. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med.* 2011; 365(24): 2268–2276.
46. Opie LH, Schwartz PJ. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med.* 2012; 366(12): 1159.
47. Murray KT. Ibutilide. *Circulation.* 1998; 97: 493–497.
48. Bernard EO, Schmid ER, Schmidlin D, et al. Ibutilide versus amiodarone in atrial fibrillation: a double-blinded, randomized study. *Crit Care Med.* 2003; 31: 1031–1034.

49. Guo GB, Ellenbogen KA, Wood MA, et al. Conversion of atrial flutter by ibutilide is associated with increased atrial cycle length variability. *J Am Coll Cardiol.* 1996; 27: 1083–1089.
50. Kowey PR, VanderLugt JT, Luderer JR. Safety and risk/benefit analysis of ibutilide for acute conversion of atrial fibrillation/flutter. *Am J Cardiol.* 1996; 78 (Suppl. 8A): 46–52.
51. Boriani G, Lubinski A, Capucci A, et al. A multicentre, double-blind randomized crossover comparative study on the efficacy and safety of dofetilide vs sotalol in patients with inducible sustained ventricular tachycardia and ischaemic heart disease. *Eur Heart J.* 2001; 22: 2180–2191.
52. Torp-Pedersen C, Møller 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: 857–865.
53. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. *Circulation*. 1988; 77: 392–397.
54. Garratt CJ, Antoniou A, Griffith MJ, et al. Use of intravenous adenosine in sinus rhythm as a diagnostic test for latent pre-exitation. *Am J Cardiol.* 1990; 65: 868–873.
55. Jaeggi E, Chiu C, Hamilton R, et al. Adenosine-induced atrial pro-arrhythmia in children. *Can J Cardiol*. 1999; 15: 169–172.

# BÖLÜM 18

# Yeni Kuşak Oral Antikoagülanlar

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## GİRİŞ

Başta Avrupa Kardiyoloji Kılavuzu (ESC) olmak üzere dünya çapındaki atriyal fibrilasyon (AF) kılavuzlarında; AF'li uygun hastalarda inmeyi önlemek için oral antikoagülan (OAK) tedavi olarak K vitamini antagonisti olmayan yani "yeni kuşak oral antikoagülanların" (YOAK) tercih edilmesi tavsiye edilmektedir. (1–4). Doğrudan faktör Xa inhibitörleri olan '***apiksaban, edoksaban, rivaroksaban***' ve doğrudan trombin inhibitörü olan '***dabigatran***' bu gruptaki ilaçları temsil etmektedir. Yapılan randomize kontrollü çalışmalar (RKÇ) sonucunda YOAK'lar, vitamin K antagonisti (VKA) olan varfarin ile kıyaslanmış ve en az (superior veya non-inferior) varfarin kadar başarılı etkinlik/güvenlik sonuçları saptanmıştır. Ayrıca rutin monitorizasyona ihtiyaç duyulmadan tahmin edilebilir bir antikoagülan etkiye sahip olduğu da gösterilmiştir (6,7). Bu nedenle mekanik protez kalp kapağı veya orta-şiddetli mitral stenozu (genellikle romatizmal kaynaklı) olmayan AF hastalarında YOAK'lar inmenin önlenmesi için VKA yerine tercih edilmesi tavsiye edilmektedir. İnme ve sistemik emboli riski *CHA2DS2-VASc skoruyla* (**Şekil 1**), kanama riski ise *HAS-BLED skoru* (**Şekil 2**) ile değerlendirilmektedir. *CHA2DS2-VASc skoru ≥2* erkeklerde ve ≥3 kadınlarda (1) (ESC kılavuzuna göre; *CHA2DS2-VASc skoru ≥1* erkeklerde ve ≥2)(2) kadınlarda iskemik riskin yüksek olduğu için uygun bir YOAK başlanmalıdır. *HAS-BLED ≥3* ise

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## KAYNAKLAR


1. Steffel J, Collins R, Antz M et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace (2021) 23, 1612–1676.
2. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373–498.
3. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation 2019;140:e125–51.
4. Andrade JG, Verma A, Mitchell LB, et al. 2018 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol 2018;34:1371-92.
5. Barnes GD, Ageno W, Ansell J, et al. Subcommittee on the Control of Anticoagulation of the International Society on Thrombosis and Haemostasis. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:1154-6.
6. Ruff CT, Giugliano RP, Braunwald E,et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955–62.
7. Chan YH, Chao TF, Lee HF, et al. Impacts of different renal function estimation formulas on dosing of DOACs and clinical outcomes. J Am Coll Cardiol 2020;76:1808–10.
8. Guo Y, Lane DA, Chen Y, et al; mAF-App II Trial investigators. Regular bleeding risk assessment associated with reduction in bleeding outcomes: the mAFA-II randomized trial. Am J Med 2020; 133: 1195–202.e2.
9. Patel MR, Mahaffey KW, Garg J, et al. the ROCKET AF Steering Committee. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
10. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365:981–92.
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139–51.
12. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093–104.
13. Alexander JH, Andersson U, Lopes RD, et al; Apixaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation (ARISTOTLE) Investigators. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. JAMA Cardiol 2016;1:673–81.
14. Lane DA, Meyerhoff J, Rohner U, et al. Atrial fibrillation patient preferences for oral anticoagulation and stroke knowledge: Results of a conjoint analysis. Clin Cardiol 2018;41:855–61.
15. Kubitza D, Becka M, Zuehlsdorf M, et al. Effect of food, an antacid, and the H2 antagonist ranitidine on the absorption of BAY 59-7939 (rivaroxaban), an oral, direct factor Xa inhibitor, in healthy subjects. J Clin Pharmacol 2006;46:549–58.

16. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2020;76:594–622.
17. Cuker A, Siegal D. Monitoring and reversal of direct oral anticoagulants.Hematology Am Soc Hematol Educ Program 2015;2015:117–24.
18. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. N Engl J Med 2017;377:431–41.
19. Fanikos J, Murwin D, Gruenenfelder F, et al. Global use of idarucizumab in clinical practice: outcomes of the RE-VECTO Surveillance Program. Thromb Haemost 2020;120:27–35.
20. Connolly SJ, Crowther M, Eikelboom JW, et al.; ANNEXA-4 Investigators. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med 2019;380:1326–35.
21. Shaw JR, Li N, Vanassche T, et al. Predictors of preprocedural direct oral anticoagulant levels in patients having an elective surgery or procedure. Blood Adv 2020;4:3520–7.
22. Douketis JD, Spyropoulos AC, Kaatz S, et al. BRIDGE Investigators. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015;373:823-33.
23. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020.
24. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 2019;381:1103–13.
25. Lip GY, Hammerstingl C, Marin F, et al; X-TRA study and CLOT-AF registry investigators. Left atrial thrombus resolution in atrial fibrillation or flutter: results of a prospective study with rivaroxaban (XTRA) and a retrospective observational registry providing baseline data (CLOT-AF). Am Heart J 2016;178:126–34.
26. Ezekowitz MD, Pollack CV Jr, Halperin JL,et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. Eur Heart J 2018;39:2959–71.
27. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 Guidelines for the early management of acute ischemic stroke: a guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50:e344–418.
28. Ahmed N, Audebert H, Turc G, et al.Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11-13 November 2018. Eur Stroke J 2019;4:307–17.
29. Bai Y, Guo SD, Deng H, et al. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-regression analysis. Age Ageing 2018;47:9.
30. Janion-Sadowska A, Papuga-Szela E, Lukaszuk R, et al. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and thrombocytopenia. J Cardiovasc Pharmacol 2018;72:153–60.
31. Guimaraes HP, Lopes RD, de Barros E, et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med 2020;383:2117–26.
32. Nijenhuis VJ, Brouwer J, Delewi R, et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med 2020;382:1696–707.

# BÖLÜM 19

# Pulmoner Arteriyel Hipertansiyon Tedavisinde Kullanılan İlaçlar

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## GİRİŞ

Pulmoner arteriyel hipertansiyon (PAH), pulmoner vasküler sistemin patolojik yeniden şekillenmesiyle karakterize, pulmoner arter basıncının artmasına ve nihayetinde sağ ventrikül yetmezliğine, hipoksiye ve ölüme yol açan, nadir, heterojen bir hastalık durumu ailesidir. Kadınlarda daha sık (%80) görülmektedir. Hastalığın ortalama tanı konma yaşı 53 yaştır. Pulmoner hipertansiyona bağlı ölüm, tedavi edilmediği takdirde, sağ ventrikül yetmezliğinden kaynaklanır. Dinlenme konumunda pulmoner arter ortalama basıncının (oPAB)≥25 mmHg olması ve bunun sağ kalp kateterizasyonu ile gösterilmiş olması durumunda pulmoner hipertansiyondan bahsedilebilir (1-3). Son güncellemede 2018'deki altıncı WSPH'de pulmoner hipertansiyon ve PAH tanımı değiştirilmiş ve PAH'ı tanımlamak için>20 mmHg gibi daha düşük bir mPAP cutoff değerinin kullanılması önerilmiştir.

Bu bölümde genel anlamda pulmoner hipertansiyon tedavisinden ziyade daha özel bir alt grubu oluşturan 1. Grup olan Pulmoner arteriyel hipertansiyon (PAH) tedavisinde kullanılan spesifik ilaç gruplarından bahsedilmesi hedeflenmiştir. Pulmoner hipertansiyon neticesinde gelişen sağ kalp yetmezliği ve nihayetinde sol kalp yetmezliği tedavisinde kullanılan ilaçlara ilgili bölümlerde değinilmiştir.

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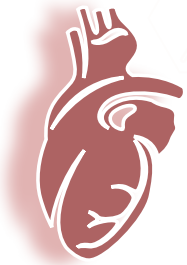
## KAYNAKLAR


1. Galie N, Hoeper MM, Humbert M, Torbicki A, et al. Guidelines on diagnosis and treatment of pulmonary hypertension. European Heart Journal 2009;30, 2493-2537.
2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119. doi: 10.1093/eurheartj/ehv317. Epub 2015 Aug 29. PMID: 26320113.
3. Galie N, Torbicki A, Barst R, Dartevelle P, et al. Guidelines on diagnosis and treatment of pulmonary hypertension. European Heart Journal 2004;25, 2243-2278.
4. Toshner M Tajsic T, Oerrell NW. Pulmonary hypertension:advences in pathogenesis and treatment. British Medical Bulletin 2010;94:21-32.
5. McLaughlin VV, Archer S L,Badesh DB, Barst RJ, et al. ACCP/AHA 2009 Expert consensus document on pulmonary hypertension. J Am Coll Cardiol 2009.
6. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346(12):896–903.
7. Bolli MH, Boss C, Binkert C, et al. The discovery of a N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N′-propylsulfamide (Macitentan), an orally active, potent, dual endothelin receptor antagonist. J Med Chem. 2012;55(17):7849–61.
8. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46(3):529–35.
9. Corbin JD, Beasley A, Blount MA, Francis SH. High lung PDE5: a strong basis for treating pulmonary hypertension with PDE5 inhibitors. Biochem Biophys Res Commun. 2005;334(3):930–8.
10. Lee AJ, Chiao TB, Tsang MP. Sildenafil for Pulmonary Hypertension. Annals of Pharmacotherapy. 2005;39(5):869-884. doi:10.1345/aph.1E426
11. Barnett CF, Machado RF. Sildenafil in the treatment of pulmonary hypertension. Vasc Health Risk Manag. 2006;2(4):411-422. doi:10.2147/vhrm.2006.2.4.411
12. Oudiz R, Brundage B, Galiè N, et al. Tadalafil for the Treatment of Pulmonary Arterial Hypertension. J Am Coll Cardiol. 2012 Aug, 60 (8) 768–774.
13. Wrishko, Rebecca E., et al. "Pharmacokinetic interaction between tadalafil and bosentan in healthy male subjects." The Journal of Clinical Pharmacology 48.5 (2008): 610-618.
14. Fan, You-Fei, et al. "The phosphodiesterase-5 inhibitor vardenafil reduces oxidative stress while reversing pulmonary arterial hypertension." Cardiovascular research 99.3 (2013): 395-403.
15. Jing, Zhi-Cheng, et al. "Vardenafil in pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled study." American journal of respiratory and critical care medicine 183.12 (2011): 1723-1729.
16. Ghofrani, Hossein-Ardeschir, et al. "Riociguat for the treatment of pulmonary arterial hypertension." N Engl J Med 369 (2013): 330-340.
17. Schermuly, Ralph T., et al. "Riociguat for the treatment of pulmonary hypertension." Expert opinion on investigational drugs 20.4 (2011): 567-576.

18. Barst, Robyn J., et al. "Beraprost therapy for pulmonary arterial hypertension." Journal of the American College of Cardiology 41.12 (2003): 2119-2125.
19. Saji, T., Ozawa, Y., Ishikita, T., Matsuura, H., & Matsuo, N. (1996). Short-term hemodynamic effect of a new oral PGI2 analogue, beraprost, in primary and secondary pulmonary hypertension. The American journal of cardiology, 78(2), 244-247.
20. Galiè, N., Humbert, M., Vachiéry, J. L., Vizza, C., Kneussl, M., Manes, A., ... & Arterial Pulmonary Hypertension and Beraprost European Trial (ALPHABET) Study Group. (2002). Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. Journal of the American College of Cardiology, 39(9), 1496-1502.
21. Barst, R. J., Rubin, L. J., Long, W. A., McGoon, M. D., Rich, S., Badesch, D. B., ... & Crow, J. W. (1996). A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. New England Journal of Medicine, 334(5), 296-301.
22. McLaughlin, V. V., Shillington, A., & Rich, S. (2002). Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation, 106(12), 1477-1482.
23. Sitbon, O., Humbert, M., Nunes, H., Parent, F., Garcia, G., Hervé, P., ... & Simonneau, G. É. (2002). Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. Journal of the American College of Cardiology, 40(4), 780-788.
24. Olschewski, H., Simonneau, G., Galiè, N., Higenbottam, T., Naeije, R., Rubin, L. J., ... & Seeger, W. (2002). Inhaled iloprost for severe pulmonary hypertension. New England Journal of Medicine, 347(5), 322-329.
25. Olschewski, H., Walmrath, D., Schermuly, R., Ghofrani, H. A., Grimminger, F., & Seeger, W. (1996). Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. Annals of Internal Medicine, 124(9), 820-824.
26. McLaughlin, V. V., Gaine, S. P., Barst, R. J., Oudiz, R. J., Bourge, R. C., Frost, A., ... & Treprostinil Study Group. (2003). Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. Journal of cardiovascular pharmacology, 41(2), 293-299.
27. Sitbon, O., Channick, R., Chin, K. M., Frey, A., Gaine, S., Galiè, N., ... & McLaughlin, V. V. (2015). Selexipag for the treatment of pulmonary arterial hypertension. New England Journal of Medicine, 373(26), 2522-2533.



# BÖLÜM 20

# Pulmoner Tromboemboli Hastasına Yaklaşım ve Tedavisi

*Nigar DİRİCAN* [1]

## GİRİŞ

Pulmoner tromboembolizm (PTE), trombüsün pulmoner arteri tıkamasıyla gelişen, yaşamı tehdit eden bir hastalıktır. Genellikle derin ven trombozu (DVT)'nun komplikasyonu olarak meydana gelir, genellikle alt ekstremitenin proksimal (iliyak, femoral, popliteal) venlerinden kaynaklıdır.

Hemostaz, doku faktörü tarafından başlatılan kan pıhtılaşması, trombin ve fibrin oluşumuyla sonuçlanan, dolaşım sisteminin bütünlüğünü koruyan süreçtir. Patolojik süreçler, hemostazın düzenleyici mekanizmalarını aştığında, trombin oluşumu artarak trombozu başlatır. (1) Patogenezde Virchow triadının; "vasküler venöz staz, hiperkoagülabilite ve endotelyal hasarın" rolü vardır. (2)

PTE nispeten yaygın bir durumdur, genel popülasyonda tahmini insidansı 1000 kişi-yılında 0,5 ila 1,0'dir ve 30 günlük mortalitesi %9-11, 3 aylık mortalitesi %9-17'dir.(3,4) PTE insidansi yaşamın yedinci on yılında keskin bir şekilde artar, 50 yaşındaki insidansın altı katına kadar çıkar.(5) Son yıllardaki veriler, başta PTE olmak üzere VTE oranlarının arttığını ve son kırk yılda neredeyse iki katına çıktığını göstermiştir.(6) Bu eğilim, yaşlanan nüfus, artan kanser riski ve tanı yöntemlerinin daha iyi kullanılabilirliği ve duyarlılığı ile ilişkili olabilir. Aynı zamanda daha iyi tedavi seçenekleri, kılavuzlara bağlılık ve görüntüleme cihazlarının yaygınlaşması nedeniyle vaka ölüm oranlarının düştüğü saptanmıştır. (7)

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seri olmayan olgularda; Edoxaban veya rivaroksaban DMAH a alternatif olarak düşünülmelidir.

Uzatılmış tedavide dabigatran, rivoraksaban ve apiksabanın kullanımı birçok çalışmada araştırılmıştır. RE-MEDY çalışmasında, günde iki doz 150 mg kullanılan dabigatranın, tekrarlayan VTE ataklarını engellemede varfarin kadar etkili ve kanama açısından güvenli olduğu görülmüştür. (39)

Randomize bir çalışmada 1197 hastanın uzun süreli tedavileri (6-12 aylık) 20 mg/gün rivaroksaban veya varfarin ile tamamlanarak, 20 mg/gün rivaroksaban/plasebo kontrollü uzatılmış antikoagülan tedavi uygulandığında; rivaroksaban nüks riskini belirgin olarak azaltırken, majör kanama insidansında fark saptanmamıştır. (40)

Apiksabanla yapılmış plasebo kontrollü uzatılmış antikoagülan tedavi çalışmasında 2.5 mg/gün apiksabanın kanama riskini arttırmadan plaseboya göre anlamlı olarak VTE riskini azalttığı bildirilmiştir. (41)

Düşük doz aspirinin VTE nüksünü önlemede etkisini belirlemek amacıyla yapılan iki çalışmada, antikoagülan tedavisini tamamladıktan sonra iki yıl boyunca aspirin alan hastalarda plaseboya göre nüks %30-35 oranında daha az görülmüştür. (42,43) Bununla birlikte daha yeni bir çalışmada rivaroksabanın sekonder profilakside aspirine göre üstünlüğü gösterilmiştir.(44)

PTE'de ilk üç aylık tedavi dönemi sonlandıktan sonra antikoagülan tedavi altındaki hastaların belli aralıklarla kanama ve nüks riski açısından değerlendirilmeleri gerekmektedir. Kesin bir süre tanımlanmamakla birlikte, en fazla bir yıl olması önerilmektedir.

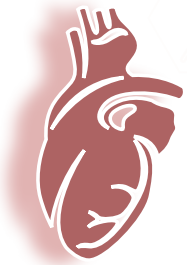
## KAYNAKLAR


1. Furie F, Furie BC. Mechanisms of thrombus formation. The New England Journal of Medicine; 2008;359:938–49. doi: 10.1056/NEJMra0801082.
2. Dickson BC. Venousthrombosis: on the history of Virchow's triad. The University of Toronto Medical Journal; 2004;81:166-71.
3. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest; 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026.
4. Flinterman LE, van Hylckama Vlieg A, Cannegieter SC, et al. Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. PLoS Medicine; 2012 Jan;9(1):e1001155. doi: 10.1371/journal.pmed.1001155.
5. Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations—United States, 2007–2009. MMWR Morb Mortal Wkly Rep. 2012;61(22):401–4.
6. 6. Huang W, Goldberg RJ, Anderson FA, et al. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). American Journal of Medicine; 2014;127(9): 829-39.e5. doi: 10.1016/j.amjmed.2014.03.041.

7. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal; 2020 Jan 21;41(4):543-603. doi: 10.1093/eurheartj/ehz405.
8. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry. Journal of the American College of Cardiology; 2011 Feb 8;57(6):700-6. doi: 10.1016/j.jacc.2010.05.071.
9. Ortel TL, Neumann I, Ageno W, et al. American society of hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Advances; 2020;4(19):4693–738
10. Kurnicka K, Lichodziejewska B, Goliszek S,et al. Echocardiographic pattern of acute pulmonary embolism: analysis of 511 consecutive patients. Journal of the American Society of Echocardiography; 2016 Sep;29(9):907-13. doi: 10.1016/j.echo.2016.05.016
11. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation; 2007;116(4):427–33. doi: 10.1161/CIRCULATIONAHA.106.680421.
12. Cavallazzi R, Nair A, Vasu T, et al. Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Medicine; 2008;34(12):2147–56. doi: 10.1007/s00134-008-1214-5.
13. Ali MR, Salim Hossain M, Islam MA, et al. Aspect of thrombolytic therapy: a review. Scientific World Journal; 2014;2014:586510. doi: 10.1155/2014/586510.
14. STREPTASE®[Internet].2007.https://pdf.hres.ca/dpd_pm/00003639.PDF
15. FDA. ACTIVASE (alteplase) Prescribing information. 2015
16. Konstantinides S, Geibel A, Heusel G,et al. Heparin plus Alteplase Compared with Heparin Alone in Patients with Submassive Pulmonary Embolism. New England Journal of Medicine; 2002 Oct 10;347(15):1143-50. doi: 10.1056/NEJMoa021274.
17. 17.Chaherjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, majör bleeding, and intracranial hemorrhage: a metaanalysis. JAMA; 2014; 311(23):2414–2421. doi: 10.1001/jama.2014.5990.
18. Zhang Z, Zhai Z, Liang L et al. Lower dosage of recombinant tissue- type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. Thrombosis Research; 2014;133:357-63. doi: 10.1016/j.thromres.2013.12.026.
19. Wang C, Zhai Z, Yang Y, et al. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism: a randomized, multicenter, controlled trial. Chest; 2010 Feb;137(2):254-62. doi: 10.1378/chest.09-0765.
20. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). The American Journal of Cardiology;2013; 111:273. doi: 10.1016/j.amjcard.2012.09.027.
21. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. New England Journal of Medicine;2014;370:1402-11. doi: 10.1056/NEJMoa1302097.
22. Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated Heparin for treatment of venous thromboembolic disease. Annals of Internal Medicine;2001;134:191-202. doi: 10.7326/0003-4819-134-3-200102060-00009.
23. Morris TA. New synthetic antithrombotic agents for venous thromboembolism: pentasaccharides, direct thrombin inhibitors, direct Xa inhibitors. Clinics in Chest Medicine; 2010;31:707-18. doi: 10.1016/j.ccm.2010.06.006.

24. Lee GM, Arepally GM. Heparin-induced thrombocytopenia. American Society of Hematology Education Program;2013:668-74. doi: 10.1182/asheducation-2013.1.668.
25. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest; 2012;141(Suppl 2):495-530. doi: 10.1378/chest.11-2303.
26. Kayaalp SO. Antitrombotik ilaçlar. Kayaalp SO (editör). Rasyonel Tedavi Yönünden Tıbbi Farmakoloji. 9. Baskı. Ankara: Hacettepe Taş Kitapçılık, 2000:584-617.
27. Beinema M. Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon. Thrombosis Haemostasis; 2008;100(6):1052–7.
28. Mearns ES, Kohn CG, Song JS, et al. Meta-analysis to assess the quality of international normalized ratio control and associated outcomes in venous thromboembolism patients. Thrombosis Research; 2014;134(2):310–9. doi: 10.1016/j.thromres.2014.05.035.
29. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest; 2012;141(Suppl 2):44-88. doi: 10.1378/chest.11-2292.
30. Eldredge JB, Spyropoulos AC. Direct oral anticoagulants in the treatment of pulmonary embolism. Current Medical Research and Opinion; 2018 Jan;34(1):131-140. doi: 10.1080/03007995.2017.1364227
31. Verdecchia P, Angeli F, Aita A, et al. Why switch from warfarin to NOACs? Internal and Emergency Medicine; 2016 Apr;11(3):289-93. doi: 10.1007/s11739-016-1411-0
32. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. Journal of Thrombosis and Thrombolysis;2015 Feb;39(2):155-65. doi: 10.1007/s11239-014-1102-5.
33. Raschi E, Bianchin M, Ageno W,et al. Risk-Benefit Profile of Direct-Acting Oral Anticoagulants in Established Therapeutic Indications: An Overview of Systematic Reviews and Observational Studies. *Drug Safety.* Drug Saf 2016;39;1175-1187(30)
34. Long B, Koyfman A. Best clinical practice: controversies in outpatient management of acute pulmonary embolism. *The Journal of Emergency Medicine*; 2017 May;52(5):668-679. doi: 10.1016/j.jemermed.2016.11.020.
35. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Annals of the Rheumatic Diseases*; 2019 Oct;78(10):1296-1304. doi: 10.1136/annrheumdis-2019-215213
36. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding duration of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping therapy: analysis of individual participants' data from seven trials. *British Medical Association* 2011 May 24;342:d3036. doi: 10.1136/bmj.d3036.
37. Prandoni P, Barbar S, Milan M, et al. The risk of recurrent thromboembolic disorders in patients with unprovoked venous thromboembolism: news cenarios and opportunities. *European Journal of Internal Medicine*; 2014 Jan;25(1):25-30. doi: 10.1016/j.ejim.2013.09.005
38. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*; 12 Feb;141(2 Suppl):e419S-e496S. doi: 10.1378/chest.11-2301.
39. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *New England Journal of Medicine*; 2013 Feb 21;368(8):709-18. doi: 10.1056/NEJMoa1113697.

40. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *New England Journal of Medicine;* 2012 Apr 5;366(14):1287-97. doi: 10.1056/NEJMoa1113572.
41. Agnelli G, Buller HR, Cohen A, et al. AMPLIFY-EXT investigators. Oral apixaban for extended treatment of venous thromboembolism. *New England Journal of Medicine*; 2013 Feb 21;368(8):699-708. doi: 10.1056/NEJMoa1207541
42. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. New England Journal of Medicine; 2012 May 24;366(21):1959-67. doi: 10.1056/NEJMoa1114238.
43. Brighton TA, Eikelboom JW, Mann K, et al. Low dose aspirin for preventing recurrent venous thromboembolism. *New England Journal of Medicine*;2012;367:1979-87. doi: 10.1056/NEJMoa1210384
44. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *New England Journal of Medicine;* 2017;376:1211-22. doi: 10.1056/NEJMoa1700518.



# BÖLÜM 21

# Acil Serviste Aort Diseksiyonu Hastasına Yaklaşım ve Tedavisi

*Deniz ORAY* [1]

## GİRİŞ VE TANIM

Tüm dünyada ölümlerin %30'undan kardiyovasküler hastalıklar sorumlu tutulmaktadır. Dünya geneline benzer şekilde koroner arter hastalığı (KAH) ülkemizde de önde gelen ölüm nedenlerindendir.

Aort diseksiyonu (AD), penetran aort ülseri, intramural hematom, anevrizma kaçağı ve rüptüre abdominal aort anevrizmaları, akut aort sendromları olarak adlandırılırlar. Aort duvarının intima ve media tabakaları arasında oluşan yırtık sonucu, intima tabakasının kan akış yönünde distale doğru ayrılarak kanın lümen dışında olması AD olarak adlandırılır. En önemli predispozan faktörler hipertansiyon ve aterosklerozdur (1).

Tanısı zor konulan mortalitesi yüksek bir vasküler hastalıktır. Hastane içi tanı alabilenlerin mortalitesi %27' dir. Hastaneye ulaşanlarda mortalite riski her geçen dakika artmaktadır (6 saatte % 23, 24 saatte % 50, 1 haftada % 68). Bu sebeple acil servislerde hızlıca tanınıp tedavi planlaması için kalp damar cerrahisi ile görüşülmelidir. Ölmeden önce tanı konulamayan hastaların oranı %22' dir (2).

AD, anatomik ve fonksiyonel tutulumlarına göre Stanford ve DeBakey sınıflamaları ile sınıflandırılırlar. Süre baz alındığında, 2 haftadan kısa süreli AD akut, 2 hafta ile 2 ay içerisinde olanlar subakut AD, 2 aydan uzun süreli olanlar kronik AD olarak adlandırılırlar (3). Tablo 1'de sınıflamalardan bahsedilmektedir.

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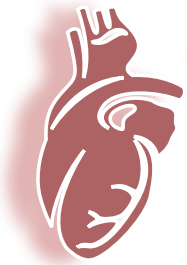
## KAYNAKLAR


1. Smith LM, Mahler SA. Kardiyovasküler hastalık. Tintinalli Acil Tıp, kapsamlı bir çalışma kılavuzu (Eroğlu SE, Özhaseneker A, Çev. Ed.). İstanbul: Nobel Tıp Kitapevleri Tic. Ltd. Şti.; 2021.
2. Hagan PG, Nienaber CA, Isselbacher EM, et al: The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA 283: 897, 2000.
3. Isselbacher EM, Preventza O, Hamilton Black J 3rd et al: 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease:A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022 Dec 13;80(24):e223-e393
4. Erbel R, Aboyans V, Boileau C et al: 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014 Nov 1;35(41):2873-926.
5. Merchant RM, Topjian AA, Panchal AR, et al. Part 1: executive summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020;142
6. Suzuki T, Isselbacher EM, Nienaber CA, Pyeritz RE, Eagle KA, Tsai TT, Cooper JV, Januzzi JL Jr., Braverman AC, Montgomery DG, Fattori R, Pape L, Harris KM, Booher A, Oh JK, Peterson M, Ramanath VS, Froehlich JB. Type– selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol 2012;109:122 –127.



# BÖLÜM 22

# Periferik Arter Hastalıklarının Medikal Tedavisi

*Ezgi POLAT OCAKLI* [1]

## GİRİŞ

Koroner arterler ve aorta dışında kalan arterlerde (karotid ve vertebral arterler, çölyak ve mezenterik arterler, renal arterler ve üst ve alt ekstremite arterleri) meydana gelen daralma ve tıkanıklığa neden olan duruma periferik arter hastalığı denir. Periferik arter hastalıklarının en sık etkeni aterosklerozdur. Serebrovasküler hastalıklar, arteriyosklerozis obliterans ve Buerger hastalığı (tromboangiitis obliterans) aterosklerotik periferik arter hastalığına örnek olarak verilebilir.

Periferik arter hastalığı (PAH) varlığında, kardiyovasküler (KV) olay gelişim riskinde artma olur. Altta yatan neden çoğunlukla ateroskleroz olduğundan, aterosklerozun yavaşlatılması ve kan akımının devamını sağlamak hedeflenir. Bu nedenle tedavinin temelini, aterosklerotik risk faktörlerinin modifikasyonu (lipit düzeylerinin kontrolü, kan basıncı kontrolü, diyabet kontrolü) amaçlı medikal tedavinin düzenlenmesi oluşturur. Ayrıca sigaranın bırakılması ve egzersiz yapılması önerilir. *Amerikan Kalp Derneği (AHA),* **sınıf 1** öneri ile hastaların her kontrolünde sigara içme durumlarının sorgulanması gerektiği üzerinde durulmaktadır (1). Ayrıca sigara içmeye devam eden hastalara danışmanlık verilmesi ve vareniklin, bupropion ve/veya nikotin replasman tedavisi ile farmakolojik tedaviyi içeren bir sigarayı bırakma tedavi planı geliştirme konusunda hastalara yardım edilmesi önerilmektedir (1).

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oksetin ile semptomlarda hafifleme gözlenmiştir(71). Endotelin reseptörlerinin antagonisti olan bosentan çeşitli çalışmalarda dijital ülser riskini büyük ölçüde azalttığı (72) ve dolayısıyla RP'de gözlenen semptomları hafifletme potansiyeline sahip olduğu gözlemlenmiştir. İnositol nikotinat (bir nikotinik asit türevi) ve naftidrofuril oksalat'ın, hafif /orta şiddette hastalıkta bazı cesaret verici sonuçlar vermiştir. B-blokerler, kanıtlar iyi olmasa da geleneksel olarak kontrendikedir. Torakoskopik sempatektomi şiddetli semptomları olan hastalarda endikedir ve esas olarak ağrının giderilmesini sağlar (73).

## KAYNAKLAR


1. Gerhard-Herman MD, Gornik HL, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017 Mar 21;135(12):e726-e779.
2. Kithcart AP, Beckman JA. ACC/AHA Versus ESC Guidelines for Diagnosis and Management of Peripheral Artery Disease: JACC Guideline Comparison. J Am Coll Cardiol 2018;72:2789–801.
3. Aboyans V, Ricco JB, Bartelink MEL, et al. ESC Scientific Document Group. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018 Mar 1;39(9):763-816.
4. Management of Peripheral Arterial Disease: Lifestyle Modifications and Medical Therapies R. Wilson King, MDa,b , Mario Enrico Canonico, MDb,c , Marc P. Bonaca, MD, MPH b,d , Connie N. Hess, MD, MHS b,d
5. Norgren L, Hiatt WR, Dormandy JA, eet al.; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease. Int Angiol 2007; 26: 82–157.
6. Squires H, Simpson EL, Meng Y, et al. A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. Health Technol Assess 2011; 15: 1–210.
7. Stiefel MF, Spiotta AM, Udoetuk JD et al. Intra-arterial papaverine used to treat cerebral vasospasm reduces brain oxygen. Neurocrit Care. 2006; 4(2):113-8.
8. Platz J, Baráth K, Keller E, et al. Disruption of the blood–brain barrier by intra-arterial administration of papaverine: a technical note. Neuroradiology. 2008; 50(12):1035-9.
9. McGuinness B, Gandhi D. Endovascular management of cerebral vasospasm. Neurosurg Clin N Am. 2010; 21(2):281-90.
10. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. J Urol. 2018;200(3):633-641.
11. Salonia A, Bettocchi C, Carvalho J, et al. EAU Guidelines on sexual and reproductive health. The Netherlands: European Association of Urology;2020.

12. Weber AA, Hohlfeld T, Strobach H, et al. Oral naftidrofuryl prevents platelet hyperreactivity ex vivo and inhibits functional desensitization to prostacyclin in hypercholesterolemic rabbits. *J Cardiovasc Pharmacol.* 1993;21(2):332–338.
13. Conte MS, Pomposelli FB, Clair DG, et al. Society for vascular surgery practice guidelines for the atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg.* 2015;61(3):2S–41S.e1.
14. Michiels C, Arnould T, Janssens D, et al. Effects of naftidrofuryl on hypoxia-induced activation and mortality of human endothelial cells. *J Pharmacol Exp Ther.* 1993;267(2):904–911.
15. Wiernsperger NF. Serotonin, 5-HT2 receptors, and their blockade by naftidrofuryl: a targeted therapy of vascular diseases. *J Cardiovasc Pharmacol.* 1994;23(suppl 3):S37–43.
16. De Clerck F. The role of serotonin in thrombogenesis. Clin Physiol Biochem. 1990;8(Suppl 3):40–49.
17. Wiernsperger NF. Serotonin, 5-HT2 receptors, and their blockade by naftidrofuryl: a targeted therapy of vascular diseases. J Cardiovasc Pharmacol. 1994;23(Suppl 3):S37–S43
18. Zaidi TN, McIntire LV, Farrell DH, et al. Adhesion of platelets to surface-bound fibrinogen under flow. Blood. 1996;88:2967– 2972.
19. Le Dévéhat C, Khodabandehlou T, Mosnier M. Effect of naftidrofuryl on platelet aggregation in plasma from aspirin treated patients: an in vitro study. Clin Hemorheol Microcirc. 2000;22:197–204. 29.
20. Meng Y, Squires H, Stevens JW, et al. Cost-effectiveness of cilostazol, naftidrofuryl oxalate, and pentoxifylline for the treatment of intermittent claudication in people with peripheral arterial disease. *Angiology.* 2014;65(3):190–197.
21. Squires H, Simpson E, Meng Y, et al. A systematic review and economic evaluation of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease. *Health Technol Assess.* 2011;15(40):1–210.
22. Stevens J, Simpson E, Harnan S, et al. Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication. *Br J Surg.* 2012;99(12):1630–1638.
23. Peripheral arterial disease: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2020 Dec 11. PMID: 32073808.
24. Goldsmith DR, Wellington K. Naftidrofuryl: a review of its use in the treatment of intermittent claudication. Drugs Aging. 2005;22:967– 977
25. Ward A, Clissold SP. Pentoxifylline. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drugs. 1987 Jul;34(1):50-97.
26. Zhang M, Xu YJ, Mengi SA, et al. Therapeutic potentials of pentoxifylline for treatment of cardiovascular diseases. Exp Clin Cardiol. 2004 Summer;9(2):103-11.
27. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med. 2000 Nov;109(7):523-30.
28. Ciuffetti G, Mercuri M, Ott C, et al. Use of pentoxifylline as an inhibitor of free radical generation in peripheral vascular disease. Results of a double-blind placebo-controlled study. Eur J Clin Pharmacol. 1991;41(6):511-5.
29. Aviado DM, Porter JM. Pentoxifylline: a new drug for the treatment of intermittent claudication. Mechanism of action, pharmacokinetics, clinical efficacy and adverse effects. Pharmacotherapy. 1984 Nov-Dec;4(6):297-307.
30. Aviado DM, Dettelbach HR. Pharmacology of pentoxifylline, a hemorheologic agent for the treatment of intermittent claudication. Angiology. 1984 Jul;35(7):407-17.

31. Garcia FA, Pinto SF, Cavalcante AF, et al. Pentoxifylline decreases glycemia levels and TNF-alpha, iNOS and COX-2 expressions in diabetic rat pancreas. Springerplus. 2014;3:283.
32. Singh Y, Mikrou P. Use of prostaglandins in duct-dependent congenital heart conditions. Arch Dis Child Educ Pract Ed. 2018 Jun;103(3):137-140.
33. Hanchanale V, Eardley I. Alprostadil for the treatment of impotence. Expert Opin Pharmacother. 2014 Feb;15(3):421-8.
34. Noé L, Peeters K, Izzi B, et al. Regulators of platelet cAMP levels: clinical and therapeutic implications. Curr Med Chem. 2010;17(26):2897–905.
35. Gresele P, Momi S, Falcinelli E. Anti-platelet therapy: phosphodiesterase inhibitors: anti-platelet therapy. Br J Clin Pharmacol. 2011;72(4):634–46.
36. Wallis RM, Corbin JD, Francis SH, et al. Tissue distribution of phosphodiesterase families and the effects of sildenafil on tissue cyclic nucleotides, platelet function, and the contractile responses of trabeculae carneae and aortic rings in vitro. Am J Cardiol. 1999;83(5):3–12
37. Paul S, Feoktistov I, Hollister AS, et al. Adenosine inhibits the rise in intracellular calcium and platelet aggregation produced by thrombin: evidence that both effects are coupled to adenylate cyclase. Mol Pharmacol. 1990;37(6): 870–5.
38. Sun B, Le SN, Lin S, et al. New mechanism of action for cilostazol: interplay between adenosine and cilostazol in inhibiting platelet activation. J Cardiovasc Pharmacol. 2002;40(4):577–85.
39. Liu Y, Shakur Y, Yoshitake M, et al. Cilostazol (pletal®): a dual inhibitor of cyclic nucleotide phosphodiesterase type 3 and adenosine uptake. Cardiovasc Drug Rev. 2001;19(4): 369–86
40. Yan R, Yan R, Li S, et al. The critical roles of cyclic AMP/cyclic AMP-dependent protein kinase in platelet physiology. Front Biol China. 2009;4(1):7–14.
41. Sudo T, Ito H, Kimura Y. Phosphorylation of the vasodilatorstimulated phosphoprotein (VASP) by the anti-platelet drug, cilostazol, in platelets. Platelets. 2003;14(6):381–90.
42. Adelstein RS, Conti MA, Hathaway DR, Klee CB. Phosphorylation of smooth muscle myosin light chain kinase by the catalytic subunit of adenosine 3': 5'-monophosphatedependent protein kinase. J Biol Chem. 1978;253(23):8347–50.
43. Nishioka K, Nishida M, Ariyoshi M, et al. Cilostazol suppresses angiotensin II–Induced vasoconstriction via protein kinase A–mediated phosphorylation of the transient receptor potential canonical 6 channel. Arterioscler Thromb Vasc Biol. 2011;31(10):2278–86.
44. Manickavasagam S, Ye Y, Lin Y, et al. The cardioprotective effect of a statin and cilostazol combination: relationship to akt and endothelial nitric oxide synthase activation. Cardiovasc Drugs Ther. 2007;21(5):321–30
45. Borgognone A, Pulcinelli FM. Reduction of cAMP and cGMP inhibitory effects in human platelets by MRP4-mediated transport. Thromb Haemost. 2012;108(5):955–62.
46. Guarino ML, Massimi I, Alemanno L, et al. MRP4 over-expression has a role on both reducing nitric oxide-dependent antiplatelet effect and enhancing ADP induced platelet activation. J Thromb Thrombolysis. 2020.
47. Ito H, Uehara K, Matsumoto Y, et al. Cilostazol inhibits accumulation of triglyceride in aorta and platelet aggregation in cholesterol-fed rabbits. PLoS One. 2012;7(6):e39374.
48. Motta NAV, Brito FCF. Cilostazol exerts antiplatelet and antiinflammatory effects through AMPK activation and NF-kB inhibition on hypercholesterolemic rats. Fundam Clin Pharmacol. 2016;30(4):327–37.
49. Tani T, Uehara K, Sudo T, et al. Cilostazol, a selective type III phosphodiesterase inhibitor, decreases triglyceride and increases HDL cholesterol levels by increasing lipoprotein lipase activity in rats. Atherosclerosis. 2000;152(2):299–305.

50. Toyota T, Oikawa S, Abe R, et al. Effect of cilostazol on lipid, uric acid and glucose metabolism in patients with impaired glucose tolerance or type 2 diabetes mellitus: a double-blind, placebo-controlled study. Clin Drug Investig. 2001;21(5):325–35
51. Bedenis R, Stewart M, Cleanthis M, et al.Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014;2014(10):CD003748.
52. Pletal. https://www.accessdata.fda.gov/drugsatfda_docs/label/ 2007/020863s021lbl.pdf. Accessed 2/5/2021.
53. Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (cilostazol: a study in long-term effects). J Vasc Surg. 2008;47(2):330–336.e2.
54. Castellsague J, Perez-Gutthann S, Calingaert B, et al. Characterization of new users of cilostazol in the UK, spain, sweden, and germany: characterization of new users of cilostazol. Pharmacoepidemiol Drug Saf. 2017;26(6):615–24
55. European medicines agency recommends restricting use of cilostazol-containing medicines. European Medicines Agency. 2013. https://www.ema.europa.eu/en/documents/press-release/ european-medicines-agency-recommends-restricting-usecilostazol-containing-medicines_en.pdf.
55. European medicines agency recommends restricting use of cilostazol-containing medicines. European Medicines Agency. 2013. https://www.ema.europa.eu/en/documents/press-release/ european-medicines-agency-recommends-restricting-usecilostazol-containing-medicines_en.pdf.
56. taylor dj, Amato lj. hands et al. 1996. Changes in energy metabolism of calf muscle in patients with in termittent claudication assessed by 31P magnetic resonance spectroscopy: a phase II open study. Vasc. Med. 1: 241–245.
57. Cipolla Mj, Nıcoloffet A al. 1999. Propionyl-L-carnitine dilates human subcutaneous arteries through an endothelium-depe ndent mechanism. J. Vasc.Surg. 29: 1097–1103.
58. Arker B , Green ga , Skew Cd et al . 2001. Effect of propionyl-L -carnitine on exercise performance in peripheral arteri al disease. Med. Sci. Sports Exercise 33: 1415–1422.
59. Diamond BJ, Shiflett SC, Feiwel N, et al. Ginkgo biloba extract: mechanisms and clinical indications. Arch Phys Med Rehabil. 2000;81:668–678.
60. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication: a meta-analysis of randomized trials. Am J Med. 2000;108:276–281.
61. Sierpina VS, Wollschlaeger B, Blumenthal M. Ginkgo biloba. Am Fam Phys. 2003;68:923–926.
62. Ito H, Taniyama Y, Iwakura K, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. J Am Coll Cardiol 1999: 33:654–660
63. Kurdal AT. Raynaud hastalığı ve üst ekstremite küçük arter tıkayıcı hastalığı. In: Polat A, Akay HT, Köksl C, Bozkurt AK, editörler. Damar. Konu 17. İstanbul: Bayçınar Tıbbi Yayıncılık; 2019. s. 553-58
64. Landry GJ: Current medical and surgical management of Raynaud's syndrome. J Vasc Surg. 2013, 57:1710-6. 10.1016/j.jvs.2013.03.012
65. Fries R. Shariat K, et al. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation 2005 Nov 8; 112(19):2980-5.
66. Caglayan E, et al. Arch Intern Med. 2012:172:1182-4
67. Shenoy PD, et al. Rheumatol. 2010;49:2420-8.
68. Wollersheim H, Thien T, Fennis J, et al: Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. Clin Pharmacol Ther. 1986, 40:219-25. 10.1038/clpt.1986.166

69. Pope J, Fenlon D, Thompson A, et al: Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev. 1998, 2:CD000956. 10.1002/14651858.CD000956
70. Teh LS, Manning J, Moore T, et al: Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. Br J Rheumatol. 1995, 34:636 41. 10. 1093/rheumatology/34.7.636
71. Bolte MA, Avery D: Case of fluoxetine-induced remission of Raynaud's phenomenon--a case report. Angiology. 1993, 44:161-3. 10.1177/000331979304400213
72. Baumhäkel M, Böhm M: Recent achievements in the management of Raynaud's phenomenon. Vasc Health Risk Manag. 2010, 6:207-14. 10.2147/vhrm.s5255
73. Landry GJ: Current medical and surgical management of Raynaud's syndrome. J Vasc Surg. 2013, 57:1710-6. 10.1016/j.jvs.2013.03.012

# BÖLÜM 23

# Depo Hastalıklarının ve İnfiltratif Hastalıkların Kardiyak Tedavileri

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## GİRİŞ

Kardiyak etkilenmenin olduğu depo hastalıkları, infiltratif veya kalıtımsal bazı hastalıkların sınıflandırmalarına bakıldığında, kendi grupları içinde kardiyak etkilenmenin olduğu hastalıklar olarak incelendikleri veya çoğunlukla klinik prezentasyonları gereği hipertrofik veya restriktif kardiyomyopati başlığı altında incelendikleri görülmektedir. Ancak bunula birlikte bu tanıma net olarak uymayan durumlar da mevcuttur. AHA (American Heart Assosiation) tarafından önerilen kardiyomyopati sınıflandırılmasında hastalığın primer veya predominant olarak kardiyak tutulum yapıyor olması veya sistemik (multiorgan) bir hastalığın kardiyak tutulumu şeklinde ortaya çıkıyor olmasına göre primer ve sekonder kardiyomyopatiler şeklinde iki sınıfa ayrılmaktadır. Primer kardiyomyopatiler genetik, mikst ve kazanılmış olarak, sekonder kardiyomyopatiler ise infiltratif, depo, toksisite, endomyokardiyal, inflamatuvar, endokrin, kardiyofasiyal, nöromuskuler/nörolojik, nutrisyonel eksiklik, otoimmun/kollagen, elektrolit imbalansı, kanser terapisi sonucu olmak üzere alt gruplara ayrılmaktadır. (1) Bu bölümde kardiyak açıdan tedavileri incelenecek olan hastalıklar çoğunlukla sekonder kardiyomyopati sınıflandırılmasındaki depo ve infiltratif hastalık grubundadır. Primer nedenden bağımsız olarak tüm kardiyomyopati türleri için

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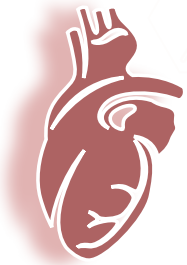
## KAYNAKLAR


1. Maron B.J., Towbin J.A. , Thiene G. Et al. - Contemporary Definitions and Classification of the Cardiomyopathies- An American Heart Association Scientific Statement From the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention- Originally published27 Mar 2006https://doi.org/10.1161/CIRCULATIONAHA.106.174287. *Circulation*. 2006;113:1807–1816
2. Kittleson M. M. , Maurer M.S., Ambardekar A.V. et al. and On behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology- Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association-*Circulation*- Originally published1 Jun 2020https://doi.org/10.1161/CIR.0000000000000792Circulation. 2020;142:e7–e22
3. Benson M.D. , Buxbaum J.N. et al. - Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee- 2018 Dec;25(4):215-219. doi: 10.1080/13506129.2018.1549825. Epub 2019 Jan 7.
4. Garcia-Pavia P., Rapezzi C., Adler Y. et al.- Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases- *European Heart Journal*, Volume 42, Issue 16, 21 April 2021, Pages 1554-1568, https://doi.org/10.1093/eurheartj/ehab072
5. Papingiotis G, Basmpana L, Farmakis D.- Cardiac amyloidosis: epidemiology, diagnosis and therapy- *European Society of Cardiology Journals*- e-Journal of Cardiology Practice- e-Journal of Cardiology Practice - Volume 19. Vol. 19, N° 19 - 21 Apr 2021
6. Solomon SD, Adams D, Kristen A et al. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis.-***Circulation.*** 2019; 139:431–443. doi: 10.1161/CIRCULATIONAHA.118.035831
7. Benson MD, Dasgupta NR, Rissing SM, et al.- Safety and efficacy of a TTR specific antisense oligonucleotide in patients with transthyretin amyloid cardiomyopathy- ***Amyloid***. 2017; 24:219–225. DOI: 10.1080/13506129.2017.1374946
8. Castaño A., Helmke S., Alvarez J. et al.- Diflunisal for ATTR cardiac amyloidosis- *Heart Fail*. 2012 Nov-Dec;18(6):315-9. doi: 10.1111/j.1751-7133.2012.00303.x. Epub 2012 Jul 2.
9. Mathew S. Maurer, M.D., Jeffrey H et al., for the ATTR-ACT Study Investigators*- Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy- N Engl J Med 2018; 379:1007-1016 DOI: 10.1056/NEJMoa1805689
10. Tafamidis (Rx)- *Medscape*- Drugs & Diseases-Brand and Other Names: Vyndamax-Classes: Cardiovascular, Other
11. Radulescu D., Buzdugan E., Stoicescu L. Et al.- Current status of cardiac manifestations in Fabry disease and their treatment- *Med Pharm Rep*. 2021 Aug; 94(Suppl No 1): S19–S21. Published online 2021 Aug 10. doi: 10.15386/mpr-2221
12. Biegstraaten M. , Arngrímsson R. , Barbey F. Et al. - Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document- *Orphanet Journal of Rare Diseases* volume 10, Article number: 36 (2015)
13. Germain D.P. , Charrow J. , Desnick R.J. - Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease- *J Med Genet*: first published as 10.1136/med genet-2014-102797 on 20 March 2015
14. Replagal® Summary of Product Characteristics- Available at:http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000369/WC500053612.pdf (2014), Accessed 19th Oct 2017

15. Hughes D.A., Elliott P.M., Shah J. Et al.- Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomized, double-blind, placebo-controlled clinical trial of agalsidase alfa- *Heart*. 2008 Feb;94(2):153-8. doi: 10.1136/hrt.2006.104026. Epub 2007 May 4.
16. Beck M. , Hughes D., Kampmann C. et al. - Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: A Fabry Outcome Survey analysis- *Molecular Genetics and Metabolism Reports* Volume 3, June 2015, Pages 21-27
17. Fabrazyme Prescribing Information- Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103979s5135lbl.pdf (2010)
18. Germain D.P., Waldek S., Banikazemi M. Et al.- Sustained, Long-Term Renal Stabilization After 54 Months of Agalsidase β Therapy in Patients with Fabry Disease- *JASN* May 2007, 18 (5) 1547-1557; DOI: https://doi.org/10.1681/ASN.2006080816
19. Wilbert S. Aronow, Management of cardiac hemochromatosis- *Arch Med* Sci 2018; 14, 3: 560–568 DOI: https://doi.org/10.5114/aoms.2017.68729 Copyright © 2017 Termedia & Banach
20. Wasserman AJ, Richardson DW, Baird CL, et al. Cardiac hemochromatosis simulating constrictive pericarditis. *Am J Med.* 1962;32:316–23
21. Kremastinos D.T., Farmakis D.- Iron Overload Cardiomyopathy in Clinical Practice- *Circulation*. 2011;124:2253–2263- Originally published15 Nov 2011https://doi.org/10.1161/CIRCULATIONAHA.111.050773Circulation.
22. Dabestani A, Child JS, Henze E, et al. Primary hemochromatosis: anatomic and physiologic characteristics of the cardiac ventricles and their response to phlebotomy. *Am J Cardiol* 1984; 54: 153-9.
23. Mamtani M., Kulkarni H.- Influence of iron chelators on myocardial iron and cardiac function in transfusion-dependent thalassemia: a systematic review and meta-analysis- *Br J Haematol*. 2008 Jun;141(6):882-90.doi: 10.1111/j.1365-2141.2008.07122.x. Epub 2008 Mar 18.
24. Pepe A. , Meloni A. , Rossi G. Et al. - A T2* MRI prospective survey on heart iron in thalassemia major patients treated with deferasirox versus deferiprone and desferrioxamine in monotherapy- *Journal of Cardiovascular Magnetic Resonance* volume 13, Article number: O21 (2011)
25. Deferoxamine (Rx)- *Medscape*- Drugs & Diseases-Brand and Other Names:Desferal-Classes: Chelators
26. Farmaki K. , Tzoumari I. , Pappa C. - Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major- *Br J Haematol.* 2010 Feb;148(3):466-75.doi: 10.1111/j.1365-2141.2009.07970.x. Epub 2009 Nov 12.
27. Deferiprone (Rx)- *Medscape*- Drugs & Diseases-Brand and Other Names:Ferriprox -Classes: Chelators
28. Deferasirox (Rx)- *Medscape*- Drugs & Diseases-Brand and Other Names: Exjade, Jadenu, Jadenu Sprinkle -Classes: Chelators
29. Cappellini M.D. , Cohen A., Piga A. Et al.- A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia- *Blood.* 2006 May 1;107(9):3455-62. doi: 10.1182/blood-2005-08-3430. Epub 2005 Dec 13.
30. Modell B., Khan M., Darlison M. et al. - Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance- *Journal of Cardiovascular Magnetic Resonance* volume 10, Article number: 42 (2008)
31. Anderson L.J., Holden S., Davis B. et al.- Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload- *European Heart Journal*, Volume 22, Issue 23, 1 December 2001, Pages 2171–2179, https://doi.org/10.1053/euhj.2001.2822

32. Harshaw-Ellis K.S. -Cardiac Sarcoidosis- American Collage of Cardiology, expert anaylsis- May 20, 2021
33. Birnie D.H., Nery P.B., Ha A.C. et al. – Cardiac Sarcoidosis- *J Am Coll Cardiol*. 2016 Jul, 68 (4) 411–421
34. Nair V., Belanger E.C., Veinot J.P.- Lysosomal storage disorders affecting the heart: a review- *Cardiovascular Pathology* Volume 39, March–April 2019, Pages 12-24
35. Güngör D., Kruijshaar M.E. , Plug I. - Impact of enzyme replacement therapy on survival in adults with Pompe disease: results from a prospective international observational study- *Orphanet Journal of Rare Diseases* volume 8, Article number: 49 (2013)
36. Nascimbeni A.C. , Fanin M. , Angelini C. et al.- Autophagy dysregulation in Danon disease- *Cell Death & Disease* volume 8, pagee2565 (2018)
37. D'souza R.S. ,Levandowski C., Slavov D. Et al. - Danon Disease: Clinical Features, Evaluation, and Management- *Circ Heart Fail*. 2014 Sep; 7(5): 843–849. doi: 10.1161/CIRCHEARTFAILURE.114.001105
38. Braunlin E.A., Harmatz P.R., Scarpa M. et al.- Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management- *J Inherit Metab Dis*. 2011; 34(6): 1183–1197. Published online 2011 Jul 9. doi: 10.1007/s10545-011-9359-8
39. Okuyama T., Tanaka A., Suzuki Y. et al.- Japan Elaprase® Treatment (JET) study: Idursulfase enzyme replacement therapy in adult patients with attenuated Hunter syndrome (Mucopolysaccharidosis II, MPS II)- *Molecular Genetics and Metabolism* Volume 99, Issue 1, January 2010, Pages 18-25
40. Concolino D., Deodato F., Parini R. - Enzyme replacement therapy: efficacy and limitations- *Ital J Pediatr.* 2018; 44(Suppl 2): 120. Published online 2018 Nov 16. doi: 10.1186/s13052-018-0562-1



# BÖLÜM 24

# Kardiyovasküler Alanda Proton Pompa İnhibitörleri

*Ahmet Yekta TÜZÜN* [1]

## GİRİŞ

Proton pompası inhibitörleri (PPI'ler), gastrik parietal hücre membranının lümenal yüzeyinde bulunan ve gastrik asit salgılanmasının son basamağı olan hidrojen-potasyum ATPaz pompasına geri dönüşümsüz olarak bağlanmak suretiyle inhibe ederek gastrik asit sekresyonunu baskılar.

Bu ilaç grubu temelde peptik ülser hastalığı, dispepsi, gastroözofagial reflü hastalığı, NSAİD grubunun yaratabileceği gastrik hasarın primer veya sekonder profilaksisinde, Zolinger Elison Sendromu gibi hipergastrinemi ve hiperasidite ile giden hastalıklarda ve Helicobacter pylori eradikasyon tedavisinin bir bileşeni olarak kullanılmaktadır.

PPI'leri parietal hücrede bulunan HK-ATPase pompasını aktif halini inhibe eder ve bu pompa en uzun açlıktan sonraki ilk öğün ile en yüksek aktif pompa sayısına ulaşılacağından, bu sebepten uzun süreli açlıktan sonra (gece açlığı) en yüksek aktif pompa sayısına ulaşılacağından,, *PPİ'ler günün ilk öğününden yaklaşık 20-30 dakika önce uygulanmalıdır. Bu farmakokinetik etki grup etkisi olduğundan bütün PPI'lar için geçerlidir.* Çoğu kişide, günde bir kez doz, istenen düzeyde asit inhibisyonu sağlamak için yeterlidir ve ara sıra gerekli olan ikinci bir doz, akşam yemeğinden önce uygulanmalıdır (1).

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» **Dimetil arginin dimetilamino hidrolaz (DDAH) enzimini PPİ'lar inhibe etmektedir.**
» **DDAH; asimetrik dimetil arginin (ADMA) %80'inin temizlenmesinden sorumludur.**
» **ADMA → NOS (nitrik oksitsentetaz)'ı inhibe eder.**

**PPİ → DDAH (↓) → ADMA (↑)→ NOS (↓)→ NO (↓↓) → Vasküler direnç (↑) → İnflamasyonu ve trombozisi uyarır**

Vasküler komplikasyonlarla ilgili bir diğer mekanizma ise PPI'ların irreversible bloke ettiği proton pompalarının sadece gastrik pariyetal hücrelerde değil aynı zamanda hücre lizozomlarında da benzer proton pompaları inhibe edilmiş olur. PPI'lar ayrıca damar sistemini kaplayan endotel hücrelerinin lizozomlarındaki proton pompalarına da bağlanır. Lizozomal asiditenin kronik olarak bozulması, lizozomal enzimlerin işlevini bozar. Böylece endotel hücresinde protein aggregatlarının birikmesi ve proteazların bozulması gerçekleşir. Endotelyal yaşlanmanın hızlanması ile vasküler inflamasyon ve böylece ateroskleroz ve koroner arter hastalığı riskinde artış meydana gelmiş olur (17).

Proton pompası inhibitörleri

» **Endotelyal lizozomal proton pompa inhibisyonu ↓**
» **Lizozomal asidifikasyonda azalma ↓**
» **Azalmiş lizozomal enzim aktivasyonu ↓**
» **Protein aggregatlarinin birikimi**
» **Endotelyal hasar → stroke demans ve koroner enfarktüs riskinde artış.**

## KAYNAKLAR


1. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000; 118:S9.
2. Pharmacist's Letter [Internet] Stockton, CA: Therapeutic Research Center; 2019. Proton pump inhibitors: appropriate use and safety concerns; 2019 Feb [cited 2019 Mar 27].
3. Eid SM, Boueiz A, Paranji S, Mativo C, Landis R, Abougergi MS. Patterns and predictors of proton pump inhibitor overuse among academic and non-academic hospitalists. Intern Med. 2010;49(23):2561-8.
4. Corleto VD, Festa S, Di Giulio E, et al. Proton pump inhibitor therapy and potential long-term harm. Curr Opin Endocrinol Diabetes Obes 2014;21:3-8.
5. W. Zhu, K. Hong. Potential cardiovascular risks of proton pump inhibitors in the general population Int. Heart J., 58 (2) (2017 Apr 06), pp. 163-166
6. D.E. Freedberg, L.S. Kim, Y.X. Yang. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the american gastroenterological as-

sociation, Gastroenterology 152 (4) (2017 Mar) 706–715
7. Kang DO, An H, Park GU ve ark. Miyokard Enfarktüsü Sonrası Steroid Olmayan Anti-İnflamatuvar İlaçlarla İlişkili Kardiyovasküler ve Kanama Riskleri. J Am Coll Cardiol 2020; 76:518.
8. Smecuol E, Pinto Sanchez MI, Suarez A, et al. Low-dose aspirin affects the small bowel mucosa: results of a pilot study with a multidimensional assessment. Clin Gastroenterol Hepatol. 2009;7:524–9.
9. Luo JC, Peng YL, Chen TS, et al. Clopidogrel inhibits angiogenesis of gastric ulcer healing via downregulation of vascular endothelial growth factor receptor 2. J Formos Med Assoc. 2016;115:764–72.
10. Lanza FL, Chan FK, Quigley EM, Practice Parameters Committee of the American College of Gastroenterology Am J Gastroenterol. 2009;104(3):728.
11. Graham DY, Agrawal NM, Campbell DR ve ark. Uzun süreli nonsteroid antiinflamatuvar ilaç kullanıcılarında ülser önleme: mizoprostol ve lansoprazole ilişkin çift kör, randomize, çok merkezli, aktif ve plasebo kontrollü bir çalışmanın sonuçları. Arch Intern Med 2002; 162:169.
12. Papatheodoridis GV, Sougioultzis S, Archimandritis AJ. Helicobacter pylori ve nonsteroidal antiinflamatuar ilaçların peptik ülser hastalığı üzerindeki etkileri: sistematik bir derleme. Clin Gastroenterol Hepatol 2006; 4:130.
13. Björnsson E, Abrahamsson H, Simrén M, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006;24(6):945.
14. Prescribers Digital Reference [Whippany, NJ: PDR, LLC; 2019. Plavix (clopidogrel bisulfate) FDA Drug Safety Communication; 2009 Nov 17 cited 2019 Mar
15. Toh JW, Ong E, Wilson R. Hypomagnesaemia associated with long-term use of proton pump inhibitors. Gastroenterol Rep (Oxf). 2015 Aug;3(3):243-53.
16. Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation. (2013) 128:845–53.
17. Yepuri G, Sukhovershin R, Nazari-Shafti TZ, et al. Proton pump inhibitors accelerate endothelial senescence. Circ Res.(2016) 118:e36–e42.