



## BÖLÜM 30

### Anjiyotensin Dönüştürücü Enzim İnhibitörleri ve Anjiyotensin Reseptör Blokörleri

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#### GİRİŞ

Tanı ve tedavi yöntemlerindeki tüm gelişmelere rağmen, akut koroner sendromlar (AKS) özellikle de ST yükselmeli miyokard enfarktüsü (STEMI) endüstrileşmiş dünyada önemli bir halk sağlığı problemi olmaya devam etmektedir ve gelişmekte olan ülkelerde önemli bir artış göstermektedir (1). Son dönemde duyarlılığı daha yüksek belirteçlerin kullanıma girmesiyle AKS'ler içerisinde STEMI oranı düşmekle beraber (2) erken dönem mortalite oranı %5-6, ilk 1 yıl mortalite oranı %7-18 arasındadır (3,4).

Modern tıpta STEMI yönetimi, 20. yüzyılın başlarında klinik gözlem ve sonrasında koroner yoğun bakım ünitesi fazlarındayken, teknolojinin gelişimi ve reperfüzyon dönemiyle beraber büyük bir atılım yakalamıştır (5). Reperfüzyon dönemiyle beraber, önce fibrinoliz sonrasında primer perkütan girişim ve buna eşlik eden kılavuza yönelik optimal medikal tedavinin rutine dönüşmesi, kanıta dayalı tedavinin uygulanmasını arttırmış ve STEMI sonrası tüm klinik sonuçları iyileştirmiştir (6).

Renin - Anjiyotensin - Aldosteron sistemi (RAAS) normal fizyolojide kardiyovasküler sistemin önemli bir parçasıdır. Kan basıncının yük-

seltilmesi, sodyum retansiyonu, arterler üzerinde vazokonstriksiyon ve adrenal bezden aldosteron salgılanması önemli fonksiyonları arasındadır. Ayrıca, kalpte pozitif inotropik ve kronotropik etkiler gösterir, nörohumoral sistem üzerinden susama, tuz iştahı, sempatik sistem aktivasyonu ve vazopressin salgılanmasında önemli rolleri mevcuttur (7). Bütün bu etkiler normal fizyolojide bir insanda homeostazinin devamı için elzem olsa da miyokard enfarktüsünde RAAS'ın aktivasyonu, oksidatif strese, endotelial disfonksiyona ve inflamasyona sebep olarak kardiyovasküler sistem üzerinde zararlı etkiler oluşturmaktadır (8,9).

Anjiyotensin Dönüştürücü Enzim (ACE) inhibitörleri ve Anjiyotensin II Reseptör Blokörleri (ARB) RAAS'ın STEMI geçiren hastalarda oluşturduğu etkileri ortadan kaldırmak amacıyla uzun zamandan beri kullanılmakta olup optimal medikal tedavi içinde yer almaktadır. Güncel olarak STEMI sonrası sol ventrikül ejeksiyon fraksiyonu (LVEF) <%40 olan veya kalp yetersizliği semptomları olan hastalarda, diyabetiklerde, hipertansif hastalarda, kontrendikasyon yoksa kronik böbrek hastalarında ACE inhibitörleri rutin tedavide önerilmektedir. ACE inhibitörlerini tolere edemeyen hastalarda da ARB'ler aynı şekilde önerilmektedir.

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cel kılavuzlar STEMI geçiren hastalarda, anterior lokalizasyon olması veya LVEF<%40 olması veya kalp yetersizliği semptomları olması halinde ACE inhibitörlerini kesin olarak birinci basamak tedavide erken dönemde başlanmak üzere önermektedir. Bu özellikleri barındırmayan hastalarda da aynı kanıt düzeyinde olmamakla birlikte kuvvetli öneri mevcuttur. Herhangi bir sebeple ACE inhibitörü kullanamayan hastalarda da ARB'ler aynı şekilde önerilmektedirler.

Anjiyotensin dönüştürücü enzim inhibitörleri ve ARB'ler yan etki profilleri düşük, birçok farklı mekanizma ile kardiyoprotektif etki gösteren, uygun maliyetli ilaç gruplarıdır. Hipertansiyonu olan, kalp yetersizliği olan veya STEMI geçiren hastalarda, herhangi bir engel bulunmadığında, bu ilaçlar tedavi seçenekleri arasında öncelikli olarak düşünülmelidir.

## KAYNAKLAR

- Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. *Circulation*. 2015;132(17):1667–1678. doi: 10.1161/CIRCULATIONAHA.114.008720
- Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. *New England Journal of Medicine*. 2010;362(23):2155–2165. doi: 10.1056/NEJMoa0908610
- Rosamond WD, Chambless LE, Heiss G, et al. Twenty-two-year trends in incidence of myocardial infarction, coronary heart disease mortality, and case fatality in 4 US communities, 1987-2008. *Circulation*. 2012;125(15):1848–1857. doi: 10.1161/CIRCULATIONAHA.111.047480
- Ford ES, Roger VL, Dunlay SM, et al. Challenges of ascertaining national trends in the incidence of coronary heart disease in the United States. *Journal of the American Heart Association*. 2014;3(6). doi: 10.1161/JAHA.114.001097
- Morrow DA, Fang JC, Fintel DJ, et al. Evolution of critical care cardiology: transformation of the cardiovascular intensive care unit and the emerging need for new medical staffing and training models: a scientific statement from the American Heart Association. *Circulation*. 2012;126(11):1408–1428. doi: 10.1161/CIR.0b013e31826890b0
- Wasfy JH, Borden WB, Secemsky EA, et al. Public reporting in cardiovascular medicine: accountability, unintended consequences, and promise for improvement. *Circulation*. 2015;131(17):1518–1527. doi: 10.1161/CIRCULATIONAHA.114.014118
- Bader M. Tissue renin-angiotensin-aldosterone systems: Targets for pharmacological therapy. *Annual Review of Pharmacology and Toxicology*. 2010;50:439–465. doi: 10.1146/annurev.pharmtox.010909.105610
- Scirica BM, Libby P, Morrow DA, ST-Elevation Myocardial Infarction. In: Bonow RO, Libby P, Mann DL, Tomaselli GF, Bhatt DP, Solomon SD, Braunwald E. (eds.) *Braunwald's Heart Disease, 2 Vol Set, 12th Edition, A Textbook of Cardiovascular Medicine*. Philadelphia: Elsevier; 2022 p. 2689-2753.
- Schmieder RE, Hilgers KF, Schlaich MP, et al. Renin-angiotensin system and cardiovascular risk. *The Lancet*. 2007;369(9568):1208–1219. doi: 10.1016/S0140-6736(07)60242-6
- Guyton AC, Hall JE. *Textbook of Medical Physiology*. Philadelphia, PA: Elsevier; 2021. p. 229-244.
- Wu CH, Mohammadmoradi S, Chen JZ, et al. Renin-Angiotensin System and Cardiovascular Functions. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2018;38(7):E108–116. doi: 10.1161/ATVBAHA.118.311282
- Gupta P, Franco-Saenz R, Mulrow PJ. Locally generated angiotensin II in the adrenal gland regulates basal, corticotropin-, and potassium-stimulated aldosterone secretion. *Hypertension*. 1995;25(3):443–448. doi: 10.1161/01.hyp.25.3.443
- Cano A, Miller RT, Alpern RJ, et al. Angiotensin II stimulation of Na-H antiporter activity is cAMP independent in OKP cells. *American Journal of Physiology*. 1994;266(6 Pt 1). doi: 10.1152/ajpcell.1994.266.6.C1603
- Harrison-Bernard LM. The renal renin-angiotensin system. *Advances in Physiology Education*. 2009;33(4):270–274. doi: 10.1152/advan.00049.2009
- Dzau VJ. Theodore Cooper Lecture: Tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension*. 2001;37(4):1047–1052. doi: 10.1161/01.hyp.37.4.1047
- Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. *American Journal of Physiology-Cell Physiology*. 2007;292(1). doi: 10.1152/ajpcell.00287.2006
- Ferrario CM. Role of angiotensin II in cardiovascular disease therapeutic implications of more than a century of research. *Journal of the Renin-Angiotensin-Aldosterone System*. 2006;7(1):3–14. doi: 10.3317/jraas.2006.003
- Xu Z, Li W, Han J, Zou, et al. Angiotensin II induces kidney inflammatory injury and fibrosis through binding to myeloid differentiation protein-2 (MD2). *Scientific Reports*. 2017;7. doi: 10.1038/srep44911
- Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al. Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. *Circulation*. 2000;101(12):1372–1378. doi: 10.1161/01.cir.101.12.1372
- Eguchi S, Kawai T, Scalia R, et al. Understanding Angiotensin II Type 1 Receptor Signaling in Vascular Pathophysiology. *Hypertension*. 2018;71(5):804–810. doi: 10.1161/HYPERTENSIONAHA.118.10266

21. Namsolleck P, Recarti C, Foulquier S, et al. AT(2) receptor and tissue injury: therapeutic implications. *Current Hypertension Reports*. 2014;16(2). doi: 10.1007/s11906-013-0416-6
22. Williams GH. Aldosterone biosynthesis, regulation, and classical mechanism of action. *Heart Failure Reviews*. 2005;10(1):7–13. doi: 10.1007/s10741-005-2343-3
23. Holst JP, Soldin OP, Guo T, et al. Steroid hormones: Relevance and measurement in the clinical laboratory. *Clinics in Laboratory Medicine*. 2004;24(1):105–118. doi: 10.1016/j.cll.2004.01.004
24. Geerling JC, Loewy AD. Aldosterone in the brain. *American Journal of Physiology-Renal Physiology*. 2009;297(3). doi: 10.1152/ajprenal.90399.2008
25. Dandona P, Dhindsa S, Ghanim H, et al. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. *Journal of Human Hypertension*. 2007;21(1):20–27. doi: 10.1038/sj.jhh.1002101
26. Bissessor N, White H. Valsartan in the treatment of heart failure or left ventricular dysfunction after myocardial infarction. *Vascular Health and Risk Management*. 2007;3(4):425.
27. Prabhu SD, Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis. *Circulation Research*. 2016;119(1):91–112. doi: 10.1161/CIRCRESAHA.116.303577
28. Kannel WB, Sorlie P, Mcnamara PM. Prognosis after initial myocardial infarction: The Framingham study. *American Journal of Cardiology*. 1979;44(1):53–59. doi: 10.1016/0002-9149(79)90250-9
29. Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *The New England Journal of Medicine*. 1983;309(6):331–336. doi: 10.1056/NEJM198308113090602
30. Pfeffer JM, Pfeffer MA, Fletcher PJ, et al. Progressive ventricular remodeling in rat with myocardial infarction. *American Journal of Physiology*. 1991;260(5 Pt 2). doi: 10.1152/ajpheart.1991.260.5.H1406
31. Eaton LW, Weiss JL, Bulkley BH, et al. Regional cardiac dilatation after acute myocardial infarction: recognition by two-dimensional echocardiography. *The New England Journal of Medicine*. 1979;300(2):57–62. Available from: 10.1056/NEJM197901113000202
32. Gaudron P, Eilles C, Ertl G, et al. Early remodelling of the left ventricle in patients with myocardial infarction. *European Heart Journal*. 1990;11 Suppl B:139–146. doi: 10.1093/eurheartj/11.suppl\_b.139
33. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation*. 1990;81(4):1161–1172. doi: 10.1161/01.cir.81.4.1161
34. Ruiz-Ortega M, Lorenzo O, Rupérez M, et al. Angiotensin II activates nuclear transcription factor kappaB through AT(1) and AT(2) in vascular smooth muscle cells: molecular mechanisms. *Circulation Research*. 2000;86(12):1266–1172. doi: 10.1161/01.res.86.12.1266
35. Zahradka P, Werner JP, Buhay S, et al. NF-κB activation is essential for angiotensin II-dependent proliferation and migration of vascular smooth muscle cells. *Journal of Molecular and Cellular Cardiology*. 2002;34(12):1609–1621. doi: 10.1006/jmcc.2002.2111
36. Griendling KK, Minieri CA, Ollerenshaw JD, et al. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circulation Research*. 1994;74(6):1141–1148. doi: 10.1161/01.res.74.6.1141
37. Vieira JL, Mehra MR, Heart Failure, In: Bhatt DL (ed) *Opie's Cardiovascular Drugs: A Companion to Braunwald's Heart Disease*. 9th ed. Philadelphia: Elsevier; 2021 p. 147–231.
38. O'Gara PT, Kushner FG, Ascheim DD, et al. 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;127(4):e362–425. doi: 10.1161/CIR.0b013e-3182742cf6
39. 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. *The Lancet*. 1993;342(8875):821–828.
40. Køber L, Torp-Pederson C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *The New England Journal of Medicine*. 1995;333(25):49. doi: 10.1056/NEJM199512213332503
41. 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. *The New England Journal of Medicine*. 1992;327(10):669–677. doi: 10.1056/NEJM199209033271001
42. Van Den Akker M, Spigt MG, De Raeve L, et al. The SMILE study: a study of medical information and lifestyles in Eindhoven, the rationale and contents of a large prospective dynamic cohort study *BMC Public Health*. 2008;8:19. doi: 10.1186/1471-2458-8-19
43. Nicolosi GL, Latini R, Marino P, et al. The prognostic value of predischARGE quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 trial. *European Heart Journal*. 1996;17(11):1646–1656. doi: 10.1093/oxfordjournals.eurheartj.a014747
44. Flather M, Pipilis A, Collins R, et al. Randomized controlled trial of oral captopril, of oral isosorbide mononitrate and of intravenous magnesium sulphate started early in acute myocardial infarction: Safety and haemodynamic effects: Isis-4 (fourth international study of infarct survival) pilot study investigators. *European Heart Journal*. 1994;15(5):608–619. doi: 10.1093/oxfordjournals.eurheartj.a060556

45. Chinese Cardiac Study Collaborative Group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *The Lancet* 1995;345(8951):686–687. doi: 10.1016/S0140-6736(95)90866-8
46. Swedberg K, Held P, Kjeksus 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). *The New England Journal of Medicine*. 1992;327(10):678–684. doi: 10.1056/NEJM199209033271002
47. Welch TD, Yang EH, Reeder GS, et al. Modern management of acute myocardial infarction. *Current Problems in Cardiology*.2012;37(7):237–310. doi: 10.1016/j.cpcardiol.2012.03.002
48. Swedberg K, Held P, Kjeksus J, et al. Effects of the Early Administration of Enalapril on Mortality in Patients with Acute Myocardial Infarction. *The New England Journal of Medicine*. 2010;327(10):678–684. doi: 10.1056/NEJM199209033271002
49. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *The New England Journal of Medicine*. 2004;351(20):2058–2068. doi: 10.1056/NEJMoa042739
50. Kim KH, Choi BG, Rha SW, et al. Impact of renin angiotensin system inhibitor on 3-year clinical outcomes in acute myocardial infarction patients with preserved left ventricular systolic function: a prospective cohort study from Korea Acute Myocardial Infarction Registry (KAMIR). *BMC Cardiovascular Disorders*. 2021;21(1):251. doi: 10.1186/s12872-021-02070-x
51. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both. *New England Journal of Medicine*. 2003;349(20):1893–1906. doi: 10.1056/NEJMoa032292
52. Dickstein K, Kjeksus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: The OPTIMAAL randomised trial. *The Lancet*. 2002;360(9335):752–760. doi: 10.1016/S0140-6736(02)09895-1
53. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England Journal of Medicine*. 2014;371(11):132–133. doi: 10.1056/NEJMoa1409077
54. Pfeffer MA Claggett B, Lewis EF, et al. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction. *The New England Journal of Medicine* 2021;385(20):1845-1855. doi:10.1056/NEJMoa2104508.
55. Ibanez B, James S, Agewall S, Antunes MJ, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal*. 2018;39(2):119–177. doi: 10.1093/eurheartj/ehx393
56. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*. 2021;42(36):3599–3726. doi: 10.1093/eurheartj/ehab368
57. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation*. 1998;97(14):1411–1420. doi: 10.1161/01.cir.97.14.1411
58. Mira ML, Silva MM, Manso CF. The Scavenging of Oxygen Free Radicals by Angiotensin Converting Enzyme Inhibitors: The Importance of the Sulfhydryl Group in the Chemical Structure of the Compounds. *Annals of the New York Academy of Sciences*. 1994;723(1):439–441.
59. Taylor AA, Siragy H, Nesbitt S. Angiotensin Receptor Blockers: Pharmacology, Efficacy, and Safety. *The Journal of Clinical Hypertension*. 2011;13(9):677. doi: 10.1111/j.1751-7176.2011.00518.x
60. Proud D, Kaplan AP. Kinin Formation: Mechanisms and Role in Inflammatory Disorders. *Annual Review of Immunology*. 1988;6:49-83 doi: 10.1146/annurev.iy.06.040188.000405
61. Kramer HJ, Townsend RR, Griffin K, et al. KDOQI US Commentary on the 2017 ACC/AHA Hypertension Guideline. *American Journal of Kidney Diseases*. 2019;73(4):437–458. doi: 10.1053/j.ajkd.2019.01.007