

# BÖLÜM 29



## VARFARİN VE PARENTERAL ANTİKOAGÜLANLAR

Bekir DEMİRTAŞ<sup>1</sup>

### VARFARİN

Varfarin günümüze kadarki olan süreçte en yaygın ve uzun süredir kullanılan oral antikoagülan ajandır. Tarihsel gelişimine baktığımızda ilk oral antikoagülan (OAK) olarak 1950'li yıllarda tedavide kullanılmaya başlanmıştır. Her ne kadar 2002 yılından itibaren kullanıma giren yeni nesil oral antikoagülan (YOAK) ajanlara (rivaroksaban, dabigatran, apiksaban ve edoksaban) eğilim artsa da halen birçok endikasyonla ve bu ajanların kullanımının mümkün olmadığı durumlarda kullanılmaktadır. Ayrıca maliyet etkin olması diğer bir avantajıdır. Yan etki profili, komplikasyonları, komplikasyon halindeki tedavi yaklaşımları ve bilinen bir antidotunun olması yönüyle iyi bilinen bir ilaçtır. En önemli bilinen yan etkisi kanama olup, kanama harici yan etkileri daha nadir görülmektedir. İntrakranial kanama en ciddi yan etkisidir. Diğer endikasyonlarla kullanılan ilaçlar ve besinlerden metabolizması etkilenebilir. Dikkatli takip ve doz ayarlaması ile yan etki gelişmesi ihtimali oldukça azalır.

### ETKİ MEKANİZMASI VE FARMAKOKİNETİK

Varfarin vitamin-K epoksit redüktaz enzimini inhibe eder ve vitamin-K inaktivasyonu yapar. Böylece karaciğerde üretilen vitamin-K bağımlı pıhtılaşma faktörleri olan FII, FVII, FIX ve FX sentezini inhibe ederek antikoagülan etki gösterir.<sup>1</sup> Plazmada %97 oranında albümine bağlanır, yarılanma ömrü 36-48 saattir. Karaciğerde bulunan CYP<sub>2C9</sub> ve vitamin-K epoksit redüktaz enzimleri ile inaktif metabolitlerine dönüştürülüp idrar ve dışkı yolu ile atılır.<sup>2</sup> Bu enzimlerdeki genetik varyasyonlar,

<sup>1</sup> Uzm. Dr., Çankırı Devlet Hastanesi, Kardiyoloji Bölümü, bkrdemirtas@gmail.com

PCI işlemine kadar sınıf I kanıt düzeyi ile fondaparinuxs önermektedir.<sup>39</sup> 2020 ESC NSTEMI kılavuzunda ise PCI işlemi sırasında ek doz UHF yapılması kaydı ile sınıf I kanıt düzeyi ile önermektedir.<sup>38</sup> 2013 ACC/AHA kılavuzunda hastane yatışından itibaren 8 gün ya da revaskülarizasyona kadar sınıf I kanıt düzeyi ile önermektedir. 2017 ESC STEMI kılavuzunda ise streptokinaz verilen hastalarda IV olarak verilmesini sınıf IIa kanıt düzeyi ile önermektedir. Primer PCI planlanan hastalarda her iki kılavuzda da katater trombozu riski nedeniyle sınıf III kanıt düzeyi ile fondaparinuxs önerilmemektedir.<sup>40,41</sup> OASIS- 5 çalışmasında STEMI hastalarında enoksaparin ile karşılaştırılmıştır. Etkinlik benzer olmakla birlikte majör kanama fondaparinuxs kolunda daha az görülmüştür. Ancak katater ilişkili trombüs insidansında artış görülmesi nedeniyle ek doz UHF PCI sırasında yapılması önerilmiştir.<sup>50</sup> 2019 ESC PTE tanı ve tedavi kılavuzunda ise antikoagülan parenteral olarak verilecekse DMAH veya fondaparinuxsu sınıf I kanıt düzeyi ile önermektedir.<sup>26</sup>

## KAYNAKLAR

1. Holford NH. Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. *Clin Pharmacokinet.* 1986;11(6):483-504. doi:10.2165/00003088-198611060-00005
2. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest.* 2001;119(1 Suppl):8S-21S. doi:10.1378/chest.119.1\_suppl.8
3. Millican EA, Lenzini PA, Milligan PE, et al. Genetic-based dosing in orthopedic patients beginning warfarin therapy. *Blood.* 2007;110(5):1511-1515. doi:10.1182/blood-2007-01-069609
4. Camm AJ. The RE-LY study: Randomized Evaluation of Long-term anticoagulant therapy: dabigatran vs. warfarin. *Eur Heart J.* 2009;30(21):2554-2555. doi:10.1093/eurheartj/ehp384
5. 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;1(2):84-91. doi:10.1161/CIRCOUTCOMES.108.796185
6. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210
7. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association [published correction appears in *Circulation.* 2020 Jan 14;141(2):e33]. *Circulation.* 2019;139(10):e56-e528. doi:10.1161/CIR.0000000000000659
8. Pisters R, Lane DA, Marin F, et al. Stroke and thromboembolism in atrial fibrillation. *Circ J.* 2012;76(10):2289-2304. doi:10.1253/circj.cj-12-1036
9. Lip GY, Nieuwlaar 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;137(2):263-272. doi:10.1378/chest.09-1584
10. Pisters R, Lane DA, Nieuwlaar R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100. doi:10.1378/chest.10-0134
11. 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 [published correction appears in *Eur Heart J*. 2021 Feb 1;42(5):507] [published correction appears in *Eur Heart J*. 2021 Feb 1;42(5):546-547] [published correction appears in *Eur Heart J*. 2021 Oct 21;42(40):4194]. *Eur Heart J*. 2021;42(5):373-498. doi:10.1093/eurheartj/ehaa612
12. 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: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society [published correction appears in *J Am Coll Cardiol*. 2019 Jul 30;74(4):599]. *J Am Coll Cardiol*. 2019;74(1):104-132. doi:10.1016/j.jacc.2019.01.011
  13. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867. doi:10.7326/0003-4819-146-12-200706190-00007
  14. Sjalander S, Sjögren V, Renlund H, et al. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thromb Res*. 2018;167:113-118. doi:10.1016/j.thromres.2018.05.022
  15. Amin A, Deitelzweig S, Jing Y, et al. Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use—learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. *J Thromb Thrombolysis*. 2014;38(2):150-159. doi:10.1007/s11239-013-1048-z
  16. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039
  17. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638
  18. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907
  19. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears in *N Engl J Med*. 2010 Nov 4;363(19):1877]. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561
  20. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med*. 2016;375(25):2423-2434. doi:10.1056/NEJMoa1611594
  21. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med*. 2017;377(16):1513-1524. doi:10.1056/NEJMoa1708454
  22. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med*. 2019;380(16):1509-1524. doi:10.1056/NEJMoa1817083
  23. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394(10206):1335-1343. doi:10.1016/S0140-6736(19)31872-0
  24. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J*. 2019;40(46):3757-3767. doi:10.1093/eurheartj/ehz732
  25. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States [published correction appears in *Circulation*. 2018 Oct 9;138(15):e425]. *Circulation*. 2018;138(15):1519-1529. doi:10.1161/CIRCULATIONAHA.118.035418
  26. 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;41(4):543-603. doi:10.1093/eurheartj/ehz405
  27. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11(1):21. Published 2013 Sep 20. doi:10.1186/1477-9560-11-21

28. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808. doi:10.1056/NEJMoa1302507
29. Hokusai-VTE Investigators, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism [published correction appears in *N Engl J Med*. 2014 Jan 23;370(4):390]. *N Engl J Med*. 2013;369(15):1406-1415. doi:10.1056/NEJMoa1306638
30. Writing Committee Members, Otto CM, Nishimura RA, 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 [published correction appears in *J Am Coll Cardiol*. 2021 Feb 2;77(4):509] [published correction appears in *J Am Coll Cardiol*. 2021 Mar 9;77(9):1275]. *J Am Coll Cardiol*. 2021;77(4):e25-e197. doi:10.1016/j.jacc.2020.11.018
31. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease [published correction appears in *Eur J Cardiothorac Surg*. 2022 Jan 13;]. *Eur J Cardiothorac Surg*. 2021;60(4):727-800. doi:10.1093/ejcts/ezab389
32. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39(34):3165-3241. doi:10.1093/eurheartj/ehy340
33. Mihm AE, Hicklin HE, Cunha AL, et al. Direct oral anticoagulants versus warfarin for the treatment of left ventricular thrombosis. *Intern Emerg Med*. 2021;16(8):2313-2317. doi:10.1007/s11739-021-02788-8
34. Robinson AA, Trankle CR, Eubanks G, et al. Off-label Use of Direct Oral Anticoagulants Compared With Warfarin for Left Ventricular Thrombi. *JAMA Cardiol*. 2020;5(6):685-692. doi:10.1001/jama-cardio.2020.0652
35. Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: Past, Present, and Future. *Pharmaceuticals (Basel)*. 2016;9(3):38. Published 2016 Jul 4. doi:10.3390/ph9030038
36. Hirsh J, O'Donnell M, Eikelboom JW. Beyond unfractionated heparin and warfarin: current and future advances. *Circulation*. 2007;116(5):552-560. doi:10.1161/CIRCULATIONAHA.106.685974
37. Davoren A, Aster RH. Heparin-induced thrombocytopenia and thrombosis. *Am J Hematol*. 2006;81(1):36-44. doi:10.1002/ajh.20490
38. 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 [published correction appears in *Eur Heart J*. 2021 May 14;42(19):1908] [published correction appears in *Eur Heart J*. 2021 May 14;42(19):1925] [published correction appears in *Eur Heart J*. 2021 May 13;]. *Eur Heart J*. 2021;42(14):1289-1367. doi:10.1093/eurheartj/ehaa575
39. 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 [published correction appears in *J Am Coll Cardiol*. 2014 Dec 23;64(24):2713-4. Dosage error in article text]. *J Am Coll Cardiol*. 2014;64(24):e139-e228. doi:10.1016/j.jacc.2014.09.017
40. 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;39(2):119-177. doi:10.1093/eurheartj/ehx393
41. 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. *J Am Coll Cardiol*. 2013;61(4):e78-e140. doi:10.1016/j.jacc.2012.11.019
42. Hirsh J, Fuster V. Guide to anticoagulant therapy. Part 1: Heparin. *American Heart Association. Circulation*. 1994;89(3):1449-1468. doi:10.1161/01.cir.89.3.1449
43. Dempfle CE, Zharkowa U, Elmas E, et al. Heptest-STAT, a new assay for monitoring of low-molecular-weight heparins, is not influenced by pregnancy-related changes of blood plasma. Th-

romb Haemost. 2009;102(5):1001-1006. doi:10.1160/TH08-09-0560

44. 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;344:e553. Published 2012 Feb 3. doi:10.1136/bmj.e553
45. 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*. 2011;378(9792):693-703. doi:10.1016/S0140-6736(11)60876-3
46. Reed MD, Bell D. Clinical pharmacology of bivalirudin. *Pharmacotherapy*. 2002;22(6 Pt 2):1055-1115. doi:10.1592/phco.22.10.1055.33616
47. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. *N Engl J Med*. 2015;373(11):997-1009. doi:10.1056/NEJMoa1507854
48. 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 [published correction appears in *Lancet*. 2014 Nov 22;384(9957):1848]. *Lancet*. 2014;384(9957):1849-1858. doi:10.1016/S0140-6736(14)60924-7
49. De Caterina R, Husted S, Wallentin L, et al. Anticoagulants in heart disease: current status and perspectives. *Eur Heart J*. 2007;28(7):880-913. doi:10.1093/eurheartj/ehl492
50. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol*. 2007;50(18):1742-1751. doi:10.1016/j.jacc.2007.07.042