



## BÖLÜM 2

# KARDİYOVASKÜLER CERRAHİDE FARMAKOLOJİK TEDAVİ

Hakkı Kürşat ÇETİN<sup>1</sup>

### GİRİŞ

Kardiyovasküler cerrahlar için, her ne kadar ameliyat yapmak günlük pratiğin en önemli kısmı olarak görülse de bu alanda kullanılan ilaçların bilinmesi kardiyovasküler ameliyatların başarısını arttırdığı gibi, olası komplikasyonları da azaltacaktır. Kardiyovasküler cerrahide kullanılan ilaçlar bazen kardiyoloji bölümü ile ortaklık gösterebilmektedir. Bu yazıda, kardiyovasküler cerrahide en sık kullanılan medikal tedaviler olan antitrombotik tedaviler, anti-koagülan tedaviler, vazoaktif ajanlar ve trombolitik tedavilerden bahsedilmiştir.

### ANTİTROMBOTİK TEDAVİ

#### Trombosit İşlevi

Trombositler, en küçük kan hücreleri olup, hemostaz ve trombozda öncül görevler yaparlar. Megakaryositler tarafından kemik iliğinde üretilirler. Damarlarda görülen hasar sonrası aktifleşirler (1). Hasarlı damarların subendotelial yüzeyini hedeflerler, Yüzeyindeki glikoprotein 1b-IX-V reseptör kompleksi, hasarlanmış damar kollajenle-

rine von Willebrand faktör aracılığıyla bağlanır. Adezyon hücrede aktivasyonu başlatır, ardından matris bileşenleri (laminin,kollajen,fibronektin), hormonlar (epinefrin, vazopressin), trombin ve trombosit kaynaklı oluşan maddeler (tromboksan A2, adenosin difosfat) tepkimeleri başlatır. Aktifleşmiş trombositler birbirine fibrinojen aracılığıyla bağlanır ve agregasyon oluşur (Birincil agregasyon). Bu aşamada reversibl olan tepkime, trombositlerden oluşan granüller ve membran kaynaklı araşidonik asitten (AA) tromboksan A2 (TxA2) oluşumu sonrası irreversibl hale gelir. Fibrinojen bağlanması, vWF ile GP 2b/3a çapraz bağları pıhtılaşma için trombositleri sabitleyerek kanamada ilk durdurucu rolü oynarlar (2).

#### Antitrombotik İlaçlar

Trombosit çalışmasını, trombüs formasyonunu engelleyici işlevleri vardır. Trombositlerin aktivasyon ve agregasyon süreçlerine anahtar enzimler aracılığıyla negatif etki ederler. Koroner arter hastalığı, Serebrovasküler hastalık ve periferik arter hastalığı gibi arteriyel hastalıkların profilaksisinde ve tedavisinde, vasküler girişimlerin ardından ise ikincil koruma amaçlı kullanılırlar.

<sup>1</sup> Uzm. Dr., Sağlık Bilimleri Üniversitesi Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi, Kalp ve Damar Cerrahisi AD, hakkikursatcvs@gmail.com



## KAYNAKLAR

1. Jurk K, Kehrel BE. Platelets: physiology and biochemistry. *Semin Thromb Hemost* 2005;31:381-92.
2. Clemetson KJ. Platelets and primary haemostasis. *Thromb Res* 2012;129:220-4.
3. Clappers N, Brouwer MA, Verheugt FW. Antiplatelet treatment for coronary heart disease. *Heart* 2007;93:258-65.
4. Verheugt FW, Smith SC Jr. The lady aspirin for cardiovascular disease. *Lancet* 2005;366:1148-50.
5. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17
6. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, and Society for Vascular Surgery. *J Vasc Surg* 2011;54:32-58.
7. Wenger NK. 2011 ACCF/AHA focused update of the guidelines for the management of patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (updating the 2007 Guideline) highlights for the clinician. *Clin Cardiol* 2012;34:73-8
8. Arnett DK, Blumenthal RS, Albert Duroker AB, Goldberger ZD, Hahn E], et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease
9. Pamukcu B. A review of aspirin resistance; delimitation, possible mechanisms. detection with platelet function tests, and its clinical outcomes. *Thromb Thrombolysis* 2007;23:213-22
10. Donadini MP, Bellesini. Squizzato A. Aspirin Plus Clopidogrel vs Aspirin Alone for Preventing Cardiovascular Events Among Patients at High Risk for Cardiovascular Events. *JAMA* 2018;320:593-4.
11. Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA, et al. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133:776-814.
12. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15,
13. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045-57.
14. Angiolillo D, Bhatt DI, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. *Am J Cardiol* 2009;103:40-51.
15. Hagemeyer CF, Peter K. Targeting the platelet integrin GPIIb/IIIa. *Curr Pharm Des* 2010;16:4119-33.
16. Coughlin SR. Protease-activated receptors in hemostasis, thrombosis and vascular biology. *Thromb Haemost* 2005;3:1800-14.
17. De Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *Cochrane Database Syst Rev* 2007;3:CD001820.
18. Barlas RS, Loke YK, Mamas MA, Bettencourt-Silva IH, Ford I, Clark AB, et al. Effect of Antiplatelet Therapy (Aspirin + Dipyridamole Versus Clopidogrel) on Mortality Outcome in Ischemic Stroke. *Am J Cardiol* 2018;122:1085-90.
19. Greving JP, Diener HC, Reitsma JB, Bath PM, Csiba L, Hacke W, et al. Antiplatelet Therapy After Noncardioembolic Stroke. *Stroke* 2019;50:1812-8.
20. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med* 2001;344:1608-21.
21. Chin P. Reviewing the reality: why we need to change. *Eur Heart J Suppl* 2005;7:15-20.
22. Apeno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:44-88.
23. Donketic ID. Pharmacologic properties of the new oral anticoagulants: a clinician oriented review with a focus on perioperative management. *Curr Pharm Des* 2010;16:3436-1h
24. Couris R, Taaronis G, McCloskey W, Dertel L, Dalal G, Dryer et al. Dietary vitamin & variability affects International Normalized Ratio (INR) coagulation Indices. *Int J Vitam Nutr Res* 2006;76:65-74.
25. Amishrambodhi therapy and prevention of thrombosis, 9th ed ACCP Guidelines *Chest* 2012;141:152-84.



26. Will DM, Nicawhat R, Chark NP, Ansell I, Halbrook A, Skor I, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv* 2018;2:3257-91.
27. Mite I. Blood coagulation and anticoagulant, fibrinolytic, platelet drugs. In: Brunton L, Chabner BA, Knollman R editors. *Goodman & Gilman's The pharmacological basis of therapeutics*, 12th ed. New York: McGraw Hill Medical; 2011. p. 848-76.
28. Ruschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a standard care nomogram. A randomized controlled trial. *Ann Intern Med* 1993;119:874-81.
29. Harter K, Levine M, Henderson SO. Anticoagulation drug therapy: a review. *West J Emerg Med* 2015;16:11-7.
30. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. *Blood* 2008;111:4871-9.
31. van Dongen C, van den Belt AG, Prins MH, Lensing AV. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2004;4:CD001100.
32. Ozaslan E, Ozkan M, Cicin I, Benekli M, Kocer M, Uysal M, et al. Effectiveness and Safety of LMWH Treatment in Patients With Cancer Diagnosed With Non-High-Risk Venous Thromboembolism: Turkish Observational Study (TREBECA). *Clin Appl Thromb Hemost* 2018;24:973-9.
33. Buller HR, Davidson BL, Decousus H, Galus A, Gent M, Piovella F, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695-702.
34. Morris TA. New synthetic antithrombotic agents for venous thromboembolism: inhibitors, direct Xa pentasaccharides, direct thrombin inhibitors. *Clin Chest Med* 2010;31:707-18.
35. Kreuz R. Pharmacodynamic and pharmacokinetic basics of rivaroxaban. *Fundam Clin Pharmacol* 2012;26:27-32.
36. Kubitzka D, Becka M, Roth A, Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr Med Res Opin* 2008;24:2757-65.
37. Vanassche T, Verhamme P, Wells PS, Segers A, Ageno W, Brekelmans MPA, et al. Impact of age, comorbidity, and polypharmacy on the efficacy and safety of edoxaban for the treatment of venous thromboembolism: An analysis of the randomized, double-blind Hokusai-VTE trial. *Thromb Res* 2018;162:7-14.
38. Eriksson BI, Borris IC, Friedman R, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75.
39. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORDA): a randomised trial. *Lancet* 2009;373:1673-80.
40. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-9.
41. Lassen MR, Ageno W, Borris IC, Lieberman IR, Rosencher Bandelh al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86.
42. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342-52.
43. Carrier M, Abou-Nassar K, Mallick R, Tagalakis V, Shivakumar S, Schattner A, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med* 2019;380:711-9.
44. Begelman SM, Hurting M, Aghababian RV, McCollum H. Heparin-induced thrombocytopenia from thromboembolism treatment. *Intern Med* 2005;258:5.
45. Lee C, Ansell E. Direct thrombin inhibitors. *R Pharmacol* 2011;72:581-92.
46. Ganetsky M, Babu KM, Salhanick SD, Brown R, Bo Dabigatran: review of pharmacology and manage bleeding complications of this novel oral anticoagulant. *Toxicol* 2011;7:281-7.
47. Bozkurt Ak. Periferik Arter ve Ven Hastalıkları Tedavi Kılavuzu 2016, İstanbul: Bayçınar Tıbbi 2016.
48. Norgren L, Hiatt WR, Dormandy A, Naylor R, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC I). *J Vasc Surg* 2007;45:5-67.



49. Abovans V, Criqui MH, Abraham P, Allison MA, Creager MA, Dichm G. et al. Measurement and interpretation of the ankle-brachial index—a scientific statement from American Heart Association. *Circulation* 2012;126:2890-909 extremity manifestations
50. McDermott MM, Guralnik IM, Ferrucci L, Tian L, Liu K, Liao Y, et al. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation* 2008;117:2484-91.
51. Roger VL, Go AS, Lloyd-Jones DM, Benjamin E, Berry ID, Borden WB, et al. Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation* 2012;125:188-97.
52. Heald CL, Fowkes FG, Murray GD, Price IF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review. *Atherosclerosis* 2006;189:61-9.
53. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;300:197-208.
54. Abovans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 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 arteries Endorsed 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;39:763-816.
55. de Donato G, Setacci F, Mele M, Giannace G, Galzerano G, Setacci C. Restenosis after Coronary and Peripheral Intervention: Efficacy and Clinical Impact of Cilostazol. *Ann Vasc Surg* 2017;41:300-7.
56. Chapman TM, Goa KL. Cilostazol: a review of its use in intermittent claudication. *Am J Cardiovasc Drugs* 2003;3:117-38.
57. Pratt CM. Analysis of the cilostazol safety database. Analysis by the cilostazol safety database. *Am J Cardio* 2001;728:35'
58. Borkurt AK. Periferik arter ve ven hastalıkları. Ulusal Tedavi Kilavuzu. 1. Baskı. İstanbul: Baygıncar Tıbbi Yayınları; 2016
59. Reich T, Gillings D. Effects of pentoxifylline on severe intermittent claudication. *Angiology* 1987;38:651-6.
60. Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels J. Pentoxifylline for intermittent claudication. *Cochrane Database Syst Rev* 2015;9:CD005262.
61. Goldsmith DR, Wellington K. Naftidrofuryl: a review of its use in the treatment of intermittent claudication. *Drugs Aging* 2005;22:967-77.
62. Meng Y, Squires H, Stevens JW, Simpson E, Hannan S, Thomas S, et al. Cost-effectiveness of cilostazol, naftidrofuryl oxalate, and pentoxifylline for the treatment of intermittent claudication in people with peripheral arterial disease *Angiology* 2014;65:190-7.
63. Kim M, Lee JS, Kim SW. Acute kidney injury associated with naftidrofuryl oxalate overdose. *Clin Exp Nephrol* 2013;17:437-8.
64. Hiatt WR. Carnitine and peripheral arterial disease. *Ann N Y Acad Sci* 2004;1033:92-8
65. Brevetti G, Diehm C, Lambert D. European multicenter study on propionyl-L-carnitine in intermittent claudication ] *Am Coll Cardiol* 1999;34:1618-24.
66. Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Clinical use and molecular mechanisms of action of extract of Ginkgo biloba leaves in cardiovascular diseases, *Cardiovasc Drug Rev* 2004;22:309-19.
67. Nicolai CR, Randermacher MH, Stokmans RA, Broos PP et al Ginkgo biloba *Cochran Database Syst Rev* 2013;6: CD006888
68. Dib IC, Dedeyan S. Purported benefits of inositol niacinate. *Am J Health Syst Pharm* 2004;61:307-8.
69. Clissold SP, Lynch S, Sorkin EM. Buflomedil. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in peripheral and cerebral vascular diseases. *Drugs* 1987;33:430-60.
70. Hassanshahi M, Khabbazi S, Peymanfar Y, Hassanshahi A, Hosseini-Khah Z, Su YW, et al. Critical limb ischemia: Current and novel therapeutic strategies. ] *Cell Physiol* 2019 Jan 13. (Epub ahead of print]
71. Powell RJ, Goodney P, Mendelsohn FO, Mon EK, Annex BH. Safety and efficacy of patient specific-



- ic intramuscular injection of HGF plasmid gene therapy on limb perfusion and wound healing in patients with ischemic lower extremity ulceration: results of the HGF-0205 trial. *J Vasc Surg* 2010;52:1525-30.
72. Tateishi-Yuyama E, Matsubara H, Murohara T, Ikeda U, Shintani S, Masaki H, et al. Therapeutic angiogenesis for patients with limb ischemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet* 2002;360:427-35.
73. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, et al. Effect of Granulocyte- Macrophage Colony-Stimulating Factor With or Without Supervised Exercise on Walking Performance in Patients With Peripheral Artery Disease: The PROPEL Randomized Clinical Trial. *AMA* 2017;318:2089-98.
74. Carmeliet P, Collen D. Gene targeting and gene transfer studies of the biological role of the plasminogen/plasmin system. *Thromb Haemost* 1995;74:429-36.
75. U.S. National Institutes of Health. A service of the U.S. National
76. Jackson NIV: Tang, his Simplitey nino acid sequence or streptokinase and is homology with serine proteases *Biochemistry* 1982;21:6620-5.
- I. GUSTO investigators, Am international randomized trial comparing four thrombolytic strategies for acute myocardia infarction. *N Engl J Med* 1993;329:673-82.
77. Bannish BE, Chernysh IN, Keener J1P, Fogelson AL, Weiv Jw. Molecular and Physical Mechanisms of Fibrinolysis and Trombolysis from Mathematical Modeling and Experiments *Sci Rep* 2017;7:6914.
78. Collen D, Schlott B, Engelborghs Y, Van Hoef B, Hartmann M.Linen HR, et al. On the mechanism of the activation of human plasminogen by recombinant staphylokinase. *J Biol Chem* 1993;268:8284-9.
79. Gulba DC, Bode C, Runge MS, Huber K. Thrombolytic agents.-an overview. *Ann Hematol* 1996;73:927.
80. del Zoppo G), Higashida RT, Furlan A), Pessin MS, Rowley HA. Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke* 1998;29:4-11.
81. Pohl G, Kenne L, Nilsson B, Einarsson M. Isolation and characterization of three different carbohydrate chains from melanoma tissue plasminogen activator. *Eur biochem* 1987;170:69-75.