



BÖLÜM 95

Protez Kapak Hastalarında Antitrombotik Tedavi

*Ahmet GÜNER¹, Semih KALKAN²
Emrah BAYAM³, Macit KALÇIK⁴
Mehmet ÖZKAN⁵*

ANTİTROMBOTİK TEDAVİ VE GENEL HASTA YÖNETİMİ

Kapak replasmanı yapılan hastalarda antitrombotik tedaviye genel bakış

Prostetik kalp kapakları, protez kapak trombozu ve tromboembolik komplikasyonlar da dahil olmak üzere bir dizi kapak patolojisine sahip olabilir¹⁻⁴. Bu hem kapağın kan akışı üzerindeki etkisi, türbülans ve staz oluşturması hem kapak malzemesine bağlı olarak gelişir. Bu nedenle, kapak replasmanı sonrası antitrombotik ilaçların kullanılması, tedavinin önemli bir bölümünü oluşturur. Bu amaçla yaygın olarak kullanılan farmakolojik ajanlar arasında, varfarin, asenokumarol ve fenprokumon gibi K vitamini antagonistleri (VKA) ve aspirin, dipiridamol ve klopidoğrel gibi antiplateletler bulunur⁵. Daha da önemlisi, pıhtılaşma faktörlerinin veya trombositlerin etkisini inhibe ederek bu ilaçlar doğal olarak hastaları kanamaya yatkın hale getirir; tedavi stratejileri, tromboembolizm riski ile kanama riski arasında bir denge bulmalıdır.

Vitamin K antagonistleri

Varfarin ve diğer kumarin türevlerini içeren VKA, 1954 yılında ABD’de tromboembolik komplikasyonların hem birincil hem ikincil önlenmesi için için ruhsatlandırılmıştır⁶. Varfarin gibi kumarin türevleri etkilerini K vitamini antagonistize ederek gösterirler, böylece K vitaminine bağlı pıhtılaşma faktörleri II, VII, IX ve X’in yanı sıra doğal anti-koagülanlar, protein C ve protein S’nin sentezini inhibe ederler⁷. Bununla birlikte, varfarinin etkisi oldukça öngörülemezdir ve doz-yanıt özellikleri önemli ölçüde dalgalanabilir. Bu nedenle, varfarinin güvenli ve etkili kullanımı için, genellikle kullanımdan önce uluslararası normleştirilmiş orana (INR) dönüştürülen protrombin zamanı kullanılarak antikoagülasyon derecesi düzenli olarak izlenmelidir⁸. Subterapötik INR’leri olan hastalar, tromboembolik hastalıklarının ilerlemesi ile tedavi başarısızlığına yatkındır³. Antitrombotik tedavi olmadan, majör emboli riski yıllık %4 iken antitrombotik tedavi ile bu oran %1’e düşer⁹.

¹ Uzm. Dr. Ahmet GÜNER, S.B. S.B.Ü. Mehmet Akif Ersoy Göğüs Kalp ve Damar Cerrahisi Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü ahmetguner488@gmail.com

² Uzm. Dr. Semih KALKAN, S.B. S.B.Ü. Erzurum Bölge Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü semihby1@gmail.com

³ Uzm. Dr. Emrah BAYAM, S.B. S.B.Ü. Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Bölümü emrah_bayam@hotmail.com

⁴ Doç. Dr. Macit KALÇIK, Hitit Üniversitesi Tıp Fakültesi Kardiyoloji AD. macitkalcik@yahoo.com

⁵ Prof. Dr. Mehmet ÖZKAN, Ardahan Üniversitesi Sağlık Bilimleri Fakültesi, Kardiyoloji AD., memoozkan1@gmail.com



KAYNAKLAR

- 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 [published correction appears in *Circulation*. 2021 Feb 2;143(5):e229]. *Circulation*. 2021;143(5):e72-e227. doi:10.1161/CIR.0000000000000923
- Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2017; 38:2739-91.
- Gündüz S, Kalçık M, Gürsoy MO, Güner A, Özkan M. Diagnosis, treatment & management of prosthetic valve thrombosis: the key considerations. *Expert Rev Med Devices*. 2020 Mar;17(3):209-221.
- Özkan M, Gündüz S, Biteker M, Astarcioglu MA, Çevik C, Kaynak E, Yıldız M, Oğuz E, Aykan AÇ, Ertürk E, Karavelioglu Y, Gökdeniz T, Kaya H, Gürsoy OM, Çakal B, Karakoyun S, Duran N, Özdemir N. Comparison of different TEE-guided thrombolytic regimens for prosthetic valve thrombosis: the TROIA trial. *JACC Cardiovasc Imaging*. 2013; 6(2):206-16.
- Leiria TLL, Lopes RD, Williams JB, Katz JN, Kalil RAK, Alexander JH. Antithrombotic therapies in patients with prosthetic heart valves: guidelines translated for the clinician. *J Thromb Thrombolysis*. 2011; 31(4):514-522.
- Kessler CM. Urgent reversal of warfarin with prothrombin complex concentrate: where are the evidence-based data? *J Thromb Haemost*. 2006; 4(5):963-966.
- 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
- Kalçık M, Yesin M, Gürsoy MO, Gündüz S, Karakoyun S, Astarcioglu MA, Bayam E, Cerşit S, Özkan M. Comparison of the INR Values Measured by CoaguChek XS Coagulometer and Conventional Laboratory Methods in Patients on VKA Therapy. *Clin Appl Thromb Hemost*. 2017; 23(2):187-194.
- Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89(2):635-641.
- Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, Wells PS. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165(10):1095-106.
- Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2):e576S-e600S.
- Goldhaber SZ. "Bridging" and mechanical heart valves. *Circulation*. 2006;113(4):470-472.
- Montalescot G, Polle V, Collet JP, et al. Low molecular weight heparin after mechanical heart valve replacement. *Circulation*. 2000; 101(10):1083-1086.
- Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206-1214.
- Duraes AR, de Souza Lima Bitar Y, Schonhofen IS, Travassos KSO, Pereira LV, Filho JAL, Neto MG, Junior RA, Roevers L. Rivaroxaban Versus Warfarin in Patients with Mechanical Heart Valves: Open-Label, Proof-of-Concept trial-The RIWA study. *Am J Cardiovasc Drugs*. 2021; 21(3):363-371.
- Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89(2):635-641.
- Puskas J, Gerdisch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the Prospective Randomized On-X Valve Anticoagulation Clinical Trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg*. 2014;147(4):1202-1211.
- Aikins J, Koomson A, Ladele M, Al-Nusair L, Ahmed A, Ashry A, Harky A. Anticoagulation and antiplatelet therapy in patients with prosthetic heart valves. *J Card Surg*. 2020; 35(12):3521-3529.
- Patriquin C, Crowther M. Treatment of warfarin-associated coagulopathy with vitamin K. *Expert Rev Hematol*. 2011; 4(6):657-65.
- Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J. Thromb. Haemost*. 2006; 4(9):1853-1863.
- Crowther MA, Garcia D, Ageno W et al. Oral vitamin K effectively treats international normalised ratio (INR) values in excess of 10. Results of a prospective cohort study. *Thromb Haemost*. 2010; 104(1):118-121.
- Lee A, Crowther M. Practical issues with vitamin K antagonists: elevated INRs, low time-in-therapeutic range, and warfarin failure. *J. Thromb Thrombolysis* 2011; 31(3):249-258.
- Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. *Arch Intern Med*. 2003; 163(20):2469-2473.
- Heras M, Chesebro JH, Fuster V, et al. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. *J Am Coll Cardiol*. 1995;25(5):1111-1119. doi:10.1016/0735-1097(94)00563-6
- Colli A, Mestres CA, Castella M, Gherli T. Comparing warfarin to aspirin (WoA) after aortic valve replacement with the St. Jude Medical Epic heart valve bioprosthesis: results of the WoA Epic pilot trial. *J Heart Valve Dis*. 2007;16(6):667-671.
- Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular



- lar disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e576S-e600S. doi:10.1378/chest.11-2305
27. Sundt TM, Zehr KJ, Dearani JA, et al. Is early anticoagulation with warfarin necessary after bioprosthetic aortic valve replacement?. *J Thorac Cardiovasc Surg*. 2005;129(5):1024-1031. doi:10.1016/j.jtcvs.2004.11.028
28. Mérie C, Køber L, Skov Olsen P, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA*. 2012;308(20):2118-2125. doi:10.1001/jama.2012.54506
29. Guimarães HP, Lopes RD, de Barros E Silva PGM, et al. Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve. *N Engl J Med*. 2020;383(22):2117-2126. doi:10.1056/NEJMoa2029603
30. Gupta T, Kalra A, Kolte D, et al. Regional Variation in Utilization, In-hospital Mortality, and Health-Care Resource Use of Transcatheter Aortic Valve Implantation in the United States. *Am J Cardiol*. 2017;120(10):1869-1876. doi:10.1016/j.amjcard.2017.07.102
31. Rodés-Cabau J, Masson JB, Welsh RC, et al. Aspirin Versus Aspirin Plus Clopidogrel as Antithrombotic Treatment Following Transcatheter Aortic Valve Replacement With a Balloon-Expandable Valve: The ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) Randomized Clinical Trial. *JACC Cardiovasc Interv*. 2017;10(13):1357-1365. doi:10.1016/j.jcin.2017.04.014
32. Zuo W, Yang M, He Y, Hao C, Chen L, Ma G. Single or dual antiplatelet therapy after transcatheter aortic valve replacement: an updated systemic review and meta-analysis. *J Thorac Dis*. 2019;11(3):959-968. doi:10.21037/jtd.2019.01.87
33. Yanagawa B, Mazina A, Bhatt DL, et al. Subclinical bioprosthetic aortic valve thrombosis: clinical and translational implications. *Curr Opin Cardiol*. 2017;32(2):137-146. doi:10.1097/HCO.0000000000000373
34. Mazer CD, Bhatt DL, Verma S. Anticoagulation Following TAVR: No Clear Answer Yet. *J Am Coll Cardiol*. 2019;73(1):22-28. doi:10.1016/j.jacc.2018.11.012
35. Makkar RR, Fontana G, Jilaihawi H, et al. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. *N Engl J Med*. 2015;373(21):2015-2024. doi:10.1056/NEJMoa1509233
36. Chakravarty T, Patel A, Kapadia S, et al. Anticoagulation After Surgical or Transcatheter Bioprosthetic Aortic Valve Replacement. *J Am Coll Cardiol*. 2019;74(9):1190-1200. doi:10.1016/j.jacc.2019.06.058
37. Jose J, Sulimov DS, El-Mawardi M, et al. Clinical Bioprosthetic Heart Valve Thrombosis After Transcatheter Aortic Valve Replacement: Incidence, Characteristics, and Treatment Outcomes. *JACC Cardiovasc Interv*. 2017;10(7):686-697. doi:10.1016/j.jcin.2017.01.045
38. Jochheim D, Barbanti M, Capretti G, et al. Oral Anticoagulant Type and Outcomes After Transcatheter Aortic Valve Replacement. *JACC Cardiovasc Interv*. 2019;12(16):1566-1576. doi:10.1016/j.jcin.2019.03.003
39. Windecker S, Tijssen J, Giustino G, et al. Trial design: Rivaroxaban for the prevention of major cardiovascular events after transcatheter aortic valve replacement: Rationale and design of the GALILEO study. *Am Heart J*. 2017;184:81-87. doi:10.1016/j.ahj.2016.10.017
40. Goldstone AB, Chiu P, Baiocchi M, et al. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med*. 2017;377:1847-57.
41. Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. *JAMA*. 2015;313(14):1435-1442. doi:10.1001/jama.2015.3164
42. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. *JAMA*. 2014;312(13):1323-1329. doi:10.1001/jama.2014.12679
43. Massel DR, Little SH. Antiplatelet and anticoagulation for patients with prosthetic heart valves. *Cochrane Database Syst Rev*. 2013;2013(7):CD003464. Published 2013 Jul 9. doi:10.1002/14651858.CD003464.pub2
44. Chaudhary R, Garg J, Krishnamoorthy P, et al. On-X Valve: The Next Generation Aortic Valve. *Cardiol Rev*. 2017;25(2):77-83. doi:10.1097/CRD.0000000000000105
45. Puskas J, Gerdtsch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *J Thorac Cardiovasc Surg*. 2014;147(4):1202-1211. doi:10.1016/j.jtcvs.2014.01.004
46. Puskas JD, Gerdtsch M, Nichols D, et al. Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement. *J Am Coll Cardiol*. 2018;71(24):2717-2726. doi:10.1016/j.jacc.2018.03.535
47. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2012;33:2451-2496.
48. Pengo V, Cucchini U, Denas G, et al. Standardized Low-Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery An Inception Cohort Management Study. *Circulation* 2009;119:2920-2927.
49. Gürsoy, Mustafa Ozan et al. "A global perspective on mechanical prosthetic heart valve thrombosis: Diagnostic and therapeutic challenges." *Anatol J Cardiol*. 2016;16(12):980-989. doi:10.14744/AnatolJCardiol.2016.7486
50. Özkan M, Gürsoy OM, Astarcioglu MA, et al. Real-time three-dimensional transesophageal echocardiography in the assessment of mechanical prosthetic mitral valve ring thrombosis. *Am J Cardiol* 2013; 112: 977-83. doi:



- 10.1016/j.amjcard.2013.05.032
51. Gürsoy, Mustafa Ozan et al. "The current status of fluoroscopy and echocardiography in the diagnosis of prosthetic valve thrombosis-a review article." *Echocardiography*. 2015;32(1):156-164. doi:10.1111/echo.12721
 52. Bayam E, Kalçık M, Gürbüz AS, et al. The relationship between heparanase levels, thrombus burden and thromboembolism in patients receiving unfractionated heparin treatment for prosthetic valve thrombosis. *Thromb Res*. 2018;171:103-110.
 53. Lengyel M, Vegh G, Vándor L. Thrombolysis is superior to heparin for non-obstructive mitral mechanical valve thrombosis. *J Heart Valve Dis*. 1999;8:167-173.
 54. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017 June 20;135(25):e1159-e1195
 55. Karthikeyan G, Senguttuvan NB, Joseph J, et al. Urgent surgery compared with fibrinolytic therapy for the treatment of left-sided prosthetic heart valve thrombosis: a systematic review and meta-analysis of observational studies. *Eur Heart J*. 2013;34:1557-1566.
 56. Castilho FM, De Sousa MR, Mendonça AL, et al. Thrombolytic therapy or surgery for valve prosthesis thrombosis: systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:1218-1228.
 57. Karthikeyan G, Math RS, Mathew N, et al. Accelerated infusion of streptokinase for the treatment of left-sided prosthetic valve thrombosis: a randomized controlled trial. *Circulation*. 2009;120:1108-1114.
 58. Özkan M, Gündüz S, Gürsoy OM, et al. Ultraslow thrombolytic therapy: A novel strategy in the management of PROsthetic MEchanical valve Thrombosis and the predictors of outcome: The Ultra-slow PROMETEE trial. *Am Heart J*. 2015;170(2):409-418. doi:10.1016/j.ahj.2015.04.025
 59. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; 33: 2451-96.
 60. Weiss BM, von Segesser LK, Alon E, et al. Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984-1996. *Am J Obstet Gynecol* 1998; 179: 1643-53.
 61. Özkan M, Çakal B, Karakoyun S, et al. Thrombolytic therapy for the treatment of prosthetic heart valve thrombosis in pregnancy with low-dose, slow infusion of tissue-type plasminogen activator. *Circulation*. 2013;128(5):532-540. doi:10.1161/CIRCULATIONAHA.113.001145
 62. Gündüz S, Özkan M, Yesin M, et al. Prolonged infusions of low-dose thrombolytics in elderly patients with prosthetic heart valve thrombosis. *Clin Appl Thromb Hemost*. 2017 Apr;23 (3):241-247.
 63. Lengyel M, Horstkotte D, Völler H, Mistiaen WP. Working Group Infection, Thrombosis, Embolism and Bleeding of the Society for Heart Valve Disease. Recommendations for the management of prosthetic valve thrombosis. *J Heart Valve Dis* 2005; 14: 567-75.
 64. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25(5):457-507.
 65. Özkan M, Gürsoy OM, Atasoy B, et al. Management of acute ischemic stroke occurred during thrombolytic treatment of a patient with prosthetic mitral valve thrombosis: continuing thrombolysis on top of thrombolysis. *Anadolu Kardiyol Derg* 2012; 12:689-90.
 66. Yesin M, Karakoyun S, Kalçık M, et al. Status of the epicardial coronary arteries in non-ST elevation acute coronary syndrome in patients with mechanical prosthetic heart valves (from the TROIA-ACS trial). *Am J Cardiol*. 2018 Aug 15;122(4):638-644.