

BÖLÜM 21



Kronik Karaciğer Hastalığında Atriyal Fibrilasyon Yönetimi

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GİRİŞ

Atriyal fibrilasyon (AF), 2010 yılında küresel olarak tahminen 33,5 milyon AF'li birey ile dünya çapında en yaygın aritmidir (1). Birçok kişi asemptomatik veya teşhis edilmemiş olduğundan AF'nin gerçek prevalansı muhtemelen çok daha yüksektir. AF için ileri yaş, alkol, sigara, obezite, diyabetes mellitus, hipertansiyon, kalp yetmezliği, iskemik kalp hastalığı ve kalp kapak hastalığı gibi çok sayıda risk faktörü olmasına rağmen, AF riskiyle ilgili hala yanıtlanmamış birçok soru vardır. Kardiyovasküler risk faktörlerinin önlenmesi ve yapısal kalp hastalığının tedavisi, AF'den kaynaklanan morbidite ve mortaliteyi azaltmaya yardımcı olabilir (2).

Kronik karaciğer hastalığı (KKH), trombosit sayısı, trombosit agregasyonu, pihtlaşma faktörleri, doğal inhibitörler ve fibrinolizin değiştirilmiş regülasyonu nedeniyle kanamanın yanı sıra tromboza da eğilimlidir (3,4). Karaciğer yetmezliğinin şiddetinin genellikle Child-Pugh (CP) sınıflandırmasına göre belirlenir ve Sınıf A, B, C sırasıyla hafif, orta ve şiddetli karaciğer

yetmezliğini temsil eder (5). Pihtlaşma faktörlerinin azalması genellikle karaciğer yetmezliğinin şiddeti ile ilişkilidir (6). AF hastalarında KKH siktir, çünkü hem AF Hemde KKH ortak risk faktörleri vardır. Karaciğer hastalığı, AF için risk sınıflandırma şemalarının çoğu herhangi bir noktayı hesaba katmasa da, karaciğer sirozu varlığının artan iskemik inme riski ile ilişkili olduğu bulundu (7-11).

AF'li hastalarda gastrointestinal ve karaciğer hastalıkları yaygındır. Karaciğer ve gastrointestinal sistem hastalıkları, otonomik modülasyon ve inflamasyon dahil olmak üzere çeşitli mekanizmalar yoluyla AF riskine katkıda bulunabilir. Tersine, AF ve AF'nin ablasyon, antiaritmik ilaçlar ve antikoagüllerle tedavisi gastrointestinal ve karaciğer komplikasyonlarının ve hastalıklarının gelişimini etkileyebilir.

AF'NİN PATOFİZYOLOJİSİ

AF patogenezinin iki önemli hipotezi, duyarlı bir atriyal substrat üzerindeki ektopik tetiklemelerin veya hızlı tetiklenen iletilerin yüksek

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KAYNAKLAR

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 study. *Circulation*. 2014; 129: 837–847.
2. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386; 154–162.
3. Qamar A, Vaduganathan M, Greenberger NJ, et al. Oral anticoagulation in patients with liver disease. *J Am Coll Cardiol* 2018;71:2162–2175.
4. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med*. 2011;365:147–156.
5. Albers I, Hartmann H, Bircher J, et al. Superiority of the Child-Pugh classification to quantitative liver function tests for assessing prognosis of liver cirrhosis. *Scand J Gastroenterol*. 1989;24:269–276.
6. Plessier A, Denninger MH, Consigny Y, et al. Coagulation disorders in patients with cirrhosis and severe sepsis. *Liver Int*. 2003;23:440–448.
7. Wijarnpreecha K, Boonpheng B, Thongprayoon C, et al. The association between non-alcoholic fatty liver disease and atrial fibrillation: a meta-analysis. *Clin Res Hepatol Gastroenterol*. 2017;41:525–532.
8. Alonso A, Misialek JR, Amiin MA, et al. Circulating levels of liver enzymes and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities cohort. *Heart*. 2014;100:1511–1516.
9. Karajamaki AJ, Pätsi OP, Savolainen M, et al. Non-alcoholic fatty liver disease as a predictor of atrial fibrillation in middle-aged population (OPERA Study). *PLoS One* 2015;10:e0142937.
10. Targher G, Mantovani A, Pichiri I, et al. Non-alcoholic fatty liver disease is associated with an increased prevalence of atrial fibrillation in hospitalized patients with type 2 diabetes. *Clin Sci*. 2013;125: 301–309.
11. Kuo L, Chao TF, Liu CJ, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? *J Am Heart Assoc*. 2017;6:e005307.
12. Chen PS, Chen LS, Fishbein MC, et al. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. *Circ Res*. 2014;114: 1500–1515.
13. Goette A, Kalman JM, Aguinaga L, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Heart Rhythm*. 2017;14, e3–e40.
14. Asrani SK, Devarbhavi H, Eaton J, et al. Burden of liver disease in the World. *J Hepatol*. 2019 Jan;70(1):151–171
15. Mwalitsa JP, Maimone S, Filomia R, et al. Atrial fibrillation in patients with cirrhosis. *Liver International*. 2016;36.3: 395–400
16. Djousse L, Levy D, Benjamin EJ, et al. Longterm alcohol consumption and the risk of atrial fibrillation in the Framingham Study. *Am J Cardiol*. 2004;93:710–713.
17. Frost L and Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med*. 2004;164: 1993–1998.
18. Kodama S, Saito K, Tanaka S, et al. Alcohol consumption and risk of atrial fibrillation: a meta-analysis. *J Am Coll Cardiol*. 2011;57:427–436.
19. Larsson SC, Drca N and Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose response metaanalysis. *J Am Coll Cardiol*. 2014;64: 281–289
20. Maki T, Toivonen L, Koskinen P, et al. Effect of ethanol drinking, hangover, and exercise on adrenergic activity and heart rate variability in patients with a history of alcohol-induced atrial fibrillation. *Am J Cardiol*. 1998;82:317–322.
21. McManus DD, Yin X, Gladstone R, et al. Alcohol consumption, left atrial diameter, and atrial fibrillation. *J Am Heart Assoc*. 2016;5(9),e004060..
22. Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol*. 2011;9: 524–530.
23. Karajamaki AJ, Pätsi OP, Savolainen M, et al. Non-alcoholic fatty liver disease as a predictor of atrial fibrillation in middle-aged population (OPERA Study). *PLoS One* 2015; 10: e0142937.
24. Markus MRP, Meffert PJ, Baumeister SE, et al. Association between hepatic steatosis and serum liver enzyme levels with atrial fibrillation in the general population. *Atherosclerosis* 2016;245: 123–131.
25. Sinner MF, Wang N, Fox CS, et al. Relation of circulating liver transaminase concentrations to risk of new-onset atrial fibrillation. *Am J Cardiol* 2013; 111: 219–224.
26. Targher G, Mantovani A, Pichiri I, et al. Nonalcoholic fatty liver disease is associated with an increased prevalence of atrial fibrillation in hospitalized patients with type 2 diabetes. *Clin Sci (Lond)*. 2013; 125: 301–309.
27. Targher G, Valbusa F, Bonapace S, et al. Nonalcoholic fatty liver disease is associated with an increased incidence of atrial fibrillation in patients with type 2 diabetes. *PLoS One*. 2013; 8:e57183.
28. Wijarnpreecha K, Boonpheng B, Thongprayoon C, et al. The association between non-alcoholic fatty liver disease and atrial fibrillation: a metaanalysis. *Clin Res Hepatol Gastroenterol*. 2017; 41:525–532.
29. Long MT, Yin X, Larson MG, et al. Relations of liver fat with prevalent and incident atrial fibrillation in the Framingham Heart Study. *J Am Heart Assoc*. 2017; 6, pii: e005227.
30. Goland S, Shimoni S, Zornitzki T, et al. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. *J Clin Gastroenterol*. 2006; 40:949–955.
31. Hallsworth K, Hollingsworth KG, Thoma C, et al. Cardiac structure and function are altered in adults with non-alcoholic fatty liver disease. *J Hepatol*. 2013; 58: 757–762.
32. Bonapace S, Perseghin G, Molon G, et al. Nonalcohol-

- lic fatty liver disease is associated with left ventricular diastolic dysfunction in patients with type 2 diabetes. *Diabetes Care.* 2012; 35:389–395.
33. Ndumele CE, Nasir K, Conceição RD, et al. Hepatic steatosis, obesity, and the metabolic syndrome are independently and additively associated with increased systemic inflammation. *Arterioscler Thromb Vasc Biol.* 2011; 31: 1927–1932.
 34. Hamirani YS, Katz R, Nasir K, et al. Association between inflammatory markers and liver fat: the multi-ethnic study of atherosclerosis. *J Clin Exp Cardiol.* 2014; 5. pii: 1000344.
 35. Liu YC, Hung CS, Wu YW, et al. Influence of non-alcoholic fatty liver disease on autonomic changes evaluated by the time domain, frequency domain, and symbolic dynamics of heart rate variability. *PLoS One* 2013; 8: e61803.
 36. Sun W, Zhang D, Sun J, et al. Association between non-alcoholic fatty liver disease and autonomic dysfunction in a Chinese population. *QJM.* 2015; 108: 617–624.
 37. Olshansky B. Interrelationships between the autonomic nervous system and atrial fibrillation. *Prog Cardiovasc Dis.* 2005; 48: 57–78.
 38. Ozveren O, Izgi C, Eroglu E, et al. Doppler tissue evaluation of atrial conduction properties in patients with non-alcoholic fatty-liver disease. *Ultrason Imaging.* 2016; 38: 225–235.
 39. Targher G, Day CP and Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med.* 2010; 363: 1341–1350.
 40. Musso G, Olivetti C, Cassader M, et al. Obstructive sleep apnea-hypopnea syndrome and nonalcoholic fatty liver disease: emerging evidence and mechanisms. *Semin Liver Dis.* 2012; 32: 49–64.
 41. Kanagalal R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation.* 2003; 107: 2589–2594.
 42. Gaeta M, Bandera F, Tassinari F, et al. Is epicardial fat depot associated with atrial fibrillation? A systematic review and metaanalysis. *Europace.* 2017; 19: 747–752.
 43. Friedman DJ, Wang N, Meigs JB, et al. Pericardial fat is associated with atrial conduction: the Framingham Heart Study. *J Am Heart Assoc.* 2014; 3; e000477.
 44. Anthony S, Fausi H. Harrison principles of internal medicine, Clifford lane 19th edition, chapter 365. 2059.
 45. Aursulesei V, Vasincu D, Timofte D, et al. New mechanism of valve sicle migrations. *Gen. Physiol. Biophys.* 2016; 35: 287–298.
 46. Calborean V, Miscoci SA, Istratoae O, et al. Correlation Between Liver Cirrhosis and Risk of Cardiac Arrhythmias. *Rev Chim.* 2018; 69, 1527–1532.
 47. Wu, Victor Chien-Chia, et al. Risk of cardiac arrhythmias in patients with chronic hepatitis B and C infections—A 13-year nationwide population-based study. *Journal of Cardiology.* 2019; 74.4: 333–338
 48. Emoto T, Yamashita T, Sasaki N, et al. Analysis of gut microbiota in coronary artery disease patients: a possible link between gut microbiota and coronary artery disease. *J Atheroscler Thromb.* 2016; 23: 908–921.
 49. Lim GB. Heart failure: gut flora-pathogenic role in chronic heart failure. *Nat Rev Cardiol.* 2016; 13: 61.
 50. Marques FZ, Mackay CR and Kaye DM. Beyond gut feelings: how the gut microbiota regulates blood pressure. *Nat Rev Cardiol.* 2018; 15(1), 20–32. DOI: 10.1038/nrccardio.2017.120.
 51. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med.* 2013; 368: 1575–1584.
 52. Leung C, Rivera L, Furness JB, et al. The role of the gut microbiota in NAFLD. *Nat Rev Gastroenterol Hepatol.* 2016; 13: 412–425.
 53. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med.* 2013; 19: 576–585.
 54. Wang Z, Klipfell E, Bennett BJ. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature.* 2011; 472: 57–63.
 55. Yu L, Meng G, Huang B, et al. A potential relationship between gut microbes and atrial fibrillation: trimethylamine N-oxide, a gut microbe-derived metabolite, facilitates the progression of atrial fibrillation. *Int J Cardiol.* 2018; 255: 92–98.
 56. Serrano M, Moreno-Navarrete JM, Puig J, et al. Serum lipopolysaccharide-binding protein as a marker of atherosclerosis. *Atherosclerosis.* 2013; 230: 223–227.
 57. Pastori D, Carnevale R, Nocella C, et al. Gut-derived serum lipopolysaccharide is associated with enhanced risk of major adverse cardiovascular events in atrial fibrillation: effect of adherence to Mediterranean diet. *J Am Heart Assoc.* 2017; 6. pii: 005784.
 58. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci U S A.* 2010; 107: 4691–14696.
 59. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014; 505: 559–563.
 60. Martinez-Gonzalez MA, Toledo E, Arós F, et al. Extra virgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevención con Dieta Mediterránea) trial. *Circulation.* 2014; 130: 18–26.
 61. Mitsou EK, Kakali A, Antonopoulou S, et al. Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. *Br J Nutr.* 2017; 117: 1645–1655.
 62. Lin K, Chen X, Zhang L, et al. Proton pump inhibitors as also inhibitors of atrial fibrillation. *Eur J Pharmacol.* 2013; 718: 435–440.
 63. Stollberger C and Finsterer J. Treatment of esophagitis/vagitis-induced paroxysmal atrial fibrillation by proton-pump inhibitors. *J Gastroenterol.* 2003; 38: 1109.
 64. Weigl M, Gschwantler M, Gatterer E, et al. Reflux esophagitis in the pathogenesis of paroxysmal atrial fibrillation: results of a pilot study. *South Med J.* 2003; 96: 1128–1132.

65. Huang CC, Chan WL, Luo JC, et al. Gastroesophageal reflux disease and atrial fibrillation: a nationwide population-based study. *PLoS One* 2012; 7: e47575
66. Aparci M, Uz O, Atalay M, et al. May hypomagnesemia; caused by proton pump inhibitor; increase atrial fibrillation risk? *Int J Cardiol.* 2016; 207: 141.
67. Denton-Beaumont RN, Banning AS and Gershlick AH. Malabsorption causing failure of pharmacological therapy in the treatment of atrial fibrillation. *Int J Cardiol.* 2008; 128:e87–e88.
68. Hakeam HA and Al-Sanea N. Effect of major gastrointestinal tract surgery on the absorption and efficacy of direct acting oral anticoagulants (DOACs). *J Thromb Thrombolysis.* 2017; 43:343–351.
69. Rottenstreich A, Barkai A, Arad A, et al. The effect of bariatric surgery on direct-acting oral anticoagulant drug levels. *Thromb Res.* 2018; 163:190–195.
70. Kroll D, Stirnimann G, Vogt A, et al. Pharmacokinetics and pharmacodynamics of single doses of rivaroxaban in obese patients prior to and after bariatric surgery. *Br J Clin Pharmacol.* 2017; 83: 1466–1475.
71. Sogaard KK, Horváth-Puhó E, Gronbaek H, et al. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol.* 2009;104:96–101.
72. Wu H, Nguyen GC. Liver cirrhosis is associated with venous thromboembolism among hospitalized patients in a nationwide US study. *Clin Gastroenterol Hepatol.* 2010;8:800–805.
73. Agnelli G, Eriksson BI, Cohen AT, et al. Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran. *Thromb Res.* 2009; 123: 488–497.
74. Abraham NS, Noseworthy PA, Yao X, et al. Gastrointestinal safety of direct oral anticoagulants: a large population-based study. *Gastroenterology.* 2017; 152: 1014–1022.e1.
75. Douros A, Azoulay L, Yin H, et al. Non-vitamin K antagonist oral anticoagulants and risk of serious liver injury. *J Am Coll Cardiol.* 2018; 71:1105–1113.
76. Tripodi A and Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med.* 2011; 365:147–156.
77. Efird LM, Mishkin DS, Berlowitz DR, et al. Stratifying the risks of oral anticoagulation in patients with liver disease. *Circ Cardiovasc Qual Outcomes.* 2014; 7: 461–467.
78. Kuo L, Chao TF, Liu CJ, et al. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? *J Am Heart Assoc.* 2017; 6. pii:e005307
79. Goriacko P and Veltri KT. Safety of direct oral anticoagulants versus warfarin in patients with chronic liver disease and atrial fibrillation. *Eur J Haematol.* 2018; 100: 488–493.
80. Pastori D, Lip GH, Farcomeni A, et al. Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants. *Int J Cardiol.* 2018; 264: 58–63.
81. Graff J and Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. *Clin Pharmacokinet.* 2013;52: 243–254.
82. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J.* 2018; 39:1330–1393.
83. Lee SR, Lee HJ, Choi EK, et al. Direct oral anticoagulants in patients with atrial fibrillation and liver disease. *J Am Coll Cardiol.* 2019;73:3295–3308.
84. Wang CL, Wu VC, Kuo CF, et al. Efficacy and safety of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with impaired liver function: a retrospective cohort study. *J Am Heart Assoc.* 2018;7:e009263.
85. Chokesuwtanaskul R, Thongprayoon C, Bathini T, et al.. Efficacy and safety of anticoagulation for atrial fibrillation in patients with cirrhosis: a systematic review and metaanalysis. *Dig Liver Dis.* 2019;51:489–495.
86. Acosta RD, Abraham NS, Chandrasekhara V, et al. ASGE Standards of Practice Committee. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc.* 2016; 83: 3–16.866.
87. Chan FKL, Goh KL, Reddy N, et al. Management of patients on antithrombotic agents undergoing emergency and electiveendoscopy: joint Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) practice guidelines. *Gut.* 2018; 67: 405–417.
88. Vassallo P and Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. *JAMA.* 2007; 298: 1312–1322.
89. Cangemi DJ, Krill T, Weideman R, et al. A comparison of the rate of gastrointestinal bleeding in patients taking non vitamin K antagonist oral anticoagulants or warfarin. *Am J Gastroenterol.* 2017; 112: 734–739.
90. Vorperian VR, Havighurst TC, Miller S, et al. Adverse effects of low dose amiodarone: a metaanalysis. *J Am Coll Cardiol.* 1997; 30: 791–798.
91. Patel V and Sanyal AJ. Drug-induced steatohepatitis. *Clin Liver Dis.* 2013; 17: 533–546.
92. Flack KE, Desai J, Kolb JM, et al. Major gastrointestinal bleeding often is causedby occult malignancy in patients receiving warfarin or dabigatran to prevent stroke and systemic embolism from atrial fibrillation. *Clin Gastroenterol Hepatol.* 2017; 15: 682–690.
93. Potpara TS and Lip GY. Postapproval observational studies of non-vitamin K antagonist oral anticoagulants in atrial fibrillation. *JAMA..* 2017; 317: 1115–1116.
94. Ntaios G, Papavasileiou V, Makaritsis K, et al. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and metaanalysis. *Stroke.* 2017; 48: 2494–2503.

95. Miller CS, Dorreen A, Martel M, et al. Risk of gastrointestinal bleeding in patients taking non-vitamin K antagonist oral anticoagulants: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2017; 15: 1674–1683.e1673.
96. Freedman B, Camm J, Calkins H, et al. Screening for atrial fibrillation: a report of the AF-SCREEN international collaboration. *Circulation.* 2017; 135: 1851–1867.
97. Marzec LN, Wang J, Shah ND, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol.* 2017; 69: 2475–2484.
98. Kubitz D, Roth A, Becka M, et al. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol.* 2013;76:89–98.
99. Steffel J, Collins R, Antz M, et al. External reviewers. 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.
100. 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 in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019;140:e125–e151.
101. LaFromboise TD. American Indian mental health policy. *Am Psychol.* 1988;43:388–397.