BÖLÜM 27

Romatolojik Hastalıklarda Atriyal Fibrilasyon

Zeynep KAYA [1]

GİRİŞ

Atriyal fibrilasyon (AF) genel popülasyonda en sık görülen aritmidir. Hipertansiyon, diyabet, obezite, yaş, kalp kapak hastalığı ve kardiyomiyopati gibi çeşitli risk faktörleri AF riskini artırmaktadır (1). Çalışmalar, sistemik enflamasyonun AF'yi indükleyebileceğini göstermiştir (2,3). Tümör nekroz faktörü alfa (TNF-α), interlökin (IL)-2, IL-6 ve C-reaktif protein (CRP) gibi sistemik inflamatuar belirteçler AF gelişimi ile ilişkilendirilmiştir (2-4). Romatizmal hastalıklar da dahil olmak üzere birçok hastalık sistemik inflamasyon ile ilişkilidir.

Son zamanlarda yapılan çalışmalar sonucunda, otoimmün bozukluklar ve AF arasında bir ilişki olduğu gösterilmiştir (5, 6). Anti-M2 reseptörü (7), anti-B-adrenerjik reseptör (8), anti-ısı şoku proteini (9), anti-Na+/K+ pompası (10) ve antimiyozin otoantikorlarının (11) AF ile ilişkili olduğu gösterilmiştir (12, 13, 14).

Bu otoantikorlar inflamasyon ve atriyal fibrozisi tetikleyebilir (15), atriyal miyokardiyumunu AF gelişimine yatkın hale getirebilir (16).

AF'nin patogenezi çok faktörlü olsa da, anormal ventrikülovasküler homeostatik mekanizmalar ventriküler dolum basınçlarını ve dolayısıyla sol atriyal basınç ve gerilmeyi artırarak AF gelişiminde primer rol oynayabilir (17, 18, 19).

Bu mekanizmalara ek olarak inflamasyonun AF gelişimine yol açan sinyal yolaklarını etkilediği böylelikle yapısal kardiyovasküler hastalıklara ve AF ye neden olduğu bilinmektedir. İnflamatuar yükün azaltılmasının, prognozu olumlu yönde iyileştirdiği için, tedavi öncelikle sistemik inflamasyonu hedef almalıdır. Romatizmal hastalıklara bağlı AF tedavisinde de diğer AF tedavisi gibi antikoagulan, ritm kontrol tedavi, katater ablasyon, pacemaker gibi tedaviler düşünülebilir.

Birçok romatizmal hastalıkta AF riskinin arttığı yapılan çalışmalarda gösterilmiştir.

ROMATOİD ARTRİT VE ATRİYAL FİBRİLASYON

Romatoid artrit (RA), inflamatuar artrite neden olan ve sinovyal eklem tutulumunun yanı

[1] Uzm. Dr., Malatya Eğitim ve Araştırma Hastanesi, İç Hastalıkları AD. Romatoloji BD. zeynepkaya00@gmail.com

Gut tanılı hastalarda AF riskinin araştırıldığı az sayıda çalışma mevcuttur (70,71). İngilterede yapılan bir çalışmada, gut tanılı hastalarda AF için risk oranı 1,09 saptanmıştır (70) 2004-2013 yılları arasında yapılan diğer bir çalışmada, osteoartrit ile karşılaştırıldığında, gut hastalığı olan kişilerde yeni AF için risk oranı 1,13 saptanmıştır (72).

Gut hastalığının özellikleri olan hiperürisemi (73-76), oksidatif stres (77,78) ve kronik enflamasyon (79-81) AF riskini artırmaktadır ve, bu da gut hastalığındaki yüksek AF riskini açıklayabilir.

Gut tedavisinde kullanılan allopurinol, oksidatif stres ile fibrozisi önleyerek AF riskini azaltmektadır (82). Yaşlılarda yapılan yeni bir kohort çalışmasında allopurinol ile AF riskinde azalma tespit edilmiştir (83). Bu etkiye, ksantin oksido-redüktaz inhibisyonu yoluyla allopurinole bağlı oksidatif stresin azaltılması (84) veya daha önce kalp yetmezliğinde belirtildiği gibi allopurinolün endotelyal disfonksiyonu iyileştirmesi aracılık ediyor olabilir (85). Allopurinol ayrıca serum ürat seviyesini (sUA), ürat kristal birikimini ve ilişkili kronik enflamasyonu azaltarak AF riskini azaltabilir (86). Bu veriler, gut hastalığında hiperürisemi, oksidatif stres ve kronik enflamasyonun AF riskine katkıda bulunabileceği hipotezine yol açmaktadır.

KAYNAKLAR

1. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ*. 2018;361:k1453
2. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *Eur Heart J*. 2005;26:2083–2092.
3. Liu T, Li G, Li L, Korantzopoulos P. Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. *J Am Coll Cardiol*. 2007;49:1642–1648.
4. Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol*. 2012;60:2263–2270.
5. Ahlehoff O, Gislason GH, Jorgensen CH, Lindhardsen J, Charlot M, Olesen JB, Abildstrom SZ, Skov L, Torp-Pedersen C, Hansen PR. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. *Eur Heart J*. 2012;33:2054–2064.
6. Emilsson L, Smith JG, West J, Melander O, Ludvigsson JF. Increased risk of atrial fibrillation in patients with coeliac disease: a nationwide cohort study. *Eur Heart J*. 2011;32:2430–2437.
7. Baba A, Yoshikawa T, Fukuda Y, Sugiyama T, Shimada M, Akaishi M, Tsuchimoto K, Ogawa S, Fu M. Autoantibodies against M2-muscarinic acetylcholine receptors: new upstream targets in atrial fibrillation in patients with dilated cardiomyopathy. *Eur Heart J*. 2004;25:1108–1115.
8. Stavrakis S, Yu X, Patterson E, Huang S, Hamlett SR, Chalmers L, Pappy R, Cunningham MW, Morshed SA, Davies TF, et al. Activating autoantibodies to the beta-1 adrenergic and m2 muscarinic receptors facilitate atrial fibrillation in patients with Graves' hyperthyroidism. *J Am Coll Cardiol*. 2009;54:1309–1316.
9. Mandal K, Jahangiri M, Mukhin M, Poloniecki J, Camm AJ, Xu Q. Association of anti-heat shock protein 65 antibodies with development of postoperative atrial fibrillation. *Circulation*. 2004;110:2588–2590.
10. Bagrov AY, Fedorova OV, Roukoyatkina NI, Zhabko EP. Effect of endogenous digoxin-like factor and digoxin antibody on myocardial Na+, K(+)-pump activity and ventricular arrhythmias in acute myocardial ischaemia in rats. *Cardiovasc Res*. 1993;27:1045–1050.
11. Maixent JM, Paganelli F, Scaglione J, Levy S. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 1998;9:612–617.
12. Baba A, Yoshikawa T, Fukuda Y, Sugiyama T, Shimada M, Akaishi M, Tsuchimoto K, Ogawa S, Fu M. Autoantibodies against M2-muscarinic acetylcholine receptors: new upstream targets in atrial fibrillation in patients with dilated cardiomyopathy. *Eur Heart J*. 2004;25:1108–1115.
13. Fu M. Autoantibodies in atrial fibrillation: actors, biomarkers or bystanders? How far have we come? *Cardiology*. 2009;112:178–179.
14. Maixent JM, Paganelli F, Scaglione J, Levy S. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 1998;9:612–617.
15. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation*. 1997;96:1180–1184.
16. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, Wildevuur CR, Eijsman L, Trouwborst A, Hack CE. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves

C-reactive protein and is associated with postoperative arrhythmia. *Circulation*. 1997;96:3542–3548.
17. Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol*. 1998;32:1221–1227.
18. Leite-Moreira AF, Correia-Pinto J, Gillebert TC. Afterload induced changes in myocardial relaxation: a mechanism for diastolic dysfunction. *Cardiovasc Res*. 1999;43:344–353.
19. Shaikh AY, Wang N, Yin X, Larson MG, Vasan RS, Hamburg NM, Magnani JW, Ellinor PT, Lubitz SA, Mitchell GF, et al. Relations of arterial stiffness and brachial flow-mediated dilation with new-onset atrial fibrillation: The framingham heart study. *Hypertension*. 2016;68:590–596.
20. Outcomes of acute myocardial infarction in patients with rheumatoid arthritis (Epub ahead of print) Elbadawi A, Ahmed HMA, Elgendy IY, et al. *Am J Med.* 2020
21. Risk of incident atrial fibrillation in patients with rheumatoid arthritis: a systematic review and meta-analysis. Ungprasert P, Srivali N, Kittanamongkolchai W. *Int J Rheum Dis.* 2017;20:434–441.
22. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. Lazzerini PE, Capecchi PL, Laghi-Pasini F. *Eur Heart J.* 2017;38:1717–1727.
23. Arrhythmic risk in rheumatoid arthritis: the driving role of systemic inflammation. Lazzerini PE, Capecchi PL, Acampa M, Galeazzi M, Laghi-Pasini F. *Autoimmun Rev.* 2014;13:936–944.
24. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. Lindhardsen J, Ahlehoff O, Gislason GH, et al. *BMJ.* 2012;344:0.
25. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. Lazzerini PE, Capecchi PL, Laghi-Pasini F. *Eur Heart J.* 2017;38:1717–1727.
26. Cardiac arrhythmias in autoimmune diseases. Gawałko M, Balsam P, Lodziński P, Grabowski M, Krzowski B, Opolski G, Kosiuk J. *Circ J.* 2020;84:685–694.
27. Characterization, pathogenesis, and clinical implications of inflammation-related atrial myopathy as an important cause of atrial fibrillation. Packer M. *J Am Heart Assoc.* 2020;9:0.
28. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; 68(Suppl. 2): ii1–ii44.
29. Bengtsson K, Forsblad-d'Elia H, Lie E, et al. Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. *Arthritis Res Ther* 2017; 19: 102.
30. Exarchou S, Lie E, Lindström U, et al. Mortality in ankylosing spondylitis: results from a nationwide population-based study. *Ann Rheum Dis* 2016; 75: 1466–1472.
31. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017; 76: 17–28.
32. Szabo SM, Levy AR, Rao SR, et al. Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: a population-based study. *Arthritis Rheum* 2011; 63: 3294–3304.
33. Morovatdar N, Watts GF, Bondarsahebi Y, et al. Ankylosing spondylitis and risk of cardiac arrhythmia and conduction disorders: a systematic review and meta analysis. *Curr Cardiol Rev* 2021; 17: e150521193326.
34. Bengtsson K, Forsblad-d'Elia H, Lie E, et al. Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. *Ann Rheum Dis* 2018; 77: 541–548.
35. Dik VK, Peters MJ, Dijkmans PA, et al. The relationship between disease-related characteristics and conduction disturbances in ankylosing spondylitis. *Scand J Rheumatol* 2010; 39: 38–41.
36. Forsblad-d'Elia H, Wallberg H, Klingberg E, et al. Cardiac conduction system abnormalities in ankylosing spondylitis: a cross-sectional study. *BMC Musculoskelet Disord* 2013; 14: 237.
37. Brunner F, Kunz A, Weber U, et al. Ankylosing spondylitis and heart abnormalities: do cardiac conduction disorders, valve regurgitation and diastolic dysfunction occur more often in male patients with diagnosed ankylosing spondylitis for over 15 years than in the normal population. *Clin Rheumatol* 2006; 25: 24–29.
38. Bartels CM, Buhr KA, Goldberg JW, Bell CL, Visekruna M, Nekkanti S, et al. Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. *J Rheumatol*. 2014;41:680–687.
39. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271:840–844.
40. Wang TJ, Parise H, Levy D, D'Agostino RB, Wolf PA, Vasan RS, et al. Obesity and the Risk of New-Onset Atrial Fibrillation. *JAMA*. 2004;292:2471.
41. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, et al. Chronic Kidney Disease Is Associated With the Incidence of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2011;123:2946–2953
42. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation*. 2001;104:2886–2891.
43. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Svendsen JH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ*. 2012;344:e1257–e1257.
44. Kristensen SL, Lindhardsen J, Ahlehoff O, Erichsen R, Lamberts M, Khalid U, et al. Increased risk of atrial

fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace*. 2014;16:477–484.
45. Kim SC, Liu J, Solomon DH. The risk of atrial fibrillation in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2014;73:1091–1095.
46. Bacani AK, Crowson CS, Roger VL, Gabriel SE, Matteson EL. Increased incidence of atrial fibrillation in patients with rheumatoid arthritis. *Biomed Res Int*. 2015;2015:809514.
47. Barnado A, Carroll RJ, Casey C, Wheless L, Denny JC, Crofford LJ. Phenome-Wide Association Studies Uncover a Novel Association of Increased Atrial Fibrillation in Male Patients With Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)*. 2018;70:1630–1636.
48. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation*. 1997;96:1180–1184.
49. Emilsson L, Smith JG, West J, Melander O, Ludvigsson JF. Increased risk of atrial fibrillation in patients with coeliac disease: a nationwide cohort study. *Eur Heart J*. 2011;32:2430–2437.
50. Ahlehoff O, Gislason GH, Jorgensen CH, Lindhardsen J, Charlot M, Olesen JB, Abildstrom SZ, Skov L, Torp-Pedersen C, Hansen PR. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study. *Eur Heart J*. 2012;33:2054–2064.
51. Maixent JM, Paganelli F, Scaglione J, Levy S. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 1998;9:612–617.
52. Baba A, Yoshikawa T, Fukuda Y, Sugiyama T, Shimada M, Akaishi M, Tsuchimoto K, Ogawa S, Fu M. Autoantibodies against M2-muscarinic acetylcholine receptors: new upstream targets in atrial fibrillation in patients with dilated cardiomyopathy. *Eur Heart J*. 2004;25:1108–1115.
53. Stavrakis S, Yu X, Patterson E, Huang S, Hamlett SR, Chalmers L, Pappy R, Cunningham MW, Morshed SA, Davies TF, et al. Activating autoantibodies to the beta-1 adrenergic and m2 muscarinic receptors facilitate atrial fibrillation in patients with Graves' hyperthyroidism. *J Am Coll Cardiol*. 2009;54:1309–1316.
54. Mandal K, Jahangiri M, Mukhin M, Poloniecki J, Camm AJ, Xu Q. Association of anti-heat shock protein 65 antibodies with development of postoperative atrial fibrillation. *Circulation*. 2004;110:2588–2590.
55. Baba A, Yoshikawa T, Fukuda Y, Sugiyama T, Shimada M, Akaishi M, Tsuchimoto K, Ogawa S, Fu M. Autoantibodies against M2-muscarinic acetylcholine receptors: new upstream targets in atrial fibrillation in patients with dilated cardiomyopathy. *Eur Heart J*. 2004;25:1108–1115.
56. Maixent JM, Paganelli F, Scaglione J, Levy S. Antibodies against myosin in sera of patients with idiopathic paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 1998;9:612–617.
57. Melduni RM, Cooper LT, Gersh BJ, Warrington KJ, Bailey KR, McEvoy MT, Kita H, Lee HC. Association of Autoimmune Vasculitis and Incident Atrial Fibrillation: A Population-Based Case-Control Study. J Am Heart Assoc. 2020 Sep 15;9(18):e015977.
58. Dalbeth N, Haskard DO. Mechanisms of inflammation in gout. *Rheumatology* 2005;44:1090–6. 10.1093/rheumatology/keh640
59. Clarson LE, Hider SL, Belcher J, et al.. Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK clinical practice research datalink. *Ann Rheum Dis* 2015;74:642–7. 10.1136/annrheumdis-2014-205252
60. Clarson LE, Chandratre P, Hider SL, et al.. Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2015;22:335–43. 10.1177/2047487313514895
61. Kuo CF, Yu KH, See LC, et al.. Risk of myocardial infarction among patients with gout: a nationwide population-based study. *Rheumatology* 2013;52:111–7. 10.1093/rheumatology/kes169
62. Krishnan E, Svendsen K, Neaton JD, et al.. Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008;168:1104–10. 10.1001/archinte.168.10.1104
63. Cohen SD, Kimmel PL, Neff R, et al.. Association of Incident Gout and Mortality in Dialysis Patients. *Journal of the American Society of Nephrology* 2008. November;19:2204–10. 10.1681/ASN.2007111256
64. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007;116:894–900. 10.1161/CIRCULATIONAHA.107.703389
65. Krishnan E. Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. *Rheumatology* 2010;49:1229–38. 10.1093/rheumatology/keq037
66. Krishnan E. Gout and coronary artery disease: Epidemiologic clues. *Curr Rheumatol Rep* 2008;10:249–55. 10.1007/s11926-008-0039-0
67. Brand FN, McGee DL, Kannel WB, et al.. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. *Am J Epidemiol* 1985;121:11–18. 10.1093/oxfordjournals.aje.a113972
68. Niskanen LK, Laaksonen DE, Nyyssönen K, et al.. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Intern Med* 2004;164:1546–51.10.1001/archinte.164.14.1546
69. Fang J,Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA* 2000;283:2404–10.
70. Kuo C-F, Grainge MJ, Mallen C, et al.. Impact of gout on the risk of atrial fibrillation. *Rheumatology* 2016;55:721–8. 10.1093/rheumatology/kev418
71. Kim SC, Liu J, Solomon DH. Risk of incident atrial fibrillation in gout: a cohort study. *Ann Rheum Dis* 2016;75:1473–8. 10.1136/annrheumdis-2015-208161
72. Mantovani A, Rigolon R, Civettini A. Hyperuricemia is associated with an increased prevalence of paroxys-

mal atrial fibrillation in patients with type 2 diabetes referred for clinically indicated 24-h Holter monitoring. *J Endocrinol Invest* 2017. July 15.
73. Kuwabara M, Niwa K, Nishihara S, et al.. Hyperuricemia is an independent competing risk factor for atrial fibrillation. *Int J Cardiol* 2017;231:137–42. 10.1016/j.ijcard.2016.11.268
74. Xu X, Du N, Wang R, et al.. Hyperuricemia is independently associated with increased risk of atrial fibrillation: A meta-analysis of cohort studies. *Int J Cardiol* 2015;184:699–702. 10.1016/j.ijcard.2015.02.038
75. Chuang S-Y, Wu C-C, Hsu P-F, et al.. Hyperuricemia and incident atrial fibrillation in a normotensive elderly population in Taiwan. *Nutrition, Metabolism and Cardiovascular Diseases* 2014;24:1020–6. 10.1016/j.numecd.2014.03.012
76. Liu Y. Hyperuricemia and risk of atrial fibrillation. *J Atr Fibrillation* 2014;6:967 10.4022/jafib.
77. Hanna N, Cardin S, Leung TK. Differences in atrial versus ventricular remodeling in dogs with ventricular tachypacing-induced congestive heart failure. *Cardiovasc Res* 2004;63:236–44. 10.1016/j.cardiores.2004.03.
78. Li D, Shinagawa K, Pang L, et al.. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation* 2001;104:2608–14. 10.1161/hc4601.099402
79. Aviles RJ, Martin DO, Apperson-Hansen C, et al.. Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003;108:3006–10. 10.1161/01.CIR.0000103131.70301.4F
80. Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? *Eur Heart J* 2006;27:136–49. 10.1093/eurheartj/ehi645
81. Gaudino M, Andreotti F, Zamparelli R, et al.. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? *Circulation* 2003;108 Suppl 1:195II-–9. 10.1161/01.cir.0000087441.48566.0d
82. Sakabe M, Fujiki A, Sakamoto T, et al.. Xanthine oxidase inhibition prevents atrial fibrillation in a canine Model of atrial pacing-induced left ventricular Dysfunction. *J Cardiovasc Electrophysiol* 2012;23:1130–5. 10.1111/j.1540-8167.2012.02356.x
83. Singh JA, Yu S. Allopurinol and the risk of atrial fibrillation in the elderly: a study using Medicare data. *Ann Rheum Dis* 2017;76:72–8. 10.1136/annrheumdis-2015-209008
84. Carro MD, Falkenstein E, Radke WJ, et al.. Effects of allopurinol on uric acid concentrations, xanthine oxidoreductase activity and oxidative stress in broiler chickens. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology* 2010;151:12–17. 10.1016/j.cbpc.2009.07.
85. Farquharson CA, Butler R, Hill A, et al.. Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation* 2002;106:221–6. 10.1161/01.CIR.0000022140.61460.1D
86. Ruggiero C, Cherubini A, Ble A, et al.. Uric acid and inflammatory markers. *Eur Heart J* 2006;27:1174–81. 10.1093/eurheartj/ehi879