5.
BÖLÜM

AKUT VE KRONİK SOL/SAĞ KALP YETERSİZLİĞİNDE FARMAKOLOJİK TEDAVİ

Serkan ÜNLÜ[1]

AKUT SOL KALP YETERSİZLİĞİNDE FARMAKOLOJİK TEDAVİ

Akut kalp yetersizliği (AKY) nedeniyle başvuran hastaların çok hızlı değerlendirilmesi ve durumlarının kontrol altına alınması gereklidir. AKY kliniği sistolik veya diyastolik fonksiyon bozukluğundan kaynaklanabilir ancak müdahale basamakları farklılık göstermez [1,2]. Yeterli oksijenizasyon O_2 inhalasyonu, noninvaziv mekanik ventilasyon veya entünbasyon ile sağlanır ve oksimetre ile takip edilebilir [3,4]. Sık ve yakın kan basıncı takibi yapılarak kan basınçları normal aralıklarda tutulmalıdır. Birden çok yoldan intravenöz katater takılmalıdır. Hasta oturur pozisyonda sürekli monitörize edilmelidir. Öncelikle hemodinamik bozukluğu ve intravasküler hacim yükünü hızla düzelten tedaviler başlanmalıdır. Diüretik ve vazodilatör ajanlar tedavinin ana yapıtaşlarıdır. Diüretik veya vazodilatör tedavinin ağırlığı hastanın kliniğine bağlı olarak ayarlanmalıdır. Yüksek kan basıncı izlenen, akut mitral yetersizliği ya da aort yetersizliğine bağlı gelişen AKY'de, arteriyel tonusu düşüren nitroprussid gibi ajanların kullanılması sistemik vasküler direnç ve sol ventrikül artyükünde düşüş sağlayarak etkili olurlar. Venöz tonusu sağlamak amacıyla vazodilatör (nitrat türevi) ajanların erken kullanımı da diüretiklerle beraber önerilmektedir. Diüretik veya vazodilatör tedavinin ağırlığı hastanın kliniğine bağlı olarak ayarlanmalıdır. Ayrıca venöz tromboembolizm profilaksisi hasta yattığı sürece uygulanmalıdır [1–4].

Oksijen Tedavisi

AKY ile başvuran hastalarda oksijen satürasyonu (SpO_2) <%90 olan hastalara destek O_2 tedavisi verilmelidir. Nazal kanül yerine yüze tam oturan maskeler tercih edilmelidir. Hipoksemi izlenmeyen hastalarda rutin olarak destek O_2 verilmesi önerilmez. Gereksiz verilen O_2 vazokonstriksiyon ve kardiyak debide düşüş yaratabilir. Kronik obstrüktif akciğer hastalığı olan hastalarda hedef SaO_2 değeri %88-92 arasındadır ve yüksek O_2 desteğine ihtiyaçları olmayabilir. Destek O_2 tedavisi ile yeterli oksijenizasyon sağlanamayan durumlarda noninvaziv mekanik ventilasyon öncelikle denenmelidir. Noninvaziv mekanik ventilasyon ile düzelmeyen veya bu işlemi tolere edemeyen solunum yetmezliği olan hastalarda entübasyon uygulanmalıdır. Oksijen doygunluğu %90 üzerinde tutulacak şekilde tedavi ayarlanmalıdır [5–8].

[1] Öğr. Gör. Dr., Gazi Üniversitesi Tıp Fakültesi, Kardiyoloji AD, unlu.serkan@gmail.com

tışı azalttığını göstermiştir [3,124,130,131]. Avrupa KY kılavuzu KY bulunan hastalarda demir eksikliğinin ve anemi varlığının incelenmesi gerektiğini ve bu klinik durumlar saptanırsa semptomları iyileştirmek ve yaşam kalitesini artırmak amacıyla iv. ferrik karboksimaltoz tedavisini (sınıf IIa) önermektedir [3]. Amerika Birleşik Devletler kılavuzları ise özel formulasyon belirtmez ve daha kısıtlı öneri düzeyi ile iv. demir tedavisini KY hastaları için önerir (sınıf IIb) [4]. Korunmuş ejeksiyon fraksiyonlu KY hastalarında ise demir tedavisinin rolü henüz ortaya konmamıştır.

KAYNAKLAR

1. Ware LB, Matthay MA. Acute Pulmonary Edema. *N Engl J Med* 2005;353(26):2788–2796.
2. West RL, Hernandez AF, O'Connor CM, Starling RC, Califf RM. A review of dyspnea in acute heart failure syndromes. *Am Heart J* 2010;160(2):209–214.
3. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *Eur J Heart Fail* 2016;18(8):891–975.
4. Yancy CW, Januzzi JLJ, Allen LA, et al. 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Task Force on Expert Consensus Decisio. *J Am Coll Cardiol* 2018;71(2):201–230.
5. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema. *N Engl J Med* 2008;359(2):142–151.
6. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ V. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. *Heart* 2010;96(7):533–538.
7. Vital FMR, Ladeira MT, Atallah ÁN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013;
8. Sepehrvand N, Ezekowitz JA. Oxygen Therapy in Patients With Acute Heart Failure. *JACC Hear Fail* 2016;4(10):783–790.
9. STAMPFER M, EPSTEIN SE, BEISER GD, BRAUNWALD E. Hemodynamic Effects of Diuresis at Rest and During Intense Upright Exercise in Patients with Impaired Cardiac Function. *Circulation* 1968;37(6):900–911.
10. Matsue Y, Damman K, Voors AA, et al. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure. *J Am Coll Cardiol* 2017;69(25):3042–3051.
11. Salvador DRK, Rey NR, Ramos GC, Punzalan FER. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure [Internet]. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2004.
12. Felker GM, Mentz RJ. Diuretics and Ultrafiltration in Acute Decompensated Heart Failure. *J Am Coll Cardiol* 2012;59(24):2145–2153.
13. Cotter G, Metzkor E, Kaluski E, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998;351(9100):389–393.
14. Ho EC, Parker JD, Austin PC, Tu J V, Wang X, Lee DS. Impact of Nitrate Use on Survival in Acute Heart Failure: A Propensity-Matched Analysis. *J Am Heart Assoc* 2016;5(2).
15. Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure. *JAMA* 2002;287(12).
16. Elkayam U, Akhter MW, Singh H, Khan S, Usman A. Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. *Am J Cardiol* 2004;93(2):237–240.
17. Sharon A, Shpirer I, Kaluski E, et al. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. *J Am Coll Cardiol* 2000;36(3):832–837.
18. Packer M, Meller J, Medina N, Gorlin R, Herman M V. Rebound Hemodynamic Events after the

Abrupt Withdrawal of Nitroprusside in Patients with Severe Chronic Heart Failure. *N Engl J Med* 1979;301(22):1193–1197.
19. Mullens W, Abrahams Z, Francis GS, et al. Sodium Nitroprusside for Advanced Low-Output Heart Failure. *J Am Coll Cardiol* 2008;52(3):200–207.
20. Finley JJ, Konstam MA, Udelson JE. Arginine Vasopressin Antagonists for the Treatment of Heart Failure and Hyponatremia. *Circulation* 2008;118(4):410–421.
21. MA K, Gheorghiade M, JC B, al et, Konstam MA. Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure<SUBTITLE>The EVEREST Outcome Trial</SUBTITLE>. *JAMA* 2007;297(12):1319–1331.
22. Goldsmith SR, Elkayam U, Haught WH, Barve A, He W. Efficacy and Safety of the Vasopressin V1A/V2-Receptor Antagonist Conivaptan in Acute Decompensated Heart Failure: A Dose-Ranging Pilot Study. *J Card Fail* 2008;14(8):641–647.
23. Gheorghiade M. Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Patients Hospitalized for Heart Failure<SUBTITLE>The EVEREST Clinical Status Trials</SUBTITLE>. *JAMA* 2007;297(12):1332.
24. Peacock WF, Hollander JE, Diercks DB, Lopatin M, Fonarow G, Emerman CL. Morphine and outcomes in acute decompensated heart failure: an ADHERE analysis. *Emerg Med J* 2008;25(4):205–209.
25. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 2013;310(23):2533–2543.
26. Liang CS, Sherman LG, Doherty JU, Wellington K, Lee VW, Hood WB. Sustained improvement of cardiac function in patients with congestive heart failure after short-term infusion of dobutamine. *Circulation* 1984;69(1):113–119.
27. Abraham WT, Adams KF, Fonarow CG. In-Hospital Mortality in Patients With Acute Decompensated Heart Failure Requiring Intravenous Vasoactive Medications. An Analysis From the Acute Decompensated Heart Failure National Registry (ADHERE). *ACC Curr J Rev* 2005;14(10):26.
28. Cuffe MS. Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart Failure<SUBTITLE>A Randomized Controlled Trial</SUBTITLE>. *JAMA* 2002;287(12):1541.
29. Aranda JM, Schofield RS, Pauly DF, et al. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: A prospective, randomized trial. *Am Heart J* 2003;145(2):324–329.
30. Packer M, Colucci W, Fisher L, et al. Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure. *JACC Hear Fail* 2013;1(2):103–111.
31. Ørstavik Ø, Ata SH, Riise J, et al. Inhibition of phosphodiesterase-3 by levosimendan is sufficient to account for its inotropic effect in failing human heart. *Br J Pharmacol* 2014;171(23):5169–5181.
32. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. *Circulation* 1999;100(23):2312–2318.
33. Delahaye F, Gevigney G de. Is the optimal dose of angiotensin-converting enzyme inhibitors in patients with congestive heart failure definitely established? Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necess. *J Am Coll Cardiol* 2000;36(7):2096–2097.
34. Burnett H, Earley A, Voors AA, et al. Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction. *Circ Hear Fail* 2017;10(1).
35. Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;355(9215):1575–1581.
36. Cohn JN, Tognoni G. A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure. *N Engl J Med* 2001;345(23):1667–1675.
37. McMurray JJ V, Östergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362(9386):767–771.
38. Granger CB, McMurray JJ V, Yusuf S, et al. Effects

of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;362(9386):772–776.

39. Solomon SD, Claggett B, Desai AS, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction. *Circ Hear Fail* 2016;9(3).
40. Desai AS, McMurray JJ V, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. *Eur Heart J* 2015;36(30):1990–1997.
41. McMurray JJ V, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N Engl J Med* 2014;371(11):993–1004.
42. M. MT, L. JJ, A. AL, et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction. *J Am Coll Cardiol* 2021;77(6):772–810.
43. McMurray JJ V, Krum H, Abraham WT, et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. *N Engl J Med* 2016;374(16):1521–1532.
44. Fang JC. Angiotensin-Converting Enzyme Inhibitors or β-Blockers in Heart Failure. *Circulation* 2005;112(16):2380–2382.
45. Sliwa K, Norton GR, Kone N, et al. Impact of initiating carvedilol before angiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure. *J Am Coll Cardiol* 2004;44(9):1825–1830.
46. Willenheimer R, Veldhuisen DJ van, Silke B, et al. Effect on Survival and Hospitalization of Initiating Treatment for Chronic Heart Failure With Bisoprolol Followed by Enalapril, as Compared With the Opposite Sequence. *Circulation* 2005;112(16):2426–2435.
47. Santema BT, Ouwerkerk W, Tromp J, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet (London, England)* 2019;394(10205):1254–1263.
48. Zannad F, McMurray JJ V, Krum H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. *N Engl J Med* 2011;364(1):11–21.
49. Pitt B, Remme W, Zannad F. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *ACC Curr J Rev* 2003;12(4):57.
50. Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, et al. Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure. *Am Heart J* 2010;160(6):1156–1162.
51. Ellison DH. Diuretic Therapy and Resistance in Congestive Heart Failure. *Cardiology* 2001;96(3–4):132–143.
52. Wile D. Diuretics: a review. *Ann Clin Biochem* 2012;49(5):419–431.
53. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJS. Diuretics for heart failure [Internet]. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2012.
54. Tanaka A, Node K. Emerging roles of sodium-glucose cotransporter 2 inhibitors in cardiology. *J Cardiol* 2017;69(3):501–507.
55. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med* 2020;383(15):1425–1435.
56. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;396(10254):819–829.
57. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;380(24):2295–2306.
58. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017;377(7):644–657.
59. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med* 2021;384(2):117–128.
60. Tanboğa İH, Topçu S, Aksakal E, et al. The Risk of Atrial Fibrillation With Ivabradine Treatment: A Meta-analysis With Trial Sequential Analysis of More Than 40000 Patients. *Clin Cardiol* 2016;39(10):615–620.
61. Martin RIR, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation as-

sociated with ivabradine treatment: meta-analysis of randomised controlled trials. *Heart* 2014;100(19):1506–1510.
62. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376(9744):875–885.
63. The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. *N Engl J Med* 1997;336(8):525–533.
64. Gheorghiade M, Patel K, Filippatos G, et al. Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial. *Eur J Heart Fail* 2013;15(5):551–559.
65. Ahmed A, Rich MW, Love TE, et al. Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. *Eur Heart J* 2005;27(2):178–186.
66. Gheorghiade M, Veldhuisen DJ van, Colucci WS. Contemporary Use of Digoxin in the Management of Cardiovascular Disorders. *Circulation* 2006;113(21):2556–2564.
67. Cohn JN, Johnson G, Ziesche S, et al. A Comparison of Enalapril with Hydralazine–Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure. *N Engl J Med* 1991;325(5):303–310.
68. Taylor AL, Ziesche S, Yancy C, et al. Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure. *N Engl J Med* 2004;351(20):2049–2057.
69. Anand IS, Win S, Rector TS, Cohn JN, Taylor AL. Effect of Fixed-Dose Combination of Isosorbide Dinitrate and Hydralazine on All Hospitalizations and on 30-Day Readmission Rates in Patients With Heart Failure. *Circ Hear Fail* 2014;7(5):759–765.
70. investigators G-H. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372(9645):1223–1230.
71. Reddy YN V, Borlaug BA. Heart Failure With Preserved Ejection Fraction. *Curr Probl Cardiol* 2016;41(4):145–188.
72. Andersen MJ, Borlaug BA. Heart Failure with Preserved Ejection Fraction: Current Understandings and Challenges. *Curr Cardiol Rep* 2014;16(7).
73. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2010;32(6):670–679.
74. Sharma K, Kass DA. Heart Failure With Preserved Ejection Fraction. *Circ Res* 2014;115(1):79–96.
75. Paulus WJ, Flachskampf FA, Smiseth OA, Fraser AG. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology: reply. *Eur Heart J* 2007;28(21):2686–2687.
76. McMurray JJ V, Teerlink JR, Cotter G, et al. Effects of Tezosentan on Symptoms and Clinical Outcomes in Patients With Acute Heart Failure. *JAMA* 2007;298(17):2009.
77. Filippatos G, Anker SD, Bohm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J* 2016;37(27):2105–2114.
78. Https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-002168-17/HU. Efficacy and safety of finerenone in subjects with chronic heart failure at high risk of recurrent heart failure decompensation.
79. Felker GM, Butler J, Collins SP, et al. Heart Failure Therapeutics on the Basis of a Biased Ligand of the Angiotensin-2 Type 1 Receptor. *JACC Hear Fail* 2015;3(3):193 LP – 201.
80. Mitrovic V, Seferovic PM, Simeunovic D, et al. Haemodynamic and clinical effects of ularitide in decompensated heart failure. *Eur Heart J* 2006;27(23):2823–2832.
81. Mitrovic V, Luss H, Nitsche K, et al. Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: a double-blind, placebo-controlled, ascending-dose trial. *Am Heart J* 2005;150(6):1239.
82. Zakeri R, Burnett JC. Designer natriuretic peptides: a vision for the future of heart failure therapeutics. *Can J Physiol Pharmacol* 2011;89(8):593–601.
83. Https://clinicaltrials.gov/ct2/show/NCT02071602. CD-NP (Cenderitide) Therapy for the Preservation of Left Ventricular Function (BELIEVE III).
84. Lapp H, Mitrovic V, Franz N, et al. Cinaciguat (BAY 58-2667) Improves Cardiopulmonary Hemodynamics in Patients With Acute Decompensated

Heart Failure. *Circulation* 2009;119(21):2781–2788.

85. Gheorghiade M, Greene SJ, Filippatos G, et al. Cinaciguat, a soluble guanylate cyclase activator: results from the randomized, controlled, phase IIb COMPOSE programme in acute heart failure syndromes. *Eur J Heart Fail* 2012;14(9):1056–1066.
86. Erdmann E, Semigran MJ, Nieminen MS, et al. Cinaciguat, a soluble guanylate cyclase activator, unloads the heart but also causes hypotension in acute decompensated heart failure†. *Eur Heart J* 2012;34(1):57–67.
87. Gheorghiade M, Greene SJ, Butler J, et al. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. *JAMA* 2015;314(21):2251–2262.
88. Pieske B, Maggioni AP, Lam CSP, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study. *Eur Heart J* 2017;38(15):1119–1127.
89. Teerlink JR, Metra M, Felker GM, et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet* 2009;373(9673):1429–1439.
90. Metra M, Cotter G, Davison BA, et al. Effect of Serelaxin on Cardiac, Renal, and Hepatic Biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) Development Program. *J Am Coll Cardiol* 2013;61(2):196–206.
91. Teerlink JR, Diaz R, Felker GM, et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N Engl J Med* 2021;384(2):105–116.
92. Arcaro A, Lembo G, Tocchetti CG. Nitroxyl (HNO) for treatment of acute heart failure. *Curr Heart Fail Rep* 2014;11(3):227–235.
93. Sabbah HN, Tocchetti CG, Wang M, et al. Nitroxyl (HNO): A novel approach for the acute treatment of heart failure. *Circ Heart Fail* 2013;6(6):1250–1258.
94. Https://clinicaltrials.gov/ct2/show/NCT01870778. Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF (RELAX-AHF-2).
95. Malik FI, Hartman JJ, Elias KA, et al. Cardiac Myosin Activation: A Potential Therapeutic Approach for Systolic Heart Failure. *Science (80-)* 2011;331(6023):1439–1443.
96. Teerlink JR, Felker GM, McMurray JJ V, et al. Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure: The ATOMIC-AHF Study. *J Am Coll Cardiol* 2016;67(12):1444–1455.
97. Khan H, Metra M, Blair JEA, et al. Istaroxime, a first in class new chemical entity exhibiting SERCA-2 activation and Na–K-ATPase inhibition: a new promising treatment for acute heart failure syndromes? *Heart Fail Rev* 2009;14(4):277–287.
98. Shah SJ, Blair JEA, Filippatos GS, et al. Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: results from the Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in P. *Am Heart J* 2009;157(6):1035–1041.
99. Gheorghiade M, Blair JEA, Filippatos GS, et al. Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent. *J Am Coll Cardiol* 2008;51(23):2276–2285.
100. Piazza G, Goldhaber SZ. The Acutely Decompensated Right Ventricle. *Chest* 2005;128(3):1836–1852.
101. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care* 2010;14(5):R169.
102. Klein M. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. *Yearb Med* 2011;2011:231–233.
103. Inglessis I, Shin JT, Lepore JJ, et al. Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. *J Am Coll Cardiol* 2004;44(4):793–798.
104. Critoph C, Green G, Hayes H, et al. Clinical Outcomes of Patients Treated With Pulmonary Vasodilators Early and in High Dose After Left

Ventricular Assist Device Implantation. *Artif Organs* 2015;40(1):106–114.
105. Baker WL, Radojevic J, Gluck JA. Systematic Review of Phosphodiesterase-5 Inhibitor Use in Right Ventricular Failure Following Left Ventricular Assist Device Implantation. *Artif Organs* 2015;40(2):123–128.
106. LÖLLGEN H, DREXLER H. Use of inotropes in the critical care setting. *Crit Care Med* 1990;18(Supplement):S61.
107. MURPHY MB, ELLIOTT WJ. Dopamine and dopamine receptor agonists in cardiovascular therapy. *Crit Care Med* 1990;18(Supplement):S19.
108. Mehra MR, Ventura HO, Kapoor C, Stapleton DD, Zimmerman D, Smart FW. Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 1997;80(1):61–64.
109. Movsesian M, Stehlik J, Vandeput F, Bristow MR. Phosphodiesterase inhibition in heart failure. *Heart Fail Rev* 2008;14(4):255–263.
110. Ruffolo RR. Review: The Pharmacology of Dobutamine. *Am J Med Sci* 1987;294(4):244–248.
111. Koch-Weser J, Sonnenblick EH, Frishman WH, LeJemtel TH. Dobutamine: A New Synthetic Cardioactive Sympathetic Amine. *N Engl J Med* 1979;300(1):17–22.
112. Rubin LJ, Handel F, Peter RH. The effects of oral hydralazine on right ventricular end-diastolic pressure in patients with right ventricular failure. *Circulation* 1982;65(7):1369–1373.
113. Kiely D. Haemodynamic and endocrine effects of type 1 angiotensin II receptor blockade in patients with hypoxaemic cor pulmonale. *Cardiovasc Res* 1997;33(1):201–208.
114. Butorov S, Butorov A, Kanygina O. US socio-political thought on the forms of government in the post-Soviet states. *OOO "Zhurnal "Voprosy Istor* 2020;2020(10–4):42–48.
115. Quaife RA, Christian PE, Gilbert EM, Datz FL, Volkman K, Bristow MR. Effects of Carvedilol on Right Ventricular Function in Chronic Heart Failure. *Am J Cardiol* 1998;81(2):247–250.
116. Giardini A, Lovato L, Donti A, et al. A pilot study on the effects of carvedilol on right ventricular remodelling and exercise tolerance in patients with systemic right ventricle. *Int J Cardiol* 2007;114(2):241–246.
117. Beck-da-Silva L, Bold A De, Davies RA, et al. Effect of Bisoprolol on Right Ventricular Function and Brain Natriuretic Peptide in Patients With Heart Failure. *Congest Hear Fail* 2004;10(3):127–132.
118. Skhiri M, Hunt SA, Denault AY, Haddad F. Evidence-Based Management of Right Heart Failure: a Systematic Review of an Empiric Field. *Rev Española Cardiol* 2010;63(4):451–471.
119. Alajaji W, Baydoun A, Al-Kindi SG, Henry L, Hanna MA, Oliveira GH. Digoxin therapy for cor pulmonale: A systematic review. *Int J Cardiol* 2016;223:320–324.
120. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endo. *Eur Heart J* 2016;37(1):67–119.
121. Ghofrani H-A, D'Armini AM, Grimminger F, et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. *N Engl J Med* 2013;369(4):319–329.
122. Crielaard BJ, Lammers T, Rivella S. Targeting iron metabolism in drug discovery and delivery. *Nat Rev Drug Discov* 2017;16:400–23.
123. Stoltzfus RJ. Defining iron-deficiency anemia in public health terms: time for reflection. *J Nutr* 2001;131:565S–7S.
124. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron Deficiency in Heart Failure: An Overview. *JACC Heart Fail* 2019;7(1):36-46.
125. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737–44.
126. Bolger AP, Bartlett FR, Penston HS, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol* 2006;48:1225–7.

127. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. *Schweiz Med Wochenschr* 1970;100:301–3.
128. Geisser P. Safety and efficacy of iron(III)-hydroxide polymaltose complex / a review of over 25 years experience. *Arzneimittelforschung* 2007;57:439-452.
129. Cook JD. Diagnosis and management of iron-deficiency anaemia. *Best Pract Res Clin Haematol* 2005;18:319-332.
130. Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in irondeficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016;18:786–95.
131. Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart. *Eur J Heart Fail* 2018;20:125-133