

## BÖLÜM 10

# PULMONER EMBOLİZM

Mehmet MERMER<sup>1</sup>

### GİRİŞ

Pulmoner embolizm (PE), son 30 yıldaki tanı ve tedavideki ilerlemelere rağmen önemli bir değişiklik göstermeyen, erken ölüm oranlarının yüksek olduğu akut dolaşım sistemi hastalığıdır (1). Pulmoner embolizm ve derin ven trombozu (DVT), venöz tromboembolizm (VTE) tanısı altında birlikte değerlendirilen, nedensel özellikle genellikle ortak olan klinik tanımlardır (2-4). Bu bölümde PE nedenlerinden sadece VTE'den bahsedilecektir.

PE, DVT başlangıcından 3-7 gün sonra ortaya çıkar ve vakaların %10'unda semptomların başlamasından sonraki bir saat içinde ölümcül olabilir, çoğu ölümcül vakalarda klinik olarak tanı alınamaz. PE, pulmoner vasküler yataktan anı tikanıklık nedeniyle, sağ ventrikül (RV) yetmezliğine neden olabilir. Ölümcül olabilen akut sağ kalp yetmezliği (ASKY) dahil tüm klinik evrede erken tanı çok önemlidir. PE, olguların %5-10'unda şok veya hipotansiyon, stabil hastaların % 50'sinde RV dilatasyonu ve / veya laboratuvar bulguları ile kötü prognoz tahmin edilebilir (5, 6).

Bilgisayarlı tomografi pulmoner anjiyografi (BTPA) ile trombus segmental seviyeye kadar

görüntülenebilir. BTPA ile aynı zamanda RV genişlemesi gösterilebilir. Yatak başında ekokardiografi acil şartlar altında kabul edilebilir bir alternatifdir. Ekokardiyografi genellikle kesin bir teşhis sağlamaz veya PE'i dışlayamaz, RV aşırı yüklenmesini ve işlev bozukluğunu gösterebilir.

Akut masif PE'de öncelikle hemodinamik durum kontrol altına alınmalıdır. PE'de ilk tedavi pulmoner vasküler yataktan yeniden kan akışını sağlamak ve erken nüksü önlemeye yönelikir (7). Trombolitik tedavi, yüksek riskli PE tespit edilen hastalarda uygulanır. Kanama riski yüksek olan hastalarda trombolitik ajanlar, fayda zarar dengesi gözetilerek doz düşürülür veya uygulanmaz (4). Ekstrakorporeal membran oksijenasyonu (EKMO) desteği, dolaşım kollapsı olan hastalarda etkili olabilir (8). Hastalığın prognozu, embolinin morfolojik boyutuna, hastanın kardiyovasküler ve pulmoner sistem durumuna, nörohumoral adaptasyon derecesine ve tedavinin potansiyel risklerine göre değişkenlik gösterir (1). PE sonrası tam reperfüzyon hastaların üçte ikisinde meydana gelir ve ölümlerin çoğunun (% 90) tedavi edilmemiş hastalarda, tanınmayan PE nedeniyle gerçekleştiği görülmektedir (9). VTE hastalarının % 5'inde kronik pulmoner hipertansiyon gelişir (10).

<sup>1</sup> Dr. Öğr. Üyesi, Göğüs Hastalıkları, Sağlık Bilimleri Üniversitesi Konya SUAM, drmmmermer@gmail.com

laktik antikoagülan olarak kullanılan DMAH'nin biyolojik birikimi olmadığını bildirdi. İki prospектив gözlemsel çalışmada: birincisi, YBÜ girişinde kreatinin klerensi 30 ml/dk veya üzerinde olan 19 hastadan oluşan ve günlük 5.000 UI subkutan dalteparin alan tek merkezli bir kohort çalışmasıdır (183). İkinci çalışma, tahmin edilen kreatinin klerensi 30 ml / dakika altında olan 138 YBÜ hastasının çok merkezli prospектив kohort çalışmasıydı (177) ve tromboprofilaksi nedeniyle günde bir kez 5.000 UI deri altı dalteparin almıştır. Her iki çalışmada da hiçbir DMAH biyobirikim oluşmadı. Dalteparin ağır böbrek yetmezliği olan kritik hastalarda kullanımının önerilmesine karşın, Dalteparin dışındaki DMAH'lerin böbrek yetmezliği olan hastalarda etkisi tartışılmalıdır.

## YBÜ Hastalarında Mekanik Tromboprofilaksi

YBÜ hastalarında antikoagülan tedavi kontrendike olduğunda, alt ekstermité DVT önlenmesi amaçlı kademeli kompresyon çorapları (KKÇ) veya aralıklı pnömatik kompresyon (APK) kullanımı önerilmiştir (79, 137). YBÜ hastalarında DVT profilakisisi için KKÇ veya APK içeren randomize kontrollü 5 çalışma (192); bunlardan biri akut miyokard enfarktüslü hastalarda yapıldı (193) ve diğer üçü travma hastalarında yapıldı (193-195). Bu dört çalışmada mekanik profilaksi yapılan veya DMAH alan 791 hasta değerlendirildi. Bir diğer çalışmada hasta tek bacağına KKÇ uygulandı. Tüm çalışmalarda DVT insidansı KKÇ ile daha düşüktü (% 10'a karşı % 0) (193). APK'yi KKÇ ile birleştirilerek tedavi uygulanan YBÜ hastalarında, sadece KKÇ uygulananlardan daha etkili bulunmadı (196). Diğer bir çalışmada mekanik profilaksi beraberinde DMAH verilen YBÜ hastalarında, sadece mekanik profilaksi uygulanlara nisbeten DVT daha düşük gözlandı (197). DVT tespit edilmiş ise KKÇ veya APK kullanımı kontrendikedir (83).

## KAYNAKLAR

1. Bělohlávek J DV, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Experimental & Clinical Cardiology*. 2013;18(2):129.
2. White RHJC. The epidemiology of venous thromboembolism. 2003;107(23\_suppl\_1):I-4-I-8.
3. Davies RA PV. pulmoner embolism. In: Bersten AD SN, editor. OH'S INTENSIVE CARE MANUAL. China: Elsevier Ltd; 2014. p. 392-400.
4. Essien EO RP, Mathai SC. Pulmonary Embolism. *Med Clin North Am*. 2019;May;103(3):549-64.
5. KE W. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest* 2002;121:877-905.
6. Konstantinides SJCoic. Pulmonary embolism: impact of right ventricular dysfunction. 2005;20(6):496-501.
7. Members ATF, Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2008;29(18):2276-315.
8. Yamamoto T. Management of patients with high-risk pulmonary embolism: a narrative review. *Journal of intensive care*. 2018;6(1):16.
9. Nijkeuter M, Hovens MM, Davidson BL, Huisman MVJC. Resolution of thromboemboli in patients with acute pulmonary embolism: a systematic review. 2006;129(1):192-7.
10. Kearon CJC. Natural history of venous thromboembolism. 2003;107(23\_suppl\_1):I-22-I-30.
11. Smith SB, Geske JB, Kathuria P, Cuttica M, Schimmel DR, Courtney DM, et al. Analysis of national trends in admissions for pulmonary embolism. 2016;150(1):35-45.
12. Joffe HV, Kucher N, Tapson VF, Goldhaber SZJC. Upper-extremity deep vein thrombosis: a prospective registry of 592 patients. 2004; 110(12):1605-11.
13. Pineda LA, Hathwar VS, Grant BJJC. Clinical suspicion of fatal pulmonary embolism. 2001;120(3):791-5.
14. Moser KM, Fedullo PF, LitteJohn JK, Crawford RJJ. Frequent asymptomatic pulmonary embo-

- lism in patients with deep venous thrombosis. 1994;271(3):223-5.
15. Dalen JE, Fccp M. Pulmonary Embolism: What Have We Learned Since Virchow?\* Natural History, Pathophysiology, and Diagnosis. *chest*. 2002;122:1440-56.
  16. van Beek EJ, Brouwers EM, Song B, Stein PD, Oudkerk MJCr. Clinical validity of a normal pulmonary angiogram in patients with suspected pulmonary embolism—a critical review. 2001;56(10):838-42.
  17. Anderson Jr FA, Spencer FAJC. Risk factors for venous thromboembolism. 2003;107(23\_suppl\_1):I-9-I-16.
  18. Bounameaux HJTL. Factor V Leiden paradox: risk of deepvein thrombosis but not of pulmonary embolism. 2000;9225(356):182-3.
  19. NORDSTRÖM M, Lindblad BJA. Autopsy-verified venous thromboembolism within a defined urban population—the city of Malmö, Sweden. 1998;106(1-6):378-84.
  20. Oger E, Thrombosis E-GsgJ, haemostasis. Incidence of venous thromboembolism: a community-based study in Western France. 2000;83(05):657-60.
  21. Becattini C, Agnelli G, Prandoni P, Silingardi M, Salvi R, Taliani MR, et al. A prospective study on cardiovascular events after acute pulmonary embolism. 2004;26(1):77-83.
  22. Toft H, Horvath-Puho E, Pedersen L, Baron JA, Prandoni PJTL. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. 2007;370(9601):1773-9.
  23. Torbicki A PA, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, at all. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2008;29:2276-315.
  24. Kakkar VV HC, Flanc C, Clarke MB. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969;2:230-2.
  25. McIntyre KM, Sasahara AAJTAjoc. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. 1971;28(3):288-94.
  26. Molloy WD, Lee K, Girling L, Schick U, Prewitt RMJARoRD. Treatment of shock in a canine model of pulmonary embolism. 1984;130(5):870-4.
  27. Sekhri V MNaa. Management of massive and nonmassive pulmonary embolism. *Arch Med Sci*. 2012 Dec 20;8(6):957-69.
  28. Hull RD, Raskob GE, Hirsh J, Jay RM, Leclerc JR, Geerts WH, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. 1986;315(18):1109-14.
  29. Sergysels R. Pulmonary gas exchange abnormalities in pulmonary embolism. In: Morpurgo M ePENYMD, 1994. p89-96.
  30. Kasper W, Geibel A, Tiede N, Just HJTL. Patient foramen ovale in patients with haemodynamically significant pulmonary embolism. 1992;340(8819):561-4.
  31. Karalezli A. Derleme|Review PEDg.
  32. Qaseem A SV, at al. Current Diagnosis of Venous Thromboembolism in Primary Care: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Fam Med*. 2007;Jan; 5:57-62.
  33. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. 2005;172(8):1041-6.
  34. Kasper W, Konstantinides S, Geibel A, Olszewski M, Heinrich F, Grosser KD, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multi-center registry. 1997;30(5):1165-71.
  35. Konstantinides SV MG, Becattini C, Bueno H, Geersing GJ, Harjola VP, at al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *European Heart Journal*. 2019;00:1-61.
  36. van der Hulle T CW, Kooij S, Beenen LFM, van Bemmel T, van Es J, at al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017;390:289-97.
  37. Raja AS GJ, Qaseem A, Denberg TD, Fitterman N, Schuur JD. Evaluation of patients With Suspected Acut Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Commiittee of the American Collage of Physicians. *Ann Intern Med*. 2015;163:701-11.
  38. Kelly J, Rudd A, Lewis RR, Hunt BJJAoIM. Plasma D-dimers in the diagnosis of venous thromboembolism. 2002;162(7):747-56.
  39. Kollef MH, Zahid M, Eisenberg PRJCcm. Predictive value of a rapid semiquantitative D-dimer as-

- say in critically ill patients with suspected venous thromboembolic disease. 2000;28(2):414-20.
40. Marino PL. (2013) MstIBFeP, US. Wolters Kluwer Health/Lippincott Williams & Wilkins.
41. Giannitsis E, Müller-Bardorff M, Kurowski V, Weidtmann B, Wiegand U, Kampmann M, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. 2000;102(2):211-7.
42. Ribeiro A LP, Juhlin-Dannfelt A, et al. Doppler echocardiography in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J. 1997;134:479-87.
43. Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jäckle S, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. 2002;106(10):1263-8.
44. Kanar BG SA, Göl G, Oğur E, Kavas M, Atas H, Mutlu B. . Timing and magnitude of regional right ventricular function and their relationship with early hospital mortality in patients with acute pulmonary embolism. . Anatol J Cardiol. 2019 Jun;22(1):26-32. doi: 10.14744.
45. Ten Wolde M TI, Mulder JWM, et al. . Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. Circulation. 2003;107(16):2082-4.
46. Konstantinides SV TA, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. . Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the Endorsed by the European Respiratory Society (ERS). Eur Heart J. 2014;35(43):3033-80.
47. Boscheri A WC, Langer M, Schoen S, Wiedemann B, Stolte D, at al. Correlation of heart-type fatty acid-binding protein with mortality and echocardiographic data in patients with pulmonary embolism at intermediate risk. Am Heart J. 2010;160(2):294-300.
48. Puls M DC, Lankeit M, Olschewski M, Binder L, Geibel A, Reiner C, Schäfer K, Hasenfuss G, Konstantinides S. Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism. Eur Heart J. 2007; 28 (2):224-9.
49. Zhan ZQ WC, Nikus KC, et al. . Electrocardiogram patterns during hemodynamic instability in patients with acute pulmonary embolism. Ann Noninvasive Electrocardiol 2014;;19::543-51.
50. Goldhaber SZ BH. Pulmonary embolism and deep vein thrombosis. Lancet 2012;379:1835-46.
51. Gottschalk A SP, Goodman LR, et al. Overview of Prospective Investigation of Pulmonary Embolism Diagnosis II. Semin Nucl Med. 2002;32:173-82.
52. Stein PD FS, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354:2317-27.
53. Im DJ HJ, Han KH, et al. Acute pulmonary embolism: retrospective cohort study of the predictive value of perfusion defect volume measured with dual-energy CT. AJR Am J Roentgenol. 2017;209:1015-22.
54. Moore AJE WJ. Imaging of acute pulmonary embolism: an update. Cardiovasc Diagn Ther. 2018 Jun;8(3):225-43.
55. Parker JA CR, Grady E, et al. SNM practice guideline for lung scintigraphy 4.0. J Nucl Med Technol. 2012;40:57-65.
56. Wells PS GJ, Anderson DR, Kearon C, Gent M, Turpie AG, at al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med Clin N Am. 1998;129:997-1005.
57. Anderson DR KS, Rodger MA, Kovacs MJ, Morris T, Hirsch A, at al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA 2007;298:2743 53.
58. Mattsson S JL, Leide Svegborn S, et al. Radiation dose to patients from radiopharmaceuticals: a compendium of current information related to frequently used substances. Ann ICRP. 2015;44:7-321.
59. Öncel G ÖD. Çift Kaynak Çift Enerji Bilgisayarlı Tomografi Teknik ve Klinik Uygulamaları. Türkiye Klinikleri J Radiol-Special Topics. 2014;7:1-11.
60. Guanella R RM. Serial limited versus single complete compression ultrasonography for the diagnosis of lower extremity deep vein thrombosis. Semin Respir Crit Care Med. 2012;33:144-50.
61. Da Costa Rodrigues J AS, Combescure C, Le Gal G, Perrier A. Diagnostic characteristics of lower limb venous compression ultrasonography in suspected pulmonary embolism: a meta-analysis. J Thromb Haemost. 2016;14:1765 72.
62. Le Gal G RM, Sanchez O, Roy PM, Baba-Ahmed M, Perriers A, at al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed

- tomography in suspected patients. *Thromb Haemost.* 2006;95:963-6.
63. Righini M LGG, Aujesky D, Roy PM, Sanchez O, Verschuren F. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet.* 2008;371:1343-1345.
  64. Bova C G, Misuraca G, Serafini O, Crocco F, Greco A, Noto A. Diagnostic utility of echocardiography in patients with suspected pulmonary embolism. *Am J Emerg Med.* 2003;21:180-3.
  65. Kurzyna M TA, Pruszczyk P, Burakowska B, Fiążkowska A, Kober J at all. Disturbed right ventricular ejection pattern as a new Doppler echocardiographic sign of acute pulmonary embolism. *Am J Cardiol* 2002;90:507-11.
  66. Roy PM CI, Durieux P, Chatellier G, Sors H, Meyer G. Systematic review and meta-analys is of strategies for the diagnosis of suspected pulmonary embolism. *BMJ* 2005;331:259.
  67. Kucher N LC, Do "rnho" fer T, Windecker S, Meier B, Hess OM. Novel management strategy for patients with suspected pulmonary embolism. *Eur Heart J.* 2003;24(4):366-76.
  68. Grifoni S OI, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation.* 2000;101:2817-22.
  69. Kasper W KS, Geibel A, et al. Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism. *Heart.* 1997;77:346-9.
  70. Segal JB SM, Hofmann LV, at all. Management of venous thromboembolism: a systematic review for a practice guideline. *Ann Intern Med.* 2007;146(3):211-22.
  71. Beckman JA DK, Sasahara AA, et al. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic PE. *Thromb Haemost.* 2003;89:953-8.
  72. Kearon C KS, Agnelli G, et al. Antithrombotic therapy for VTE: ACCP evidence-based clinical practice guidelines. *Chest.* 2008;133:454-545.
  73. Harenberg J RP, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. *Haemostasis.* 1996;26:127-39.
  74. Raschke RA RB, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a 'standard care' nomogram. A randomized controlled trial. *Ann Intern Med.* 1993;119(9):874-81.
  75. VF T. Treatment of pulmonary embolism: anti-coagulation, thrombolytic therapy, and complications of therapy. *Crit Care Clin.* 2011;27:825-39.
  76. Garcia DA BT, Weitz JI, Samama MM.. ; (Suppl): Parenteral anticoagulants. *Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:* American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141.
  77. Bethesda M. Protamine Sulfate. *AHFS Drug Information.* American Society of Health System Pharmacists. 2012:1618-20.
  78. Derneği TT. Pulmoner Tromboembolizm Tani Ve Tedavi Uzlaşı Rapo. 2015.
  79. SZ G. Pulmonary Embolism. In: Zipes L, Bonow, Mann, Tomaselli, editor. *Braunvald's Heart Disease E-Book*2019.
  80. Buller HR DB, Decousus H, et al. . ;: Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med.* 2003;349:1695-702.
  81. TA M. New synthetic antithrombotic agents for venous thromboembolism: pentasaccharides, direct thrombin inhibitors, direct Xa inhibitors. *Clin Chest Med.* 2010;31:707-18.
  82. Fondaparinux. Gold Standard. *DRUG MONOGRAPH*2019.
  83. Kearon C AE, Ornelas J, et al. : . () , 10.1016/j.chest.2015.11.026. Antithrombotic therapy for VTE disease. *CHEST guideline and expert panel report.* *Chest* 2016;149(2):315-52.
  84. Bell WR ST, DeMets DL. The clinical features of submassive and massive pulmonary emboli. *Am J Med.* 1977 62(3):355-60.
  85. Stein PD AA, Henry JW, et al. Fever in acute pulmonary embolism. *Chest.* 2000;117:39-42.
  86. Admon AJ SC, Gershengorn HB, Wunsch H, and Cooke CR, . () Dec; () . doi: . Hospital-Level Variation in ICU Admission and Critical Care Procedures for Patients Hospitalized for Pulmonary Embolism. *Chest.* 2014;146(6):1452-61.
  87. Bova C SO, Prandoni P, Lankeit M, Konstantinides S, Vanni S, Jiménez D. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. *Eur Respir J.* 2014 44(3):694-703.
  88. Becattini C AG, Lankeit M, Masotti L, Pruszczyk P, Casazza F. Acute pulmonary embolism: mortality prediction by the 2014 European Society of

- Cardiology risk stratification model. Eur Respir J. 2016;48(3):780-6.
89. Jiménez D KD, Tapson V, Briese B, Schreiber D, Lobo JL, et al. Derivation and validation of multi-marker prognostication for normotensive patients with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med. 2014;189(6):718-26.
  90. Meyer G1 VE, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370(15):1402-11.
  91. Jimenez D LJ, Fernandez-Golfin C, Portillo AK, Nieto R, Lankeit M, Konstantinides S, et al. Effectiveness of prognosticating pulmonary embolism using the ESC algorithm and the Bova score. Thromb Haemost. 2016;115:827-34.
  92. Hobohm L HK, Hasenfuss G, Munzel T, Konstantinides S, Lankeit M. Comparison of risk assessment strategies for not-high-risk pulmonary embolism. Eur Respir J. 2016;47:1170-8.
  93. Fernandez C BC, Sanchez O, Prandoni P, Lankeit M, Konstantinides S, et al. Validation of a model for identification of patients at intermediate to high risk for complications associated with acute symptomatic pulmonary embolism. Chest. 2015;148:211-8.
  94. Aujesky D1 RP, Verschuren F, Righini M, Osterwalder J, Egloff M, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet. 2011;378(2):41-8.
  95. Kostrubiec M PP, Bochowicz A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. Eur Heart J. 2005;26:2166-72.
  96. Sanchez O TL, et al. Prognostic factors for pulmonary embolism: the PREP study, a prospective multicenter cohort study. Am J Respir Crit Care Med. 2010;181:168-73.
  97. Dellas C PM, Lankeit M, et al. Elevated heart-type fatty acid binding protein levels on admission predict adverse outcome in normotensive patients with acute pulmonary embolism. J Am Coll Cardiol. 2010;55:2150-7.
  98. Green EM GM. Management of acute right ventricular failure in the intensive care unit. Curr Heart Fail Rep. 2012;9:228-35.
  99. Mercat A DJ, Meyer G, Teboul JL, Sors H. Hemodynamic effects of fluid loading in acute massive pulmonary embolism. Crit Care Med. 1999;27:540-4.
  100. Kabrhel C RR, Channick R, et al. A Multidisciplinary Pulmonary Embolism Response Team: Initial 30-Month Experience With a Novel Approach to Delivery of Care to Patients With Submassive and Massive Pulmonary Embolism. Chest. 2016;150(2):384-93.
  101. Rali PM CG, 10.1164/rccm.201711-2302CI. Submassive pulmonary embolism. Am J Respir Crit Care Med. 2018;198(5):588-98.
  102. KE W. Major pulmonary embolism. Crit Care Clin. 2011;27:885-906.
  103. Marti C JG, Konstantinides S, Combescure C, Sanchez O, Lankeit M, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2015;36:605-14.
  104. Wan S QD, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004;110:744-9.
  105. Hamel E PG, Vincentelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. Chest. 2001;120:120-5.
  106. S K. Thrombolysis in submassive pulmonary embolism – Yes. J Thromb Haemost. 2003;1:1127-9.
  107. JE. D. Thrombolysis in submassive pulmonary embolism – No. J Thromb Haemost. 2003;1:1130-2.
  108. Konstantinides S GA, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347:1143-50.
  109. Wang C ZZ, Yang Y, et al. Efficacy and Safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism. Chest. 2010;137:254-62.
  110. Kiser TH BE, Clark B, Ho PM, Allen RR, Moss M, et al. Half-Dose Versus Full-Dose Alteplase for Treatment of Pulmonary Embolism. Crit Care Med. 2018;46(10):1617-25.
  111. Aggarwal V NC, Lee A, Bashir R. Acute Management of Pulmonary Embolism Expert Analysis. American College of Cardiology Foundation. 2017;12:1-12.
  112. Avgerinos ED CR. Catheter-directed interventions for acute pulmonary embolism. J Vasc Surg. 2015;61:559-65.
  113. Adusumalli S GB. Trends in catheter-directed thrombolysis and systemic thrombolysis for the

- treatment of pulmonary embolism. *Am Heart J.* 2019;207:83–8.
114. Avgerinos ED LN, El-Shazly OM, et al. Improved early right ventricular function recovery but increased complication with catheter directed interventions compared to anticoagulation alone for submassive pulmonary embolism. *J Vasc Surg Venous Lymphat Disord* 2016;4 (3):268–75.
  115. Braaten JV GR, Francis CW. Ultrasound reversibly disaggregates fibrin fibers. *Thromb Haemost.* 1997;78:1063–8.
  116. Francis CW BA, Lee S, Cox C. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. *Ultrasound Med Biol.* 1995;21:419–24.
  117. Kaymaz C AO, Tanboga IH, Hakgor A, Yilmaz F, Ozturk S. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: a meta-analysis. *Curr Vasc Pharmacol.* 2018;16:179–89.
  118. Kucher N BP, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation* 2014;129:479–86.
  119. Avgerinos E CR. Pulmonary Embolism: Presentation, Natural History, and Treatment. In: Sidawy AN PB, editor. Rutherford's Vascular Surgery and Endovascular Therapy. E-Book: google book; 2018.
  120. Engelberger RP KN. Catheter-based reperfusion treatment of pulmonary embolism. *Circulation.* 2011;124:2139–44.
  121. Meneveau N SM, Blonde MC, Legalry P, Didier-Petit K, Briand F, et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest.* 2006;129:1043–50.
  122. Fukuda I DK. Surgical Embolectomy for Acute Pulmonary Thromboembolism. *Ann Vasc Dis.* 2017;10(2):107–14.
  123. Samoukovic G MT, deVarennes B. The role of pulmonary embolectomy in the treatment of acute pulmonary embolism: a literature review from 1968 to 2008. *Interact Cardiovasc Thorac Surg.* 2010;11:265–70.
  124. Group PS. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation* 2005;112:416–22.
  125. Weinberg A TV, Ramzy D. Massive Pulmonary Embolism: Extracorporeal Membrane Oxygenation and Surgical Pulmonary Embolectomy. *Semin Respir Crit Care Med.* 2017;38(1):66–72.
  126. Miyazaki K HM, Kuwahara Y, Ishida T, Sugiyama K, Hamabe Y. Extracorporeal cardiopulmonary resuscitation for massive pulmonary embolism in a “hybrid emergency room”. *Am J Emerg Med.* 2019;19:30043–9.
  127. Douflé G FN. Monitoring during extracorporeal membrane oxygenation. *Curr Opin Crit Care.* 2016;22(3):230–8.
  128. Kane EV CC, Dobbie R, et al. A populationbased study of venous thrombosis in pregnancy in Scotland 1980–2005. *Eur J Obstet Gynecol Reprod Biol.* 2013;169:223–9.
  129. Knight M KS, Brocklehurst P, et al. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12 Oxford. 2014.
  130. van der Pol LM TC, Bistervels IM, Ainle FN, van Bemmel T, Bertoletti L. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. *N Engl J Med.* 2019;380:1139–49.
  131. Simcox LE OL, Tower C, Greer LA. Pulmonary thrombo-embolism in pregnancy: diagnosis and management. *Breathe.* 2015;11 (4):282–9.
  132. Romualdi E DF, Rancan E, Squizzato A, Steidl L, Middeldorp S. Anticoagulant therapy for venous thromboembolism during pregnancy: a systematic review and a meta-analysis of the literature. *J Thromb Haemost.* 2013;11:270–81.
  133. Kenneth V LJ, AND Sterling M. Acute Pulmonary Embolism. In: Joseph E. Parrillo RPD, editor. Critical Care Medicine Principles of Diagnosis and Management in Adult. Philadelphia: Elsevier; 2019. p. 670–89.
  134. van der Pol LM TC, Bistervels IM, Ainle F, van Bemmel T, Bertoletti L. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. *N Engl J Med.* 2019;380(12):1139–49.
  135. Cook D CM, Meade M, Rabbat C, Griffith L, Schiff D, et al. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *Crit Care Med.* 2005;33:1565–71.
  136. Minet C LM, Savoye PY, Menez C, Ruckly S, Bonadona A, et al. Pulmonary embolism in me-

- chanically ventilated patients requiring computed tomography: Prevalence, risk factors, and outcome. *Crit Care Med.* 2012;40:3202–8.
137. Geerts WH BD, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:381S–453S.
  138. Darze ES LA, Guimaraes AG, Guedes RA, Santos AB, de Moura SS, et al. Incidence and clinical predictors of pulmonary embolism in severe heart failure patients admitted to a coronary care unit. *Chest.* 2005;128:2576–80.
  139. Shorr AF WM. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost.* 2009;101:139–44.
  140. Cook D AJ, Weaver B, McDonald E, Meade M, Crowther M. Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients. *J Crit Care.* 2000;15:127–32.
  141. Laporte S MP, Décousus H, et al. the RIETE Investigators. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism. Findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation.* 2008;117:1711–6.
  142. Schonhfer B KB. Prevalence of deep-vein thrombosis in the leg in patients with acute exacerbation of chronic obstructive lung disease. *Respiration.* 1998;65:173–7.
  143. Gunen H GG, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. *European Respiratory Journal.* 2010;35:1243–8.
  144. Moser KM LJ, Nachtwey FJ, Spragg RG. Deep venous thrombosis and pulmonary embolism. Frequency in a respiratory intensive care unit. *JAMA.* 1981;246:1422–4.
  145. Cade J. High risk of the critically ill for venous thromboembolism. *Crit Care Med.* 1982;10(7):448–50.
  146. Cook D MM, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med.* 2011;364:1305–14.
  147. Harris LM CG, Booth FV, Hassett Jr JM, Leney G, Ricotta JJ. Screening for asymptomatic deep vein thrombosis in surgical intensive care patients. *J Vasc Surg.* 1997;26:764–9.
  148. Perkins GD MD, Davies S, Gao F. Discrepancies between clinical and postmortem diagnoses in critically ill patients: an observational study. *Crit Care Clin.* 2003;7:129–32.
  149. McLeod AG GW. Venous thromboembolism prophylaxis in critically ill patients. *Crit Care Clin.* 2011;27:765–80.
  150. Timsit JF FJ, Boyer JM, Martin JB, Misset B, Renaud B, et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. *Chest.* 1998;114:207–13.
  151. Chastre J CF, Bouchama A, Viau F, Benacerraf R, Gibert C. Thrombosis as a complication of pulmonary-artery catheterization via the internal jugular vein: prospective evaluation by phlebography. *N Engl J Med.* 1982;306:278–81.
  152. Mai C HD. Upper-extremity deep venous thrombosis: a review. *Am J Med.* 2011;124:402–7.
  153. Munoz FJ MP, Poggio R, Valle R, Barron M, Guil M, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. *Chest.* 2008;133:143–8.
  154. Ibrahim EH IM, Prentice D, Sherman G, Kollef MH, Shannon W. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. *Crit Care Med.* 2002;30:771–4.
  155. Raad II LM, Khalil SA, Costerton JW, Lam C, Bodey GP. The relationship between the thrombotic and infectious complications of central venous catheters. *JAMA.* 1994;271:1014–6.
  156. Kollef MH LN, Ahrens TS, et al. The use of continuous intravenous sedation is associated with prolongation of mechanical ventilation. *Chest.* 1998;114:541–8.
  157. Minet C PL. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. *Crit Care Clin.* 2015;19(1):287–94.
  158. Schultz DJ BK, Washington L, Goodman LR, Quickel RR, Lipchik RJ, et al. Incidence of asymptomatic pulmonary embolism in moderately to severely injured trauma patients. *J Trauma.* 2004;56:727–31.
  159. Bahloul M CA, Dammak H, Medhioub F, Abid L, Ksibi H, et al. Posttraumatic pulmonary embolism in the intensive care unit. *Ann Thorac Med.* 2011;6:199–206.
  160. Katz JN KK, Becker RC. Beyond thrombosis: the versatile platelet in critical illness. *Chest.* 2011;139:658–68.

161. Sathe PM PU. D Dimer in acute care. *Int J Crit Illn Inj Sci.* 2014;4:229–32.
162. Crowther MA CD, Griffith LE, Devereaux PJ, Rabbat CC, Clarke FJ, et al. Deep venous thrombosis: clinically silent in the intensive care unit. *J Crit Care.* 2005;20:334–40.
163. Fraser JD AD. Deep venous thrombosis: recent advances and optimal investigation with US. *Radiology.* 1999;211:9–24.
164. Kory PD PC, Shiloh AL, Mayo PH, DiBello C, Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. *Chest.* 2011;139:538–42.
165. Dagadaki O BK, Mariolis T, Balopoulos G and Myriantheis P. Necessity of the periodical ultrasound assessment of the peripheral venous system in intensive care unit patients. *Ultrasound in Med & Biol.* 2019;45(2):367-73.
166. Patel S KE, Cascade PN. Pulmonary embolism: optimization of small pulmonary artery visualization at multi-detector row CT. *Radiology.* 2003;227:455–60.
167. Remy-Jardin M PM, Goodman LR, Gefter WB, Gottschalk A, Mayo JR, et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. *Radiology.* 2007;245:315–29.
168. Schwebel C ChC, Magne S, Minet C, Garrouste-Orgeas M, Bonadona A, et al. Safety of intrahospital transport in ventilated critically ill patients: a multicenter cohort study. *Crit Care Med.* 2013;41:1919–28.
169. Miniati M MS, Pratali L, Di Ricco G, Marini C, Formichi B, et al. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. *Am J Med.* 2001;110:528–35.
170. Pruszczynski P TA, Pacho R, Chlebus M, Kuch-Wocial A, Pruszynski B, et al. Noninvasive diagnosis of suspected severe pulmonary embolism: transesophageal echocardiography vs spiral CT. *Chest.* 1997;112:722–8.
171. Collins R SA, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med.* 1988;318(18):1162–73.
172. Mismetti P L-SS, Tardy B, Cucherat M, Buchmuller A, Delsart D, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a metaanalysis of randomised clinical trials. *Thromb Haemost.* 2000;83:14–9.
173. Kapoor M KY, Tessler S. Subcutaneous heparin prophylaxis significantly reduces the incidence of venous thromboembolic events in the critically ill. *Crit Care Med.* 1999;27:A69.
174. Fraisse F HL, Couland JM, Simonneau G, Beddock B, Feissel M, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med.* 2000(161):1109–14.
175. Ho KM CS, Pilcher D. Omission of early thromboprophylaxis and mortality in critically ill patients: a multicenter registry study. *Chest.* 2011 140:1436–46.
176. Arnold DM DL, Clarke FJ, Tkaczyk AJ, Heels-Ansdell D, Ztyaruk N, et al. Bleeding during critical illness: a prospective cohort study using a new measurement tool. *Clin Invest Med.* 2007;30:93–102.
177. Cook D DJ, Meade M, Guyatt G, Ztyaruk N, Granton J, et al. Venous thromboembolism and bleeding in critically ill patients with severe renal insufficiency receiving dalteparin thromboprophylaxis: prevalence, incidence and risk factors. *Crit Care Clin.* 2008;12:32.
178. Mismetti P LS, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg.* 2001;88:913–30.
179. Geerts WH JR, Code CI, Chen E, Szalai JP, Saibil EA, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med.* 1996;336:701–7.
180. Kleber FX WC, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. *Am Heart J.* 2003;145:614–21.
181. Alhazzani W LW, Jaeschke RZ, Murad MH, Cade J, Cook DJ. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med.* 2013;41:2088–98.

182. Kearon C AE, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e419S–94S.
183. Rabbat CG CD, et al. Dalteparin thrombo-prophylaxis for critically ill medical-surgical patients with renal insufficiency. *Journal of Critical Care*. 2005;20(4):357–63.
184. Vahtera A VS, Pettilä V, Kuitunen A. Plasma anti-FXa level as a surrogate marker of the adequacy of thromboprophylaxis in critically ill patients: A systematic review. *Thrombosis Research*. 2016;139 10–6.
185. Malinoski D JF, Ewing T, et al. Standard prophylactic enoxaparin dosing leads to inadequate anti-Xa levels and increased deep venous thrombosis rates in critically ill trauma and surgical patients. *J Trauma*. 2010;68 874–9.
186. Haas CE NJ, Raghavendran K, Mihalko W, Beres J, Ma Q, et al. Pharmacokinetics and pharmacodynamics of enoxaparin in multiple trauma patients. *J Trauma*. 2005;59:1336–43.
187. Dorffler-Melly J dJE, Pont AC, Meijers J, Vroom MB, Buller HR, et al. . . ;. Bioavailability of subcutaneous low-molecular-weight heparin to patients on vasopressors. *Lancet*. 2002;359:849–50.
188. Priglinger U DKG, Geppert A, Joukhadar C, Graf S, Berger R, et al. . . ;. Prophylactic anticoagulation with enoxaparin: is the subcutaneous route appropriate in the critically ill? *Crit Care Med*. 2003;31:1405–9.
189. Mayr AJ DM, Jochberger S, Fries D, Klingler A, Joannidis M, et al. Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin. *Thromb Res*. 2002;105:201–4.
190. Robinson S ZA, Strom T, Larsen TB, Rasmussen B, Toft P. Enoxaparin, effective dosage for intensive care patients: double-blinded, randomised clinical trial. *Crit Care*. 2010;14(2):R41.
191. Lim W DF, Eikelboom JW, Crowther MA. Meta-analysis: lowmolecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*. 2006;144:673–84.
192. Limpus A CW, McDonald E, Thalib L . . . ;. quiz/ discussion, 411-2. Mechanical thromboprophylaxis in critically ill patients: a systematic review and meta-analysis. *Am J Crit Care*. 2006;15:402–10.
193. Kierkegaard A NL. Graduated compression stockings in the prevention of deep vein thrombosis in patients with acute myocardial infarction. *Eur Heart J*. 1993;14:1365–8.
194. Elliott CG DT, Egger M, Orme JF, Clemmer TP, Horn SD, et al. Calf-thigh sequential pneumatic compression compared with plantar venous pneumatic compression to prevent deep-vein thrombosis after non-lower extremity trauma. *J Trauma*. 1999;47:25–32.
195. Ginzburg E CS, Lopez J, Jackowski J, Brown M, Hameed SM. Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. *Br J Surg*. 2003;90:1338–44.
196. Vignon P DP, Renault A, Mathonnet A, Paleiron N, Imbert A, et al. Intermittent pneumatic compression to prevent venous thromboembolism in patients with high risk of bleeding hospitalized in intensive care units: the CIREA1 randomized trial. *Intensive Care Med*. 2013;39:872–80.
197. Agnelli G PF, Buoncristiani P, Severi P, Pini M, D'Angelo A, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med*. 1998;339:80–5.

