SUPPLEMENTARY MATERIAL

PICO questions and recommendations supported by weaker evidence

1) PRETRANSPLANT PERIOD

1.1) Should patients listed for LT receive specific therapy to correct coagulation disorders before undergoing invasive procedures? (Continued)

1.1.4- In elective procedures associated with a high risk of bleeding (table 1), thrombopoietin agonists could be recommended prior to the procedure to increase the platelet count, although the potential risk of derived portal vein thrombosis should be taken into account[1,2] (Recommendation 2B).

1.3) Should patients at risk of portal vein thrombosis receive thromboprophylaxis while awaiting LT? (Continued)

1.3.2- Thromboprophylaxis may not be universally recommended to prevent portal vein thrombosis[3] (Recommendation 2B).

1.3.3- Surveillance should be based on dynamic imaging techniques in patients at increased risk of portal vein thrombosis according to the criteria listed in table 3 (main document)[4-7] (Recommendation 1C).

1.4) Should patients with portal vein thrombosis receive anticoagulation or other interventions to prevent progression of thrombosis while awaiting LT? (Continued)

1.4.8- Direct acting oral anticoagulants should not be used routinely in this setting[8-10] (Recommendation 2B). If a patient awaiting LT is receiving a direct acting oral

anticoagulant, its specific antidote should be available in the transplant institution for use before LT[8-10] (Recommendation 1B).

1.6) Should patients listed for LT receive specific therapy to correct coagulation disorders?

1.6.1- In the absence of active bleeding, no specific haemostatic intervention is required to correct abnormalities in conventional coagulation tests inherent to end stage liver disease[11-14] (Recommendation 1B). The use of vitamin K, antifibrinolytic agents and thrombopoietin agonists is not routinely recommended in asymptomatic patients[15,16] (Recommendation 1C).

2) INTRAOPERATIVE PERIOD

2.1) Should cirrhotic patients admitted to the hospital for LT undergo prophylactic correction of altered standard coagulation tests? (Continued)

2.1.4- No specific haemostatic intervention is required to correct alterations in conventional coagulation tests immediately before LT. In patients with a platelet count < 30,000/μL and/or fibrinogen <1 g/L, replacement therapy can be considered taking into account baseline thromboelastography if available[17] (Recommendation 1C).

2.1.5- The optimal dose of tranexamic acid, for either prophylactic or therapeutic purposes is unknown. In most centres, an initial intravenous dose of 5-10 mg/Kg is administered, with or without a subsequent continuous perfusion of 5-10 mg/Kg/h as appropriate (Recommendation 2C).

2.2) Should patients admitted to the hospital for LT revert the effect of anticoagulant or antiplatelet therapy prior to surgery? (Continued)

2.2.5- In patients with an INR>3.5 the administration of a prothrombin complex can be considered. The optimal dosing is unknown, but it is advised to avoid >20-25 IU/kg[18-21] (Recommendation 2C).

2.2.6- In patients receiving low molecular weight heparin, protamine sulfate can be administered if the interval from the last heparin dose is <12 hours and there is intraoperative coagulopathic bleeding. Assessment of anti-Xa can aid in evaluating the residual heparin effect[22] (Recommendation 2B).

2.2.7- No specific recommendation can be issued regarding the use of prothrombin complex[18,23] (Recommendation 2C).

2.4) Should patients with intraoperative haemostatic abnormalities receive replacement of coagulation factors or platelets? (Continued)

2.4.3- Frozen plasma is not recommended except in cases with massive bleeding[24]. The usual dosing is 10-15 mL/kg (Recommendation 2C).

2.5) Should patients undergoing LT receive tranexamic acid intraoperatively to reverse hyperfibrinolysis?

2.5.1- If thromboelastography is available, the prophylactic use of tranexamic acid can be tailored on a case by case basis according to established algorithms (table 2 from the main document) [25-27] (Recommendation 1C).

3) POSTRANSPLANT PERIOD

3.2) Should patients receive thromboprophylaxis after LT to prevent venous thromboembolism? (Continued)

3.2.3- Pharmacological thromboprophylaxis with low molecular weight heparin should be tailored according to the individual risk of thrombosis according to the Caprini scale[28] (online calculator available at: Caprini Score for DVT Risk Calculator (mdapp.co)). Patients at low risk of thrombosis (Caprini 1-2) do not require pharmacological thromboprophylaxis. Patients with moderate risk of thrombosis (Caprini 3-4) should start low molecular weight heparin 24 hours after surgery. In patients at high risk of thrombosis (Caprini>4), low molecular weight heparin should be started 12 hours after surgery whenever possible[29,30] (Recommendation 1C).

3.4) Should patients receive specific therapy to prevent portal vein or hepatic vein thrombosis after LT? (Continued)

3.4.2- There is no evidence to support the universal prescription of anticoagulant therapy to prevent portal vein or hepatic vein thrombosis after LT[31] (Recommendation 2C).

3.4.3- In patients meeting criteria to start therapeutic low molecular weight heparin, this should be prolonged at least 2 months after LT, and individualised thereafter[32] (Recommendation 1C).

3.7) Should patients with pretransplant antiplatelet therapy resume these drugs after LT?

3.7.1- In patients at high risk of thrombosis, antiplatelet therapy may be resumed as soon as possible, within the first 24 hours after LT, provided that the platelet count is >30,000/µL and in the absence of bleeding complications[33,34] (Recommendation 2B).

3.7.2- In patients with moderate or low risk of thrombosis, antiplatelet therapy can be initiated between postoperative days 5 to 7 provided that the platelet count is >30 000/µL – 50 000/µL[33,34] (Recommendation 2B).

3.7.3- The combination of anticoagulant and antiplatelet therapy is not formally contraindicated after LT except in patients with ongoing bleeding complications[33,34] (Recommendation 2B).

3.8) Should patients receive specific therapy to prevent hepatic artery thrombosis early after LT?

3.8.1- There is no evidence to support the universal prescription of antiplatelet therapy to prevent hepatic artery thrombosis after LT[31,35,36] (Recommendation 2C).

3.8.2- Antiplatelet therapy (aspirin 100 mg/day) can be used from the early postoperative period in patients with risk factors of hepatic artery thrombosis (table 4 from the main document). Careful evaluation of risks and benefits is required in patients with low platelet count <30 000-50 000/µL[35,37-39] (Recommendation 2C).

3.8.3- In patients meeting criteria to start antiplatelet therapy to prevent hepatic artery thrombosis, this should be prolonged at least 6 months after LT, and individualized thereafter[37] (Recommendation 1C).

3.9) Should patients with hepatic artery thrombosis after LT receive specific haemostatic management?

3.9.1- Endovascular therapy could be indicated in patients with hepatic artery thrombosis and preserved liver graft function. Catheter directed fibrinolysis with urokinase plasminogen activator is preferred over tissue type plasminogen activator due to the inherent risk of bleeding after LT. Low dose heparin can also be administered[40-42] (Recommendation 2C).

3.9.2- After catheter directed fibrinolysis, continuous intravenous sodium heparin infusion for 48 to 72 hours can be considered. The dose of sodium heparin should be

adjusted to the target activated partial thromboplastin time ratio between 1.5 and 2[41,42]. (Recommendation 2C).

3.9.3- If fibrinolysis is successful, antiplatelet therapy with aspirin (100 mg daily) should be maintained for at least 6 months[41,42] (Recommendation 1C).

3.9.4- If a stent is placed in the hepatic artery, continuous intravenous sodium heparin infusion is recommended during the procedure, and combined antiplatelet therapy with clopidogrel 75 mg od and aspirin 100 mg od should be maintained for 1 month in patients receiving bare stents, or for 6 months in patients receiving covered or drug-eluting stents. Lifetime antiplatelet therapy with aspirin 100 mg od is advised[42] (Recommendation 1C).

3.9.5- If surgical thrombectomy and reanastomosis is performed, a single intraoperative dose of intravenous aspirin (300 mg) can be considered. After the procedure, antiplatelet therapy with aspirin 100 mg od should be started as soon as possible and maintained long term[42] (Recommendation 1C).

3.9.6- In case of retransplantation, no specific recommendation can be issued regarding the need for antiplatelet therapy. Decisions should be made on a case by case basis (Recommendation 1C).

3.9.7- Antiplatelet therapy alone can be a valid therapeutic option in patients with hepatic artery thrombosis incidentally diagnosed beyond the first postoperative year and in the absence of clinical repercussion (Recommendation 2C).

<u>3.10) Should patients with portal vein or hepatic vein thrombosis after LT receive specific haemostatic management?</u>

3.10.1- In patients with portal vein thrombosis, anticoagulation with low molecular weight heparin should be recommended for at least 6 months (or at least 12 months if mesenteric or splenic veins are involved)[43] (Recommendation 1C).

3.10.2- In patients with portal vein thrombosis undergoing surgical or percutaneous thrombectomy, low molecular weight heparin (with or without subsequent conversion to vitamin K antagonists) for at least 6 months is recommended (or at least 12 months if mesenteric or splenic veins are involved)[43] (Recommendation 1C).

3.10.3- In patients with portal vein stenosis requiring stenting, lifetime antiplatelet therapy with aspirin 100 mg od may be administered[44] (Recommendation 1C).

3.10.4- In patients with portal vein thrombosis requiring stenting, anticoagulation with low molecular weight heparin (with or without subsequent conversion to vitamin K antagonists) for at least 6 months is recommended, followed by lifetime antiplatelet therapy with aspirin 100 mg od (Recommendation 1C).

3.10.5- In patients with hepatic vein thrombosis, anticoagulation with low molecular weight heparin for 3-6 months is recommended with subsequent conversion to lifetime vitamin K antagonists (Recommendation 1C).

3.10.6- In patients with hepatic vein stenosis undergoing percutaneous angioplasty or stenting, continuous intravenous sodium heparin infusion is recommended during the procedure. Low molecular weight heparin should be administered for 3 months. Then, patients should receive lifetime antiplatelet therapy with aspirin 100 mg od (Recommendation 1C).

REFERENCES

1. Takyar V, Etzion O, Heller T, et al. Complications of percutaneous liver biopsy with Klatskin needles: a 36-year single-centre experience. *Aliment Pharmacol Ther.* 2017;45(5): 744-753.

2. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol.* 2010;8(10): 877-883.

3. Nery F, Chevret S, Condat B, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology.* 2015;61(2): 660-667.

4. Francoz C, Belghiti J, Vilgrain V, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut.* 2005;54(5): 691-697.

5. Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation.* 2000;69(9): 1873-1881.

6. Zocco MA, Di Stasio E, De Cristofaro R, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. *J Hepatol.* 2009;51(4): 682-689.

7. Stine JG, Wang J, Shah PM, et al. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: A matched case-control study. *Liver Int.* 2018;38(1): 94-101.

8. De Gottardi A, Trebicka J, Klinger C, et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. *Liver Int.* 2017;37(5): 694-699.

9. Intagliata NM, Henry ZH, Maitland H, et al. Direct Oral Anticoagulants in Cirrhosis Patients Pose Similar Risks of Bleeding When Compared to Traditional Anticoagulation. *Dig Dis Sci.* 2016;61(6): 1721-1727.

10. Priyanka P, Kupec JT, Krafft M, Shah NA, Reynolds GJ. Newer Oral Anticoagulants in the Treatment of Acute Portal Vein Thrombosis in Patients with and without Cirrhosis. *Int J Hepatol.* 2018;2018: 8432781.

11. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol.* 2015;63(3): 743-752.

12. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med.* 2011;365(2): 147-156.

13. Tripodi A, Salerno F, Chantarangkul V, et al. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology.* 2005;41(3): 553-558.

14. Lisman T, Leebeek FW, Mosnier LO, et al. Thrombin-activatable fibrinolysis inhibitor deficiency in cirrhosis is not associated with increased plasma fibrinolysis. *Gastroenterology.* 2001;121(1): 131-139.

15. Aldrich SM, Regal RE. Routine Use of Vitamin K in the Treatment of Cirrhosis-Related Coagulopathy: Is it A-O-K? Maybe Not, We Say. *P T.* 2019;44(3): 131-136.

16. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. *Liver Int.* 2017;37(6): 778-793.

17. Biancofiore G, Blasi A, De Boer MT, et al. Perioperative hemostatic management in the cirrhotic patient: a position paper on behalf of the Liver Intensive Care Group of Europe (LICAGE). *Minerva Anestesiol.* 2019;85(7): 782-798.

18. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl): e44S-e88S.

19. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl): e326S-e350S.

20. Tischendorf M, Fuchs A, Zeuzem S, Lange CM. Use of prothrombin complex concentrates in patients with decompensated liver cirrhosis is associated with thromboembolic events. *J Hepatol.* 2019;70(4): 800-801.

21. Lisman T, Kleiss S, Patel VC, et al. In vitro efficacy of pro- and anticoagulant strategies in compensated and acutely ill patients with cirrhosis. *Liver Int.* 2018;38(11): 1988-1996.

22. van Veen JJ, Maclean RM, Hampton KK, et al. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis.* 2011;22(7): 565-570.

23. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. *Am J Hematol.* 2019;94(6): 697-709.

24. Rassi AB, d'Amico EA, Tripodi A, et al. Fresh frozen plasma transfusion in patients with cirrhosis and coagulopathy: Effect on conventional coagulation tests and thrombomodulin-modified thrombin generation. *J Hepatol.* 2020;72(1): 85-94.

25. Gorlinger K, Perez-Ferrer A, Dirkmann D, et al. The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. *Korean J Anesthesiol.* 2019;72(4): 297-322.

26. Molenaar IQ, Warnaar N, Groen H, Tenvergert EM, Slooff MJ, Porte RJ. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant.* 2007;7(1): 185-194.

27. Shimauchi T, Yamaura K, Higashi M, Abe K, Yoshizumi T, Hoka S. Fibrinolysis in Living Donor Liver Transplantation Recipients Evaluated Using Thromboelastometry: Impact on Mortality. *Transplant Proc.* 2017;49(9): 2117-2121.

28. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon.* 2005;51(2-3): 70-78.

29. Vivas D, Roldan I, Ferrandis R, et al. Perioperative and Periprocedural Management of Antithrombotic Therapy: Consensus Document of SEC, SEDAR, SEACV, SECTCV, AEC, SECPRE, SEPD, SEGO, SEHH, SETH, SEMERGEN, SEMFYC, SEMG, SEMICYUC, SEMI, SEMES, SEPAR, SENEC, SEO, SEPA, SERVEI, SECOT and AEU. *Rev Esp Cardiol (Engl Ed).* 2018;71(7): 553-564.

30. De Pietri L, Montalti R, Nicolini D, Troisi RI, Moccheggiani F, Vivarelli M. Perioperative thromboprophylaxis in liver transplant patients. *World J Gastroenterol.* 2018;24(27): 2931-2948.

31. Surianarayanan V, Hoather TJ, Tingle SJ, Thompson ER, Hanley J, Wilson CH. Interventions for preventing thrombosis in solid organ transplant recipients. *Cochrane Database Syst Rev.* 2021;3: CD011557.

32. Sharshar M, Yagi S, Iida T, et al. Liver transplantation in patients with portal vein thrombosis: A strategic road map throughout management. *Surgery.* 2020;168(6): 1160-1168.

33. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart

Association Task Force on practice guidelines. *J Am Coll Cardiol.* 2014;64(22): e77-137.

34. Cao D, Chandiramani R, Capodanno D, et al. Non-cardiac surgery in patients with coronary artery disease: risk evaluation and periprocedural management. *Nat Rev Cardiol.* 2021;18(1): 37-57.

35. Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant.* 2009;9(4): 746-757.

36. Wolf DC, Freni MA, Boccagni P, et al. Low-dose aspirin therapy is associated with few side effects but does not prevent hepatic artery thrombosis in liver transplant recipients. *Liver Transpl Surg.* 1997;3(6): 598-603.

37. Marin-Gomez LM, Bernal-Bellido C, Alamo-Martinez JM, et al. Intraoperative hepatic artery blood flow predicts early hepatic artery thrombosis after liver transplantation. *Transplant Proc.* 2012;44(7): 2078-2081.

38. Silva MA, Jambulingam PS, Gunson BK, et al. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. *Liver Transpl.* 2006;12(1): 146-151.

39. Warner P, Fusai G, Glantzounis GK, et al. Risk factors associated with early hepatic artery thrombosis after orthotopic liver transplantation - univariable and multivariable analysis. *Transpl Int.* 2011;24(4): 401-408.

40. Piardi T, Lhuaire M, Bruno O, et al. Vascular complications following liver transplantation: A literature review of advances in 2015. *World J Hepatol.* 2016;8(1): 36-57.

41. Thornburg B, Katariya N, Riaz A, et al. Interventional radiology in the management of the liver transplant patient. *Liver Transpl.* 2017;23(10): 1328-1341.

42. Zhu HK, Zhuang L, Chen CZ, et al. Safety and efficacy of an integrated endovascular treatment strategy for early hepatic artery occlusion after liver transplantation. *Hepatobiliary Pancreat Dis Int.* 2020;19(6): 524-531.
43. Bhangui P, Fernandes ESM, Di Benedetto F, Joo DJ, Nadalin S. Current management of portal vein thrombosis in liver transplantation. *Int J Surg.* 2020;82S: 122-127.
44. Wei BJ, Zhai RY, Wang JF, Dai DK, Yu P. Percutaneous portal venoplasty and stenting for anastomotic stenosis after liver transplantation. *World J Gastroenterol.* 2009;15(15): 1880-1885.