

## Thrombotic complications in inflammatory bowel diseases

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**SUMMARY: Thrombotic complications in inflammatory bowel diseases.**

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*Inflammatory bowel disease (IBD), Crohn's Disease (CD) and Ulcerative Colitis (UC) are associated with an increased risk of arterial and venous thromboembolism. A 2 to 3 time fold increased risk of developing thromboembolic complications was reported for IBD patients compared to general population. A systematic literature search was conducted using PubMed, Medline, Scopus, Cochrane database. The key words were: "Inflammatory Bowel Disease", "Crohn's Disease and Thrombosis", "Ulcerative Colitis and Thrombosis", "Thrombosis" and "Inflammatory Bowel Diseases and Thrombosis".*

*rombosis". Full articles and abstracts were included. Studies such as case reports, letters and commentaries were excluded from the analysis if appropriate data could not be extracted. Although no randomized controlled trials (RCTs) have been established to evaluate the efficacy of thromboprophylaxis in patients with IBD due to the incidence of VTE and PE in such patients, it is highly recommended the adoption of thromboprophylactic measures. Available prophylaxis and treatment options include pharmacological anticoagulant therapy (LMWH-Low Molecular Weight Heparin, Fondaparinux and UH-Unfractionated Heparin) and mechanical prophylaxis. In case of acute VTE patient must be treated with fibrinolytic agents and in selected non-responsive cases vascular surgery. IBD patients have an increased risk of VTE complications. Prophylaxis for VTE should be recommended in all patients who do not show contraindications to treatment.*

KEY WORDS: Inflammatory bowel disease - Venous thromboembolic complications - Deep venous thrombosis - Pulmonary embolism - Prophylaxis.

### Introduction

Inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are associated with an increased risk of arterial and venous thromboembolism (1). Bargen and Barker at the Mayo Clinic already in 1936 recognised and demonstrated the increased risk of thromboembolic events in patients affected by IBD (2, 3).

### Aim and methods

A systematic literature search was conducted us-

ing PubMed, Medline, Scopus, Cochrane database. The key words were: "Inflammatory Bowel Disease", "Crohn's Disease and Thrombosis", "Ulcerative Colitis and Thrombosis", "Thrombosis and "Inflammatory Bowel Diseases and Thrombosis". Full articles and abstracts were included. Studies such as case reports, letters and commentaries were excluded from the analysis if appropriate data could not be extracted.

### Discussion

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are important and undervalued thromboembolic complications to keep in mind that can significantly affect patient morbidity and mortality (4-6). In fact, according to latest population-cohort studies, a 2 to 3 time fold increased risk of developing thromboembolic complications was

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reported for IBD patients compared to general population (6-16). Grainge et al. and Papa et al. demonstrated in their studies that the incidence of thromboembolic events varies depending on the activity phase of the disease, suggesting that there is a higher risk of thromboembolic complications especially during IBD flares (relative risk values are similar for CD and UC) (8, 10, 13-17). These complications appear to be more common in patients younger than 40 years (7-9, 15, 18, 19) in those showing an increase in inflammatory markers and in those with other complications such as stenosis, abscess or fistulization (7, 20). The incidence of these events also seems to be correlated to the extent of the disease itself as it is shown to be higher in patients with pancolitis in UC (19, 21) and with colonic involvement in CD (20). Even though, proctocolectomy is not proved to be protective in order to prevent recurrent thromboembolic events (20). It should not be forgotten that thromboembolism is a multifactorial event that can involve both hereditary and acquired factors that can combine and reasonably increase the prothrombotic risk for the patient (15, 22, 24, 25).

Virchow triad, which includes hypercoagulability, stasis and endothelial dysfunction, explains the fundamental mechanisms of thrombosis (26-29). Two are the main pathomechanisms that have been identified to probably cause thrombosis in

IBD: alterations in coagulation and fibrinolytic systems and platelet dysfunction (10, 11, 23, 24, 26, 30, 31).

If DVT is suspected with a likely DVT Wells Score of 2 (Criteria reported in Table 1) it should be considered to perform either a proximal leg venous ultrasound within 4 hours and if this is negative a D-dimer test, or directly a D-dimer test in addition to a 24 h dosage of a parenteral anticoagulant and a proximal leg venous ultrasound within 24 hours. Whenever D-dimer results positive but the proximal leg venous ultrasound results negative the US should be repeated 6 to 8 days later (32, 33). If PE is suspected with a likely PE Wells Score of 2 (Criteria reported in Table 2) an immediate computer tomography pulmonary angiogram (CTPA) must be performed. If this is not immediately possible, parenteral anticoagulant therapy should be started promptly and it should be followed by a CTPA as soon as possible (32, 33). Although no randomized controlled trials (RCTs) have been established to evaluate the efficacy of thromboprophylaxis in patients with IBD (9, 34) due to the incidence of VTE and PE in such patients, it is highly recommended the adoption of thromboprophylactic measures. These measures are often not respected because of the lack of awareness of the importance of thrombotic risk in this type of patients and the lack of clear data on the use of oral anticoagulants in IBD (5, 10, 26, 35-37).

TABLE 1 - DVT WELLS SCORE.

Clinical feature	Points
Active cancer (treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
An alternative diagnosis is at least as likely as DVT	-2
Clinical probability simplified score	<b>Points</b>
DVT likely	2 points or more
DVT unlikely	1 points or less

TABLE 2 - PE WELL SCORE.

Clinical feature	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate >100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
Clinical probability simplified score	Points
PE likely	More than 4 points
PE unlikely	4 points or less

Two are the main kind of prophylactic measures that should be considered: pharmacological prophylaxis and non-pharmacological prophylaxis (26, 28, 29).

Non-pharmacological prophylaxis consists in the hydration of the patient and eventually in the vitamin supplementation to correct the deficiencies that can determine hyperhomocysteinemia (typically B6, B12 and Folates). If the patient has undergone surgery, he should be mobilized as early as possible and mechanical prophylaxis should be implemented. This can consist of either intermittent pneumatic compression devices (IPC) (16) or graduated compression stockings (GCS). While intermittent pneumatic compression devices reduce stasis by augmenting the pulsatile venous flow and determine secretion of tissue plasminogen activator (tPA) from the endothelial cells increasing fibrinolytic activity, graduated compression stockings (GCS) act by reducing venous stasis and inhibiting Xa coagulation pathway. GCS's drawbacks are represented by the possible onset of skin ulcers (32). Mechanical prophylaxis represents also an important measure that can be adopted in those patients who cannot receive pharmacological prophylaxis because of an active bleeding or of a high bleeding risk (16). Such patients should be switched to pharmacological prophylaxis once the risk is eliminated (9, 24, 36).

Pharmacological prophylaxis involves, as recommended by the latest American College of Chest Physicians Evidence-Based Clinical Practice, the British Society of Gastroenterology and the European Crohn and Colitis Organization guidelines, the use of low molecular weight heparin (LMWH) and unfractionated heparin (UH) (6, 9, 14, 16, 24, 38-42). Unfractionated Heparin (UH) and Low Molecular Weight Heparin (LWMH) can be administered both intravenously and subcutaneously but unfortunately oral administration is not possible because of poor absorption. 5000 units of UH are usually administered subcutaneously 2 hours to then be repeated every 8 to 12 hours (36, 43). Thromboprophylaxis in patients with IBD is recommended for hospitalized patients with exacerbations of the disease in the absence of active bleeding while it is recommended for those patients who do not show signs of severe bleeding upon admission to the hospital. According to some studies, the presence of mild-moderate bleeding should not be considered a reason to avoid the administration of thromboprophylaxis (9, 16, 35). It is also suggested in outpatients of IBD with moderate to severe disease flares that have a clinical history of VTE (16, 35). According to Kohoutova et al., thromboprophylaxis should be also suggested for all patients with active CD and for UC patients with endoscopically con-

firmed findings of extensive disease (35). Said this, the latest Consensus Statements of the Canadian Association of Gastroenterology, being based on a cost-effect for every quality-adjusted life year (QUALY) analysis, strongly discourages anticoagulant thromboprophylaxis in outpatients with active disease if there is not a history of previous VTE (16). The use of oral prophylaxis with vitamin K antagonists (VKA) for VTE has not gained much success because contrarily to UH and LMWH which are easy to use and do not need monitoring, oral anticoagulants such as Warfarin are easier to administer but need monitoring and to balance a correct dosing of the drug (44). As regards Aspirin (ASA) prophylaxis, the SPIRE trial shows no significant decrease in events of VTE compared to placebo, thus not recommending ASA as a prophylactic treatment to prevent VTE (36, 43, 45, 46). In the case of venous thromboembolism in patients with IBD, treatment is the same as for patients without IBD (24, 36). At first, it is recommended to administer the latest NICE guidelines for venous thromboembolic diseases, low molecular weight heparin (LMWH) or Fondaparinux as suggested. UH should be considered in patients with severe renal impairment (eGFR <30 ml / min / 1.73m<sup>2</sup>), with increased risk of bleeding and in patients with PE and haemodynamic instability. In the latter case, if the thrombotic obstruction is massive and is a life threatening condition, the use of fibrinolytic agents is also recommended (32). Treatment should be started as soon as possible and prolonged for at least 5 days or until INR maintains beyond 2 for at least 24 hours.

Even though it is not usually required in ileofemoral DVT, in selected cases which present good functional status, a low bleeding risk and have had symptoms for no longer than 14 days, the use of fib-

rinolytic agents can be considered as a possible therapeutic option (32, 36). When previous treatments are not achievable due to a high risk of bleeding in patients with PE or TVP affected by the presence of fluctuating thrombus despite the creation of an adequate anticoagulant therapy, the placement of a filter for the inferior vena cava should be considered as option (9, 32, 36). Another therapeutic option in the case of contraindication or failure of fibrinolytic therapy is thromboendarterectomy, which owing to high complication rates must be performed as a last therapeutic resource by vascular surgeons (36).

## Conclusions

Patients affected by IBD have a 2 to 3 time fold increased risk of developing thromboembolic complications compared to general population. Younger patients and those with other disease-related complications such as stenosis, abscess or fistulization disease are at higher risk for thromboembolic complications. Thromboembolism is a multifactorial process that must be considered in patients with IBD as it can significantly affect morbidity and mortality (47-55). Since no RCT studies have yet been conducted to clarify what the appropriate prophylactic protocol should be in patients with IBD, clinicians should follow the general guidelines for VTE prevention. Since oral pharmacological prophylaxis with VKA requires monitoring and is therefore impractical, current prophylactic options focus on anticoagulant therapy with LMWH and UH associated with mechanical prophylaxis. In case of acute non-responsive VTE, therapeutic options include anticoagulant therapy, fibrinolytic agents and in selected cases vascular surgery.

## References

1. Owczarek D, Cibor D, Głowacki MK, et al. Inflammatory bowel disease: epidemiology, pathology and risk factors for hypercoagulability. *World J Gastroenterol.* 2014;20:53-63.
2. Bagen JA, Barker NW. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. *Arch Intern Med.* 1936;58:17-31.
3. Isene R, Bernklev T, Hoie O, et al. Thromboembolism in inflammatory bowel disease: results from a prospective, population-based European inception cohort. *Scand J Gastroenterol.* 2014;49:820-5.
4. Arora Z, Wu X, Navaneethan U, et al. Non-surgical portomesenteric vein thrombosis is associated with worse long-term outcomes in inflammatory bowel diseases. *Gastroenterol Rep (Oxf).* 2016 Aug;4:210-5.
5. Chung WS, Lin CL, Hsu WH, et al. Inflammatory bowel disease increases the risks of deep vein thrombosis and pulmonary embolism in the hospitalized patients: a nationwide cohort study. *Thromb Res.* 2015;135:492-6.
6. Ra G, Thanabalan R, Ratneswaran S, et al. Predictors and safety of venous thromboembolism prophylaxis among hospitalized inflammatory bowel disease patients. *J Crohns Colitis.* 2013;7e479-85.
7. Owczarek D, Cibor D, Glowacki MK, et al. Inflammatory bowel disease: epidemiology, pathology and risk factors for

- hypercoagulability. *World J Gastroenterol.* 2014;20:53-63.
8. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet.* 2010;375:657-63.
  9. Papa A, Gerardi V, Marzo M, et al. Venous thromboembolism in patients with inflammatory bowel disease: focus on prevention and treatment. *World J Gastroenterol.* 2014;20:3173-9.
  10. Fumery M, Xiaocang C, Dauchet L, et al. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis.* 2014;8:469-79.
  11. Twig G, Zandman-Goddard G, Szyper-Kravitz M, et al. Systemic thromboembolism in inflammatory bowel disease: mechanisms and clinical applications. *Ann N Y Acad Sci.* 2005; 1051:166-73.
  12. Fornaro R, Caratto M, Barbruni G, et al. Surgical and medical treatment in patients with Acute Severe Ulcerative Colitis. *J Dig Dis.* 2015;16:558-67.
  13. Yuhara H, Steinmaus C, Corley D, et al. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2013;37:953-62.
  14. Bollen L, Vande Casteele N, Peeters M, et al. The Occurrence of Thrombosis in Inflammatory Bowel Disease Is Reflected in the Clot Lysis Profile. *Inflamm Bowel Dis.* 2015;21:2540-8.
  15. Koutroumpakis EI, Tsiolakidou G, Koutroubakis IE. Risk of venous thromboembolism in patients with inflammatory bowel disease. *Semin Thromb Hemost.* 2013;39:461-8.
  16. Nguyen GC, Bernstein CN, Bitton A, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology.* 2014;146:835-48.
  17. Paparo F, Denegri A, Revelli M, et al. Crohn's disease: value of diagnostic imaging in the evaluation of anastomotic recurrence. *Ann Ital Chir.* 2014;85:271-81.
  18. Magro F, Soares JB, Fernandes D. Venous thrombosis and prothrombotic factors in inflammatory bowel disease. *World J Gastroenterol.* 2014;20:4857-72.
  19. Vegh Z, Golovics PA, Lovasz BD, et al. Low incidence of venous thromboembolism in inflammatory bowel diseases: prevalence and predictors from a population-based inception cohort. *Scand J Gastroenterol.* 2015;50:306-11.
  20. Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol.* 2008;103:2272-80.
  21. Solem CA, Loftus EV, Tremaine WJ, et al. Venous thromboembolism in inflammatory bowel disease. *Am J Gastroenterol.* 2004;99:97-101.
  22. Miehsler W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? *Gut.* 2004;53:542-8.
  23. Pastorelli L, Dozio E, Pisani LF, et al. Procoagulatory state in inflammatory bowel diseases is promoted by impaired intestinal barrier function. *Gastroenterol Res Pract.* 2015;2015:1893-41.
  24. Papa A, Papa V, Marzo M, et al. Prevention and treatment of venous thromboembolism in patients with IBD: a trail still climbing. *Inflamm Bowel Dis.* 2015;21:1204-13.
  25. Fornaro R, Frascio M, Denegri A, et al. Chron's disease and cancer. *Ann Ital Chir.* 2009;80:119-25.
  26. Zezos P, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. *World J Gastroenterol.* 2014;20:13863-78.
  27. Fornaro R, Frascio M, Stabilini C, et al. Crohn's disease surgery: problems of postoperative recurrence. *Chir Ital.* 2008;60:761-81.
  28. Alkim H, Koksar AR, Boga S, et al. Etiopathogenesis, Prevention, and Treatment of Thromboembolism in Inflammatory Bowel Disease. *Clin Appl Thromb Hemost.* 2017 Sep;23:501-10.
  29. Kumar DR, Hanlin ER, Glurich I, et al. Virchow's Contribution to the Understanding of Thrombosis and Cellular Biology. *Clin Med Res.* 2010 Dec;8:168-72.
  30. Senchenkova E, Seifert H, Granger DN. Hypercoagulability and Platelet Abnormalities in Inflammatory Bowel Disease. *Semin Thromb Hemost.* 2015;41:582-9.
  31. Rajendran P, Rengarajan T, Thangavel J, et al. The vascular endothelium and human diseases. *Int J Biol Sci.* 2013;9:1057-69.
  32. Venous Thromboembolic Diseases: The Management of Venous Thromboembolic Diseases and the Role of Thrombophilia Testing [Internet]. National Clinical Guideline Centre (UK). London: Royal College of Physicians (UK); 2012 Jun. PMID:23638495.
  33. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet.* 1997;350:1795-8.
  34. Scarpa M, Pilon F, Pengo V, et al. Deep venous thrombosis after surgery for inflammatory bowel disease: is standard dose low molecular weight heparin prophylaxis enough? *World J Surg.* 2010;34:1629-36.
  35. Kohoutova D, Moravkova P, Kruzliak P, et al. Thromboembolic complications in inflammatory bowel disease. *J Thromb Thrombolysis.* 2015;39:489-98.
  36. Purnak T, Yuksel O. Overview of venous thrombosis in inflammatory bowel disease. *Inflamm Bowel Dis.* 2015;21:1195-203.
  37. Oldenburg B, Van Tuyl BA, van der Griend R, et al. Risk factors for thromboembolic complications in inflammatory bowel disease: the role of hyperhomocysteinaemia. *Dig Dis Sci.* 2005;50:235-40.
  38. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut.* 2011;60:571-607.
  39. Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Special situations. *J Crohns Colitis.* 2010;4:63-101.
  40. Van Assche G, Dignass A, Bokemeyer B, et al. Second European Evidence-Based Consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J Crohns Colitis.* 2013;7:1-33.
  41. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in non-surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed; American College of Chest Physicians. (2012) Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e195S-e226S.
  42. Fornaro R, Caratto E, Caratto M, et al. Post-operative recurrence in Crohn's disease. Critical analysis of potential risk factors. An update. *Surgeon.* 2015;13:330-47.
  43. Karthikeyan G, Eikelboom JW, Turpie AG, et al. Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? *Br J Haematol.* 2009;146:142-9.
  44. Thaler J, Pabinger I, Ay C. Anticoagulant Treatment of Deep Vein Thrombosis and Pulmonary Embolism: The Present State of the Art. *Front Cardiovasc Med.* 2015;2:30.
  45. Watson HG, Chee YL. Aspirin and other antiplatelet drugs in the prevention of venous thromboembolism. *Blood Rev.* 2008;22:107-16.

46. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med.* 2012;367:1979-87.
47. Parente A. Thromboembolic risk in inflammatory bowel disease. *Rev Prat.* 2014 Jun;64:759-60.
48. Zezos P, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. *World J Gastroenterol.* 2014 Oct 14;20:13863-78.
49. Chung WS, Lin CL, Hsu WH, et al. Inflammatory bowel disease increases the risks of deep vein thrombosis and pulmonary embolism in the hospitalized patients: a nationwide cohort study. *Thromb Res.* 2015 Mar;135:492-6.
50. Algahtani FH, Farag YM, Aljebreen AM, et al. Thromboembolic events in patients with inflammatory bowel disease. *Saudi J Gastroenterol.* 2016 Nov;22:423-7.
51. Alatri A, Schoepfer A, Fournier N, et al; Swiss IBD Cohort Study Group. Prevalence and risk factors for venous thromboembolic complications in the Swiss Inflammatory Bowel Disease Cohort. *Scand J Gastroenterol.* 2016 Oct;51:1200-5.
52. Fornaro R, Caratto M, Caratto E, et al. Colorectal Cancer in Patients With Inflammatory Bowel Disease: The Need for a Real Surveillance Program. *Clin Colorectal Cancer.* 2016 Sep;15:204-12.
53. Bollen L, Vande Casteele N, Ballet V, et al. Thromboembolism as an important complication of inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 2016 Jan;28:1-7.
54. Fornaro R, Caratto E, Caratto, et al. Surgery of acute severe ulcerative colitis. Subtotal colectomy: when and how to do it? *Eur Surg.* 2017;49:108-12.
55. Harbord M, Eliakim R, Bettenworth D, et al; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis.* 2017 Jul 1;11:769-84.