



Cardiovascular involvement in inflammatory bowel disease: Dangerous liaisons

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Abstract

Increasing evidence of a link between inflammatory bowel disease (IBD) and adverse cardiovascular events has emerged during the last decade. In 2014, an important number of meta-analyses and cohort studies clarified the subtle *dangerous liaisons* between gut inflammation and cardiovascular pathology. The evidence suggests that patients with IBD have a significantly increased risk of myocardial infarction, stroke, and cardiovascular mortality, especially during periods of IBD activity. Some populations (*e.g.*, women, young patients) may have an even greater risk. Current effective treatment of IBD is aimed at disease remission and seems to reduce cardiovascular risk in these patients. A beneficial effect was demonstrated for salicylates, but not for steroids or azathioprine. tumor necrosis factor- α antagonists, which are highly effective in the reduction of inflammation and in the restoration of the digestive mucosa, lead to conflicting cardiovascular effects, as they seem to reduce the risk for ischemic heart disease but increase the rate of cerebrovascular events. Future supplemental treatment strategies that may reduce the atherothrombotic risk during periods of IBD activity should be explored.

Key words: Inflammatory bowel disease; Thrombotic events; Active disease; Cardiovascular risk; Anti-tumor necrosis factor- α

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Core tip: New evidence from an important number of meta-analyses and cohort studies suggests that patients with inflammatory bowel disease (IBD) have a significantly increased risk of myocardial infarction,

stroke, and cardiovascular mortality especially during periods of active disease and particularly in some high-risk populations, such as women and younger patients. The current treatment paradigm, which is aimed at deep, sustained remission, might reduce cardiovascular risk in patients with IBD. Treatment strategies such as the supplemental administration of statins to reduce the atherothrombotic risk should be further explored.

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Inflammatory bowel disease (IBD) comprises two types of chronic intestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC).

Increasing evidence of a link between inflammatory bowel disease and adverse cardiovascular events has emerged during the last decade. The association of IBD with an increased risk of venous thromboembolic disease is now clearly recognized and has been confirmed by many studies^[1].

However, considerable heterogeneity was observed in the current study in regards to how IBD modifies the risk of arterial thromboembolic events, including cerebrovascular accidents (CVA), ischemic heart disease (IHD), and myocardial infarction (MI). The relationship of inflammatory bowel disease to heart failure (HF) is also uncertain. Two registry-based studies of approximately 17000 and 25000 patients with IBD, respectively, reported that the risk of MI in IBD patients was comparable to matched control subjects without IBD^[2,3]. In addition, in a meta-analysis of 11 studies with a total of almost 14000 patients, no increase in cardiovascular mortality was observed in the IBD group compared with the control group^[4].

In 2014, an important number of meta-analyses and cohort studies clarified these subtle dangerous liaisons between gut inflammation and cardiovascular pathology.

A meta-analysis of publications in MEDLINE, the Cochrane Library, EMBASE as well as of international conference abstracts was conducted. It included all controlled observational studies that evaluated the incidence of venous and/or arterial thromboembolic events and cardiovascular mortality in adult patients with IBD. This analysis included 33 studies that enrolled 207814 IBD patients and 5774898 controls. The risk of thromboembolic events was increased in patients with IBD, which was mainly due to an increased risk of venous thromboembolism (VTE). No increased risk of arterial thromboembolism or cardiovascular mortality in patients with IBD was

observed, but an increased risk for both ischemic heart disease and mesenteric ischemia was observed^[5].

The exact etiology of the higher occurrence of thromboembolic events is not yet completely understood, although it seems that multiple acquired and inherited factors may be involved. In patients with IBD, a persistent latent activation of hemostasis exists in cases of both active and inactive disease and is implicated in thrombotic diathesis. The detailed mechanisms of this process were recently and extensively presented in a comprehensive review. The mechanisms include the following: elevated levels of coagulation factors and products of thrombin and fibrin formation, increased markers of acquired vascular endothelial deficiencies, dysfunction of natural anticoagulants, defects in the fibrinolytic system and an elevated number of circulating platelets with increased platelet activation and an increased tendency for platelet aggregation^[1].

In a recent cohort study that included 1708 patients (648 with CD, 1060 with UC) who were followed for 35 years, the risk of venous thromboembolism was 1.03 per 1000 patients-year. The cumulative risk of VTE 15 years after the diagnosis was 1.5%, which was similar for both CD and UC, and was significantly higher in males. The risk of VTE in patients with UC was associated with extensive location of the disease (OR = 3.25, 95%CI: 1.13-9.35), the presence of a fulminant episode during the disease course (OR = 4.15, 95%CI: 1.28-13.5), smoking (OR = 3.46, 95%CI: 1.14-10.5) and the need for steroids (OR = 2.97, 95%CI: 0.99-8.92). Similarly, in regards to CD, all but one patient with VTE were smokers^[6].

In a recent study on global assays of coagulation and factor assays (procoagulant factor VIII, von Willebrand factor), the authors demonstrated that acute severe colitis is a hypercoagulable disease state. Although this hypercoagulable profile improves over time, it is still present up to 8-12 wk after hospital admission compared with control patients with quiescent, extensive UC^[7].

Another systematic review and meta-analysis included cohort and case-control studies that reported incident cases of CVA and/or IHD in patients with IBD and compared them with a non-IBD control population (or they were compared with a standardized population). The presence of IBD was associated with a modest increase in the risk of CVA, especially among women and in young patients (< 40-50 years old). IBD was also associated with a 19% increase in the risk of IHD, also primarily in women. In this study, no association was observed between IBD and an increased risk of peripheral arterial thromboembolic events^[8].

Very important data have resulted from a series of nationwide Danish population-based cohort studies that were recently published.

In a cohort of 20795 patients with new-onset

Table 1 Cardiovascular risk in inflammatory bowel disease-the liaisons

Study	Results
MEDLINE, Cochrane Library, EMBASE meta-analysis; 33 studies enrolling 207814 IBD patients and 5774898 controls ^[5]	Increased risk of venous thromboembolism Increased risk of both ischemic heart disease and mesenteric ischemia No increased risk of arterial thromboembolism No increased cardiovascular mortality
Cohort study, 1708 patients (648 Crohn's disease, 1060 ulcerative colitis), 35 yr follow-up ^[6]	A cumulative risk of venous thromboembolism after 15 yr after the diagnosis of 1.5% similar for both CD and UC
Systematic review and meta-analysis 9 studies 2424 CVA events in 5 studies and 6478 IHD events 6 studies ^[8]	Modest increase in the risk of CVA, especially among women and in young patients (< 40-50 yr old) 19% increase in the risk of IHD, primarily in women also No increased risk of peripheral arterial thromboembolic events
Cohort study, 20795 new onset IBD patients matched with 199978 controls ^[9]	Overall increased risk of MI, stroke, and cardiovascular death Increased risk during flares
Nation wide cohort study, 5436647 subjects without IBD or HF; follow up 11.8 yr 23681 IBD patients developed IBD follow up 6.4 yr 86790 Danish patients with first-time MI ^[11]	37% increased risk of hospitalization for HF in IBD Increased risk during flares
Historical cohort study 2004-2010 ^[12]	Increased risk of recurrent MI and for all-cause mortality especially during flares IBD patients had CAD at a younger age as compared with non-IBD patients
Interventional catheterization database 131 IBD patients and 524 matched controls	IBD patients less likely to be active smokers and had a lower body mass index. No difference in post-PCI outcome in patients with IBD <i>vs</i> non-IBD controls with CAD

CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; CVA: Cerebrovascular accidents; IHD: Ischemic heart disease; HF: Heart failure; MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous intervention.

IBD and a mean age of 40 years who were matched according to age and sex with 199978 controls, patients with IBD had an overall increased risk of MI, stroke, and cardiovascular death. During flares and persistent IBD activity the rate ratios of MI, stroke, and cardiovascular death were significantly increased^[9].

The same Danish team showed that IBD is associated with an increased risk of hospitalization for HF and that this risk was strongly correlated with periods of active disease^[10].

The effect of active IBD on major adverse cardiovascular outcomes after MI was studied in 86790 Danish patients with a first-time MI between 2002 and 2011. IBD was associated with hazard ratios of 1.21 (95%CI: 0.99-1.49) for recurrent MI, 1.14 (95%CI: 1.01-1.28) for all-cause mortality, and 1.17 (95%CI: 1.03-1.34) for the composite end point. Compared with the non-IBD group, IBD flares in particular were associated with increased risks of recurrent MI and all-cause mortality, whereas no increased risk was identified during remission^[11].

The correlation between IBD and coronary artery disease (CAD) was already confirmed in a smaller study, where IBD patients tended to have CAD at a younger age compared with patients without IBD; in addition, they were less likely to be active smokers and had a lower body mass index. However, in this study, the post-PCI outcome in patients with IBD and CAD was similar to that in controls with CAD but without concurrent IBD^[12].

Only a few studies have addressed the impact of the use of anti-inflammatory drugs for the management of cardiovascular risk in patients with IBD (Table 1).

One small longitudinal study included 14 patients

with IBD who were treated with salicylates alone, 11 subjects who were treated with steroids and azathioprine, 7 subjects who were treated with anti-tumor necrosis factor (TNF)- α , and 30 matched controls. The effect of therapy on pulse wave velocity (PWV) was measured at baseline and at 3.4 \pm 0.5 years later. In an adjusted model, carotid-femoral PWV increased significantly at follow-up in subjects with IBD who were treated with salicylates, but not in those who were treated with steroids and azathioprine or with anti TNF- α ^[13].

TNF- α antagonists have increasingly been used in the treatment of IBD, and they are highly effective in the reduction of the inflammatory burden and in mucosal healing in some patients. However, data on the potential impact of this anti-inflammatory effect on the risk of cardiovascular diseases (CVD) in the setting of IBD remain limited. Important evidence in regards to the role of anti TNF- α also comes from Denmark. With the same design of a nationwide, population-based cohort study, the authors addressed the risk of CVD, which was subdivided into ischemic heart disease (IHD) and cerebrovascular accidents (CVA), among patients with IBD who were followed for up to 11 years after exposure to TNF- α antagonists. The cohort consisted of 50756 patients with IBD, of whom 3109 had been exposed to TNF- α antagonists during 1999-2010. Thirty-one patients who were treated with TNF- α antagonists and 2641 patients who were not treated with TNF- α antagonists developed IHD. This yielded an adjusted HR of 0.85 (95%CI: 0.59-1.24), whereas the risk of CVA associated with TNF- α antagonists was 1.42 (95%CI: 0.82-2.45). These suggest a protective effect of TNF- α antagonists on IHD, but at the same time, the use of TNF- α antagonists might be a risk factor for

Table 2 Cardiovascular risk and inflammatory bowel disease treatment

Study	Results
Longitudinal study ^[13] 14 IBD subjects treated only with salicylates, 11 subjects treated with steroids and azathioprine, 7 subjects treated with anti TNF- α , and 30 matched controls pulse wave velocity was measured at baseline and 3.4 ± 0.5 yr later Nationwide, population-based, cohort study, patients with IBD followed for up to 11 years after exposure to TNF- α antagonists Cohort of 50756 IBD patients of whom 3109 had been exposed to TNF- α antagonists during 1999-2010 ^[14] Large retrospective study ^[15] 1986 statin exposed and 9871 unexposed subjects with IBD	Carotid-femoral pulse wave velocity increased significantly at follow-up in IBD subjects treated with salicylates, No increase of PWV in patients treated with steroids and azathioprine or anti TNF- α Protective effect of TNF- α antagonist on IHD TNF- α antagonists use might be a risk factor for CVA (increased trend, none of the values reached statistical significance) 18% reduction in initiation of oral steroids Statistical significance for atorvastatin only Greater reduction in steroid use for UC patients and no reduction in Crohn's disease Reduce hazard of anti TNF- α use, surgery and hospitalization (no statistical significance)

UC: Ulcerative colitis; IBD: Inflammatory bowel disease; CVA: Cerebrovascular accidents; IHD: Ischemic heart disease.

CVA, although none of the values reached statistical significance. Therefore, further studies are necessary to clarify this issue^[14].

The anti-inflammatory capacity of HMG-CoA-reductase inhibitors was evaluated in patients with IBD in a large retrospective study, which revealed an 18% reduction in the initiation of oral steroid use in patients with IBD (HR = 0.82; 95%CI: 0.71-0.94), and an even greater reduction in patients with UC (HR = 0.75; 95%CI: 0.62-0.91). The beneficial effect of statins in patients with IBD and whether this effect is linked to their potential to decrease the risk of atherosclerosis and inflammation requires clarification in further studies^[15].

These studies add considerable evidence to the existing literature as they confirm the substantial negative impact that IBD may have on cardiovascular outcomes. However, some variables lack statistical significance in the three studies, and thus we need further evidence regarding the use of steroids, the risk of VTE, IBD, and recurrent MI as well as exposure to anti TNF- α and CVA^[6,11,14].

However, have these recent studies changed our treatment paradigm or do they confirm that we are on the correct path? Currently, our goal is to progress beyond deep sustained remission.

The location, extension, activity, and severity of the inflammatory lesions and the potential existence of complications must be carefully evaluated in all patients at the time of diagnosis and throughout the course of the disease. This allows the selection of a targeted therapeutic strategy in a particular patient, and has important prognostic implications. An approach that uses endoscopic healing and tight control of inflammation based on the monitoring of symptoms and biomarkers is proposed. The observation of inflammatory activity is actively utilized throughout the disease course to optimize management. Certain high-risk populations (*e.g.*, those with active disease, women, and young patients) should be

counseled routinely on the modification of aggressive risk factors and adherence to the treatment guidelines.

CONCLUSION

New evidence suggests that patients with IBD have a significantly increased risk of MI, stroke, and cardiovascular mortality especially during periods of IBD activity. Some populations (*e.g.*, women, young patients) may have an increased cardiovascular risk. Effective treatment of IBD that is aimed at disease remission may also reduce the cardiovascular risk in these patients. Treatment strategies, such as supplemental statin administration during periods of IBD activity, for the reduction of atherothrombotic risk should be further explored (Table 2).

REFERENCES

- 1 **Zeos P**, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. *World J Gastroenterol* 2014; **20**: 13863-13878 [PMID: 25320522 DOI: 10.3748/wjg.v20.i38.13863]
- 2 **Ha C**, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 1445-1451 [PMID: 19491858 DOI: 10.1016/s0016-5085(08)62341-0]
- 3 **Osterman MT**, Yang YX, Brensinger C, Forde KA, Lichtenstein GR, Lewis JD. No increased risk of myocardial infarction among patients with ulcerative colitis or Crohn's disease. *Clin Gastroenterol Hepatol* 2011; **9**: 875-880 [PMID: 21749853 DOI: 10.1016/j.cgh.2011.06.032]
- 4 **Dorn SD**, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. *Am J Gastroenterol* 2007; **102**: 662-667 [PMID: 17156143 DOI: 10.1111/j.1572-0241.2006.01018.x]
- 5 **Fumery M**, Xiaocang C, Dauchet L, Gower-Rousseau C, Peyrin-Biroulet L, Colombel JF. Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: a meta-analysis of observational studies. *J Crohns Colitis* 2014; **8**: 469-479 [PMID: 24183231 DOI: 10.1016/j.crohns.2013.09.021]
- 6 **Vegh Z**, Golovics PA, Lovasz BD, Kurti Z, Gecse KB, Szita I, Balogh M, Pandur T, Lakatos L, Lakatos PL. Low incidence of venous thromboembolism in inflammatory bowel diseases: prevalence and predictors from a population-based inception cohort. *Scand J Gastroenterol* 2015; **50**: 306-311 [PMID:

- 25471148 DOI: 10.3109/00365521.2014.985708]
- 7 **Griffiths B**, Curry N, Desborough M, Henton S, Bryant RV, Travis SP, Jairath V. Evaluation of global coagulation profiles in patients with acute severe colitis: Implications for thromboprophylaxis. *J Crohns Colitis* 2015; **9** Suppl 1: S32
 - 8 **Singh S**, Singh H, Loftus EV, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 382-393.e1: quiz e22 [PMID: 23978350 DOI: 10.1016/j.cgh.2013.08.023]
 - 9 **Kristensen SL**, Ahlehoff O, Lindhardsen J, Erichsen R, Jensen GV, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death--a Danish nationwide cohort study. *PLoS One* 2013; **8**: e56944 [PMID: 23457642 DOI: 10.1371/journal.pone.0056944]
 - 10 **Kristensen SL**, Ahlehoff O, Lindhardsen J, Erichsen R, Lamberts M, Khalid U, Nielsen OH, Torp-Pedersen C, Gislason GH, Hansen PR. Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure: a Danish Nationwide Cohort study. *Circ Heart Fail* 2014; **7**: 717-722 [PMID: 25052190 DOI: 10.1161/CIRCHEARTFAILURE.114.001152]
 - 11 **Kristensen SL**, Ahlehoff O, Lindhardsen J, Erichsen R, Lamberts M, Khalid U, Nielsen OH, Torp-Pedersen C, Gislason GH, Hansen PR. Prognosis after first-time myocardial infarction in patients with inflammatory bowel disease according to disease activity: nationwide cohort study. *Circ Cardiovasc Qual Outcomes* 2014; **7**: 857-862 [PMID: 25316773]
 - 12 **Aggarwal A**, Atreja A, Kapadia S, Lopez R, Achkar JP. Conventional risk factors and cardiovascular outcomes of patients with inflammatory bowel disease with confirmed coronary artery disease. *Inflamm Bowel Dis* 2014; **20**: 1593-1601 [PMID: 25105946 DOI: 10.1097/MIB.0000000000000109]
 - 13 **Zanoli L**, Rastelli S, Inserra G, Lentini P, Valvo E, Calcagno E, Boutouyrie P, Laurent S, Castellino P. Increased arterial stiffness in inflammatory bowel diseases is dependent upon inflammation and reduced by immunomodulatory drugs. *Atherosclerosis* 2014; **234**: 346-351 [PMID: 24732573 DOI: 10.1016/j.atherosclerosis.2014.03.023]
 - 14 **Andersen NN**, Rungoe C, Andersson M, Munkholm P, Pasternak B, Jess T. Tumor Necrosis Factor-Alpha Antagonists And Cardiovascular Disease In Inflammatory Bowel Disease. European Crohn Colitis Organisation Congress, Vienna, Austria, February 14-16. 2013. Available from: URL: <https://www.ecco-ibd.eu/publications/congress-abstract-s/abstracts-2013/item/19-tumor-necrosis-factor-alpha-antagonists-and-cardiovascular-disease-in-inflammatory-bowel-disease.html>
 - 15 **Crockett SD**, Hansen RA, Stürmer T, Schectman R, Darter J, Sandler RS, Kappelman MD. Statins are associated with reduced use of steroids in inflammatory bowel disease: a retrospective cohort study. *Inflamm Bowel Dis* 2012; **18**: 1048-1056 [PMID: 21826766 DOI: 10.1002/ibd.21822]

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