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REVIEW ARTICLE

Thromboembolic events and cardiovascular mortality in inflammatory bowel diseases: A meta-analysis of observational studies☆

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Abstract

Objective: Patients with inflammatory bowel disease (IBD) are at increased risk of having venous thromboembolism. The magnitude of this risk has yet to be determined. The question of whether IBD patients have an increased risk of arterial thromboembolism and cardiovascular (CV) mortality remains controversial.
Design: We searched MEDLINE, Cochrane Library, EMBASE and international conference abstracts and included all controlled observational studies that evaluated the incidence of venous and/or arterial thromboembolic events (TE) and CV mortality in adult IBD.
Results: 33 studies enrolling 207,814 IBD patients and 5,774,898 controls and capturing 3,253,639 hospitalizations of IBD patients and 936,411,223 hospitalizations of controls reported

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; TE, thromboembolism; CV, cardiovascular; DVT, deep venous thrombosis; PE, pulmonary embolism; IHD, ischemic heart disease; RR, relative risk; OR, odds ratio.

☆ Specific author contributions:*Mathurin Fumery*: Generation, collection, assembly, interpretation of data and drafting of the manuscript.*Cao Xiaocang*: Generation, collection, assembly and interpretation of data.*Luc Dauchet*: Study design, statistical analysis, and critical revision of the manuscript.*Corinne Gower-Rousseau*: Concept and study design, interpretation of data, and critical revision of the manuscript.*Laurent Peyrin-Biroulet*: Concept and study design, interpretation of data, drafting the manuscript and approval of the final version of the manuscript.*Jean-Frederic Colombel*: Concept and study design, interpretation of data, drafting and critical revision of the manuscript and approval of the final version of the manuscript.

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a risk of arterial and/or venous TE or CV mortality were included. The risk of venous TE was increased in IBD patients compared to the general population (RR, 1.96; 95% CI, 1.67–2.30) contrary to the risk of arterial TE (RR, 1.15; 95% CI, 0.91–1.45). There was an increased risk of deep venous thrombosis (RR, 2.42; 95% CI, 1.78–3.30), pulmonary embolism (RR, 2.53; 95% CI, 1.95–3.28), ischemic heart disease (RR, 1.35; 95% CI, 1.19–1.52) and mesenteric ischemia (RR, 3.46; 95% CI, 1.78–6.71). Differences in methodology were great between studies resulting in a significant heterogeneity in all previous analysis. CV mortality in IBD patients was not increased compared to the general population (SMR, 1.03; 95% CI, 0.93–1.14).

Conclusion: The risk of TE is increased in patients with IBD. This difference is mainly due to an increased risk of venous TE. There is no increased risk of arterial TE or CV mortality in IBD patients, but an increased risk of both ischemic heart disease and mesenteric ischemia.

Contents

1. Introduction

Venous thromboembolism (TE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) is a well-known and feared complication of inflammatory bowel diseases (IBDs).[1,2] The incidence of venous TE is estimated to be 0.26% per year in both Crohn's disease (CD) and ulcerative colitis (UC).[3] However, despite several large population-based studies,[4] the true magnitude of the risk remains unclear as a result of methodological differences and heterogeneity across studies. Unlike venous TE, the risk of arterial TE and cardiovascular events in IBD is not well understood. Inflammation is involved throughout all stages of atherosclerosis pathogenesis, from plaque initiation to rupture and subsequent thrombosis.[5] C-reactive protein, often elevated during IBD flares, has also been associated with an increased risk of coronary artery disease independent of traditional cardiovascular risk factors.[6] Of note, other chronic inflammatory diseases such as rheumatoid arthritis are also associated with an increased risk of arterial TE and cardiovascular mortality.[7,8]

The aim of this meta-analysis was to determine the risk of venous and arterial TE, as well as the risk of cardio-vascular events and mortality in patients with IBD compared to the general population in referral center and population-based cohorts.

2. Materials and methods

We conducted a systematic review of the literature following the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.

2.1. Literature search and selection criteria

We conducted a computerized search of English and non-English language publications listed in the electronic

databases of PUBMED (1966 to September 2012), the Cochrane Library (to June 2012), and EMBASE (1980 to June 2012), by two independent researchers (MF, CX). We searched for the following terms: "Inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "thrombosis", "arterial thrombosis", "heart disease", "vascular disease", "atherosclerosis", "coronary artery disease", "myocardial infarction", "cerebrovascular disorders", "stroke", "mesenteric ischemia", "peripheral artery disease", "deep venous thrombosis", "pulmonary embolism", "venous thromboembolism", "mortality cause specific" and "mortality". We also hand-searched abstracts from the annual meetings of Digestive Disease Week (2009 to 2012), the United European Gastroenterology Week (2008 to 2011), and the European Crohn and Colitis Organization congress (2009 to 2012) over the past three years, as well as references from review articles, meta-analyses, and published observational studies in order to identify additional articles. We did not employ any search software. Data abstraction was carried out independently by two investigators (MF, CX) using standardized data collection form. Discrepancies in data interpretation were resolved by a discussion and re-review of the studies and by consultation with the other clinical authors (LPB, LD). We selected peer-reviewed observational controlled data (case–control and cohort studies) originating from referral center, hospital and population based-studies. If data from a single study was reported in more than one article, only the results from the most recent study were included in the meta-analysis. If a population contributed to more than one publication, each publication could be included only if different study periods were involved.

2.2. Selection criteria

Inclusion and exclusion criteria were defined before commencement of the literature search. Selected peer-reviewed studies (case control and cohort studies) were included for analyses if all participants in the study were adult patients with IBD and if they reported either (a) a risk of thrombotic events in IBD (UC or CD) patients and controls expressed as odds ratios (ORs) or relative risks (RRs) with associated 95% confidence intervals or data for calculating them or (b) cardiovascular-disease-specific Standardized Mortality Ratio (SMR) with 95% confidence interval for IBD (UC or CD).

2.3. Outcome measures

The outcome measures were defined a priori. The meta-analysis evaluated different outcome variables including venous and arterial thromboembolic events and cardiovascular mortality. We evaluated ORs or RRs of thrombosis among IBD patients versus controls, RRs or ORs of arterial TE among IBD patients versus controls, and the proportion of venous TE in IBD patients and controls. We calculated a CV-disease-specific standardized mortality ratio (SMR) in IBD patients. When data were available we evaluated the RRs or ORs of ischemic heart disease (IHD), stroke, mesenteric ischemia, peripheral artery disease, DVT and PE in IBD patients and controls.

2.4. Statistical analysis

We calculated weighted–pooled summary estimates of RR (pooled RR) for all thrombotic events combined, arterial and

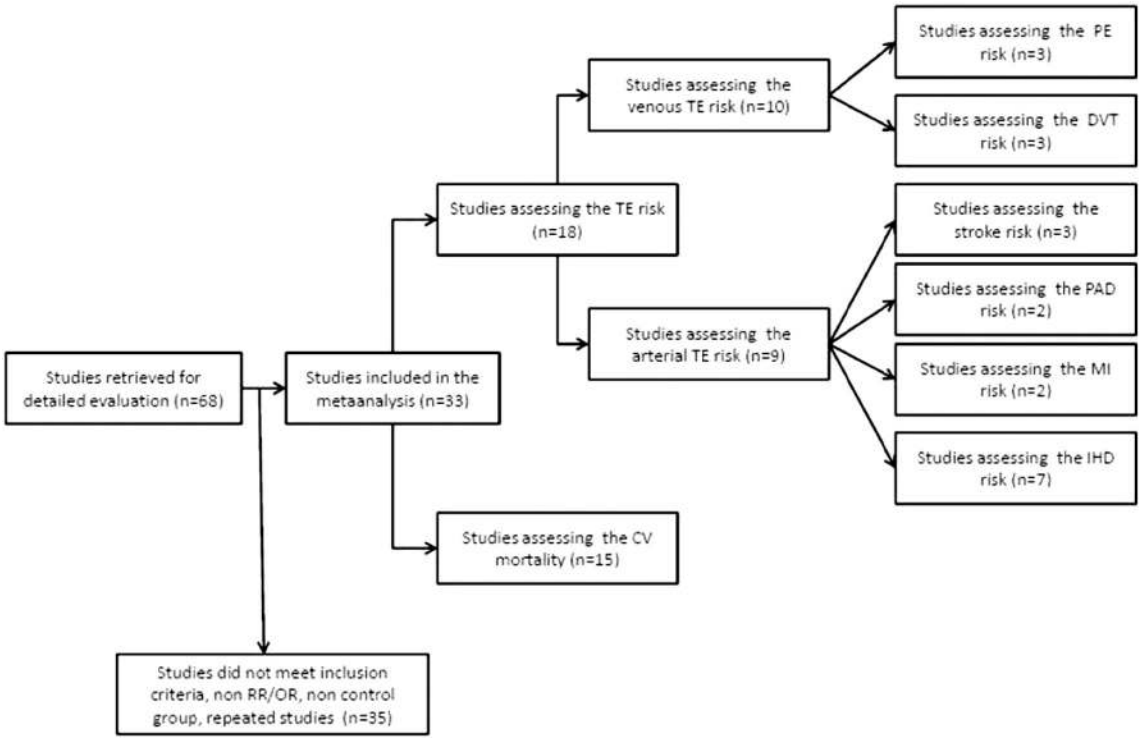

Figure 1 Flow chart of study selection. RR: relative risk, OR: odds ratio, TE: thromboembolic, CV: cardiovascular, PE: pulmonary embolism, DVT: deep venous thrombosis, PAD: peripheral artery disease, MI: mesenteric ischemia, and IHD: ischemic heart disease.

Table 1 Characteristics of the 18 studies included in the meta-analyses to assess the risk of both venous and arterial thromboembolic events in patients with IBD.

Authors	Location	Study period	Study	Data source	Population source
Bernstein CN et al.[15]	Canada	1984–2003	Cohort	IBD epidemiology database/ Manitoba Health administration database	Population
Yarur Aj et al.[16]	USA	1995–2009	Cohort	Jackson Memorial Hospital Miami	Referral center
Osterman et al.[17]	United Kingdom	1987–2003	Cohort	GPRD Database	Population
Haapamaki J et al.[18]	Finland	2006–2008	Cohort	National Health Insurance	Population
Rungoe C et al.[19]	Danmark	1997–2009	Cohort	National Patient Register	Population
Andersohn F et al.[20]	United Kingdom	1987–2005	Cohort	GPRD Database	Population
Huerta C et al.[21]	United Kingdom	1994–2000	Case–control	GPRD Database	Population
Kappelman MD et al.[23]	Danmark	1980–2007	Control	Danish National Patient Registry	Population
Grainge MJ et al.[24]	United Kingdom	1987–2001	Cohort	GPRD Database	Population
Merill A et al.[25]	USA	2008	Cohort	Use Data File of NSQIP	Population
Novacek G et al.[26]	Austria	2006–2008	Cohort	Austrian IBD center cohort/ Thrombosis Center, Austria	Referral center
Miehsler W et al.[27]	Austria	/	Cohort	Austrian Referral Center	Referral center
Bernstein CN et al.[28]	Canada	1984–1997	Cohort	Insurance plan of Manitoba	Population
Huerta C et al.[29]	United Kingdom	1994–2000	Case–control	GPRD Database	Population
Sridhar AR et al.[30]	USA	2006	Cohort	Nationwide Inpatient Sample	Hospital
Nguyen GC et al.[31]	USA	1998–2004	Cohort	Nationwide Inpatient Sample	Hospital
Saleh T et al.[32]	USA	1979–2005	Cohort	National Hospital Discharge Survey	Hospital
Inamdar S et al.[22]	USA	2009	Cohort	Nationwide Inpatient Sample	Hospital

venous thromboembolism, as well as for each outcome individually (arterial TE, IHD, Stroke, mesenteric ischemia, peripheral artery disease, venous TE, DVT, and PE). Similarly we calculated weighted–pooled summary estimates of the SMR for studies specifically evaluating CV mortality. Analyses were performed if at least two studies evaluating the same outcome could be combined.

For each meta-analysis, the method of Der Simonian and Laird[9] was used. According to this method, studies were considered as a random sample from a population of studies. Statistical heterogeneity was tested for each analysis.[10,11] Due to heterogeneity among studies a random effect model was used to analyze data. The overall effect was estimated by a weighted average of individual effects, with weights inversely proportional to the variance in observed effects. The effect measures estimated were the relative risks between the IBD and control groups, with 95% confidence intervals (CI).[12] Metaregression was performed to assess the modulation effect of pathology (UC or CD). All analyses were performed using R software[13] and metaphor package.[14]

3. Results

3.1. Literature search

Of the 68 studies identified following the literature search, 35 were excluded because of the lack of information on RRs or ORs for IBD patients and/or controls, lack of a control arm or reported confidence interval, or duplicates (Fig. 1) leaving a total of 33 eligible studies[15–47] on the risk of arterial and/or venous TE (n = 18)[15–32] or CV (n = 15) mortality in IBD patients[33–47] (Tables 1 and 2). These 33 studies enrolled 207,814 IBD patients with 5,774,898 controls (n = 29) and recorded 3,253,639 hospitalizations of IBD patients with 936,411,223 hospitalizations of controls (n = 4).

3.2. Venous thromboembolism

We identified 10 studies that assessed the risk of venous TE in IBD patients[23–32] including 72,205 IBD patients and 891,840 controls (n = 7) as well as 3,197,071 hospitalizations of IBD patients and 936,411,223 hospitalizations of controls (n = 3). The overall risk of venous TE in IBD patients was increased by 96% compared to the general population (RR, 1.96; CI 95%, 1.67–2.30) (I2 99%, Peth < 0.001) (Fig. 2). Using meta-regression analysis, the increase risk in CD was not different from the increased risk in UC (p = 0.98). The magnitude of the risk was higher in studies including IBD patients in general (RR, 2.48; 95% CI, 2.04–3.00) (I2 89%, Peth < 0.001)[23–29] as compared to studies looking at hospitalized IBD patients (RR, 1.47; 95% CI, 1.17–1.86) (I2 100%, Peth < 0.001).[30–32] In studies only considering hospitalizations, the increased risk of VTE was greater in UC than in CD patients (p = 0.0029).

Case	Case (n)	Events (n)	Controls (n)	CTL events (n)	Thrombosis risk evaluated
Patient	8072	432	80,489	3529	Ischemic heart disease, cerebrovascular disease, and peripheral artery disease
Patient	356	47	712	33	Coronary artery disease
Patient	25,327	390	235,592	3096	Myocardial infarction
Patient	2831	62	5662	79	Chronic heart disease
Patient	28,833	1175	4,541,987	243,844	Ischemic heart disease
Patient	794	88	16,554	1660	Ischemic stroke
Patient	13	1	2062	75	Mesenteric ischemia
Patient	49,799	1181	477,504	6646	Deep venous thrombosis and pulmonary embolism
Patient	13,756	139	71,672	165	Venous thromboembolism
Patient	2249	57	269,119	2608	Venous thromboembolism
Patient	86	27	1255	204	Venous thromboembolism
Patient	618	38	618	10	Venous thromboembolism
Patient	5529	374	55,290	/	Deep venous thrombosis and pulmonary embolism
Patient	168	106	16,382	6444	Deep venous thrombosis and pulmonary embolism
Hospitalization	148,229	11,741	17,261,952	2,260,802	Mesenteric ischemia, ischemic heart disease, cerebrovascular occlusion, and venous thromboembolism
Hospitalization	116,842	1933	52,2703	7213	Venous thromboembolism
Hospitalization	2,932,000	43,000	918,570,000	10,421,000	Venous thromboembolism
Hospitalization	56,568	/	56,568	/	Myocardial infarction

3.3. Deep venous thrombosis

3 studies evaluated DVT risk in IBD patients compared to the general population[23,28,29] including 55,496 IBD patients and 549,176 control patients. No data on hospitalizations of IBD patients were available. The risk was increased in IBD patients compared to the general population (RR, 2.42; 95% CI, 1.78–3.30) (I2 90%, Peth < 0.001), with no difference between CD and UC (p = 0.46).

3.4. Pulmonary embolism

We identified 3 studies assessing the risk of PE in IBD patients[23,28,29] including 55,496 IBD patients and 549,176 control patients. No data on hospitalizations of IBD patients were available. An increased risk of PE was observed in IBD patients compared to the general population (RR, 2.53; 95% CI, 1.95–3.28) (I2 80%, Peth < 0.001) with no difference between CD and UC (p = 0.69).

3.5. Arterial thromboembolism

We identified 9[15–22,30] studies that assessed the risk of arterial thrombo-embolic complications including 66,226 IBD patients and 4,883,058 controls (n = 7) and 204,797 hospitalizations of IBD patients and 17,318,520 hospitalizations of controls (n = 2). Overall, there was no increased risk of arterial thrombosis in IBD patients (RR, 1.15; 95% CI, 0.91–1.45) (I2 97%, Peth < 0.001) (Fig. 3). No difference was observed between CD and UC (p = 0.49). When the analysis was restricted to IBD patients,[15–21] excluding studies on hospitalizations, the risk of arterial TE was increased (RR, 1.28; 95% CI, 1.16–1.42) (I2 64%, Peth < 0.001), whereas it was not increased when including only studies of hospitalized patients (RR, 0.93; 95% CI, 0.56–1.54) (I2 100%, Peth < 0.001).[22,30]

3.6. Ischemic heart disease

7 studies assessed the risk of ischemic heart disease including myocardial infarction in IBD patients[15–19,22,30] and included 65,419 IBD patients and 4,864,442 control patients (n = 5) and recorded 204,797 hospitalizations of IBD patients and 17,318,520 hospitalizations of controls (n = 2). Overall, there was no increased risk of ischemic heart disease (RR, 1.23; 95% CI, 0.94–1.62) (I2 98%, Peth < 0.001) (Fig. 3). Among studies including only IBD patients,[15–19] the risk of arterial ischemic heart disease was increased (RR, 1.35; 95% CI, 1.19–1.52) (I2 74%, Peth < 0.001) (Fig. 3), whereas this risk was not increased among studies on hospitalizations[22,30] (RR, 0.86; 95% CI, 0.40–1.84) (I2 100%, Peth < 0.001), with no difference between UC and CD (p = 0.89).

3.7. Stroke

We identified 3 studies assessing the risk of stroke in IBD patients[15,20,30] including 8,866 IBD patients and 97,043

Table 2 Characteristics of the 15 studies included in the meta-analyses to assess the risk of cardiovascular mortality in IBD patients.

Authors	Location	Years at diagnosis	Study	Study source	IBD population size (n)	CD population size (n)	CD CV SMR (CI 95%)	UC population size (n)	UC CV SMR (CI 95%)
Wolters FL et al.[36]	Europe Multicenter	1991–1993	Cohort	Population based	380	380	1.49 (0.74–2.66)		
Jess T et al.[37]	Danmark	1962–1987	Cohort	Population based	374	374	0.9 (0.4–1.4)		
Prior P et al.[38]	United Kingdom	1932–76	Cohort	Hospital based	513	513	0.8 (0.4–1.3)		
Winther KV et al.[39]	Danmark	1962–1987	Cohort	Population based	1160			1160	1.07 (0.8–1.3)
Gyde S et al.[40]	United Kingdom	1940–76	Cohort	Hospital based	676			676	0.9 (0.4–1.0)
Davoli M et al.[41]	Italy	1970–89	Cohort	Hospital based	508			508	0.64 (0.26–1.3)
Viscido A et al.[42]	Italy	1964–95	Cohort	Hospital based	2066			2066	0.8 (0.5–1.1)
Hoie E et al.[33]	Europe Multicenter	1997–1993	Cohort	Population based	775			775	1.07 (0.71–1.54)
Ekbom A et al.[43]	Sweden	1965–83	Cohort	Population based	3978	1469	1.1 (0.9–1.4)	2509	0.9 (0.9–1.1)
Masala G et al.[44]	Italy	1978–92	Cohort	Population based	920	231	0.65 (0.24–1.41)	689	0.67 (0.45–0.95)
Romberg-campus M et al.[34]	Netherlands	1991–2002	Cohort	Population based	1187	476	1.2 (0.5–2.3)	630	1.2 (0.7–1.8)
Jess T et al.[45]	USA	1940–2001	Cohort	Population based	692	314	0.9 (0.3–1.8)	378	0.6 (0.2–1.3)
Persson PG et al.[46]	Sweden	1955–1984	Cohort	Population based	2798	1251	0.94 (0.7–1.24)	1547	1.11 (0.91–1.35)
Manninen P et al.[35]	Finland	1986–2007	Cohort	Population based	1915	550	1.28 (0.68–2.18)	1254	1.04 (0.76–1.41)
Jess et al.[47]	Danmark	1982–2010	Cohort	Population based	51,441	15,361	1.39 (1.28–1.51)	36,080	1.20 (1.1.26)

controls (n = 2) and recorded 148,229 hospitalizations of IBD patients and 17,261,952 hospitalizations of controls (n = 1). The risk of stroke did not differ between IBD patients and the general population (RR, 0.79; 95% CI, 0.51–1.23) (I2 94%, Peth < 0.001) (Fig. 3), with no difference between CD and UC (p = 0.62).

3.8. Peripheral artery disease

We identified 2 studies assessing the risk of peripheral artery disease n IBD patients[15,20] including 8,072 IBD patients and 80,489 controls (n = 1) and 148,229 hospitalizations of IBD patients and 17,261,952 hospitalizations of controls (n = 1). The risk of peripheral artery disease did not differ between IBD patients and the general population (RR, 0.78; 95% CI, 0.46–1.32) (I2 87%, Peth < 0.001) (Fig. 3).

3.9. Mesenteric ischemia

We identified 2 studies assessing the risk of mesenteric ischemia in IBD patients[21,30] including 13 IBD patients and 2,062 controls (n = 1) and 148,229 hospitalizations of IBD patients and 17,261,952 hospitalizations of controls (n = 1). A significant increased risk of mesenteric ischemia was observed in IBD patients compared to the general population (RR, 3.46; 95% CI, 1.78–6.71) (I2 90%, Peth < 0.001) (Fig. 3).

3.10. Cardiovascular mortality

We identified 15 studies evaluating CV mortality among IBD patients[33–47] (Table 2): 10 were population-based and 4 were hospital-based studies. A total of 69,383 IBD patients (15,361 CD and 36,080 UC) were included. Overall, cardiovascular mortality was not increased among IBD patients when compared to the general population (pooled SMR, 1.03; 95% CI, 0.93–1.14) (I2 70%, Phet < 0.001) (Fig. 4). Similar results were observed for CD and UC patients, with SMRs of 1.12 (95% CI, 0.94–1.32) and 0.98 (95% CI, 0.86–1.12) respectively. In a sensitivity analysis excluding the largest and most recent study,[47] the RR was 0.96 (0.80–1.16) (I2 0%, Phet = 0.999). All the previous results have been summarized in Table 3.

3.11. Heterogenity and publication bias

A statistical heterogeneity was observed for all analysis. The first analysis evaluating the risk of overall risk of thrombosis was associated with significant heterogeneity among studies (I2 98%, Peth < 0.001). A funnel plot (Supplementary Fig. 1) showed some asymmetry and suggested publication bias, as there were few studies with high precision (large sample size) and large RR. Nevertheless, the result of Egger's regression test for asymmetry was not significant (egger = 0.93). For the pooled analysis of cardiovascular mortality the funnel plot (Supplementary Fig. 2) showed some asymmetry (egger = 0.47) and there was a significant heterogeneity among studies (I2 70%, p < 0.05, Phet < 0.001).

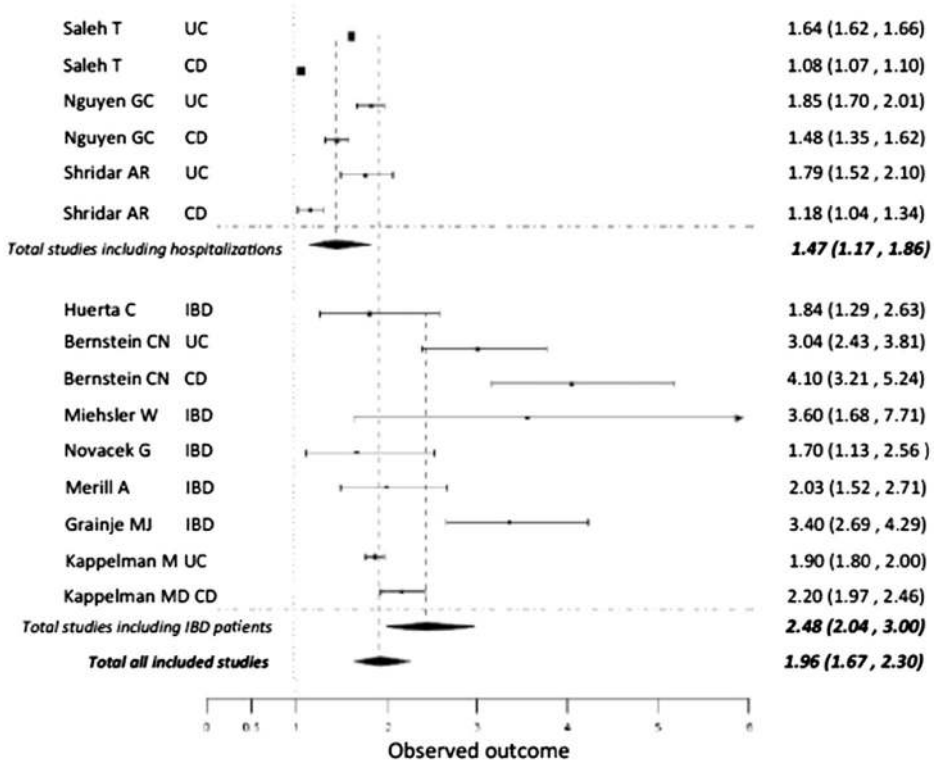

Figure 2 Meta-analysis of studies on venous thromboembolic events in IBD patients in both studies considering hospitalizations and IBD patients. CD, Crohn's disease; UC, ulcerative colitis.

4. Discussion

This is the first meta-analysis of observational studies designed to assess incidence of both venous and arterial thromboembolic events as well as cardiovascular mortality in patients with IBD. Despite great heterogeneity in design and clinical setting, our findings demonstrate that patients with IBD are at major risk for venous thromboembolism and mesenteric ischemia and, to a lesser degree, arterial thromboembolism and ischemic heart disease. Importantly, we did not find an increase in the risk of cardiovascular mortality in IBD patients.

Venous thromboembolic complications, including DVT and PE[1] have been shown to be associated with IBD, but the magnitude of the thromboembolic risk is somewhat disputed.[48] When analyzing a total of 5,982,712 patients and 939,664,862 hospitalizations, we found a 60% increase in the risk of TE in patients with IBD compared to the general population. This increase was largely attributed to venous TE events including both DVT and PE. Similar to the study by Grainge et al.,[24] the risk of venous TE was lower in studies that included only hospitalized IBD patients. While this observation may initially appear counterintuitive given that hospitalized patients typically have the most severe disease, it may be explained by the use of prophylactic heparin in hospitalized patients in accordance with international recommendations.[49,50] Reduction of venous thromboembolism by low molecular weight heparin or the new orally bioavailable anticoagulants,[51–54] may be further highlighted in future guidelines for both hospitalized and ambulatory patients. In studies including only inpatients, VTE increased risk was greater in UC than in CD patients ($p = 0.0029$). However, prophylaxis should be recommended both in UC and in CD.

Several studies have shown an increased carotid intima-media thickness in IBD patients, including pediatric cases, suggesting that atherosclerosis may be an early complication of these diseases.[55–58] When compared to the general population, the overall risk of arterial thrombosis was not significantly increased in IBD patients. However, there was a significant increased risk of ischemic heart disease and mesenteric ischemia. This increased risk was observed despite the absence of the traditional cardiovascular risk factors such as arterial hypertension, dyslipidemia, diabetes mellitus, age, male and family history of cardiovascular disease.[16,18] The magnitude of the risk was similar in patients with CD who are more often smokers than the general population and in patients with UC who are often non-smokers.[59] Chronic inflammation may be the most important driver of cardiovascular complications in IBD. C-reactive protein and interleukin-6, often elevated during IBD flares, have been associated with an increased risk of coronary artery disease and mesenteric ischemia independent of other cardiovascular risk factors.[6,60–62] In IBD, the increased expression of CD40L by platelets appears to contribute to the pro-inflammatory response[1,63] while in atherosclerosis, the inflammation caused by CD40L–CD40 interaction leads to unstable plaque resulting in thrombosis.[64]

An increase in CV mortality compared to the general population is well documented in rheumatoid arthritis (RA)

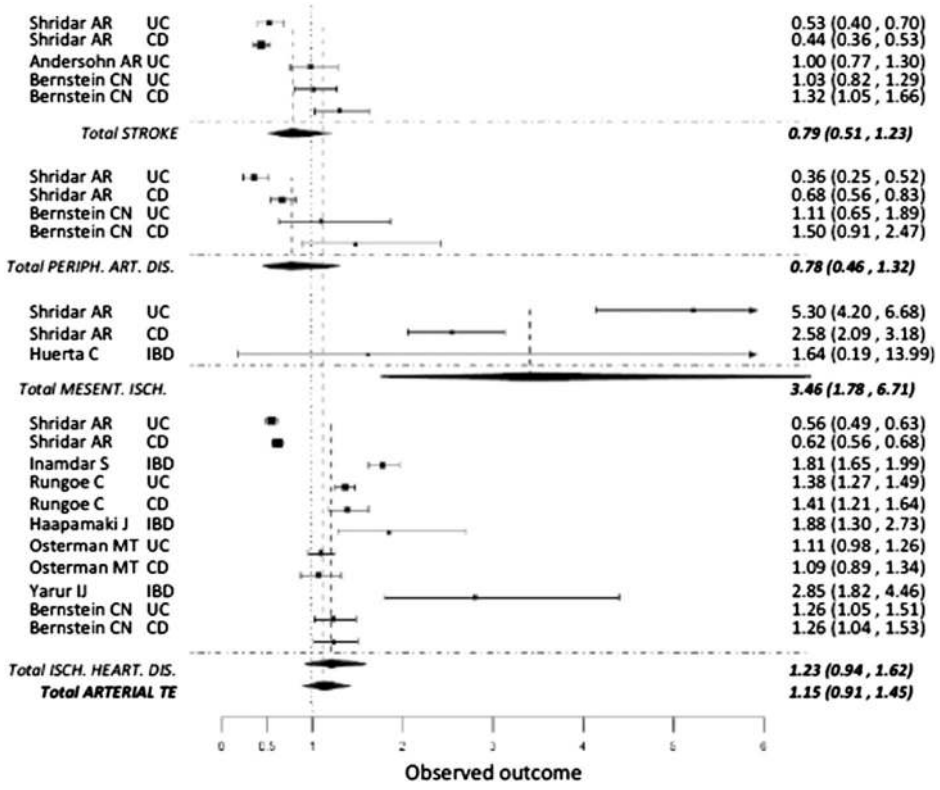

Figure 3 Meta-analysis of studies on arterial thromboembolic events in IBD patients, including stroke, peripheral artery disease (Periph. Art. Dis.), mesenteric ischemia (Mesent. Isch.) and ischemic heart disease (Isch. Heart Dis.). TE, thromboembolism; CD, Crohn's disease; UC, ulcerative colitis.

with higher death rates resulting from ischemic heart disease and cerebrovascular occlusion.[7,8] As a result, aggressive cardiovascular disease primary prevention has become standard of care in RA.[65] In contrast, a meta-analysis of 11 observational studies published 5 years ago found no increased risk of CV mortality in IBD patients.[66] We confirmed and reinforced these findings by pooling 69,383 patients including those from the most recent European studies.[33–35,47] In RA part of this risk appears to be mediated by long-term inflammation. Traditional CV risk factors as smoking or metabolic syndrome also play an important role.[67] In IBD, the impact of systemic inflammation on the cardiovascular risk may be different. Moreover, except smoking, more common in patients with Crohn's disease,[68] the prevalence and impact of traditional cardiovascular risk factors remains unknown. This discrepancy between IBD and RA may also be explained by the inclusion in most IBD studies of a majority of young patients with a follow-up of less than 5 years.

Our study is not without limitations. We included cohorts from a variety of clinical settings with differences in diagnostic criteria, age at enrollment, period at risk and study design. In addition, the methodology, inclusion criteria and outcome measures differed between studies. Some studies are population-based cohorts, some are from referral centers, and others look only at hospitalized patients through discharge databases. As expected we found statistically significant heterogeneity among the studies included in this meta-analysis. Therefore we used a random-effect model to give an estimate of variability.[69] Statistical heterogeneity was identified, because the magnitude of the association was different between studies. However the risk was consistent despite different study designs, populations and methods. Therefore our results confirmed higher risk of venous TE in IBD. The high heterogeneity observed suggests that relative risk may differ according to clinical setting therefore precise relative risk is hard to assess. In addition there were not enough studies to statified analysis by clinical setting. We determined that cohort source (patients or hospitalizations) explained some of the observed heterogeneity. Studies from large administrative databases of hospital admissions were included in the analysis. These studies report opposite results than other included studies. These different results may be explained by methodological defect. In addition, these studies have an important weight in the overall analysis. For this reason, sub-analysis including these studies was separately performed. Of note, most of the studies we included were retrospective with a relatively short average median duration of follow-up. Furthermore, well-established risk factors for TE such as smoking, personal or family history of cardiovascular events or BMI were not available in all studies and our results therefore could not be adjusted for them. Also, as a result of missing data, we were also unable to take into account age, sex, disease extension, disease severity and disease duration. Finally, we could not analyze the impact of IBD-related

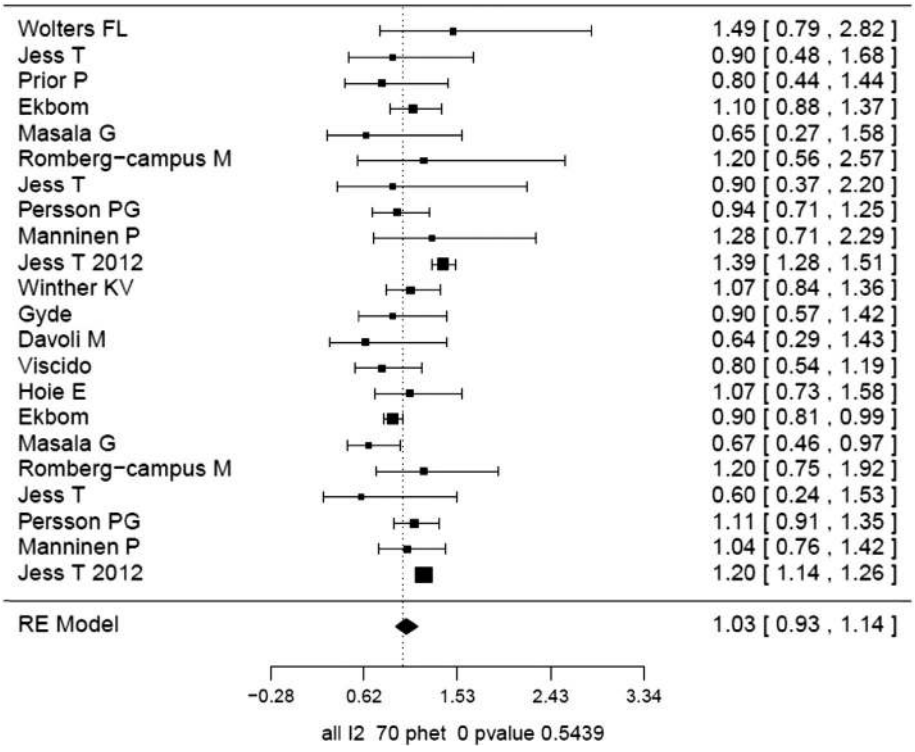

Figure 4 Meta-analysis of studies evaluating cardiovascular mortality in IBD patients.

medications on our findings. This underlines the fact that new prospective high quality studies evaluating the risk of thrombosis in IBD are required.

In conclusion, IBD is associated with an overall increased risk of thrombovascular events. As a result, the prevention of DVT and PE in particular should be at the forefront of gastroenterologists' concerns. Unfortunately this is not the case: in a recent survey involving 591 US physicians, 29% were unaware of any recommendations addressing pharmacologic prophylaxis included in American College of Gastroenterology IBD guidelines. Furthermore only 35% reported that they would give pharmacologic VTE prophylaxis to a hospitalized patient with severe ulcerative colitis.[70] In clinical practice, one study found that only 50% of patients hospitalized for severe ulcerative colitis at a referral center received pharmacologic venous thromboembolism prophylaxis.[71] With respect to the risk of ischemic heart disease and mesenteric ischemia in IBD patients, more studies are needed to further characterize risk factors such as whether a tight control of inflammation could ultimately prevent these potentially devastating events.

Disclosures

No conflicts of interest exist in this manuscript for any author.

Table 3 Relative risk of venous and arterial thromboembolism in inflammatory bowel disease patients.

	All studies (RR, CI 95%)	Studies including IBD patients (RR, CI 95%)	Studies including hospitalizations of IBD patients (RR, CI 95%)
Venous and arterial thromboembolism	1.60 [1.44–1.77]	1.90 [1.69–2.14]	1.13 [0.95–1.35]
Venous thromboembolism	1.96 [1.67–2.30]	2.48 [2.04–3.00]	1.47 [1.17–1.86]
Deep venous thrombosis	2.42 [1.78–3.30]	/	/
Pulmonary Embolism	2.53 [1.95–3.28]	/	/
Arterial thromboembolism	1.15 [0.91–1.45]	1.28 [1.16–1.42]	0.93 [0.56–1.54]
Ischemic heart disease	1.23 [0.94–1.62]	1.35 [1.19–1.52]	0.86 [0.40–1.84]
Stroke	0.79 [0.51–1.23]	1.11 [0.94–1.33]	/
Peripheral artery disease	0.78 [0.46–1.32]	/	/
Mesenteric ischemia	3.46 [1.78–6.71]	/	/

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2013.09.021.

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