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

Mathurin Fumery, Cao Xiaocang, Luc Dauchet, Corinne Gower-Rousseau, Laurent Peyrin-Biroulet, Jean-Frédéric Colombel

Objectives: 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

Abstract

Inflammatory bowel disease; Venous thromboembolism; Arterial thromboembolism; Cardiovascular mortality; Ischemic heart disease

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.

Received 25 July 2013; received in revised form 22 September 2013; accepted 24 September 2013

Available online at www.sciencedirect.com

ScienceDirect

Journal of Crohn’s and Colitis (2014) 8, 469–479

© 2013 European Crohn’s and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

http://dx.doi.org/10.1016/j.crohns.2013.09.021

Corinna Gower-Rousseau: Concept and study design, interpretation of data, and critical revision of the manuscript. Jean-Frédéric Colombel: Concept and study design, interpretation of data, and approval of the final version of the manuscript.

Corresponding author at: Henry D. Janowitz Division of Gastroenterology, One Gustave L. Levy Place, Box 1069, New York, NY 10029, USA.

E-mail address: jean-frederic.colombel@mssm.edu (J.-F. Colombel).

Contributed equally to this article.
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.

© 2013 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

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 venous.
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 Laird9 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 software13 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 studies15–47 on arterial and/or venous TE (n = 18)15–32 or CV (n = 15) mortality in IBD patients33–47 (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 patients23–32 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).
3.3. Deep venous thrombosis

3 studies evaluated DVT risk in IBD patients compared to the general population\textsuperscript{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) (I\textsuperscript{2} 90%, \textit{P} \textless 0.001), with no difference between CD and UC (\textit{p} = 0.46).

3.4. Pulmonary embolism

We identified 3 studies assessing the risk of PE in IBD patients\textsuperscript{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, 1.78–3.30) (I\textsuperscript{2} 80%, \textit{P} \textless 0.001), with no difference between CD and UC (\textit{p} = 0.69).

3.5. Arterial thromboembolism

We identified 9\textsuperscript{15–22,30} studies that assessed the risk of arterial thromboembolic 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) (I\textsuperscript{2} 97%, \textit{P} \textless 0.001) (Fig. 3). No difference was observed between CD and UC (\textit{p} = 0.49). When the analysis was restricted to IBD patients,\textsuperscript{15–19} excluding studies on hospitalizations, the risk of arterial TE was increased (RR, 1.28; 95% CI, 1.16–1.42) (I\textsuperscript{2} 64%, \textit{P} \textless 0.001), whereas it was not increased when including only studies of hospitalized patients (RR, 0.93; 95% CI, 0.56–1.54) (I\textsuperscript{2} 100%, \textit{P} \textless 0.001).\textsuperscript{22,30}

3.6. Ischemic heart disease

7 studies assessed the risk of ischemic heart disease including myocardial infarction in IBD patients\textsuperscript{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) (I\textsuperscript{2} 98%, \textit{P} \textless 0.001) (Fig. 3). Among studies including only IBD patients,\textsuperscript{15–19} the risk of arterial ischemic heart disease was increased (RR, 1.35; 95% CI, 1.19–1.52) (I\textsuperscript{2} 74%, \textit{P} \textless 0.001) (Fig. 3), whereas this risk was not increased among studies on hospitalizations\textsuperscript{22,30} (RR, 0.86; 95% CI, 0.40–1.84) (I\textsuperscript{2} 100%, \textit{P} \textless 0.001), with no difference between UC and CD (\textit{p} = 0.89).

3.7. Stroke

We identified 3 studies assessing the risk of stroke in IBD patients\textsuperscript{15,20,30} including 8,866 IBD patients and 97,043
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%, P = 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 in 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%, P = 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%, P = 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%, P = 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%, P = 0.999). All the previous results have been summarized in Table 3.

### 3.11. Heterogeneity 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%, P = 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, P = 0.001).
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, have been shown to be associated with IBD, but the magnitude of the thromboembolic risk is somewhat disputed. 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., 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. Reduction of venous thromboembolism by low molecular weight heparin or the new orally bioavailable anticoagulants 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. 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. 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. In IBD, the increased expression of CD40L by platelets appears to contribute to the pro-inflammatory response while in atherosclerosis, the inflammation caused by CD40L–CD40 interaction leads to unstable plaque resulting in thrombosis.

An increase in CV mortality compared to the general population is well documented in rheumatoid arthritis (RA)
with higher death rates resulting from ischemic heart disease and cerebrovascular occlusion. As a result, aggressive cardiovascular disease primary prevention has become standard of care in RA. In contrast, a meta-analysis of 11 observational studies published 5 years ago found no increased risk of CV mortality in IBD patients. We confirmed and reinforced these findings by pooling 69,383 patients including those from the most recent European studies. 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. 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, 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. 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 stratified 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...
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. 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. 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] | / | / |
Financial support

None.

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.

References

1. Danese S, S, A. Papa, S. Saibeni, A. Repici, A. Malesci, M. Vecchi. Inflammation and coagulation in inflammatory bowel disease: The clot thickens. Am. J. Gastroenterol. 2007;102:174–86.

2. Bergen JA, Barker NW. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. Arch. Intern. Med. 1936;58:17–31.

3. Murthy SK, Nguyen GC. Venous thromboembolism in inflammatory bowel disease: an epidemiological review. Am. J. Gastroenterol. 2011;106:713–8.

4. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, Sandborn WJ. Long-term complications, extraintestinal manifestations, and mortality in adult Crohn’s disease in population-based cohorts. Inflamm. Bowel Dis. 2011;17:471–8.

5. Hansson G. Inflammation, atherosclerosis, and coronary artery disease. N. Engl. J. Med. 2005;352(16):1685–95 (21).

6. Cao JJ, Arnold AM, Manolio TA, Polak JF, Psaty BM, Hirsch CH, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. Circulation 2007;116:32–8.

7. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaillle D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59(2):1690–7.

8. Avina-Zubieta JA, Thomas J, Sadatsafavi M, A.J Lehman, D. Lacaillle, Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann. Rheum. Dis. 2012;71:1524–9.

9. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control. Clin. Trials 1986;7:177–88.

10. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat. Med. 2002;21:1539–58.

11. Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:100–29.

12. Altman DG. Confidence intervals for the number needed to treat. BMJ 1998;317:1309–12.

13. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing3-90051-07-0; 2012 (URL, http://www.R-project.org/).

14. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 2010;36:1–48.

15. Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. Clin. Gastroenterol. Hepatol. 2008;6:41–5.

16. Yarur AJ, Deshpande AR, Pechman DM, Tamariz L, Abreu MT, Sussman DA. Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. Am. J. Gastroenterol. 2011;106:741–7.

17. 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;9:875–80.

18. Haapamäki J, Roine RP, Turunen U, Färkkilä MA, Arkkilä PE. Increased risk for coronary heart disease, asthma, and connective tissue diseases in inflammatory bowel disease. J. Crohns Colitis 2011;5:41–7.

19. Rungoe C, Basit S, Ranthe WF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. Gut 2012;62:689–94.

20. Andersohn F, Waring M, Garbe E. Risk of ischemic stroke in patients with Crohn’s disease: a population-based nested case–control study. Inflamm. Bowel Dis. 2010;16:1387–92.

21. Huerta C, Rivero E, Montoro MA, Garcia-Rodriguez LA. Risk factors for intestinal ischaemia among patients registered in a UK primary care database: a nested case control study. Aliment. Pharmacol. Ther. 2011;33:969–78.

22. Inamdar SS, Altafi SS, Sultan S. Increased risk of coronary artery disease among patients with inflammatory bowel disease. Gastroenterology 2012;142(Suppl 1):792–3.

23. Kappelman MD, Horvath-Puho E, Sandler RS, Rubin DT, Ullman TA, Pedersen L, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut 2011;60:937–43.

24. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet 2010;20(375):657–63.

25. Merrill A, Millham F. Increased risk of postoperative deep vein thrombosis and pulmonary embolism in patients with inflammatory bowel disease: a study of National Surgical Quality Improvement Program patients. Arch. Surg. 2012;147:120–4.

26. Novacke G, Weltermann A, Sobala A, Tilg H, Petritsch W, Reinisch W, et al. Inflammatory bowel disease is a risk factor for recurrent venous thromboembolism. Gastroenterology 2010;139:779–87.

27. Miehlke W, Reinisch W, Valic E, Osterode W, Tillinger W, Feichtenschlager T, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut 2004;53:342–8.

28. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb. Haemost. 2001;85:430–4.

29. Huerta CC, Johansson SS, Wallander MA, Garcia Rodriguez LA. Risk factors for postoperative deep vein thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch. Intern. Med. 2007;167(14):935–43.

30. Sridhar AR, Parasa S, Navaneethan U, Cromwell MD, Olden K. Comprehensive study of cardiovascular morbidity in hospitalized inflammatory bowel disease patients. J. Crohns Colitis 2011;5:287–94.

31. 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.

32. Saleh T, Matta F, Yaeckoub AY, Danescu S, Stein PD. Risk of venous thromboembolism with inflammatory bowel disease. Clin. Appl. Thromb. Hemost. 2011;17:254–8.

33. Höie O, Schouten LJ, Wolters FL, Solberg IC, Rils L, Mouzas IA, et al. Ulcerative colitis: no rise in mortality in a European-wide population based cohort 10 years after diagnosis. Gut 2007;56:497–503.

34. Romberg-Camps M, Kuiper E, Schouten L, Kester A, Hesselink-van de Krujs M, Limondar C, et al. Mortality in inflammatory bowel disease in the Netherlands 1991–2002: results of a population-based study: the IBD South-Limburg cohort. Inflamm. Bowel Dis. 2010;16:1397–410.

35. Manninen P, Karvonen AL, Huhtala H, Rasmussen M, Salo M, Mustaniemi L, et al. Mortality in ulcerative colitis and Crohn’s
36. Wolters FL, Russel MG, SJibbrandt J, Schouten LJ, Odes S, Riis L, et al. Crohn’s disease: increased mortality 10 years after diagnosis in a Europe-wide population based cohort. *Gut* 2006;55:510–8.

37. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Mortality and causes of death in Crohn’s disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Gastroenterology* 2002;122:1808–14.

38. Prior P, Gyde S, Cooke WT, Waterhouse JA, R.N. Mortality in Crohn’s disease. *Gastroenterology* 1981;80:307–12.

39. Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. *Gastroenterology* 2003;125:1576–82.

40. Gyde S, Prior P, Dew MJ, Saunders V, Waterhouse JA, Allan RN. Mortality in ulcerative colitis. *Gastroenterology* 1982;83:43–8.

41. Davoli M, Prantera C, Berto E, Scribano ML ML, D’ippolito D. Mortality among patients with ulcerative colitis: Rome 1970–1989. *Eur. J. Epidemiol.* 1997;13:189–94.

42. Viscido A, Bagnardi V, G.C., Annese V, Frieri G, D’Arienzo A, et al. Survival and causes of death in Italian patients with ulcerative colitis. A GISC nationwide study. *Dig. Liver Dis.* 2001;33:686–92.

43. Ekborn A, Helmick CG, Zack M, Holmberg L, Adami HO, et al. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. *Gastroenterology* 1992;103:954–60.

44. Masala G, Bagnoli S, Cerotti M, Saieva C, Trallori G, Zanna I, et al. Divergent patterns of total and cancer mortality in ulcerative colitis and Crohn’s disease patients: the Florence IBD study 1978–2001. *Gut* 2004;53:1309–13.

45. Jess T, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ, et al. Survival and cause-specific mortality in patients with inflammatory bowel disease: a long-term outcome study in Olmsted County, Minnesota, 1940–2004. *Gut* 2006;55:1248–54.

46. Persson PG, Bernell O, Leijonmarck CE, Farahmand BY, Hellers G, Ahlbom A, et al. Survival and cause-specific mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology* 1996;110:1339–45.

47. Jess T, Frisli M, Simonsen J. Trends in overall and cause-specific mortality among patients with inflammatory bowel disease from 1982 to 2010. *Clin. Gastroenterol. Hepatol.* 2013;11:43–8.

48. Koutroubakis IE. IBD: which patients with IBD are at risk of venous thromboembolism? *Nat. Rev. Gastroenterol. Hepatol.* 2010;7:307–8.

49. Van Assche G, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, 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.

50. Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J. Crohns Colitis* 2012;6:965–90.

51. Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmüller A, Juillard-Delsart D, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb. Haemost.* 2000;83:14–9.

52. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *Prophylaxis in Medical Patients with Enoxaparin Study Group. N. Engl. J. Med.* 1999;34:793–800.

53. Eriksson BI, Borriss LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N. Engl. J. Med.* 2008;358:2765–75.

54. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;370:949–56.

55. Papa A, Santoliquido A, Danese S, et al. Increased carotid intima-media thickness in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2005;1(12):839–46.

56. Broide E, Schopan A, Zaretsky M, et al. Intima-media thickness of the common carotid artery is not significantly higher in Crohn’s disease patients compared to healthy population. *Dig Dis Sci* 2011;56:197–202.

57. Kayahan H, Sari I, Cullu N, et al. Evaluation of early atherosclerosis in patients with inflammatory bowel disease. *Dig Dis Sci* 2012;57:2137–43.

58. Aloj M, Tromba L, Di Nardo G, et al. Premature subclinical atherosclerosis in pediatric inflammatory bowel disease. *J Pediatr* 2012;161:589–94.

59. Regueiro M, Kip KE, Cheung O, et al. Cigarette smoking and age at diagnosis of inflammatory bowel disease. *Inflamm Bowel Dis* 2005;11:42–7.

60. Emerging Risk Factors Collaboration Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;375:132–40.

61. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004;351:2599–610.

62. Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women’s Health Initiative observational study. *JAMA* 2002;288:980–7.

63. Danese S, Katz JA, Salbenni S, et al. Activated platelets are the source of elevated levels of soluble CD40 ligand in the circulation of inflammatory bowel disease patients. *Gut* 2003;52:1435–41.

64. Gutgens E, Lievens D, Beckers L. CD40 and its ligand in inflammation and cardiovascular risk in rheumatoid arthritis. *Trends Rheumatol* 2007;17:118–23.

65. Peters MJ, Symmons DP, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.

66. 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;102:662–7.

67. Liao KP, Solomon DH. Traditional cardiovascular risk factors, inflammation and cardiovascular risk in rheumatoid arthritis. *Rheumatology* 2013;52:45–52.

68. Birrenbach T, Böcker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. *Inflamm Bowel Dis* 2004;10:848–59.

69. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

70. Tinsley A, Naymagon S, Trindade AJ, et al. A survey of current practice of venous thromboembolism prophylaxis in hospitalized inflammatory bowel disease patients in the United States. *J Clin Gastroenterol* 2013;47:e1–6.

71. Tinsley A, Naymagon S, Enomoto L, et al. Rates of pharmacologic venous thromboembolism prophylaxis in hospitalized patients with severe ulcerative colitis. *Inflamm Bowel Dis* 2012;18(Suppl 1):S1–S127.