



Risque d'accident artériel aigu chez les patients atteints de maladie inflammatoire chronique intestinale et impact des traitements sur le risque : analyse des bases de données médico administratives françaises PMSI et SNIIRAM

Julien Kirchgesner

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M. Julien KIRCHGESNER

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**Risque d'accident artériel aigu chez les patients atteints de maladie inflammatoire chronique
intestinale et impact des traitements sur le risque : analyse des bases de données médico
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devant le jury composé de :

M. Laurent Beaugerie et M. Fabrice Carrat, Directeurs de thèse

Mme Corinne Gower-Rousseau et M. Vito Annese, Rapporteurs

Mme Tine Jess, Mme Florence Tubach, M. Bruno Fautrel et M. Guillaume Savoye,
Examineurs

Université Pierre & Marie Curie - Paris 6
Bureau d'accueil, inscription des doctorants et base de
données
Esc G, 2^{ème} étage
15 rue de l'école de médecine
75270-PARIS CEDEX 06

Tél. Secrétariat : 01 42 34 68 35
Fax : 01 42 34 68 40
Tél. pour les étudiants de A à EL : 01 42 34 69 54
Tél. pour les étudiants de EM à MON : 01 42 34 68 41
Tél. pour les étudiants de MOO à Z : 01 42 34 68 51
E-mail : scolarite.doctorat@upmc.fr

Laboratoire de rattachement

Sorbonne Universités, UPMC Univ Paris 6, INSERM,
Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP UMRS 1136)

Responsable: Dominique Costagliola

Equipe: "Epidémiologie de la grippe et des hépatites virales: risque, pronostic et stratégies thérapeutiques"

Faculté de Médecine Pierre et Marie Curie, site Saint Antoine
27 rue Chaligny, 75571 Paris cedex 12, France

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Thesis publications

Publications

Kirchgesner J, Lemaitre M, Rudnichi A, et al. Therapeutic management of inflammatory bowel disease in real-life practice in the current era of anti-TNF agents: analysis of the French administrative health databases 2009-2014. *Aliment Pharmacol Ther* 2017;45:37–49.

Kirchgesner J, Beaugerie L, Carrat F, et al. Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study. *Gut* 2017;;gutjnl-2017-314015. doi:10.1136/gutjnl-2017-314015

Communications

Kirchgesner J, Andersen NN, Carrat F Exposure to combination therapy with thiopurines and anti-TNF agents is associated with reduced incidence of acute arterial events in patients with inflammatory bowel disease (IBD): a nationwide French cohort study

United European Gastroenterology Week (UEGW) 2017, Barcelona, October 2017

Résumé

Introduction

La maladie de Crohn (MC) et la rectocolite hémorragique (RCH) sont des maladies inflammatoires chroniques intestinales, réunies sous l'acronyme MICI. Il est considéré aujourd'hui que les MICI sont le résultat d'une réponse immunitaire intestinale inadaptée aux antigènes bactériens du microbiote intestinal chez des sujets génétiquement prédisposés et sous l'influence de facteurs d'environnement. L'histoire naturelle des MICI est composée de périodes de poussées, responsables d'une inflammation intestinale et souvent systémique, entrecoupées de périodes de rémission de durée variée, sans guérison définitive.[1]

Alors que l'athérosclérose est favorisée par l'inflammation systématique[2] et que plusieurs maladies inflammatoires chroniques, telles que la polyarthrite rhumatoïde, sont associées à un sur-risque d'accident artériel aigu,[3] ce risque reste débattu chez les patients atteints de MICI. Les résultats discordants rapportés dans la littérature pourraient s'expliquer par l'absence de prise en compte spécifique de l'impact de l'âge et de l'activité de la maladie sur le risque d'accident artériel aigu. De plus, les facteurs prédictifs d'accident artériel aigu chez les patients atteints de MICI et l'identification des populations les plus à risque restent à déterminer.

Par ailleurs, un traitement immunosuppresseur (surtout thiopurines et anti-TNFs) est utilisé chez un nombre croissant de patients au fil des années, de plus en plus tôt après le diagnostic et pour des périodes prolongées.[4] Ces traitements, en diminuant le plus souvent l'inflammation intestinale et systémique, pourraient diminuer le risque d'accident artériel aigu attribuable à l'inflammation systémique.

L'objectif de cette thèse est d'étudier le risque d'accident artériel aigu chez les patients atteints de MICI comparé à la population générale et l'impact des traitements sur ce risque, à partir des bases de données médico-administratives françaises.

Bases de données médico-administratives françaises : PMSI et SNIIRAM

Les bases de données médico-administratives françaises incluent le Programme de Médicalisation des Systèmes d'Information (PMSI) et le Système National d'Information Inter-régimes de l'Assurance Maladie (SNIIRAM). Le PMSI comprend des données de prise en charge hospitalière (publique et privée), alors que le SNIIRAM regroupe les données de prise en charge ambulatoire (Données de consommation inter-régimes (DCIR)) et le PMSI. Un identifiant anonyme unique pour chaque patient permet de chaîner les deux bases de données. Pour des raisons réglementaires, différentes périodes d'inclusion ont été considérées pour chaque travaux de cette thèse.

PMSI

Le PMSI inclut l'ensemble des hôpitaux publics et privés en France, avec une exhaustivité complète pour tous les séjours hospitaliers depuis 2008. Pour chaque hospitalisation est produit un résumé de sortie standardisé comprenant : (i) des données démographiques (date de naissance, sexe, code géographique de résidence, statut vital à la sortie de l'hôpital); (ii) les diagnostics codés selon la classification internationale des maladies 10^{ème} édition (CIM-10), comprenant le diagnostic principal défini depuis 2009 comme le motif de santé ayant motivé l'admission du patient, les diagnostics associés significatifs définis comme toute comorbidité ayant entraîné une prise en charge (diagnostique ou thérapeutique) et le diagnostic relié précisant le

contexte pathologique pour certains séjours; (iii) les actes médicaux, notamment les actes chirurgicaux classés selon la classification commune des actes médicaux (CCAM); (iv) les traitements et dispositifs médicaux remboursés en sus du séjour hospitalier, définis selon une classification révisée chaque année (molécules onéreuses et dispositifs médicaux pris en charge en sus).

SNIIRAM

En plus des données hospitalières du PMSI, le SNIIRAM comprend des données de prise en charge ambulatoire intégrées dans le DCIR. Pour chaque patient sont notamment inclus : (i) les données démographiques (date de naissance, sexe, code géographique de résidence, statut vital avec date de décès); (ii) les maladies prises en charge à 100% d'après la liste des affections longue durée (ALD) selon la CIM-10 avec la date de survenue des premiers symptômes et la date de diagnostic; (iii) les traitements délivrés en pharmacie avec le nombre de boîtes délivrées, et classés selon le type de médicament (code ATC (anatomique, thérapeutique et chimique)) et le type de boîte (code CIP (Code Identifiant de Présentation)); (iv) les bilans biologiques remboursés selon la nomenclature des actes de biologie médicale (NABM), sans information sur le résultat du bilan biologique.

L'ensemble des régimes de l'assurance maladie sont inclus dans le SNIIRAM, mais l'exhaustivité des données est incomplète pour certains régimes. Dans cette thèse, les études basées sur le SNIIRAM se limitent donc aux personnes affiliées au régime général, dont les sections locales mutualistes (environ 88% de la population générale française).

Article: Therapeutic management of inflammatory bowel disease in real-life practice in the current era of anti-TNF agents: analysis of the French administrative health databases 2009-2014 (Aliment Pharmacol Ther 2017;45:37–49)

La première partie de la thèse consistait à construire un algorithme d'identification des patients atteints de MICI et valider de façon indirecte le codage du diagnostic de MICI dans les bases de données médico-administratives françaises. En effet, en l'absence d'étude de validation du codage de MICI avec estimation d'une valeur prédictive positive nécessitant un retour physique aux dossiers médicaux, une étude descriptive exhaustive de la cohorte de patients atteints de MICI a été réalisée à partir du SNIIRAM.

Cette étude descriptive était également motivée par l'absence de données en vie réelle sur la prise en charge thérapeutique des patients atteints de MICI à l'ère des anti-TNFs. En effet, cette prise en charge a fortement évolué au cours des 10 dernières années. Des essais contrôlés randomisés ont conclu à une efficacité supérieure de l'association anti-TNFs - thiopurines (combothérapie) introduite de façon précoce, comparé à chaque monothérapie, que ce soit dans la MC ou la RCH.[5,6] Par ailleurs, peu d'essais ont évalué l'arrêt des traitements immunosuppresseurs chez des patients en rémission, principalement chez des patients atteints de MC. L'impact de ces essais sur la pratique clinique en vie réelle reste inconnu. L'objectif de cette analyse était d'étudier la prise en charge thérapeutique en vie réelle des patients atteints de MICI à l'échelle de la France.

Cette étude a été réalisée à partir des données du SNIIRAM 2009-2014. Tous les patients avec un diagnostic de MICI identifié à partir d'une déclaration d'ALD avec diagnostic avant le 31 décembre 2013 et/ou à partir d'une hospitalisation avec un

diagnostic principal ou relié de MICI (maladie de Crohn, K50; RCH, K51) entre le 1^{er} janvier 2009 et le 31 décembre 2013 ont été inclus dans la cohorte. Les patients ont été suivis soit jusqu'au 31 décembre 2014, soit jusqu'au décès. L'exposition aux différents types de traitements (5-aminosalicylés et corticoïdes oraux, méthotrexate, monothérapie thiopurines et anti-TNFs, combothérapie) pendant le suivi a été décrite pour l'ensemble de la cohorte, ainsi que la fréquence des chirurgies abdominales (colectomies, résections intestinales, drainage d'abcès intra-péritonéal, et chirurgie anopérinéales) et hospitalisations liées à l'activité de la MICI.

De plus, pour les patients âgés de plus de 18 ans incidents MICI inclus entre 2009 et 2012, sans antécédent de cancer, déficit immunitaire congénital ou infection VIH, la séquence thérapeutique (1^{ère}, 2^{ème} et 3^{ème} lignes de traitement) au cours du suivi a été décrite.

Nous avons identifié 210 001 patients atteints de MICI (100 112 avec MC et 109 889 avec RCH). La majorité des patients (54,7% n=114 930) était identifiée à partir d'une déclaration d'ALD et d'une hospitalisation concomitantes. 69 725 cas incidents étaient inclus (34 739 (49,8%) avec MC et 34 986 (50,2%) avec RCH). Le taux d'incidence de la MC et RCH était respectivement de 11,0 et 11,1 pour 100 000 personnes.

Parmi les patients incidents traités par thiopurines et/ou anti-TNFs (17 566 avec MC et 8035 avec RCH), la majorité débutait par une monothérapie thiopurines (69,1% (12 130) des patients avec MC et 78,2% (6284) des patients avec RCH). À 5 ans du diagnostic, le risque cumulé d'avoir été exposé à la monothérapie thiopurines, monothérapie anti-TNFs et combothérapie était respectivement de 43,6% (intervalle de confiance à 95% (IC 95% 42,9-44,3)), 33,8% (IC 95% 33,0-34,6) et 18,3% (IC 95% 17,7-18,9) chez les patients avec MC et 24,9% (IC 95% 24,3-25,6), 12,9% (IC 95% 12,3-13,6) et 7,4% (IC 95% 6,9-7,8) chez les patients avec RCH.

Après une première ligne de traitement de plus de 3 mois, 555 (26,2%) et 1873 (33,3%) patients avec MC ont arrêté respectivement pendant plus de 3 mois leur traitement par monothérapie thiopurines ou anti-TNFs. Ces taux étaient de 22,6% (148) et 28,1% (924) en cas de rectocolite hémorragique. L'arrêt du traitement était relié à une hospitalisation ou chirurgie en rapport avec l'activité de la MICI dans moins de 30% des cas. Environ 50% des patients avec MC et 40% des patients avec RCH reprenaient leur traitement antérieur, alors que 5% des patients avec MC et 4% des patients avec RCH arrêtaient tout traitement lié à la MICI (5-aminosalicylés, corticoïdes, méthotrexate, thiopurines et anti-TNFs).

À 5 ans du diagnostic, le risque cumulé d'avoir été hospitalisé durant plus de 48h au moins une fois en rapport avec l'activité de la MICI était de 13,5% (IC 95% 13,0–14,1) et 9,7% (IC 95% 9,2–10,2) chez les patients avec MC et RCH, respectivement.

Le risque cumulé de chirurgie digestive majeure (résection intestinale et colectomie) à 5 ans du diagnostic était de 13,5% (IC 95% 13–14,1) et 6,2% (IC 95% 5,8–6,6) chez les patients avec MC et RCH, respectivement. Parmi les patients avec RCH, le risque cumulé de colectomie à 1 an et 5 ans du diagnostic était respectivement de 3,1% (IC 95% 2,9–3,3) et 5,7% (IC 95% 5,4–6,1).

Cette étude a permis de valider de façon indirecte le diagnostic de MICI dans les bases de données médico-administratives françaises, devant les taux d'incidence attendus comparé à la littérature et l'histoire naturelle de la maladie similaire à celle observée dans d'autres études observationnelles. Par ailleurs, cette étude descriptive détaillée en vie réelle de la prise en charge thérapeutique des patients avec MICI à l'échelle nationale a montré que la majorité des patients incidents étaient traités en France selon une stratégie d'intensification progressive (« step-up approach ») débutant par une monothérapie thiopurines, plutôt qu'une introduction de la combothérapie

d'emblée avec désescalade secondaire (« top-down approach »). Alors que l'exposition aux anti-TNFs est élevée, les arrêts de traitements sont non négligeables, et pour la majorité non liés à une hospitalisation ou une chirurgie en rapport avec l'activité de la MICI.

Article: Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study (Gut 2017; gutjnl-2017-314015)

L'objectif de cette analyse était d'estimer le risque d'accidents artériels aigus chez les patients atteints de MICI comparé à la population générale à l'échelle de la France et l'impact de l'âge, du sexe et de l'activité de la maladie sur ce risque.

A partir du PMSI de 2008 à 2013, tous les patients âgés de plus de 15 ans atteints de MICI ont été identifiés et suivis jusqu'au 31 décembre 2013. Le diagnostic de MICI était basé sur un codage en diagnostic principal, relié ou associé significatif. La date d'inclusion dans la cohorte était le 1^{er} Janvier 2010 pour les sujets diagnostiqués avant 2010 et la date de 1^{ère} identification dans la base pour les sujets diagnostiqués entre 2010 et 2013. Tous les sujets étaient suivis jusqu'à la survenue de l'évènement d'intérêt ou jusqu'au 31 Décembre 2013. La population générale était constituée de l'ensemble des personnes âgées de 15 ans ou plus résidant en France, à partir des données de l'Institut national de la statistique et des études économiques (INSEE).

Les critères d'exclusion étaient appliqués de façon identique dans la population atteinte de MICI et la population générale, et identifiés du 1^{er} Janvier 2008 à la date d'entrée dans la cohorte (soit au minimum 2 ans de suivi pour chaque sujet). Les sujets avec un antécédent d'accident artériel aigu, fibrillation auriculaire, cardiomyopathie, un

antécédent de valve cardiaque prothétique, d'artériographie, de coronarographie et pontage artériel étaient exclus.

Le critère de jugement principal était la survenue d'un accident artériel aigu. Tous les accidents artériels aigus incidents (cardiopathie ischémique, accident vasculaire cérébral, embolie et thrombose artérielles périphériques à l'exclusion du territoire mésentérique) ont été identifiés. Les actes chirurgicaux (colectomie, résection intestinale, drainage d'abcès intrapéritonéal et chirurgie anopérinéale pour lésions-anopérinéales secondaires) ou hospitalisations liés à l'activité de la maladie et la présence de facteurs de risque cardiovasculaire (hypertension artérielle, dyslipidémie, diabète, obésité, intoxication tabagique et alcoolique chronique) ont été recueillis. L'incidence d'accidents artériels aigus chez les patients atteints de MICI et l'incidence attendue dans la population générale stratifiée sur le sexe, l'âge (tranche de 5 ans) et la région de domicile ont été calculées, afin d'obtenir des ratios d'incidence standardisés (SIR). Des analyses en sous-groupe ont été réalisées en fonction de l'âge, le sexe et le nombre de facteurs de risque cardiovasculaire identifiés.

Pour étudier l'impact de l'activité de la maladie sur le risque, les actes chirurgicaux ou hospitalisations liés à l'activité de la maladie ont été utilisés comme marqueur d'activité de la maladie. Une période d'activité était définie comme la période précédant et suivant de 3 mois un acte chirurgical ou une hospitalisation liés à l'activité de la MICI, soit 6 mois au total. Une analyse de survie de type modèle de Cox était réalisée pour chaque sous-type de MICI, et ajustée sur l'âge, le sexe, la région de domicile, l'activité de la maladie avant l'entrée dans la cohorte et les facteurs de risque cardiovasculaire. L'activité de la maladie était prise en compte comme une variable temps-dépendante.

210 162 patients atteints de MICI (97 708 avec MC, 112 454 avec RCH) ont été inclus. Durant 595 324 patients-années, 5554 accidents artériels aigus incidents ont été

diagnostiqués (3177 cardiopathies ischémiques (57,2%), 1715 accidents vasculaires cérébraux (30,9%) et 662 embolies ou thromboses artérielles périphériques (11,9%)). Les patients atteints de MC et RCH avaient un sur-risque d'accident artériel aigu comparé à la population générale (SIR, 1,35; IC 95%, 1,30-1,41 et 1,10; IC 95%, 1,06-1,13, respectivement). Les valeurs de SIR chez les patients de moins de 35 ans étaient parmi les plus élevées dans la MC comme dans la RCH (1,42; IC 95%, 1,09-1,75 et 1,65; IC 95%, 1,20-2,10, respectivement). Ce sur-risque était noté pour tous les sous-groupes d'accidents artériels en cas de MC et pour les cardiopathies ischémiques et accidents vasculaires cérébraux en cas de RCH. Comparé à la population générale de même sexe, les femmes atteintes de MICI étaient plus à risque que les hommes, pour tous les sous-groupes d'accidents artériels aigus, avec le risque le plus élevé chez les femmes atteintes de MC (SIR d'accident artériel aigu, 1,59; IC 95%, 1,50-1,69).

21 420 (22%) et 14 886 (13%) patients atteints de MC et RCH ont été hospitalisés en rapport avec l'activité de la MICI au cours du suivi. De façon attendue, la présence de n'importe quel facteur de risque cardiovasculaire (en dehors de l'obésité) et le sexe masculin étaient associés à un sur-risque d'accident artériel aigu. Après ajustement sur les facteurs de risque cardiovasculaire, la période de 3 mois avant et après une hospitalisation ou un acte chirurgical liés à l'activité de la MICI était associée à un sur-risque d'accident artériel aigu chez les patients atteints de MC et de RCH (Hazard ratio, 1,77; IC 95%, 1,47-2,12 et 1,87; IC 95%, 1,58-2,22, respectivement). Ce sur-risque restait significatif dans toutes les analyses de sensibilité effectuées, notamment en faisant varier la période d'activité de 3 à 1 ou 6 mois avant et après une hospitalisation ou un acte chirurgical liés à l'activité de la MICI.

Les patients atteints de MICI ont un sur-risque global d'accident artériel aigu comparé à la population générale dont le risque est le plus élevé chez les patients jeunes. Cette différence de risque pourrait s'expliquer par l'impact de l'inflammation sur le risque, variant selon les catégories d'âge. En effet, l'âge jeune au diagnostic de MC est un facteur de risque de maladie sévère, alors que la sévérité de la RCH tend à diminuer avec l'âge. Par ailleurs, le sur-risque associé aux facteurs de risque cardiovasculaire traditionnels, plus nombreux chez les patients les plus âgés, pourrait dépasser celui associé à l'inflammation chronique en rapport avec l'activité de la maladie. Les facteurs de risque cardiovasculaire plus présents chez les hommes pourraient également expliquer la différence de risque entre les 2 sexes. Concernant la différence observée entre les deux phénotypes de MICI, la MC est généralement responsable d'une inflammation systémique plus importante que la RCH.[7–9] Mais cette différence pourrait être également partiellement liée à la proportion plus élevée de fumeurs chez les patients avec MC comparée aux patients avec RCH. Dernièrement, l'activité de la maladie est un élément indépendant fort du risque dans les deux sous-types de MICI.

Exposure to combination therapy with thiopurines and anti-TNF agents is associated with reduced incidence of acute arterial events in patients with inflammatory bowel disease (IBD): a nationwide French cohort study (Oral communication, United European Gastroenterology Week (UEGW) 2017, Barcelona, October 2017)

L'objectif de ce travail était d'estimer l'impact des traitements par thiopurines et anti-TNFs sur le risque d'accidents artériels aigus chez les patients atteints de MICI.

A partir des données du SNIIRAM 2010-2014, tous les patients avec un diagnostic de MICI identifié à partir d'une déclaration d'ALD et un diagnostic avant le 31 décembre

2011 ou à partir d'une hospitalisation avec un diagnostic principal ou relié de MICI entre le 1^{er} janvier 2010 et le 31 décembre 2011 ont été inclus. Les patients avec une seule hospitalisation sans ALD ni traitement en rapport avec la MICI au cours du suivi (5-aminosalicylés, budésonide, thiopurines et anti-TNFs) étaient considérés comme ayant un diagnostic incertain de MICI et inclus seulement dans les analyses de sensibilité.

La date d'inclusion dans la cohorte était le 1^{er} mars 2010 pour les sujets diagnostiqués avant 2010 et la date de 1^{ère} identification dans la base pour les sujets diagnostiqués entre 2010 et 2011. Les patients ont été suivis soit jusqu'au 31 décembre 2014, soit jusqu'à la survenue d'un accident artériel aigu, soit jusqu'au décès.

Les critères d'exclusion étaient les mêmes que ceux de l'analyse évaluant l'impact de l'activité de la maladie sur le risque, à savoir un antécédent d'accident artériel aigu, fibrillation auriculaire, cardiomyopathie, un antécédent de valve cardiaque prothétique, d'artériographie, de coronarographie et pontage artériel. Le critère de jugement principal était également défini de façon similaire et incluait tous les accidents artériels aigus incidents (cardiopathie ischémique, accident vasculaire cérébral, embolie et thrombose artérielles périphériques à l'exclusion du territoire mésentérique).

L'exposition médicamenteuse était estimée à partir des données hospitalières et ambulatoires, les anti-TNFs (infliximab, adalimumab et golimumab) pouvant être administrés à l'hôpital et en ambulatoire alors que les thiopurines sont délivrées par période d'un mois en pharmacie. Les patients traités par infliximab étaient considérés exposés 2 mois après la perfusion alors que les patients traités par thiopurines, adalimumab et golimumab étaient considérés exposés 1 mois après la délivrance en pharmacie. La combothérapie était définie comme l'exposition concomitante aux

thiopurines et anti-TNFs. Trois modalités de traitements ont été étudiées: la monothérapie thiopurines, la monothérapie anti-TNFs et la combothérapie.

Les variables identifiées à l'entrée de la cohorte incluaient le sexe, l'âge, la durée de la MICI, l'exposition au méthotrexate, 5-aminosalicylés et antiagrégants plaquettaires dans les 3 mois précédant l'entrée dans la cohorte, les facteurs de risque cardiovasculaire (hypertension artérielle, dyslipidémie, diabète, obésité, intoxication tabagique et alcoolique chronique) et les comorbidités classiques (antécédent de pathologie chronique pulmonaire, rénale et rhumatologique, cancer, maladie veineuse thromboembolique et infection par le VIH). L'activité de la maladie était définie par une hospitalisation ou un acte chirurgical lié à la MICI et l'exposition aux corticoïdes systémiques, mise à jour tous les 6 mois durant le suivi.

La propension à être traité par chacune des 3 modalités de traitement d'intérêt (monothérapie thiopurines/monothérapie anti-TNFs/combothérapie) pendant le suivi, en fonction des comorbidités et du phénotype, de l'ancienneté et de l'activité de la MICI a été estimée par régression logistique. Le risque d'accident artériel aigu a été comparé entre les 3 groupes de traitement à l'aide d'un modèle structural marginal de Cox pondéré par l'inverse de la probabilité d'être traité.

178 360 patients atteints de MICI ont été inclus dans l'analyse principale, parmi lesquels 90 423 (50,7%) et 87 937(49,3%) étaient respectivement atteints de MC et RCH. L'âge moyen à l'entrée de la cohorte était de 46,3 ans (écart type 16,4) et 16% des patients étaient des patients incidents diagnostiqués entre 2010 et 2011. 22,8%, 13,5% et 5,6% ont été respectivement exposés à la monothérapie thiopurines, la monothérapie anti-TNFs et la combothérapie au cours du suivi.

Au total, 4376 accidents artériels aigus, dont 50,4% (2204) de cardiopathies ischémiques, 33,7% (1476) d'accidents vasculaire cérébraux et 15,9% (696) d'embolies et thromboses artérielles périphériques ont été identifiés. L'incidence brute était de 5,6 accidents artériels aigus pour 1000 personnes-années.

Comparés aux patients non exposés aux thiopurines et anti-TNFs, les patients sous monothérapie thiopurines, anti-TNFs et combothérapie avaient un risque diminué d'accident artériel aigu, mais cette diminution était seulement significative pour les patients sous combothérapie, (HR 0,91; IC 95%, 0,81-1,02; 0,89; IC 95%, 0,76-1,04 et 0,81; IC 95%, 0,66-0,99, respectivement). Des résultats similaires étaient retrouvés dans les analyses par sous-groupe d'accident artériel aigu, mais seulement significatif pour le risque de cardiopathie ischémique chez les patients exposés à la combothérapie.

La diminution du risque global d'accident artériel aigu prédominait chez les patients avec MC, notamment chez les patients sous monothérapie thiopurines, (HR 0,84; IC 95% 0,71-0,98) et combothérapie, (HR 0,71; IC 95% 0,54-0,93). Cette association était encore plus soutenue chez les hommes atteints de MC sous combothérapie (HR 0,58; IC 95% 0,40-0,83).

Des résultats similaires étaient retrouvés dans l'analyse de sensibilité incluant les patients avec un diagnostic incertain de MICI (patients sous combothérapie, HR 0,79 IC 95% 0,65-0,97).

Cette étude à partir du SNIIRAM incluant plus de 170 000 patients atteints de MICI a montré que l'exposition à la combothérapie est associée à une diminution du risque d'accident artériel aigu, avec une réduction de risque particulièrement soutenue chez les patients atteints de MC. Cette différence entre la combothérapie et les

monothérapies thiopurines et anti-TNFs pourrait s'expliquer par le maintien en rémission clinique et endoscopique plus important et plus rapide en cas de traitement par combothérapie comparé à chaque monothérapie.

Discussion

Toutes les analyses ont été réalisées à partir des bases de données médico-administratives françaises, que ce soit à partir de données exclusivement hospitalières ou de données ambulatoires et hospitalières. Certaines variables ne sont pas rapportées précisément dans ces bases de données, notamment les facteurs environnementaux comme l'exposition au tabac. Or le tabac représente un facteur de risque d'accident artériel aigu, et l'exposition au tabac est également différente selon le sous-type de MICI, avec plus de fumeurs chez les patients avec MC et moins de fumeurs chez les patients avec RCH comparé à la population générale. Concernant le risque associé à l'activité de la maladie, ce sur-risque était retrouvé quel que soit le sous-type de MICI. Par ailleurs, le tabac est associé à une évolution plus sévère de la MC et les patients exposés aux anti-TNFs et thiopurines sont plus fumeurs que les patients non exposés à ces traitements. Un potentiel biais lié à un ajustement imparfait du tabac sur le risque d'accident artériel tendrait à sous-estimer la réduction du risque associé à la combothérapie. Le sens des associations rapportées ici ne paraît donc pas altéré par une sous-estimation de l'exposition tabagique.

Nous avons stratifié les analyses sur le sexe, l'âge et le phénotype de la maladie. Ces stratifications permettent de mettre en évidence les différences d'impact de l'inflammation systémique selon les caractéristiques de chaque patient. En effet, le sur-risque d'évènement artériel aigu chez les patients jeunes et les femmes comparés

à la population générale reflète l'impact supérieur de l'inflammation systémique sur le risque dans cette population avec peu de facteurs de risques cardiovasculaires. De la même façon, l'impact plus important des traitements immunosuppresseurs sur la diminution du risque d'accident artériel aigu chez les patients avec MC, notamment les hommes, reflète le bénéfice d'une diminution de l'inflammation systémique dans la population la plus à risque. À l'ère de la médecine personnalisée, ces éléments permettent de mieux appréhender le risque d'accident artériel aigu et le bénéfice potentiel des traitements pour un individu donné.

Conclusion

Les travaux menés dans le cadre de cette thèse mettent en évidence l'impact de l'activité inflammatoire sur le risque d'accident artériel aigu et le bénéfice des traitements immunosuppresseurs sur ce risque, en complément de leur bénéfice sur le contrôle de l'inflammation digestive. Ces analyses soutiennent le concept de plus en plus répandu qu'un contrôle strict de l'inflammation pourrait limiter la survenue de complications extra-digestives liées à la MICI. La prévention des accidents artériels aigus devrait être incluse dans l'évaluation de la balance bénéfice-risque des anti-TNFs et thiopurines chez les patients atteints de MICI, en prenant compte l'âge, le sexe et le phénotype de la MICI (durée, localisation) pour chaque patient

Abstract

Atherosclerosis is now recognized as a chronic inflammatory condition. While common pathogenic processes between atherosclerogenesis and chronic inflammatory diseases have been identified, several of these diseases are at increased risk of acute arterial event and anti-inflammatory agents may represent attractive preventive treatments. Despite the fact that inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) is characterized by chronic intestinal and systemic inflammation, the existence of an increased risk of acute arterial event in IBD remains unclear. The objectives of this thesis are to assemble a nationwide cohort of IBD patients based on the French administrative health databases, in order to assess the risk of acute arterial events in IBD and the impact of immunosuppressive treatment on the risk.

Disease course and therapeutic management of IBD were first studied, in order to validate the coding diagnosis of IBD in the databases. This study revealed that the step-up approach remains the predominant strategy, while exposure to anti-TNFs is high and surgery rates are low. Treatment exposure, hospitalisation, and surgery rates are similar to current standard of care and incidence rates are in the range of those reported in other populations.

Both patients with CD and UC have a statistically significant increased risk of acute arterial events compared with the general population. The highest risk is observed in patients under the age of 55 years. Disease activity is an independent risk factor of acute arterial events, after adjustment for traditional cardiovascular risk factors, with a similar magnitude of risk in active CD and UC. Exposure to thiopurine monotherapy, anti-TNF monotherapy and combination therapy (combination of thiopurines and anti-

TNFs) are all numerically associated with a decreased risk of acute arterial events compared to unexposed patients, although the difference is only statistically significant for patients exposed to combination therapy. The magnitude in risk reduction is highest in men with CD exposed to combination therapy.

These studies support the concept that a tight control of inflammation is crucial in patients with IBD to avoid IBD-related systemic complications. Prevention of acute arterial events should be considered in the benefit-risk balance assessment of thiopurines and anti-TNFs treatment in IBD patients, according to age, sex and IBD subtype.

Keywords

- Inflammatory bowel disease
- Crohn's disease
- Ulcerative colitis
- Acute arterial events
- Cardiovascular disease
- Ischemic heart disease
- Cerebrovascular disease
- Peripheral artery disease

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disease characterized by relapsing and remitting episodes that may lead to irreversible intestinal lesions and severe disability over the life course. IBD includes Crohn's disease (CD) and ulcerative colitis (UC) with young-adult disease onset, although unclassified colitis, pediatric or elderly onsets are also possible. Treatment is based on immunosuppressive therapy that aims to induce and maintain clinical, biological and histological remission. An issue of growing concern today is the increasing proportion of IBD patients exposed to prolonged immunosuppressive therapy with unknown risk-benefit balance over lifetime.[4]

The risk of cardiovascular disease such as ischemic heart disease and cerebrovascular disease in IBD remains debated although systemic inflammation is known to be involved in atherosclerosis pathogenesis and associated with cardiovascular events.[10] Moreover, the risk of cardiovascular disease is well established in other chronic inflammatory disorders such as rheumatoid arthritis in which systemic inflammation and disease activity are associated with cardiovascular events.[3,11] In addition, anti-TNF agents reduce systemic inflammation and could decrease cardiovascular events in IBD patients, as it is increasingly suggested in patients with rheumatoid arthritis.[12] However, the impact of treatment with biologics and immunosuppressants on cardiovascular risk in IBD patients remains largely unexplored, potentially due to a lack of statistical power in most IBD populations, as seen in previous studies.[13] As long as cardiovascular risk related to IBD is not well-established, efficient prevention strategy cannot be elaborated, whereas recommendations for cardiovascular risk management in patients with rheumatoid

arthritis, ankylosing spondylitis and psoriatic arthritis have been published since 2010.[11]

French administrative health databases include the French National Health Insurance anonymised claim database (*Système National d'Information Interrégimes de l'Assurance Maladie* (SNIIRAM)) and the French hospital discharge database (*Programme de Medicalisation des Systemes d'Information* (PMSI)). Patients are unselected in the SNIIRAM and PMSI and all French residents are included because universal access to healthcare is warranted for all French residents. The SNIIRAM contains all drugs reimbursements, outpatient medical and nursing care, which have been prescribed or done by health-care professionals. The SNIIRAM does not provide any information about the medical indication for each reimbursement but contains the patient's status with respect to full reimbursement of care related to long-term diseases (LTDs) listed in the International Classification of Diseases, 10th edition (ICD-10),[14] which includes CD and UC. The PMSI concerned all French hospitals since 1997 and is designed for hospital payment since 2004. All discharge diagnoses are identified since 2006 using ICD-10.[15] The unique anonymous identifier allows linking all hospital claims of the patient and tracking the occurrence and progression of severe conditions over time. Several studies estimated the reliability of the information recorded and the accuracy of their coding in different fields,[16] and the PMSI and SNIIRAM had been used for research purposes to measure disease incidence and identify determinants of medical conditions, including cardiovascular disease.[17–20]

The general objective of this thesis is to assemble a nationwide cohort of IBD adult patients in France and assess the causes and determinants of acute arterial events in patients with IBD in the era of immunosuppressive therapy with anti-tumor necrosis factors agents. This project will test the initial hypothesis that the risk of acute arterial

events is increased in patients with IBD compared with individuals of the general population, because systemic inflammation is very often associated with IBD. The second hypothesis is that immunosuppressive treatment may be a protective factor by decreasing systemic inflammation. For testing these hypotheses, we decided to use the French administrative health databases with an appropriate sample size and data.

The specific objectives of this work are:

1. To assemble a nationwide cohort of patients with IBD and validate the coding diagnosis of IBD in the French administrative health databases, by describing the disease course and therapeutic management of IBD. This part relies on the analysis of a subcohort of the SNIIRAM linked to the PMSI and composed by all French IBD patients followed during the 2009-2014 period.
2. To assess the risk of acute arterial events including ischemic heart disease, cerebrovascular disease, and peripheral artery disease among patients with IBD compared to the general population. This part relies on the analysis of data from the PMSI 2008-2013, including all French hospital discharges during this period, therefore IBD and non-IBD patients will be included.
3. To assess the impact of immunosuppressive treatment on the risk of acute arterial events in patients with IBD. This part relies on the analysis of a subcohort of the SNIIRAM linked to the PMSI and composed by all French IBD patients followed during the 2010-2014 period.

LITTERATURE REVIEW

1. Inflammatory bowel disease

A. Epidemiology and natural history

I. Epidemiology

Firstly described in the early twentieth century,[21] IBD turned into a global disease in the last decades. Incidence of CD and UC has increased since the middle of the twentieth century in the Western world, including North America, Europe, Australia and New Zealand. In a recent meta-analysis, annual incidence rates of CD and UC ranged from 0.6 to 24.3 and 0.3 to 20.2 per 100 000 persons, respectively.[22] While global incidence seems to reach a plateau in these regions, incidence in specific populations (paediatric-onset IBD) continues to increase. [23]

Differences in terms of incidence between world regions may be partly explained by environmental factors related to industrialization and urban lifestyle, although not clearly identified. In fact, epidemiological studies revealed that the first-generation offspring from individuals who immigrated from developing countries with a low incidence of IBD to the Western world assume the same risk of developing IBD as the base population. [24,25]

Similarly, incidence dramatically increased in newly industrialized countries, following similar patterns observed in the Western world during the early twentieth century. [26] Firstly, UC incidence rises rapidly then becomes stable; subsequently, CD incidence rises and finally approaches that of UC.

The peak incidence for CD and UC is during the second and third life decade, respectively. A second peak at 60-70 years was observed, but remains controversial. Pediatric-onset IBD (occurring before 16 years of age) accounts for 7% to 20% of all IBD patients. [1] CD occurs 20% to 30% more frequently in women, whereas UC occurs slightly more frequently in men (60%).

Since IBD occurs mainly in young adults and persists throughout the lifetime with low mortality, prevalence increased in parallel with incidence. Overall, in 2015, over 1 and 2.5 million residents were respectively estimated to have IBD in the USA and Europe, and number of IBD patients in newly industrialized countries might approximate that in the Western world in 2025. [27]

II. Natural history

IBD affects the digestive tract with a sequence of flare-up episodes and remissions of varying durations. However, CD and UC differ by their disease location, progression and environmental factors.

CD might affect any part of the digestive tract, from the mouth to the anus, but mainly affects the distal ileum and the colon. CD occurs in equal proportions in: (i) the ileum; (ii) the colon; (iii) both ileum and colon. Ileo-colonic disease location might be stable over time.[28] Less than 20% of patients with colonic or ileal lesions may respectively develop ileal and colonic lesions, 10 years after diagnosis. Approximately 10% to 15% and 20% to 30% of patients at diagnosis have associated upper gastrointestinal lesions and perianal lesions, respectively. The risk of perianal lesions increased with disease duration and the cumulative risk for perianal involvement is about 50% during disease course. [1]

While the majority of patients have only primary lesions (e.g ulcerations) at diagnosis (inflammatory behavior), stricture (stricturing behavior), fistulas and/or abscess (penetrating behavior) might occur during follow-up. Complicated behavior relates to disease location, with higher risk associated with small bowel disease compared to colonic disease. Patients with CD have slightly greater mortality than the general population, notably related to CD complications and smoking-related disease.[29]

UC involves the colon and has a continuous retrograde extension from the rectum. At occurrence, lesions are limited to the rectum in one-third of patients, the colon distal to the splenic flexure in another one-third, and proximal to the splenic flexure in the remaining third. Pancolitis is observed in 25% of the patients. During the disease course, the proximal disease extent progresses, and, about 50% of patients have pancolitis 20 years after diagnosis.[30] Acute severe colitis mainly occurs in the first years of disease and disease activity tends to decrease over time.[31] Increased risk of mortality in patients with UC compared with the general population remains controversial, while mortality from UC decreased in the last decades.[29]

In some cases of colitis, the distinction between CD and UC cannot be definitively made because of the presence of overlapping features between the two diseases (unclassified IBD). However, 80% of patients with unclassified IBD at diagnosis will have a final diagnosis of CD or UC during disease course.[32]

While inflammatory bowel diseases are characterized by intestinal inflammation, persistent and severe disease activity may lead to systemic inflammation, evidenced by higher level of interleukin 6 and C-reactive protein (CRP). [33] In addition, CRP plasma level was found to be correlated with disease severity and treatment response. [34–36] Intestinal and systemic inflammation may lead to intestinal and extra-intestinal complications. Persistent histologic inflammation of the colon mucosa is associated

with an increased risk of colonic dysplasia,[37] and it is well established that IBD patients with colonic involvement are at increased risk of colorectal cancer. [38] Similarly, patients with ileal and perianal lesions are at increased risk of small bowel and anal cancer.[38]

Although the precise etiology of IBD remains unclear, some environmental factors have been associated with an increased risk of occurrence and poor disease outcomes. Notably, smoking reduces the risk of UC occurrence and increases the risk of CD occurrence and flares.[39–41] The benefit of appendectomy after appendicitis on the risk of UC remains controversial.[42]

Extraintestinal manifestations (EIM) associated with IBD are composed of various diseases, including mainly musculoskeletal, skin, ocular, and liver, pancreatic and biliary manifestations. Some EIM correlate with intestinal disease activity and are improved by treatment of the underlying disease, while other EIM are activity-independent.[43] While the underlying pathogenic pathway of these EIM seems to be related to autoimmune disorders in genetic predisposed patients, vascular disorders and notably venous thromboembolism may be associated with systemic and local inflammation. In fact, coagulation and fibrinolysis are activated due to active and chronic inflammation [44] and the increased risk of venous thromboembolism is well established in patients with IBD during active disease.[45] Thus, international guidelines recommend that all hospitalized patients with IBD should be treated with low-dose heparin for prophylaxis. [46]

B. Therapeutic management

Treatment of IBD currently involves pharmacological treatment and surgery, the latter of which is indicated for medically refractory disease, strictures, abscesses and

neoplastic lesions.[46,47] Although proctocolectomy with ileal-pouch anal anastomosis may be curative in patients with UC, postoperative complications, inflammation of the ileal pouch reservoir, and even initial misdiagnosis with CD can necessitate introduction of immunosuppressants or reoperation. Additionally, the recurrent nature of CD renders it incurable by surgical resection and multiple surgical procedures may lead to severe complications such as short bowel syndrome.

Hence, pharmacological treatment is the cornerstone of IBD management and various pharmacological treatment regimens are available for the treatment of IBD. While the majority are administered for the induction and maintenance of remission, corticosteroids (systemic corticosteroids, budesonide, and locally administered) are limited for the induction of remission, because of their side effects in long-term exposure. So far, drugs that have been shown to be able to induce and maintain remission in IBD are aminosalicylates, methotrexate, thiopurines (azathioprine and mercaptopurine), biologics targeting tumor necrosis factor (anti-TNFs), and other biologics (vedolizumab, ustekinumab).

The efficacy of aminosalicylates, as oral or local (enema, suppository) administration, is limited to mild to moderate forms of UC,[48,49] while aminosalicylates are minimally effective in patients with CD.[50] The efficacy of methotrexate has been only proven in corticosteroid-dependent forms of CD. In addition, the tolerance of methotrexate is often limited and this treatment is not compatible with pregnancy. [51] Biologic agents inhibiting gut lymphocyte trafficking (vedolizumab) or targeting the interleukin-12/23 inflammation pathway (ustekinumab) obtained their marketing authorizations in inflammatory bowel disease in November 2014 and 2016, respectively, in France.

Finally, thiopurines and anti-TNFs remain the standard treatment of IBD, either in monotherapy or combined (combination therapy). In addition, immunosuppressive

treatments are started early in the disease and are now used for prolonged periods, since studies assessing the impact of withdrawal of treatment in patients in sustained clinical remission did not provide significant results.[52,53]

I. Thiopurines

Thiopurines are used in patients with IBD since 1968,[54] and include azathioprine, mercaptopurine, and thioguanine. These purine analogues, orally administered, competitively inhibit the biosynthesis of purine nucleotides and induce apoptosis of antigen specific T cells. Once absorbed, azathioprine is almost entirely metabolised to mercaptopurine, then mercaptopurine undergoes enzymatic and non-enzymatic reduction in the presence of glutathione, which notably releases the active metabolite, 6-thioguanine nucleotides (6-TGN) and 6-methyl mercaptopurine (6-MMP).

In CD and UC, the efficacy of azathioprine for inducing remission in combination with corticosteroids, and maintenance of remission, has been shown in several prospective controlled studies and meta-analyses.[55,56] In CD, thiopurines are also used to maintain surgically-induced remission. [57]

Thiopurines are also associated with adverse events. Apart from idiosyncratic and immune mediated drug reactions, such as vomiting, diarrhea, flu-like symptoms, jaundice, rash and pancreatitis,[58] thiopurines are associated with bone marrow toxicity, hepatotoxicity, increased risk of serious infections and various cancers.

Bone marrow toxicity is related to an increased level of 6-TGN, notably in patients with specific genotype of enzyme metabolizing mercaptopurine (TPMT).[59] However it can be anticipated in the majority of cases by performing a genotyping of TPMT or starting thiopurines with lower doses and increasing it afterwards. Thiopurine-induced liver dysfunction secondary to 6-MMP can manifest as elevated liver enzymes, hepatitis,

cholestatic jaundice or nodular regenerative hyperplasia (NRH), although occurrence of NRH is associated with long-term exposure.[60] Thioguanine is not currently used in clinical practice, since the risk of severe irreversible hepatotoxicity outweighs potential clinical benefits. [61]

Several studies have shown an increased risk of serious and opportunistic infections in patients treated with thiopurines as monotherapy for IBD.[62,63] Specifically, previous studies showed that thiopurines increase the risk of viral infections.[64]

Regarding the risk of cancer, the CESAME cohort, following almost 20 000 patients with IBD in France between 2006 and 2009 provides major findings.[4,65–67] Four to six fold increased risk of lymphoma, mostly EBV-associated lymphoma has been observed in patients treated with thiopurines, although the absolute risk is low despite specific populations such as young men naïve for EBV and men aged above 65 years. [68] Additionally thiopurines current and past exposure are associated with an increased risk of non-melanoma skin cancer (NMSC).[65,69] More recently, thiopurines were associated with an increased risk of urothelial cancers and acute myeloid leukemias.[66,67]

II. Agents targeting tumor necrosis factor (Anti-TNFs)

Tumor necrosis factor is a pro-inflammatory cytokine implicated in the pathogenesis of IBD. In the early nineties, drugs targeting TNF- α were designed with biologically developed antibodies targeting TNF- α and the first randomized controlled trial assessing the efficacy of anti-TNFs in patients with IBD was published in 1997.[70] Currently, three anti-TNFs obtained the marketing authorization in the European Union: infliximab, adalimumab and golimumab. Golimumab has only the marketing

authorization for UC and certolizumab pegol is not labelled in Europe, but in the United States.

Anti-TNFs have revolutionized the medical treatment of patients with IBD, by inducing remission in severe disease, notably in patients with acute severe colitis and perianal lesions, and also maintaining remission. Indeed, anti-TNFs can markedly and rapidly reduce systemic inflammation, evidenced by decreased CRP plasma level.[71] However, almost 30% of patients will experience primary non-response and secondary non-response occurs in up to 20% of patients each year.[72,73]

Although anti-TNFs have allowed considerable advances in the treatment of IBD, there are theoretical, but serious, safety concerns.

Acute infusion reactions occurred in approximately 20% of patients exposed to infliximab, notably related to the chimeric nature of the antibody compared to fully humanized antibodies (adalimumab and golimumab).[74] Psoriasiform skin manifestations had also been associated with anti-TNFs exposure.[75]

Along with the well-known risk of reactivation of latent tuberculosis, [64] anti-TNFs exposure is associated with an increased risk of serious infections. While the risk may be not specific of the site of infection,[76] it seems to be notably increased for bacterial infections.[64]

Regarding the risk of cancer, data are still difficult to interpret, since events are rare and the majority of patients have been exposed before to thiopurines, which themselves carry an increased risk of cancer and lymphoma. However, current but not past anti-TNFs exposure has been associated with an increased risk of melanoma skin cancer.[69] It is also unclear as to whether anti-TNFs also increase the risk of lymphoma, since results are controversial in the literature.[77,78]

III. Combination therapy

The combination of infliximab and thiopurines (combination therapy) has been shown to be more effective than monotherapy with either of these drugs in patients with CD and UC.[5,6] Combination therapy is also associated with increased rates of mucosal healing, faster transition to deep remission and decreased level of systemic inflammation measured by C-reactive protein level.[79]

The benefit of such combination therapy is not well documented with adalimumab, although performed in clinical practice. A recent meta-analysis concluded that combination of adalimumab and immunomodulators does not seem superior to adalimumab monotherapy for induction and maintenance of remission and response in Crohn's disease.[80] Similarly, very few studies assessed the combination of anti-TNFs and methotrexate, with controversial results.[81] Hence, in clinical practice, combination therapy is almost always based on the association of anti-TNFs and thiopurines.

However, the use of thiopurines and anti-TNFs is associated with adverse effects shared by both drugs, notably infections and malignancies.[38,64] Several studies have shown an increased risk of serious and opportunistic infections in patients treated with anti-TNFs or thiopurines as monotherapy for IBD,[76,82–84] but it is unclear if combination therapy carries a higher risk than monotherapy. Meta-analyses and pooled analyses of randomised controlled trials do not suggest an increased risk of serious infections with combination therapy,[85–87] while an increased risk of opportunistic infections has been reported compared to anti-TNF monotherapy.[88] The risk of cancer associated with combination therapy is even less clear, with controversial findings on the risk of lymphoma compared to anti-TNF monotherapy.[77]

In conclusion, medical treatment of IBD has evolved significantly in the past two decades with the advent of anti-TNFs and combination therapy. However the benefit/risk balance of these drugs regimens remains poorly studied, notably for the combination therapy.

2. Acute arterial events

A. Epidemiology and burden of acute arterial events

Acute arterial events are cardiovascular diseases and include ischemic heart disease, cerebrovascular disease and peripheral artery disease. Cardiovascular disease is a leading cause of death in Europe and the United States.[89] In Europe, it accounts for 45% of all deaths, 49% of deaths among women and 40% among men. While the burden of cardiovascular disease was highest in the Western world during much of the twentieth century, the incidence decreased during the last decade. However, it still accounts in Europe for 11.3 million new cases in 2015.[90] The highest rates are now reported in low income countries.[91,92] This concept is defined as the epidemiological transition of cardiovascular diseases. Finally, by 2030, projections estimate that cardiovascular disease alone will be responsible for more deaths in low income countries than infectious diseases, maternal and perinatal conditions, and nutritional disorders combined. [93]

Ischemic heart disease, consisting notably of myocardial infarction, is the predominant manifestation of acute arterial events. While stable angina is the initial manifestation of ischemic heart disease in one-half of the patients, myocardial infarction is characterized by myocardial necrosis due to prolonged ischemia.[94] This ischemia is mainly related to atherosclerotic plaque rupture and endothelial erosion in the coronary arteries.

In 2010, the worldwide incidence of myocardial infarction was estimated at 195 per 100 000 person years in males and 115 per 100 000 person years in females.[91] While global incidence decreased between 1990 and 2010, the global burden of

ischemic heart disease increased by 29% (29 million disability-adjusted life-years) between 1990 and 2010.[91]

Cerebrovascular disease includes stroke and transient ischemic attack. The definition of stroke according to WHO diagnostic criteria is “rapidly developing clinical signs of focal (at times, global) disturbances of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin”. Additionally, the WHO defines a transient ischemic attack as a “brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of acute infarction”. [95] Stroke includes two subtypes, ischemic and hemorrhagic stroke. The two main physiopathological pathways of ischemic stroke are atherosclerosis or cardio-embolism. Atherosclerosis of carotid, vertebral arteries or intracranial arteries may lead to plaque rupture. Supraventricular arrhythmias, notably atrial fibrillation, or thrombogenic device, such as valve prosthesis, cause intracardiac stasis of blood and clots, which may travel through the carotid arteries until the vascular brain system. Regarding hemorrhagic strokes, there are two types: intracerebral hemorrhage and subarachnoid hemorrhage. The former is mainly associated with hypertension, but also in case of a hemorrhagic conversion of an ischemic stroke. The latter is mainly associated with craniocerebral and aneurysm rupture. According to recent data of the American Heart Association, 87% of strokes in the United States are classified as ischemic.[96] Current epidemiological data reported a global incidence of 258 per 100 000 person years, with marked differences between high-income (217 per 100 000 person years) and low-income (281 per 100 000 person years) countries.[92] Similarly to ischemic heart disease, stroke mortality rates have decreased in the past two decades, whereas the global burden is increasing, notably in low-income countries.[92]

Peripheral artery disease is the partial or complete obstruction of one or more peripheral arteries, e.g non coronary arteries. It affects in the vast majority of cases the lower extremities.[97] However, mesenteric ischemia may be included in a broader definition of peripheral artery disease. Atherosclerosis is the major leading cause of peripheral artery disease, although non occlusive mechanism such as vascular spasm can occur. A wide spectrum of severity is observed, from the absence of symptoms, in a majority of patients, to critical ischemia. Hence, disease prevalence of asymptomatic peripheral artery disease is between 3% and 10% of the population.[98] Similarly, the incidence of acute limb ischemia, which may lead to amputation, is estimated at 26 per 100 000 in the United States in 2009. Comparison of burden between high-income and low-income countries follows the same pattern compared to ischemic heart disease and cerebrovascular disease, with a higher burden of disease in low-income countries.

B. Risk factors of acute arterial events

The leading study assessing cardiovascular risk factors is the Framingham Heart Study, a large longitudinal investigation that started in 1948 in the town of Framingham, United States. Indeed in 1961, it coined for the first time in the medical literature the term 'risk factors'.[99]

Hypertension was one of the first risk factor identified in the Framingham Heart Study.[100] Hypertension is a chronic elevation of blood pressure, resulting notably in left ventricular hypertrophy and coronary artery disease. Coronary heart disease is caused by a pressure related increase in oxygen demand and a decrease in coronary oxygen supply resulting from associated atheromatous lesions. Hence, hypertension promotes atherosclerosis by inducing oxidative stress on the arterial wall.[101] Finally, systolic and diastolic blood pressure have a continuous, graded association with

cardiovascular events. Even high-normal blood pressure values are associated with an increased risk of cardiovascular disease. [102] The current definition of hypertension is a systolic blood pressure over 140mmHg and/or diastolic blood pressure over 90mmHg, based on the evidence from randomized controlled trials that treatment-induced blood pressure reduction is beneficial in patients with these blood pressure values.[103]

Elevated levels of blood lipids are well documented risk factors of acute arterial events. This association was first described in 1960.[104] Hyperlipidemia is defined as elevations of fasting total cholesterol concentration with or without elevated triglyceride concentration. Furthermore, lipids are transported in particles known as lipoproteins in the plasma. Lipoproteins are composed of several subtypes, notably high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C). In the Framingham cohort, a high level of HDL-C was associated with a decreased risk of coronary heart disease, whereas high levels of LDL-C and triglycerides were associated with an increased risk.[105] Since, these findings have been confirmed in several studies.[106] LDL-C may be accumulated in the vascular intima due to its ability to infiltrate into the endothelium and cause atherosclerosis. However, recent reinterpretation of pivotal RCTs of statins may balance the potential benefit of reduce cholesterol level, and thus, discuss the causal relation between acute arterial event and hyperlipidemia.[107]

Cardiovascular complications are now the leading causes of diabetes-related morbidity and mortality. In multiple studies, type 1 and type 2 diabetes were associated with high risk of acute arterial events.[108] Diabetes is a chronic metabolic disorder characterized by inappropriate hyperglycemia due to lack of or resistance to insulin, and impacts all components of the cardiovascular system: the microvasculature, the

larger arteries, and the heart, as well as the kidneys. Persistent hyperglycemia causes endothelial dysfunction by its different glycooxidative products. Type 2 diabetes causes insulin resistance which induces higher oxidative stress, responsible for endothelial dysfunction.[109] Closely linked to type 2 diabetes is the metabolic syndrome, predisposed by obesity and physical inactivity. According to the International Diabetes Federation, metabolic syndrome is defined by central obesity (increased waist circumference) plus any two of the following four factors: raised triglycerides, reduced HDL-C, raised blood pressure systolic over 130 mmHg or diastolic blood pressure over 85 mmHg, raised fasting plasma glucose ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes.[110] While insulin resistance is one of the main factor of endothelial dysfunction in metabolic syndrome, inflammatory processes in case of obesity may predispose to atherosclerosis. Along with the link between obesity and several cardiovascular risk factors, obesity is associated with a subacute inflammation of white adipose tissue.[111] Furthermore, white adipose tissue is characterized by an increased production and secretion of pro-inflammatory cytokines including TNF- α and interleukin-6,[111] which may promote atherosclerosis, as detailed below.

Additionally, modifiable risk factors have been also associated with an increased risk of acute arterial events. Smoking promotes atherogenic cardiovascular disease in both a dose- and a duration-dependent manner through several concurrent pathways. Smoking induces oxidative stress and endothelial dysfunction is a main consequence of smoke compounds with significant changes in initiating physiologic coagulation process.[112] Smoking also enhances platelet aggregation, impairs lipoprotein metabolism, and reduces distensibility of vessel walls.[112] Similarly, alcohol use disorder has a detrimental effect on the risk of acute arterial events. Although moderate

alcohol consumption may have a cardioprotective effect, it disappears when light to moderate drinking is mixed with irregular heavy-drinking occasions. [113]

Finally, there is a marked difference in acute arterial events risk between sexes, with a higher risk in men compared to women.[114] In both sexes, the risk of acute arterial events increases also markedly with age.[115] Differences observed between sex and age categories is mainly related to the difference in traditional cardiovascular risk factors. Indeed, in a Finnish cohort assessing the risk of coronary heart disease, differences in HDL-C and smoking explained nearly half of the risk difference between men and women. Differences in serum total cholesterol level, blood pressure, body mass index, and diabetes mellitus prevalence explained about one-third of the age-related increase in the risk among men and 50% to 60% among women. [114] Genetic factors may be also associated with the risk of acute arterial events, since family history of acute arterial events is an independent cardiovascular risk factor.[116]

In conclusion, while multiples cardiovascular risk factors have been identified since 1960, the major common factor promoting acute arterial events is atherosclerosis.

C. Atherosclerosis and inflammation

Since the early nineties, inflammatory mechanisms have been shown to be implicated in the pathogenesis of atherosclerosis,[117] which revolutionized the comprehension of atherosclerogenesis. Until then, atherosclerosis was defined as an arterial collection of cholesterol, complicated by smooth muscle cell accumulation. According to this concept, endothelial erosion led to platelet aggregation and release of platelet-derived growth factor which would trigger vascular smooth muscle proliferation in the intimal layer and form atherosclerotic lesion.

Atherosclerosis is now defined as a chronic inflammatory condition of the vessel wall. Indeed, recent findings revealed that the inflammatory response in atherosclerosis involves elements of both the innate and adaptive immunity.[10]

Regarding innate immunity, monocyte recruitment occurred in the early phase of atherosclerosis and in established atherosclerotic plaque.[118] The recruitment of monocytes involves attachment to activated endothelial cells by leukocyte adhesion molecules, known as chemokines. Mast cells were also recently highlighted as potentially participating in atherosclerosis.[119] Additionally, thrombosis and inflammation are linked with convergent pathways in atherosclerosis. Indeed, platelet activation may lead to proinflammatory cytokines secretion and release of a proinflammatory mediator known as myeloid-related protein, which serves as a biomarker for acute arterial events.[120]

The key regulatory role of adaptive immunity in atherosclerosis is supported by accumulating evidence. Dendritic cells populate atherosclerotic lesions and regional lymph nodes where they can present antigens to T cells with co-stimulatory molecules that promote the afferent limb of adaptive immunity. This activation cascade results in the expression of a set of cytokines, cell-surface molecules, and enzymes. The atherosclerotic plaque contains cytokines promoting a Th1 response, rather than a Th2 response.[121] Th1 responses generally amplify proinflammatory pathways by secretion of cytokines and appear to aggravate atherosclerosis. Conversely, cytokines of the Th2 pathway can promote antiatherosclerotic immune reactions. However, it may also induce elastolytic enzymes, which lead to the formation of aneurysms.[122] Regarding B cells, recent findings suggest that humoral immunity may attenuate rather than promote atherosclerosis. Hence in hypercholesterolemic mice, splenectomy, ablating an important B cell compartment, aggravates atherosclerosis.[123]

Furthermore, T-cell cytokines cause the production of large amounts of molecules downstream in the cytokine cascade, most notably TNF- α , which is directly involved in atherosclerogenesis.[124] Higher circulating TNF- α has also been associated with severe atherosclerosis in patients with stable angina.[125] Finally, this cytokine cascade leads to systemic inflammation, characterized by elevated levels of interleukin-6 and C-reactive protein detected in the peripheral circulation. Therefore, inflammatory biomarkers have been shown to predict risk, monitor treatments, and guide therapy. Although several biomarkers were identified during the last years, CRP measured by a highly sensitive assay remains the most widely studied. Several studies concluded that CRP level predicts ischemic heart disease, cerebrovascular disease, and cardiovascular death even after adjustment for the traditional Framingham covariates.[126,127] Values of CRP associated with an increased cardiovascular risk are notably low, since CRP level of approximately 3 mg/l is widely used as a cut-off value for increased likelihood of cardiovascular disease.[126] Additionally, analyses from randomized clinical trials assessing the efficacy of statins also suggests that a reduction of CRP may be a potential therapeutic goal, although current guidelines did not recommended this practice.[126]

Finally, the concept that atherosclerosis is a chronic inflammatory condition offers new opportunities for the prevention of acute arterial events, and the use of anti-inflammatory agents such as immunosuppressant may represent attractive treatments for the prevention of acute arterial events.

3. Acute arterial events in other chronic inflammatory diseases

A. Rheumatoid arthritis and other forms of inflammatory joint disorders

Inflammatory rheumatic diseases, including rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, are characterized by local and/or systemic inflammation, which may result in connective tissue and internal organ damage.

Since atherosclerosis is a chronic inflammatory condition as detailed above, this increase of risk may be related to shared pathogenic processes between atherosclerosis and other inflammatory chronic diseases, notably rheumatoid arthritis. Indeed, endothelial activation, promotion of Th1 response, neovascularization and collagen degradation are observed in the inflamed rheumatoid synovium.[128] (Figure 1) Cytokines such as IL-6 are also implicated in both processes. Lastly, inflammation related to rheumatoid arthritis has been associated with increased arterial stiffness,[129] and changes in lipoprotein function.[130] However, the pattern of abnormalities in lipid levels is difficult to interpret, since systemic inflammation may result in a paradoxical inversion of the usual association between the risk of acute arterial event and lipid levels (that is, an increased risk of acute arterial event being associated with low lipid levels).[131]

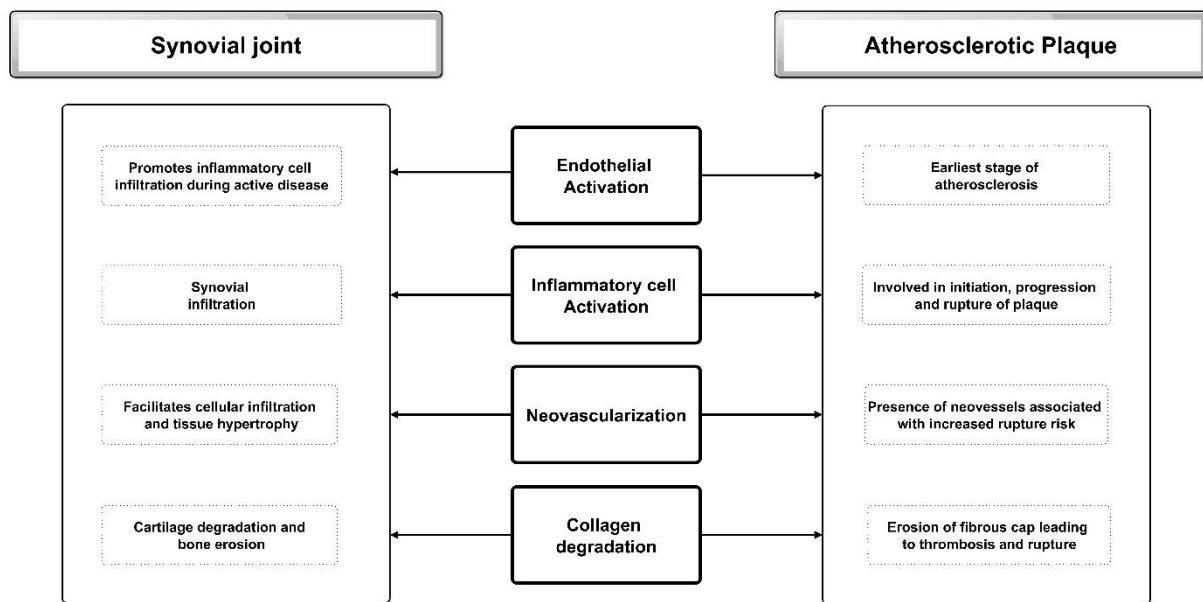


Figure 1: Major pathological features common to both atherosclerosis and the inflamed rheumatoid synovium (adapted from Skeoch et al. Nat. Rev. Rheumatol. 2015[128])

Thus, inflammatory rheumatic diseases are associated with an excess risk of cardiovascular disease, as reported for several decades.[132] Patients with rheumatoid arthritis are at increased risk of death related to cardiovascular disease, with a 50% increase for ischemic heart disease and cerebrovascular disease in men and women, reported in a recent meta-analysis.[3] The absolute risk of cardiovascular death is highest for elderly men, whereas the relative risk is highest for young women.[133] Additionally, a recent Danish cohort study reported a risk of myocardial infraction 70% higher than in the general population, and similar to that in patients with diabetes mellitus. This risk corresponded to the risk of non-rheumatoid arthritis subjects who were 10 years older.[134] This increased risk was not observed in

patients with rheumatoid arthritis before the onset of symptoms,[135] suggesting that accelerated atherosclerosis starts around the time of the onset of symptoms, and not at the time of diagnosis.

Disease activity assessed by the 28 joint disease activity score (DAS28),[136] but also the number and duration of flares[137] have been associated with an increased risk of cardiovascular disease. Moreover, this increased risk associated with disease activity is endorsed by the fact that disease-modifying antirheumatic drugs (DMARDs) reduce the risk of acute arterial events. Conventional synthetic DMARDs, such as methotrexate, as well as biologics, such as anti-TNFs have been associated with a decreased risk of acute arterial events, compared to no treatment.[138] A recent meta-analysis reported a risk of ischemic heart disease and cerebrovascular disease 30% lower in patients exposed to the two treatment regimens compared to unexposed patients. Additionally, anti-TNFs may have a specific effect on atherosclerosis independently of their anti-inflammatory effect, since TNF- α is directly involved in atherosclerogenesis.[124] In patients with rheumatoid arthritis, anti-TNFs were shown to curb platelet activation, while TNF- α induced platelet activation.[139] Anti-TNFs reduce also existing subclinical atherosclerosis, by decreasing carotid intima-media thickness and arterial stiffness. These findings suggest that anti-TNFs may not only prevent but even reverse atherosclerosis. Nevertheless, the impact of this potential antithrombotic effect compared to the impact of the anti-inflammatory effect remains unknown.[140] In contrast, corticosteroids have been associated with an increased risk of acute arterial events.[138]

Regarding ankylosing spondylitis and psoriatic arthritis, fewer studies assessed the cardiovascular risk compared to rheumatoid arthritis. However, patients with

ankylosing spondylitis and psoriatic arthritis are at increased risk of cardiovascular events, with a similar magnitude than in patients with rheumatoid arthritis.[141,142]

In 2009, the European League Against Rheumatism (EULAR) taskforce published the first guidelines regarding the cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders,[11] which were updated in 2016.[143] These guidelines endorse the fact that disease activity should be controlled optimally in order to lower the risk of acute arterial events in all patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

Furthermore, nontraditional cardiovascular risk factors were identified in patients with rheumatoid arthritis, including anticitrullinated protein antibody and rheumatoid factor positivity, extra-articular manifestations and hypothyroidism.[144,145] Since classical cardiovascular prediction models only include traditional cardiovascular risk factors, these model may inaccurately predict and notably underestimate the risk of acute arterial events in patients with rheumatoid arthritis, as reported in several studies.[146,147] Hence, EULAR guidelines recommend to adapt this prediction model for patients with rheumatoid arthritis by a 1.5 multiplication factor, if rheumatoid arthritis is not already included in the risk algorithm.[143]

B. Systemic lupus erythematosus

Cardiovascular disease is a well-documented complication of systemic lupus erythematosus. In 1976, the bimodal mortality pattern related to systemic lupus erythematosus was already described, with a first peak within 1 year after diagnosis due to active disease and renal complications, followed by a later peak, 5 years after diagnosis, due to atherosclerosis.[148] Although improved treatment lead to decreased overall mortality, mortality related to cardiovascular disease did not decrease.[149]

Patients with systemic lupus erythematosus are at increased risk of ischemic heart disease and cerebrovascular disease, compared with the general population, with a similar risk magnitude from 2 to 10 fold increase in the risk.[150,151]

Although traditional cardiovascular risk factors, notably hypertension, hyperlipidemia, smoking and diabetes mellitus are more frequent in patients with systemic lupus erythematosus,[12] disease activity was associated with an increased risk of acute arterial event after adjustment for all traditional cardiovascular risk factors.

The underlying mechanism leading to atherosclerosis in patients with systemic lupus erythematosus may be more heterogeneous compared to patients with rheumatoid arthritis, since several markers of disease activity and inflammation have been associated with acute arterial events, including renal disease, microalbuminuria, neuropsychiatric disease, and vasculitis.[12] However, atherosclerosis may be also promoted by chronic inflammation, although less defined compared to rheumatoid arthritis. Thus, higher exposure to oxidative stress has been observed in patients with systemic lupus erythematosus, which may promote atherosclerosis.

Standard guidelines regarding the cardiovascular risk management in patients with systemic lupus erythematosus are not yet available since data are scarce compared to inflammatory rheumatic diseases, but adequate control of the traditional cardiovascular risk factors is the standard of care.

4. Acute arterial events in inflammatory bowel disease

A. Risk in patients with IBD compared with healthy subjects

I. Potential links between IBD and acute arterial events

While the risk of developing venous thromboembolism in IBD, such as deep vein thrombosis, pulmonary embolism, and portal vein thrombosis is well established, [45] the magnitude of the risk of IBD-related acute arterial event remains unclear.

This concept is supported by common pathogenic processes between IBD and atherosclerosis, as well as in rheumatoid arthritis. Several pathophysiological mechanisms, including structural and functional vascular changes, as well as biochemical and genetic changes may be involved in the risk of acute arterial events in patients with IBD.[152] A recent meta-analysis reported an increased carotid intima-media thickness, which is strongly associated with atherosclerosis.[153] Arterial stiffness was also observed, independently of traditional cardiovascular risk factors.[154] Besides structural changes, microvascular endothelial dysfunction assessed by pulse arterial tonometry and brachial ultrasound was observed in patients with IBD.[155] Hypercoagulability observed in IBD may also play a role in the formation of thrombi at sites of atherosclerotic plaque ruptures. Several prothrombotic factors are increased in patients with IBD, notably during disease activity.[156] Platelet activation may be also increased, through the CD40 ligand, which is expressed on activated platelets and immune cells,[157] and plasma levels of soluble CD40 ligand are increased in IBD.[158]

Furthermore, these pathophysiological mechanisms may also support the hypothesis of a more pronounced increased risk of acute arterial event in CD as compared to UC patients. High levels of circulating cytokines and CRP are characteristic of IBD,[159] and CRP has been found to correlate with disease activity. CD patients are more prone to a higher degree of systemic inflammation compared to UC patients, amongst others evidenced by higher level of CRP production[7–9] and serum concentration of interleukin-6.[33] The difference in risk estimates between CD and UC patients could also be linked to the prothrombotic effect of hyperhomocysteinemia and low vitamin B6 plasma level, which may be related to malabsorption in CD patients. Indeed, while hyperhomocysteinemia is promoted by low vitamin B6 plasma level impairing the cystathionine-synthase activity in the transulfuration metabolic pathway of homocysteine, low vitamin B6 plasma level and hyperhomocysteinemia are independent risk factors for arterial thrombosis. [160,161] Lastly, polymorphisms in NOD2/CARD15 have been associated with both coronary atherosclerosis and IBD with a stronger link with CD.[162] NOD2/CARD15 variants may predispose to CD.[163] The microbiome may be also implicated in the atherosclerogenesis in IBD, since IBD is characterized by dysbiosis of the gut microbiota.[164] Although there is no direct link between the dysbiosis associated with IBD and atherosclerogenesis, indirect associations may support an implication of the microbiome. Indeed, a pathway linking dietary lipid intake, gut microflora and atherosclerosis has been reported using a metabolomics approach.[165]

Thus, all these pathogenic processes support an increased risk of acute arterial events in patients with IBD compared with the general population.

II. Ischemic heart disease

The risk of ischemic heart disease is the most studied event among all acute arterial events in IBD. First evidence that IBD may be associated with increased risk of ischemic heart disease came from a population-based study from the Manitoba Database by Bernstein et al.,[166] which reported an increased risk of ischemic heart disease in patients with IBD (1.26 incidence rate ratio [IRR]; 95% confidence interval [95% CI], 1.11-1.44) No difference in risk was observed between sex and subtype of IBD. In a matched cohort study from 2011 by Yarur et al.,[167] an increased hazard ratio (HR) (2.62 HR; 95 % CI, 1.50-4.57) for developing ischemic heart disease was observed in patients with IBD, after adjustment for traditional cardiovascular risk factors, white blood cell and platelet count, and anemia. A nationwide Danish population based cohort study reported a markedly increased risk of ischemic heart disease within the first year after diagnosis with IBD (2.13 IRR; 95% CI, 1.91-2.38), while the risk decreased during the following years, although remaining statistically significant (1.22 IRR; 95% CI, 1.14-1.30).[13] In contrast, another matched cohort study from United States by Ha et al. did not report an overall increased risk of ischemic heart disease, although the risk was significantly increased in women older than 40 years.[168]

Finally, two meta-analyses were recently published with conflicting conclusions. The first meta-analysis by Singh et al. reported an 19% increased risk of ischemic heart disease (1.18 OR; 95% CI, 1.08-1.31),[169] while the second meta-analysis by Fumery et al. did not report a statistically significant increased risk (1.23 RR; 95% CI, 0.94-1.62).[170] These two studies mainly differ by the inclusion of a cross-sectional study[171] only in the latter meta-analysis.

III. Cerebrovascular disease

In the study by Bernstein et al, Only CD was associated with an increased risk of cerebrovascular disease (CD, 1.32 IRR; 95% CI, 1.05-1.66; UC, 1.03 IRR; 95% CI, 0.82-1.29).[166] A recent study including only patients with CD revealed a 90% increased risk of stroke (1.91 HR; 95% CI, 1.65-2.22).[172] In contrast, Ha and colleagues reported an increased risk of cerebrovascular disease only in women with IBD younger than 40 years of age (2.1 HR; $p=0.04$).[168] Similarly to ischemic heart disease, the two meta-analyses reported conflicting results regarding the risk of cerebrovascular disease. The first meta-analysis by Singh et al. concluded to an increased risk (1.18 OR; 95% CI, 1.09-1.27),[169] while the second meta-analysis by Fumery et al. reported no difference (0.79 RR; 95%CI, 0.51-1.23).[170]

IV. Peripheral artery disease

Only 2 studies assessed the risk of peripheral artery disease in patients with IBD. The meta-analysis of Singh et al., including 148 events, did not report an increased risk (1.15 OR; 95%CI, 0.96-1.38).[169]

The exception of mesenteric ischemia should be noticed, since the highest risk associated with IBD was observed in this subgroup. In the study by Ha et al., the risk magnitude was markedly increased compared to ischemic heart disease and cerebrovascular disease (11.2 HR; $p<0.001$).[168] Indeed, mesenteric ischemia may be related to intestinal rather than systemic inflammation in patients with IBD.[159,173]

B. Predictors of acute arterial events in patients with IBD

I. Traditional cardiovascular risk factors

As in the general population, traditional cardiovascular risk factors contribute to an increased risk of acute arterial events in patients with IBD. However, traditional cardiovascular risk factors besides smoking do not seem to be over-represented in this population.

Studies assessing the prevalence of traditional cardiovascular risk factors reported conflicting results. Regarding hypertension in patients with IBD compared to control individuals, two studies reported a lower prevalence,[167,174] whereas three studies observed a higher prevalence.[168,175,176] Additionally, lower rates of diabetes, hyperlipidemia, and obesity were reported in the study by Yarur et al. [167]

As well as in patients with rheumatoid arthritis, the pattern of abnormalities in lipid levels is difficult to interpret, since systemic inflammation may result in a paradoxical inversion of the established relationship between the risk of acute arterial events and lipid levels (that is, an increased risk of acute arterial events being associated with low lipid levels).[131]

Since smoking increases the risk of CD occurrence and flares, patients with CD are more prone to be smokers compared with the general population.[39] Conversely, patients with UC are less smokers than the general population, due to the protective effect of smoking.[41]

II. Age and sex

The impact of sex on the risk of acute arterial events in patient with IBD remains unclear. Indeed, several studies reported an association between younger age and an

increased risk of acute arterial events,[13,166,177] while an increased risk of myocardial infarction was reported specifically in patients of older age.[168] In a sub-analysis of Singh et al. including only studies with sex-specific risk estimates, the magnitude of the increased risk of cerebrovascular disease was higher in young patients (age, 18–50 y) with IBD (1.84 OR; 95% CI, 1.28-2.66) as compared with older patients with IBD (1.11 OR; 95% CI, 1.02-1.21). Regarding ischemic heart disease, no difference in the risk was observed between younger and older patients with IBD.[169]

Regarding sex, the study by Ha et al. found no overall increased risk of cerebrovascular disease, whereas the risk was only significantly increased in women younger than 40 years of age.[168] In the meta-analysis of Singh et al., the risk of cerebrovascular disease was higher in women (1.28 OR; 95% CI, 1.17-1.41) compared with men (1.11 OR; 95% CI, 0.98-1.25) with IBD. The pattern was similar for the risk of ischemic heart disease, with a non significantly increased risk in men (women, 1.26 OR; 95% CI, 1.18-1.35; men, 1.05 OR; 95% CI, 0.92-1.21).[169]

However, further generalization of results is limited by the considerable heterogeneity found between studies in this meta-analysis.[169]

III. IBD subtype and disease activity

As detailed above, several pathophysiological mechanisms may support the hypothesis of a more pronounced increased risk of overall acute arterial events in CD as compared to UC patients. In the meta-analysis of Singh et al., the risk of cerebrovascular disease was slightly higher in patients with CD (1.26 OR; 95% CI, 1.14-1.39) as compared to patients with UC (1.13 OR; 95% CI, 1.05-1.23). This difference was not observed for the risk of ischemic heart disease (CD, 1.10 OR; 95% CI, 1.03-1.17; UC, 1.14 OR; 95% CI, 1.03-1.25). [169] However, these results must be

interpreted with caution, since inclusion criteria widely differed between studies included in this meta-analysis, with population based cohort studies and cohorts from tertiary referral centers. Indeed, the impact of disease activity is not assessed and may notably explained the conflicting results observed.

Only one study reported the association between disease activity and the risk of myocardial infarction and stroke, but did not include peripheral artery disease.[175] This population-based Danish study by Kristensen et al. reported an increased risk of ischemic heart disease during periods of flare (1.49 RR; 95% CI, 1.16-1.93) and persistent activity (2.05 RR; 95% CI, 1.58-2.65), but not during remission (1.01 RR; 95% CI, 0.89-1.15). Similar results were observed for cerebrovascular disease.

C. Impact of thiopurines and anti-TNFs

Thiopurines and anti-TNFs reduce systemic inflammation and could decrease cardiovascular events in patients with IBD, which has been suggested in patients with rheumatoid arthritis.

Besides pooled analyses including several auto-immune diseases, very few studies assessed the impact of treatment on the risk of acute arterial events in patients with IBD. In the study by Kristensen et al., no significant difference in the risk of ischemic heart disease (RR 1.15 versus 1.17, $p=0.88$) or cerebrovascular disease (RR 1.16 versus 1.18, $p=0.79$) were found in patients treated with immunomodulators compared with the entire IBD population.[175] Similar results were observed in another Danish population based cohort study, notably for anti-TNFs. [13] However, these studies may lack sufficient power to detect risk differences between treatment regimens.

Recently, a meta-analysis presented in 2017 at the Digestive disease week assessed the association between exposure to biologics and immunomodulators and cardiovascular events in patients with immune-mediated inflammatory diseases, including IBD, rheumatoid arthritis, psoriasis and psoriatic arthritis, and spondyloarthropathies.[178] Exposure to biologics and immunomodulators were associated with a 30% (0.70 OR; 95% CI, 0.59-0.82) and 32% (0.68 OR; 95% CI, 0.57-0.81) lower odds of cardiovascular events, respectively. In patients with IBD, only exposure to immunomodulators was associated with a significantly decreased risk of cardiovascular events (immunomodulators, 0.49 OR; 95% CI, 0.40-0.61; biologics, 0.39 OR; 95% CI, 0.05-2.86). However, considerable heterogeneity was observed and analyses were partially adjusted for disease activity only at baseline.

In conclusion, the magnitude of the risk and the independent risk factors of acute arterial events in patients with IBD remain unclear and need further investigation. Notably, further studies are required to assess the impact of treatment, after adjustment for disease activity and all traditional cardiovascular risk factors.

FRENCH ADMINISTRATIVE HEALTH DATABASES: PMSI AND SNIIRAM

In France, universal access to healthcare is guaranteed for all French residents by a public care insurance system called Social Security (*Sécurité sociale*), which was created in 1945 after the Second World War. The French Public care insurance includes several insurance schemes according to employment situation and the main insurance scheme is the general health insurance scheme, covering employees in the industry, business and service sectors, public service employees and students, and accounting for approximately 88% of the French population. The public care insurance covers the vast majority of medical expenses, while complementary coverage is provided by mutual funds or private insurance companies.

Over the years, all health insurance claims of the different schemes have converged in a single model, allowing the creation of a single database, which includes all subjects with a unique anonymous identifier from birth (or immigration) to death (or emigration).

1. PMSI

Since the nineties, diagnosis-Related-Groups (DRG) based payment, linking hospital funding to activity, has become the most common mode of hospital payment in the Western world, including North America, Europe, Australia and New Zealand.[179] In France, a DRG-based payment system was progressively introduced in 2004, and includes all public and private hospitals since January 2008. Every hospital discharge summary is standardized and included in a single database, the French hospital discharge database (*Programme de Médicalisation des Systèmes d'Information* [PMSI]).

The standardised discharge summary includes:

- Patient's demographics (sex, age, place of residence based on municipality code)
- Primary and associated discharge diagnosis codes, according to the WHO International Classification of Diseases, 10th revision (ICD-10).[15] The primary discharge diagnosis is defined by the condition that requires hospitalisation (since 2009, before defined by the most costly condition), while associated discharge diagnoses are related to coexisting conditions (up to 30 associated diagnoses reported). Another specific type of discharge diagnosis is the related diagnosis, only used in specific situations such as day hospitalization.
- Medical and surgical procedures performed, according to French Medical Common Procedure Coding System (*Classification commune des actes médicaux* [CCAM]). It notably includes digestive endoscopies and all surgical procedures.
- Costly drugs dispensed during hospitalization (notably anti-TNFs, but not thiopurines), within a list of drugs annually revised.[180]
- Medical devices, such as orthopedic prosthesis and prosthetic valve.
- Length of stay, date and modes of entry and discharge, including inhospital mortality which accounted for 57.4% of all adult deaths recorded in France between 2008 and 2013.[181]

The unique anonymous identifier allows linking all hospital claims of the patient and tracking the occurrence and progression of chronic conditions over time. Several studies have found the reliability, validity and accuracy of medical coding in the PMSI database for various diseases to be good.[16,182–185]

2. SNIIRAM

The SNIIRAM (*Système national d'information inter-régime de l'assurance maladie*) was created in 2003, with the underlying objectives of contributing to a better management of the French public care insurance and of public health politics, and informing health practitioners as regards their activity and prescriptions. It was initially only based on outpatient data, with the French National Health Insurance anonymized claim database (*données de consommation interrégimes* [DCIR]) including all outpatient reimbursed health expenditures. It was afterwards linked to the French hospital discharge database. The SNIIRAM contains:

- All data from the French hospital discharge database.
- Patient's demographics and affiliation to complementary universal health insurance (free access to healthcare for people with low income). It also includes the vital status and date of death, even for death occurring outside the hospital.
- Patient's status with respect to full reimbursement of care for long-term diseases (LTD) according to ICD-10, which includes CD and UC. Introduction of reimbursement for LTD healthcare is recommended after IBD diagnosis to ensure that patients will be fully covered for healthcare related to IBD. Full coverage is subject to prior national health insurance approval, after examination of an official form signed by a physician (general practitioner and/or gastroenterologist) certifying that the patient has CD or UC. Even if the official form for LTD healthcare is completed after IBD diagnosis, LTD healthcare has a retroactive effect since the date of disease onset. Date of disease onset is therefore reported.

- All drug reimbursements and the date of dispensation. Medications are classified according to a unique national registration code (*Code Identifiant de Présentation* [CIP]) and the Anatomical Therapeutic Chemical (ATC) Classification System. The number of packs is included, the number of tablets and strength are therefore reported.
- Date and nature of physician interactions, and procedures performed in an outpatient setting (for example upper GI endoscopy without sedation).
- Laboratory tests, according to the French classification. (*nomenclature des actes de biologie médicale* [NABM]) The date and nature of laboratory test is included without the results.

Figure 2 provides a visual overview of the SNIIRAM simplified architecture.

Finally, the SNIIRAM database is one of the largest global database of medical and administrative data in the general population, covering nearly 65 million persons and it has been used previously for large pharmacoepidemiological studies.[18,186,187]

Entire French population

Outpatient management

French National Health Insurance
anonymized claim database
(DCIR)

- All drug reimbursements and outpatient medical care
- Full reimbursement of care for specific long-term diseases (including Crohn's disease and ulcerative colitis)



Unique
anonymous
identifier

Inpatient management

French hospital discharge
database
(PMSI)

- Standardized discharge summary
 - Primary and associated discharge diagnoses (ICD-10)
 - Surgical procedures
 - Length of stay

Figure 2: Simplified architecture of the SNIIRAM

IDENTIFICATION AND THERAPEUTIC MANAGEMENT OF INFLAMMATORY BOWEL DISEASE IN THE FRENCH ADMINISTRATIVE HEALTH DATABASES

The first objective of the thesis was to assemble a nationwide cohort of patients with IBD and validate the coding diagnosis of IBD in the French administrative health databases, by describing the disease course and therapeutic management of IBD. This part relies on the analysis of data from the SNIIRAM 2009-2014. Due to the availability and quality of data, only claims reimbursed from the general health insurance scheme were explored in this work, accounting for 88% of the French population.

At this time, there is no validation study of IBD diagnosis codes in the SNIIRAM database, which should assess the positive predictive value of IBD diagnosis codes after de-anonymisation of hospital discharge summaries. However, de-anonymisation of the data is legally forbidden. Only indirect validation is therefore possible by exhaustively describing and comparing incidence rates, natural history and therapeutic management of IBD with contemporary cohorts. This descriptive analysis was also motivated by the lack of data regarding the therapeutic management of IBD in real-life practice in the current era of anti-TNFs.

All patients affiliated to the French national health insurance diagnosed with IBD were included from 2009 to 2013 and followed up until 31 December 2014. Patients with a single hospital discharge diagnosis of IBD and no pharmacy claim for any IBD medication (aminosalicylates, enteral budesonide, thiopurines, and anti-TNFs), were considered to have a non-confirmed diagnosis of IBD and therefore not included. Exposure to oral aminosalicylates, oral corticosteroids, methotrexate, thiopurines, anti-

TNFs and combination therapy, hospitalisation and surgical procedures related to IBD were assessed over time.

A total of 210 001 patients were diagnosed with IBD (CD, 100 112; UC, 109 889). Incidence rates were 11.0 for CD and 11.1 for UC per 100 000 person-years. Thiopurine monotherapy was the first-line treatment for the majority of CD and UC incident patients treated with thiopurine and anti-TNF monotherapies or combination therapy, while the use of anti-TNFs, as monotherapy or combination therapy, was high and surgery rates were low, as compared to historical data. IBD treatment withdrawal was also frequent, and generally not related to hospitalization or surgery.

1. Article: Therapeutic management of inflammatory bowel disease in real-life practice in the current era of anti-TNF agents: analysis of the French administrative health databases 2009–2014

Therapeutic management of inflammatory bowel disease in real-life practice in the current era of anti-TNF agents: analysis of the French administrative health databases 2009–2014

J. Kirchgesner^{*,†}, M. Lemaitre^{*}, A. Rudnichi^{*}, A. Racine[‡], M. Zureik^{*}, F. Carbonnel[‡] & R. Dray-Spira^{*}

^{*}Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety, Saint-Denis, France.
[†]UMR-S 1136, INSERM & UPMC Univ Paris 06, Paris, France.

[‡]Université Paris-Sud, Assistance Publique-Hôpitaux de Paris and Gastroenterology Unit, Hôpitaux Universitaires Paris Sud, Le Kremlin Bicêtre, France.

Correspondence to:

Dr R. Dray-Spira, Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety, 143-147 Blvd Anatole France, F-93285 Saint-Denis, France.
 E-mail: rosemary.dray-spira@ansm.sante.fr

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SUMMARY

Background

Management of inflammatory bowel disease (IBD) has evolved in the last decade.

Aim

To assess IBD therapeutic management, including treatment withdrawal and early treatment use in the current era of anti-TNF agents (anti-TNFs).

Methods

All patients affiliated to the French national health insurance diagnosed with IBD were included from 2009 to 2013 and followed up until 31 December 2014. Medication uses, treatment sequences after introduction of thiopurine or anti-TNF monotherapies or both (combination therapy), surgical procedures and hospitalisations were assessed.

Results

A total of 210 001 patients were diagnosed with IBD [Crohn's disease (CD), 100 112; ulcerative colitis (UC), 109 889]. Five years after diagnosis, cumulative probabilities of anti-TNF monotherapy and combination therapy exposures were 33.8% and 18.3% in CD patients and 12.9% and 7.4% in UC patients, respectively. Among incident patients who received thiopurines or anti-TNFs, the first treatment was thiopurine in 69.1% of CD and 78.2% of UC patients. Among patients treated with anti-TNFs, 45.2% and 54.5% of CD patients and 38.2% and 39.9% of UC patients started monotherapy and combination therapy within 3 months after diagnosis, respectively; 31.3% of CD and 27.1% of UC incident patients withdrew from thiopurine or anti-TNFs for more than 3 months after their first course of treatment. Five years after diagnosis, the cumulative risks of first intestinal resection in CD patients and colectomy in UC patients were 11.9% and 5.7%, respectively.

Conclusions

Step-up approach remains the predominant strategy, while exposure to anti-TNFs is high. Surgery rates are low. Treatment withdrawal in IBD is more common than expected.

INTRODUCTION

Inflammatory bowel diseases (IBD) include Crohn's disease (CD) and ulcerative colitis (UC). Medical treatment of IBD has evolved significantly in the past two decades.^{1–3} Pivotal randomised trials have demonstrated the efficacy of anti-TNF agents (anti-TNFs) as an induction and maintenance treatment of UC and CD. More recently, the combination of infliximab and azathioprine (combination therapy) was shown to be more effective than monotherapy with each drug in CD and UC patients.^{4, 5} However, thiopurines and anti-TNFs are associated with an increased risk of infection^{6–9} and cancers.¹⁰ In addition, anti-TNFs have a large impact on healthcare expenditure.¹¹ Very few trials or prospective studies, mostly performed in CD patients, have assessed the efficacy and safety of thiopurine or anti-TNF withdrawal.¹² Therefore, the optimal duration of thiopurine and/or anti-TNF therapy is unknown, and the magnitude of withdrawal in real-life practice has never been assessed.^{12, 13}

Several population-based studies have reported a high use of thiopurines and an increasing use of anti-TNFs, particularly in CD patients.^{14–17} A Danish population-based study revealed an increasing use of thiopurines and anti-TNFs over time and a parallel decrease in surgery rates.¹⁴ However, the impact of early treatment use, combination therapy trials and treatment withdrawal studies on real-life practice is unknown.^{4, 5}

The aim of this study was to assess the real-life therapeutic management of IBD, including treatment withdrawals, early treatment use, surgery rates and hospital stays, in the current era of anti-TNFs. This study was conducted in France and was based on French administrative health databases.

MATERIALS AND METHODS

Database description

French administrative health databases include the French National Health Insurance anonymised claim database [*Système National d'Information Interrégimes de l'Assurance Maladie* (SNIIRAM)] related to outpatient management and the French hospital discharge database [*Programme de Médicalisation des Systèmes d'Information* (PMSI)] related to inpatient management. These databases cover the entire French population with different schemes based on employment situation. Due to the availability and quality of data, only claims reimbursed from the general health insurance scheme were explored in this work. They account for approximately 90% of the

French population. Excluded health insurance schemes relate to specific professions and do not depend on comorbidities or medical conditions. Several studies have assessed the reliability of the recorded information and the accuracy of its coding in different fields.^{18, 19} Moreover, the PMSI and SNIIRAM have been used to measure disease incidence and identify determinants of medical conditions in various fields.^{20–24}

The SNIIRAM contains data on all drug reimbursements, and outpatient medical and nursing care prescribed or provided by health-care professionals. SNIIRAM does not provide any information on the medical indication for each reimbursement, but contains the patient's status with respect to full reimbursement of care for long-term diseases (LTD) listed in the *International Classification of Diseases*, 10th edition (ICD-10),²⁵ which includes CD and UC. The PMSI was originally designed for hospital payments; it includes all French hospitals, both public and private. The standardised discharge summary includes primary and associated discharge diagnoses according to ICD-10, surgical procedures, length of stay, modes of entry and discharge (including in-hospital death). The unique anonymous identifier is shared by SNIIRAM and PMSI, it links inpatient and outpatient management of each patient and tracks the occurrence and progression of medical conditions over time.

Study population

Every patient identified with IBD between 2009 and 2013 from the PMSI and the SNIIRAM was included. Identification of IBD cases was based on LTDs and/or hospitalisation discharges with ICD-10 codes related to CD or UC (K50 and K51, respectively). Patients with only one hospitalisation for IBD and at least one pharmacy claim for any of the following IBD medications: aminosalicylates, enteral budesonide, thiopurines and anti-TNFs were included. Since corticosteroids are widely prescribed apart from IBD, we did not include these medications in the definition. In case of multiple hospitalisations with ICD-10 codes related to both UC and CD, the most recent diagnosis at cohort entry was retained. The ICD-10 code for indeterminate colitis (K52.3) was implemented after the start of inclusion and was, therefore, not considered in this study.

Detailed individual-level information regarding hospitalisations and medical treatment were available from 1 January 2006 and 1 June 2008, respectively. Since renewal of LTDs is mandatory every year and the certification form completed by the physician includes the date

of disease onset, date of IBD diagnosis could, therefore, predate the database creation. Patients diagnosed with IBD before 1 January 2009 corresponded to prevalent cases of IBD and patients identified between 1 January 2009 and 31 December 2013 accounted for incident cases of IBD. Date of diagnosis was the first date of IBD-related in- or outpatient care (hospitalisation or full reimbursement of care related to IBD). Date of cohort inclusion was 1 January 2009 for prevalent cases and the date of IBD diagnosis for incident cases. Patients were followed until 31 December 2014, death, or last known contact date, defined by the last claim in the database, irrespective of type or indication.

Approval from the French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés; CNIL) was obtained for this study. All databases used in this study only contained anonymous patient records.

Statistical approach

Drug exposure definition and analysis. In France, infliximab and adalimumab are dispensed in hospitals or private clinics. Adalimumab and thiopurines are dispensed by pharmacies for a maximum treatment duration of 1 month at a time.²⁶ Data on anti-TNF exposure were, therefore, collected from SNIIRAM and PMSI. Patients who received infliximab were considered exposed for 2 months following the infusion, and those who received adalimumab or thiopurines were considered exposed for 1 month following delivery. Combination therapy was defined as the concomitant initiation of anti-TNFs and thiopurines in a period of 30 days. Treatment withdrawal was defined by a period of at least 3 months after the last day of estimated exposure without any new treatment delivery. Consequently, period of treatment withdrawal started 4 months after the last delivery of thiopurines or adalimumab and 5 months after the last perfusion of infliximab.

Therapeutic management. For the entire cohort, exposure to oral aminosalicylates, oral corticosteroids (above or equal to 20 mg), methotrexate, thiopurines, anti-TNFs and combination therapy, hospitalisation for longer than 1 day and surgical procedures related to IBD were assessed over time (Tables S1 and S2). Exposures to infliximab and adalimumab, as monotherapy and combination therapy, were assessed for incident patients. Among incident patients naïve to thiopurines and anti-TNFs, early introduction of thiopurines and anti-TNFs was assessed for different time periods (within 3, 6 months and within the first year after diagnosis).

Surgery included colectomies, intestinal resections, intra-abdominal abscess drainage and surgery for perianal complications, according to the French Medical Common Procedure Coding System (Table S3). Major abdominal surgery included colectomy and intestinal resection.

Treatment sequences. In order to have a minimum follow-up of 2 years, treatment sequences were assessed for incident patients included between 1 January 2009 and 31 December 2012. Since IBD drug therapy may be different in the following medical conditions,^{27–29} patients under 18 years at cohort inclusion, with a history of cancer or cancer occurrence within 3 months after cohort entry, organ transplantation, congenital immunodeficiency and HIV infection prior to cohort inclusion, were excluded from this analysis (Table S4). In addition, patient follow-up was also stopped after the occurrence of cancer or serious infections (requiring a hospitalisation) (Table S4). Patients exposed to thiopurines or anti-TNFs before the identification date could have received these drugs for diseases other than IBD. They were, therefore, excluded. First and second treatment sequences were assessed. In order to assess the causes of treatment withdrawal, exposures to oral aminosalicylates, methotrexate and oral corticosteroids were assessed in cases of thiopurine or anti-TNF withdrawal for more than 3 months. Surgical procedures and hospitalisations (either related to IBD or any hospitalisation admissions) 2 months before and after treatment withdrawal were also assessed.

Statistical analysis

The statistical analyses were performed with SAS (version 9.4) statistical software (SAS Institute, Cary, NC, USA). The results are expressed as numbers and percentages or medians and interquartile ranges. Cumulative incidences were used to estimate the cumulative probabilities of medication use, surgery and hospitalisation.

RESULTS

Patient characteristics

Patients' characteristics according to IBD phenotype are shown in Table 1. A total of 210 001 patients were included in the cohort [100 112 CD (47.7%) and 109 889 UC (52.3%)]. The majority of patients (54.7%, $n = 114\,930$) had a diagnosis of IBD from both the outpatient (long-term diseases from the SNIIRAM) and hospitalisation (PMSI) databases, 31.1% ($n = 65\,241$) had a diagnosis of IBD from the outpatient database only, and

Table 1 | Patient characteristics at cohort entry

	Crohn's disease		Ulcerative colitis		Total <i>n</i> = 210 001
	Incident patients (<i>n</i> = 34 739)	Total (<i>n</i> = 100 112)	Incident patients (<i>n</i> = 34 986)	Total (<i>n</i> = 109 889)	
Age at diagnosis	32 (23–48)	32 (23–45)	42 (29–57)	41 (29–54)	36 (26–50)
Male sex	15 451 (44.5)	42 234 (42.2)	17 514 (50.1)	54 658 (49.7)	96 892 (46.1)
Identification method					
Full reimbursement care related to inflammatory bowel disease	7493 (21.6)	29 291 (29.3)	8083 (23.1)	35 950 (32.7)	65 241 (31.1)
Hospitalisation related to IBD	8030 (23.1)	11 299 (11.3)	12 061 (34.5)	18 531 (16.9)	29 830 (14.2)
Hospitalisation and full reimbursement care related to inflammatory bowel disease	19 216 (55.3)	59 522 (59.4)	14 842 (42.4)	55 408 (50.4)	114 930 (54.7)
Year of cohort inclusion					
2009	7149 (20.6)	72 522 (72.4)	7225 (20.7)	82 128 (74.7)	154 650 (73.6)
2010	6973 (20.1)	6973 (7)	7166 (20.5)	7166 (6.5)	14 139 (6.7)
2011	7029 (20.2)	7029 (7)	7201 (20.6)	7201 (6.6)	14 230 (6.8)
2012	7175 (20.6)	7175 (7.2)	7047 (20.1)	7047 (6.4)	14 222 (6.8)
2013	6413 (18.5)	6413 (6.4)	6347 (18.1)	6347 (5.8)	12 760 (6.1)

Results are expressed as median (interquartile range) or *n* (%).

14.2% (*n* = 29 830) had a diagnosis of IBD from the hospitalisation database only. Median follow-up was 4.9 years. The majority of CD and UC patients were women [57 878 (57.8%) CD and 55 231 (50.3%) UC female patients]. Patients with CD were younger at diagnosis compared with UC patients [median age at diagnosis: 32 years (interquartile range, IQR: 23–45) and 41 years (IQR: 30–54), respectively].

Medication use, hospitalisation and surgery among the French IBD population

A total of 9986 (10%), 21 310 (21.3%) and 32 761 (32.7%) CD patients were prescribed combination therapy, anti-TNF and thiopurine monotherapies, respectively; and 5279 (5.3%) CD patients were exposed to methotrexate. 4617 (4.2%), 9310 (8.5%) and 20 504 (18.7%) UC patients were prescribed combination therapy, anti-TNF and thiopurine monotherapies, respectively; and 3240 (2.9%) UC patients were exposed to methotrexate.

During follow-up, 25 855 (25.8%) CD patients (12 948 prevalent and 12 907 incident patients) and 15 718 (14.3%) UC patients (8449 prevalent and 7269 incident patients) had an IBD-related hospitalisation. The hospitalisation rates were 109 and 58 hospitalisations per 1000 patient-years (PY) for CD and UC patients, respectively. IBD-related hospitalisations accounted for 34.3% and 21% of all hospitalisations in patients with CD and UC, respectively.

A total of 12 237 (12.2%) CD patients (7297 prevalent and 4940 incident patients) underwent at least one IBD-related surgical procedure, corresponding to 41 surgical procedures per 1000 PY. Overall, 5467 (4.8%) UC patients (3480 prevalent and 1987 incident patients) underwent at least one IBD-related surgical procedure, corresponding to 17 surgical procedures per 1000 PY.

Medication use, hospitalisation, and surgery among incident IBD patients

A total of 69 725 patients were incident cases [34 739 CD (49.8%) and 34 986 UC (50.2%)]. Incidence rates were 11 for CD and 11.1 for UC per 100 000 person-years. The number of annual incident IBD cases varied between 12 760 and 14 374 between 2009 and 2013.

Overall medication use. Among the 69 725 incident patients with IBD, the 1-year cumulative probabilities of combination therapy and anti-TNF monotherapy prescriptions were 7.1% and 14.1% in CD patients (Figure 1a) and 2.2% and 3.9% in UC patients, respectively (Figure 1b). The cumulative risk of thiopurine monotherapy 1 year after diagnosis was 30% in CD patients and 13% in UC patients (Figure 1).

Among incident patients treated with thiopurines or anti-TNFs during follow-up (17 566 CD and 8035 UC patients), the first treatment was thiopurine, anti-TNF monotherapy, and combination therapy for 12 130 (69.1%), 4361 (24.8%) and 1075 (6.1%) CD patients and

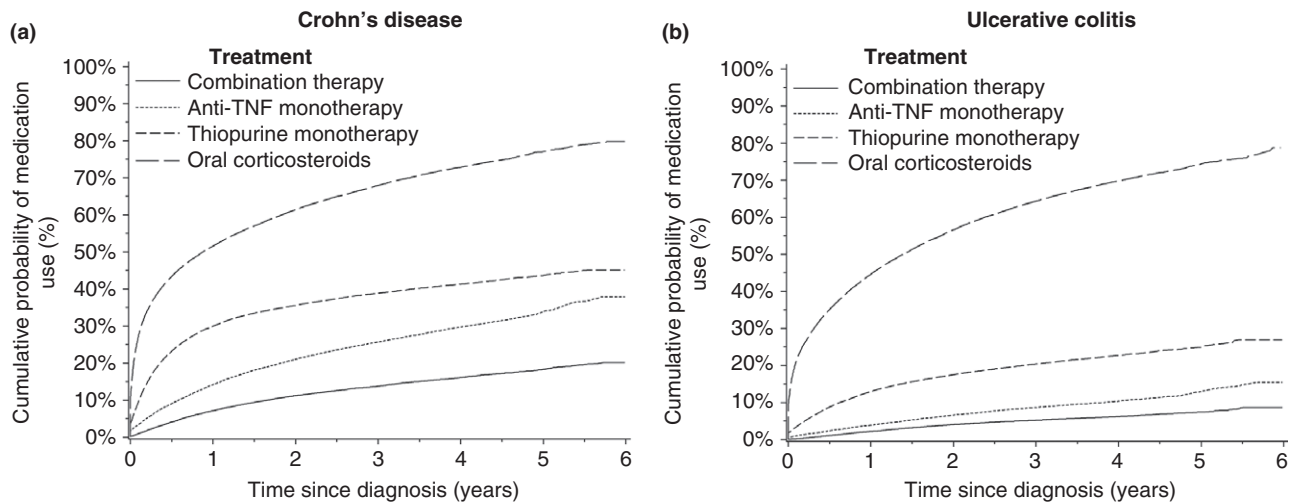


Figure 1 | Cumulative probability of combination therapy, anti-TNF, thiopurine monotherapy and oral corticosteroids use over time since diagnosis in Crohn's disease (a) and ulcerative colitis (b).

Table 2 | Incident patients exposed to thiopurines or anti-TNFs. Interval between diagnosis and treatment introduction

	Treatment introduction within 3 months after diagnosis	Treatment introduction within 6 months after diagnosis	Treatment introduction within the first year after diagnosis
Crohn's disease			
Thiopurine monotherapy	4695 (46.9)	6474 (64.7)	8068 (80.7)
Anti-TNF monotherapy	1650 (45.2)	2258 (61.8)	2828 (77.4)
Combination therapy	467 (54.5)	597 (69.7)	702 (81.9)
Ulcerative colitis			
Thiopurine monotherapy	1666 (30.8)	2543 (47)	3571 (66)
Anti-TNF monotherapy	474 (38.2)	660 (53.1)	839 (67.6)
Combination therapy	103 (39.9)	153 (59.3)	194 (75.2)

Results are expressed as *n* (%).

6284 (78.2%), 1418 (17.7%) and 333 (4.1%) UC patients, respectively.

The 5-year cumulative probabilities of combination therapy and anti-TNF monotherapy prescriptions were 18.3% and 33.8% in CD patients (Figure 1a) and 7.4% and 12.9% in UC patients, respectively (Figure 1b). The cumulative risk of thiopurine monotherapy and oral corticosteroids 5 years after diagnosis was 43.6% and 77% in CD patients and 24.9% and 74.4% in UC patients (Figure 1).

Among CD patients, 9.1% and 9.6% were prescribed infliximab and adalimumab monotherapy, respectively, during the first year of diagnosis. These rates were 3.5% and 1.9%, respectively, in UC patients (Figure S1b,d). Combination therapy was more frequent with infliximab than with adalimumab in the first year after diagnosis in CD and UC patients (4.2% vs. 3.1% and 1.7% vs. 0.6%

in CD and UC patients, respectively) (Figure S1a,c). The cumulative probabilities of methotrexate and aminosalicylates use are shown in Table S5.

A total of 4695 (46.9%), 1650 (45.2%) and 467 (54.5%) CD patients and 1666 (30.8%), 474 (38.2%) and 103 (39.9%) UC patients started thiopurine, anti-TNF monotherapy and combination therapy within 3 months after diagnosis, respectively. More than 70% of CD patients (77.4% and 81.9%) and more than 60% of UC patients (67.6% and 75.2%) started anti-TNF monotherapy and combination therapy within the first year after diagnosis, respectively. Rates of treatment introduction within the first 6 months after diagnosis are provided in Table 2.

Treatment sequences. A total of 47 572 incident patients (22 758 CD and 24 814 UC patients) aged ≥ 18 years,

with no history of cancer, congenital immunodeficiency, organ transplantation or HIV infection at cohort entry were included in the treatment sequence analysis.

A total of 5347 (23.5%) and 10 677 (46.9%) CD patients started oral corticosteroids and aminosalicylates as first-line treatment. Among patients treated with aminosalicylates as first-line treatment, 766 (7.2%) switched to anti-TNF monotherapy, 2758 (25.8%) to thiopurine monotherapy and 193 (1.8%) to combination therapy, while 6960 (65.2%) were not exposed to thiopurines or anti-TNFs. Among patients treated with oral corticosteroids as first-line treatment, 676 (12.6%) switched to anti-TNF monotherapy, 2368 (44.3%) to thiopurine monotherapy and 195 (3.6%) to combination therapy, while 2108 (39.5%) were not exposed to thiopurines or anti-TNFs. Treatment duration and number of corticosteroids course are provided in Figure S2.

As shown in Figure 2, 7317 (36.8%), 2426 (12.2%) and 610 (3.1%) CD patients naïve to thiopurines or anti-TNFs started thiopurine, anti-TNF monotherapy and combination therapy. Among patients treated for more than 3 months, 555 (26.2%) and 1873 (33.3%) withdrew treatment for more than 3 months, after a first course of anti-TNFs ($n = 2116$) and thiopurines ($n = 5631$), respectively (Figure 2). Withdrawal rates were similar between patients exposed to infliximab (25%) and adalimumab (26.7%). Hospitalisations and surgical procedures (in the 2 months before and after treatment withdrawal) were associated with less than 30% of these treatment withdrawals (Table S6); 47.9% of patients resumed their initial treatment [47.4% of patients initially treated with anti-TNFs after a median withdrawal duration of 175 days (IQR: 118–329) and 48.1% of patients initially treated with thiopurines after a median withdrawal duration of 156 days (IQR: 115–256)]. All IBD-related treatments were stopped during follow-up in 442 patients (5.7%) (4.6% and 6.1% after anti-TNF and thiopurine withdrawals, respectively).

Crohn's disease patients in whom thiopurines or anti-TNFs were not reintroduced were followed after withdrawal, for a median time of 536 days (IQR 281–866). This was also the case in the subgroup of patients who stopped all IBD-related treatments [thiopurines, anti-TNFs, methotrexate and corticosteroids; 442 patients, median follow-up after withdrawal: 418 days (IQR 236–724)].

After introduction of combination therapy, 59.4% switched to anti-TNF monotherapy and 17.9% to thiopurine monotherapy, while 16.2% remained under combination therapy during follow-up (Figure S3).

In UC, 4079 (16.4%) and 17 612 (71%) patients started oral corticosteroids and aminosalicylates as first-line treatment. Among patients treated with aminosalicylates as first-line treatment, 513 (2.9%) switched to anti-TNF monotherapy, 2969 (16.8%) to thiopurine monotherapy and 115 (0.7%) to combination therapy, while 14 015 (79.6%) were not exposed to thiopurines or anti-TNFs. Among patients treated with oral corticosteroids as first-line treatment, 158 (3.9%) switched to anti-TNF monotherapy, 790 (19.4%) to thiopurine monotherapy and 40 (1%) to combination therapy, while 3091 (75.7%) were not exposed to thiopurines or anti-TNFs. Treatment duration and number of corticosteroids course are provided in Figure S4.

A total of 4080 (21.8%), 827 (4.4%) and 183 (1%) UC patients naïve to thiopurines or anti-TNFs started thiopurine, anti-TNF monotherapy and combination therapy, respectively (Figure 3). Among patients treated for more than 3 months, 148 (22.6%) and 924 (28.1%) withdrew treatment for more than 3 months, after their first course of anti-TNFs ($n = 656$) and thiopurines ($n = 3296$), respectively (Figure 3). Withdrawal rates were similar between patients exposed to infliximab (20.1%) and adalimumab (23.7%). Hospitalisations and surgical procedures (in the 2 months before and after treatment withdrawal) were associated with less than 25% of these treatment withdrawals (Table S6). A total of 39.7% of patients resumed their initial treatment (35.8% of patients initially under anti-TNFs after a median withdrawal duration of 203 days (IQR: 119–364) and 40.4% of patients initially treated with thiopurines after a median withdrawal duration of 160 days (IQR: 119–285). All IBD-related medications were stopped during follow-up in 148 patients (3.7%) (4.1% and 3.7% after anti-TNF and thiopurine withdrawals, respectively).

Ulcerative colitis patients in whom thiopurines or anti-TNFs were not reintroduced were followed after withdrawal, for a median time of 554 days (IQR 252–872). This was also the case in the subgroup of patients who stopped all IBD-related treatments [thiopurines, anti-TNFs, methotrexate and corticosteroids; 148 patients, median follow-up after withdrawal: 363 days (IQR 206–638)].

After introduction of combination therapy, 52.6% switched to anti-TNF monotherapy and 20.4% to thiopurine monotherapy, with 24.8% remaining under combination therapy during follow-up (Figure S5).

Hospitalisation. Hospitalisations during follow-up period and lengths of stay are shown in Table 3. The 1- and 5-

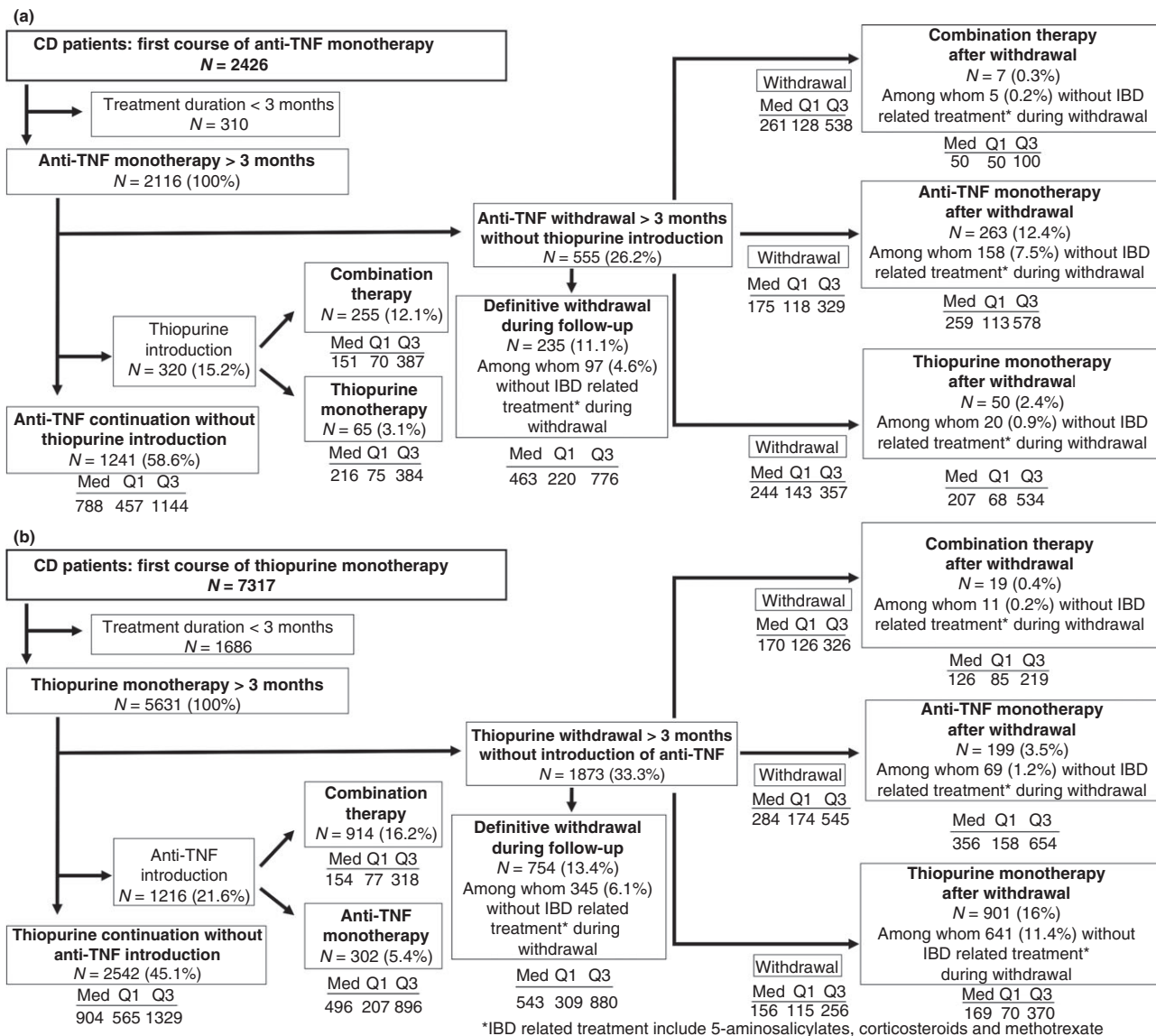


Figure 2 | Crohn's disease (CD) patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of anti-TNF (a) or thiopurine (b) monotherapy (days). Med, median; Q1, 1st quartile; Q3, 3rd quartile.

year cumulative risks of more than one IBD-related hospitalisation were 9.2% (95% CI: 8.9–9.5) and 20% (95% CI: 19.4–20.6) for CD patients and 4.4% (95% CI: 4.1–4.6) and 9.7% (95% CI: 9.2–10.2) for UC patients, respectively; 59.1% and 46% of hospitalisations within 1 and 5 years after diagnosis were related to IBD activity in CD patients, compared with 44.9% and 32.1% in UC patients, respectively. The median numbers of cumulative hospitalised days were similar for UC and CD patients (22 and 23 days, respectively, within 5 years after diagnosis).

Surgery. In CD patients, the 1- and 5-year cumulative risks of major abdominal surgery related to IBD after diagnosis were 6.2% (95% CI: 6–6.5) and 13.5% (95% CI: 13–14.1), respectively (Figure 4a). The 1- and 5-year cumulative risks of IBD-related surgery after diagnosis were 9.2% (95% CI: 8.9–9.5) and 19.3% (95% CI: 18.7–20), respectively. The most frequent surgical procedure was intestinal resection (47.5%). The cumulative risk of first intestinal resection was 5.6% (95% CI: 5.3–5.8) within 1 year after diagnosis and 11.9% (95% CI: 11.4–12.4) within 5 years after diagnosis. The cumulative risk of a

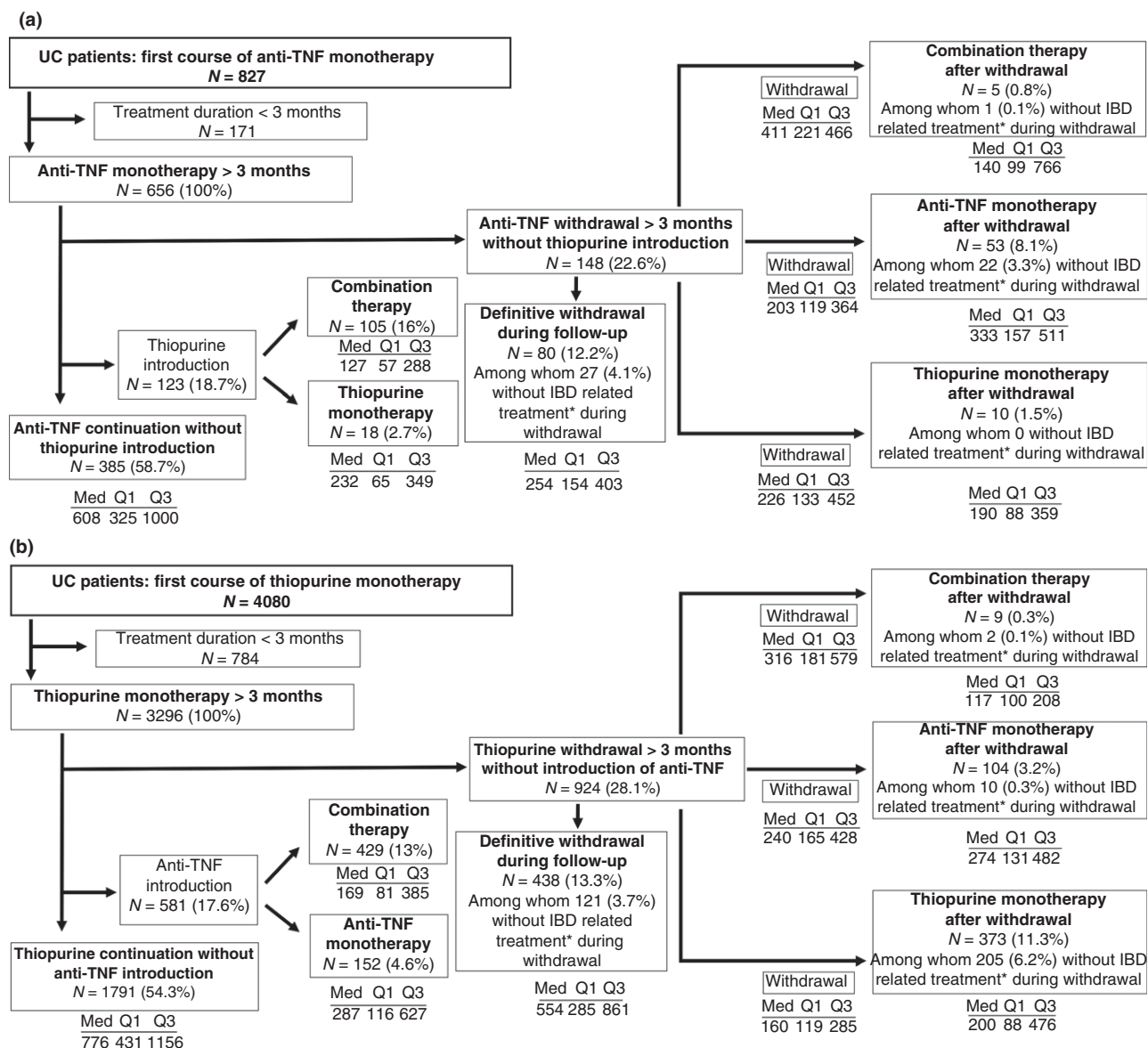


Figure 3 | Ulcerative colitis (UC) patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of anti-TNF (a) or thiopurine (b) monotherapy (days). Med, median; Q1, 1st quartile; Q3, 3rd quartile.

second resection was 10.4% (95% CI: 8.6–12.4), 5 years after the first resection. The 1- and 5-year cumulative risks of first perianal surgery after diagnosis were 2.8% (95% CI: 2.7–3) and 6.2% (95% CI: 5.8–6.6), respectively.

In UC, the 1- and 5-year cumulative risk of major abdominal surgery was 3.3% (95% CI: 3.1–3.5) and 6.2% (95% CI: 5.8–6.6), respectively (Figure 4b). The 1- and 5-year cumulative risk of surgery was 3.9% (95% CI: 3.7–4.1) and 8% (95% CI: 7.5–8.4), respectively. The 1- and 5-year cumulative risk of colectomy was 3.1% (95% CI: 2.9–3.3) and 5.7% (95% CI: 5.4–6.1), respectively.

DISCUSSION

This nationwide population-based cohort study provides a detailed description of the therapeutic management of 210 001 patients diagnosed with IBD, followed 6 years, in the current era of anti-TNFs. First, the majority of incident patients treated with immunosuppressive drugs or anti-TNFs are treated using a step-up approach, that starts with thiopurine monotherapy. Second, exposure to anti-TNFs is high. Third, more than 25% and 20% of incident IBD patients withdraw from thiopurines or anti-TNFs for more than 3 months after their first

Table 3 | Incident patients. Hospitalisation during follow-up

	Crohn's disease		Ulcerative colitis	
	1 year after diagnosis	5 years after diagnosis	1 year after diagnosis	5 years after diagnosis
Hospitalisation >24 h related to inflammatory bowel disease activity				
Patients hospitalised (N)	5561	12 843	5993	7243
Cumulative risk of being hospitalised at least once (%)	30.9	43.4	17.4	25
Length of stay (days)	6 (3–10)	6 (3–10)	6 (3–11)	7 (4–11)
Cumulative hospitalised days	11 (5–21)	14 (7–28)	10 (5–21)	14 (6–31)
Any hospitalisation >24 h				
Patients hospitalised (N)	14 414	19 570	10 396	15 336
Cumulative risk of being hospitalised at least once (%)	42.1	69.8	30.4	60
Length of stay (days)	6 (3–10)	5 (3–9)	6 (3–10)	5 (3–9)
Cumulative hospitalised days	14 (7–30)	22 (10–48)	15 (6–33)	23 (9–52)

Results are expressed as median (interquartile range) or *n* (%).

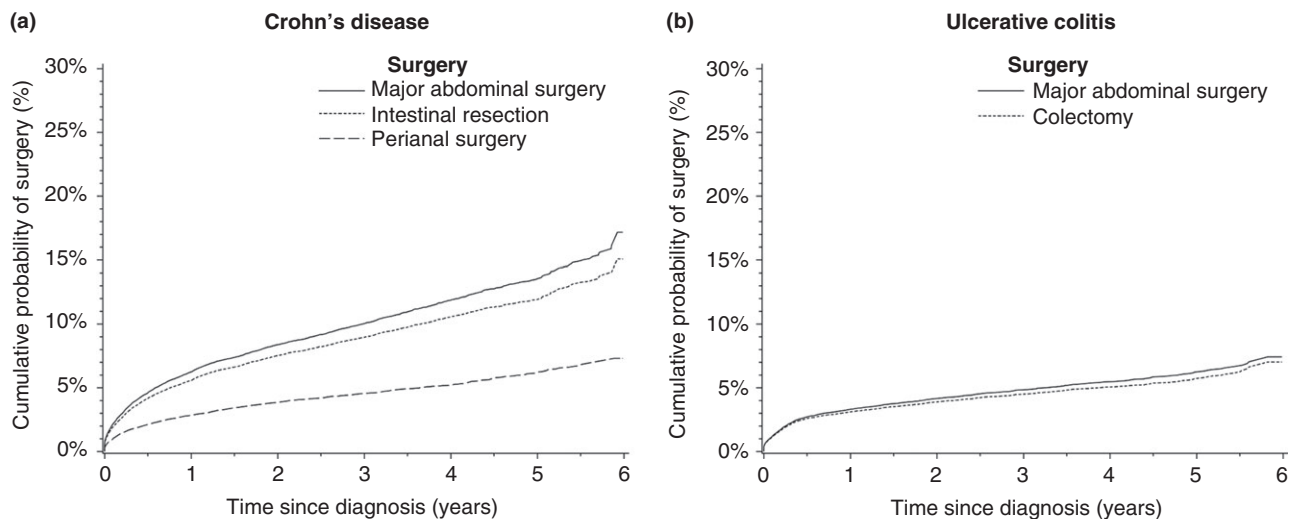


Figure 4 | Cumulative risk of first major abdominal surgery, intestinal resection and perianal surgery (a) over time in Crohn's disease and cumulative risk of first major abdominal surgery and colectomy in ulcerative colitis (b).

course of treatment, respectively. Among them, nearly 50% of CD patients and 40% of UC patients subsequently resume their initial treatment. Most of these withdrawals are not related to hospitalisations or surgical procedures.

Among incident patients who received thiopurines or anti-TNFs, the first treatment was thiopurine in the majority of patients, suggesting that the step-up approach is the predominant strategy in France. Although the higher efficacy of combination therapy as a first-line treatment has recently been shown in UC patients,⁵ it had already been demonstrated in 2010 in CD patients with the SONIC trial.⁴ If we restrict our

analysis to CD patients diagnosed between 2011 and 2013, thiopurine monotherapy was still the first-line treatment for the majority of patients (data not shown). Therefore, the SONIC trial had a limited impact on current practice. Thus, despite its higher efficacy as first-line treatment, the use of combination therapy was low. This may be due to concerns on safety of combination therapy as compared with monotherapy, although further studies are needed to define the benefit-risk balance of these strategies.

The use of anti-TNFs as monotherapy was expectedly high, particularly in CD patients, compared with cohort studies with follow-up beginning in the early 2000s.¹⁷

However, the cumulative probability of anti-TNF prescription, either as monotherapy or combination therapy, is similar to that reported by the recent prospective population-based inception IBD cohort, the EpiCom cohort.¹⁵ This cohort included incident cases diagnosed with IBD between 1 January and 31 December 2010; 21% of incident CD patients in Western European centres received anti-TNFs (as monotherapy or combination therapy) within the first year after diagnosis. In our cohort, the cumulative risk of anti-TNFs as monotherapy and combination therapy within the first year after diagnosis was 15.7% and 7.9%, respectively.

Most patients with anti-TNF, either as monotherapy or combination therapy, initiated their treatment within the first year after diagnosis. There is no consensus regarding the definition of 'early treatment use'. This study is the first to assess early treatment use rates according to several definitions in a nationwide population-based cohort.

Surgery rates observed in this study appear to be lower than historical data. A meta-analysis and a recent Danish population-based study have also shown that surgery rates in CD have declined in the last two decades. These trends are paralleled by an increased use of thiopurines and anti-TNFs. The REACT trial suggests that the earlier use of anti-TNF is associated with a reduced risk of surgery in CD patients who do not adequately respond to corticosteroids.³⁰ Although there was no blinded assessment of endoscopic healing in this trial, this benefit may be related to the prevention of bowel damage by early use of anti-TNFs. Yet, further trials are needed to confirm that early (vs. delayed) introduction of anti-TNF reduces surgery and prevents bowel damage in both CD and UC.

Our results show an unexpectedly high rate of thiopurine and anti-TNF withdrawal after a first course of treatment. Maintenance treatment withdrawal can be due to several causes; it can precede the introduction of a new treatment after withdrawal; it can be due to sustained medically or surgically induced remission; and it might also be due to loss of compliance. Noticeably, it may depend of the route of administration, as several studies suggest that adherence to adalimumab is lower than that of infliximab in IBD patients.³¹ However, in a sensitivity analysis, withdrawal rates were similar between infliximab and adalimumab, suggesting that non-adherence might not be the primary factor for treatment withdrawal. Finally, nearly 50% of CD patients and 40% of UC patients subsequently resume their initial treatment. In the few studies that assessed recapture rates

after treatment withdrawal, retreatment was successful in the majority of patients.^{32–34} A recent review on the effects of withdrawal of immunomodulators or biologic agents in IBD concluded that after 2 years of follow-up, at least 50% of patients who cease therapy have a disease relapse.¹² Similar results were observed in a recent retrospective observational study.³⁴ These findings are consistent with our results.

The hospitalisation rates of our study are similar to those of Vester-Andersen *et al.*³⁵ In this Danish cohort, 49% of CD patients and 33% of UC patients were admitted to hospital within the first year after diagnosis.³⁶ In a comparative study, the hospitalisation rates appeared to be higher in Denmark than in other European countries.³⁷ Taken together, these data suggest that hospitalisation rates for IBD in France are among the highest in Europe. Local insurance policies may explain these various rates.

This study has several strengths. The database is comprehensive in that it includes medical prescriptions and hospital stays for IBD in France. Patients are unselected in the SNIIRAM and PMSI because universal access to healthcare is guaranteed for all French residents, and there is no other insurance scheme in France. Moreover, patients were followed until 31 December 2014, death or last claim in the database, irrespective of type or indication (any outpatient care or any inpatient care). Patients for whom thiopurines or anti-TNFs were reintroduced after withdrawal were still followed during withdrawal period. Patients for whom thiopurines or anti-TNFs were not reintroduced remained followed during a substantial time after withdrawal occurrence with median follow-up of 1 year or more. Therefore, the data on medications is comprehensive. Withdrawal does not reflect any interruption in health insurance coverage or switch to a different data source. Second, the originality of our study relies on the extensive analysis of treatment sequences among incident patients in real-life practice. IBD-related drug exposure and duration for combination therapy, anti-TNF and thiopurine monotherapies, methotrexate, 5-aminosalicylates and corticosteroids, duration of treatment withdrawal, hospitalisations and surgical procedures were included in the same analysis. Finally, the sample size is large enough to study combination therapy separately from anti-TNF and thiopurine monotherapies, but also infliximab and adalimumab.

This study also has some limitations. Until now, there has been no validation study of the ICD codes related to IBD in the PMSI or SNIIRAM. However, 86% of patients were fully covered for IBD and full coverage is subject to

prior national health insurance approval, after examination of an official form signed by a physician (general practitioner and/or gastroenterologist) certifying that the patient has CD or UC, which strengthens the validity of IBD diagnosis. Furthermore, incidence rates observed in this study are in the range of those reported in a recent systematic review on IBD incidence: in European countries, reported incidence rates range between 0.6 and 24.3 per 100 000 person-years for UC and between 0.3 and 12.7 per 100 000 person-years for CD, respectively.³⁸

The follow-up of 6 years may be short compared to tertiary centres. However, the broader use of combination therapy started in 2009 with the SONIC trial. Among IBD patients, 1.7% and 5.5% were treated with combination therapy and anti-TNF monotherapy in 2009. These rates were 16.9% and 31.3% in 2014. Consequently, an increase of the follow-up before 2009 would not provide significantly more information regarding anti-TNFs and combination therapy. We did not provide data concerning other biologics prescription in case of anti-TNFs failure. Vedolizumab has the marketing authorisation for the management of IBD in France since May 2014, and ustekinumab has not the marketing authorisation for the management of IBD. In case of nominative compassionate early access programme to treatment before marketing authorisation granted by French regulatory agencies, these treatments are not collected in the SNIIRAM or PMSI. Future studies are required to assess the use of recent biologics prescription in case of anti-TNFs failure. Another potential limitation is the potential difference between drug intake and drug prescription. However, drug prescription and drug intake are similar for infliximab and inpatient administration of adalimumab. Finally, there was no information on certain relevant characteristics such as smoking behaviour and disease extent.

In conclusion, this study identified nearly 210 000 patients with IBD in France. Our data revealed that step-up approach remains the predominant strategy in France. The volume of anti-TNF prescriptions is high and surgery rates are low. High rates of thiopurine and anti-TNF withdrawal after a first course of treatment should prompt researchers to conduct more intensive research into the forms, indications and outcomes of de-escalation strategies in IBD.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. (a–d) Cumulative probability (CP) of every drug use over time since diagnosis in Crohn's

disease (left) and ulcerative colitis (right); CP of infliximab and adalimumab as combination therapy (a, c) and infliximab and adalimumab as monotherapies (b, d).

Figure S2. Crohn's disease patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of aminosalicylates (a) and oral corticosteroids (b) (days). Med, median; Q1, 1st quartile; Q3, 3rd quartile.

Figure S3. Crohn's disease patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of combination therapy (days). Med, median; Q1, 1st quartile; Q3, 3rd quartile.

Figure S4. Ulcerative colitis patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of aminosalicylates (A) and oral.

Figure S5. Ulcerative colitis patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of combination therapy (days). Med, median; Q1, 1st quartile; Q3, 3rd quartile; corticosteroids (b) (days). Med, median; Q1, 1st quartile; Q3, 3rd quartile.

Table S1. Codes used to define medication use.

Table S2. Codes used to define IBD-related hospitalisation.

Table S3. Codes used to define surgery.

Table S4. Codes used to define comorbidity.

Table S5. Incident patients: Medication use during follow-up.

Table S6. IBD patients: hospitalisation, surgery and drug exposure after anti-TNF and thiopurines withdrawal.

AUTHORSHIP

Guarantor of the article: Julien Kirchgesner.

Author contributions: JK: study concept and design; acquisition of data; statistical analysis; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. ML: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; AR: acquisition of data; critical revision of the manuscript for important intellectual content. AR: critical revision of the manuscript for important intellectual content. MZ: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. FC: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. RDS: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision. All authors took part in the revision of the manuscript and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Supplementary Table 1. Codes used to define medication use

Type of medication	Anatomical Therapeutic Chemical (ATC) classification system code
Anti-TNFs	L04AB02, L04AB04
Thiopurines	L04AX01
Methotrexate	L01BA01
5-aminosalicylates	A07EC
Oral corticosteroids	H02AB

Supplementary Table 2. Codes used to define IBD-related hospitalization

	ICD-10 codes
IBD	K50, K51
Occlusion	K56
Perianal complications	K60, K61

Supplementary Table 3. Codes used to define surgery

Type of surgery	French Medical Common Procedure Coding System
Colectomy	HHFA002, HHFA004, HHFA005, HHFA006, HHFA008, HHFA009, HHFA010, HHFA014, HHFA017, HHFA018, HHFA021, HHFA022, HHFA023, HHFA024, HHFA026, HHFA028, HHFA029, HHFA030, HHFA031
Intestinal resection	HGCA005, HGCC015, HGFA003, HGFA004, HGFA005, HGFA007, HGFC014, HGFC016, HGFC021
Perineal surgery	HKPA004, HKPA005, HKPA006, HKPA007, HKPA008
Minor surgery excluding perianal surgery	HGCA008, HGCC026, HGLA001, HHCA003, HHCC011, HPPA002, HPPC003, ZCJA002, ZCJA004

Supplementary Table 4. Codes used to define comorbidity

Comorbidity	ICD-10 codes	Anatomical Therapeutic Chemical (ATC) classification system code*	French Medical Common Procedure Coding System
Cancer	C00-C97 A00-A99, B00-B02, B05, B06, B08, B09, B15, B17, B25-B83, B95-B99, G00-G07, H00, H01.0, H03.1, H06.1, H10.0, H13.1, H19.1, H19.2, H60.0, H60.1, H60.2, H60.3, H65.0, H65.1, H66, H68.0, H70, I30.1, I33.0, I98.0, J01-J06, J10-J18, J20-J22, J36, J37, J39.0, J39.1, J85, J86, K11.3, K12.2, K23.0, K23.80, K67.3, K75.0, K80.0, K80.3, K80.4, K81.0, K83.0, K87.00, K93.0, K93.82, L00-L05, L08, L30.3, M00, M01, M49.0, M60.0, M72.6, M86, M90.0, N10, N30.0, N33.0, N39.0, N41.0, N41.2, N41.3, N45, N70.0, N71.0, N72, N73.3, N74.0, N74.1, N77.1, R57.2, R65.0, R65.1, T82.6, T82.7, T84.5, T84.6, T84.7, T85.7, U04	-	-
Serious infection	K67.3, K75.0, K80.0, K80.3, K80.4, K81.0, K83.0, K87.00, K93.0, K93.82, L00-L05, L08, L30.3, M00, M01, M49.0, M60.0, M72.6, M86, M90.0, N10, N30.0, N33.0, N39.0, N41.0, N41.2, N41.3, N45, N70.0, N71.0, N72, N73.3, N74.0, N74.1, N77.1, R57.2, R65.0, R65.1, T82.6, T82.7, T84.5, T84.6, T84.7, T85.7, U04	-	-
Congenital immunodeficiency	D80-D84	J06BA02, J06BA01 J05AX07, J05AX08, J05AX09, J05AX10, J05AX11, J05AE (except J05AE12), J05AF (except J05AG, J05AR	-
HIV	B20-B24, F024, O987, R75, Z21	(except J05AF, J05AF10), J05AR	-
Organ transplantation	T86.0-T86.4, T86.80-T86.82, T86.9, Z94.0-Z94.4, Z94.803, Z94.804, Z94.809, Z94.81, Z94.82, Z94.88, Z94.9	-	HNEA002, DZEA001, DZEA002, DZEA003, DZEA004, DZFA004, FELF009, GFEA001, GFEA002, GFEA003, GFEA004, GFEA005, GFEA006, GFEA007, HGEA002, HGEA004, HGEA005, HLEA001, HLEA002, HNEA900, JAEA003

Supplementary Table 5. Incident patients: Medication use during follow-up

	Crohn's disease		Ulcerative colitis	
	1 year after diagnosis	5 years after diagnosis	1 year after diagnosis	5 years after diagnosis
Users (N) and cumulative probability (%)				
Combination therapy ^A	2371(7.1)	4479(18.3)	727(2.2)	1628(7.4)
Adalimumab and thiopurines ^B	1027(3.1)	2252(9.8)	202(0.6)	623(3.3)
Infliximab and thiopurines ^B	1401(4.2)	2551(10.3)	556(1.7)	1148(4.9)
Anti-TNF monotherapy ^A	4738(14.1)	8375(33.8)	1295(3.9)	2748(12.9)
Adalimumab ^B	3208(9.6)	5909(24.7)	640(1.9)	1670(8.5)
Infliximab ^B	3049(9.1)	5136(20.3)	1153(3.5)	2149(9.3)
Thiopurine monotherapy	10 109(30)	12 731(43.6)	4340(13)	6481(24.9)
Methotrexate	743(2.3)	1557(7.1)	309(1)	691(3.3)
5-aminosalicylates (oral)	18 253(58.3)	19 747(67.2)	19 637(74.8)	20 890(83.6)
Corticosteroids (oral, ≥ 20mg)	16 743(51.6)	21 076(77)	12 804(44.9)	17 301(74.4)

^A Patients exposed to both adalimumab and infliximab during follow-up are counted only once;

^B Patients exposed to both adalimumab and infliximab during follow-up are counted in both groups. Results are expressed as numbers (%)

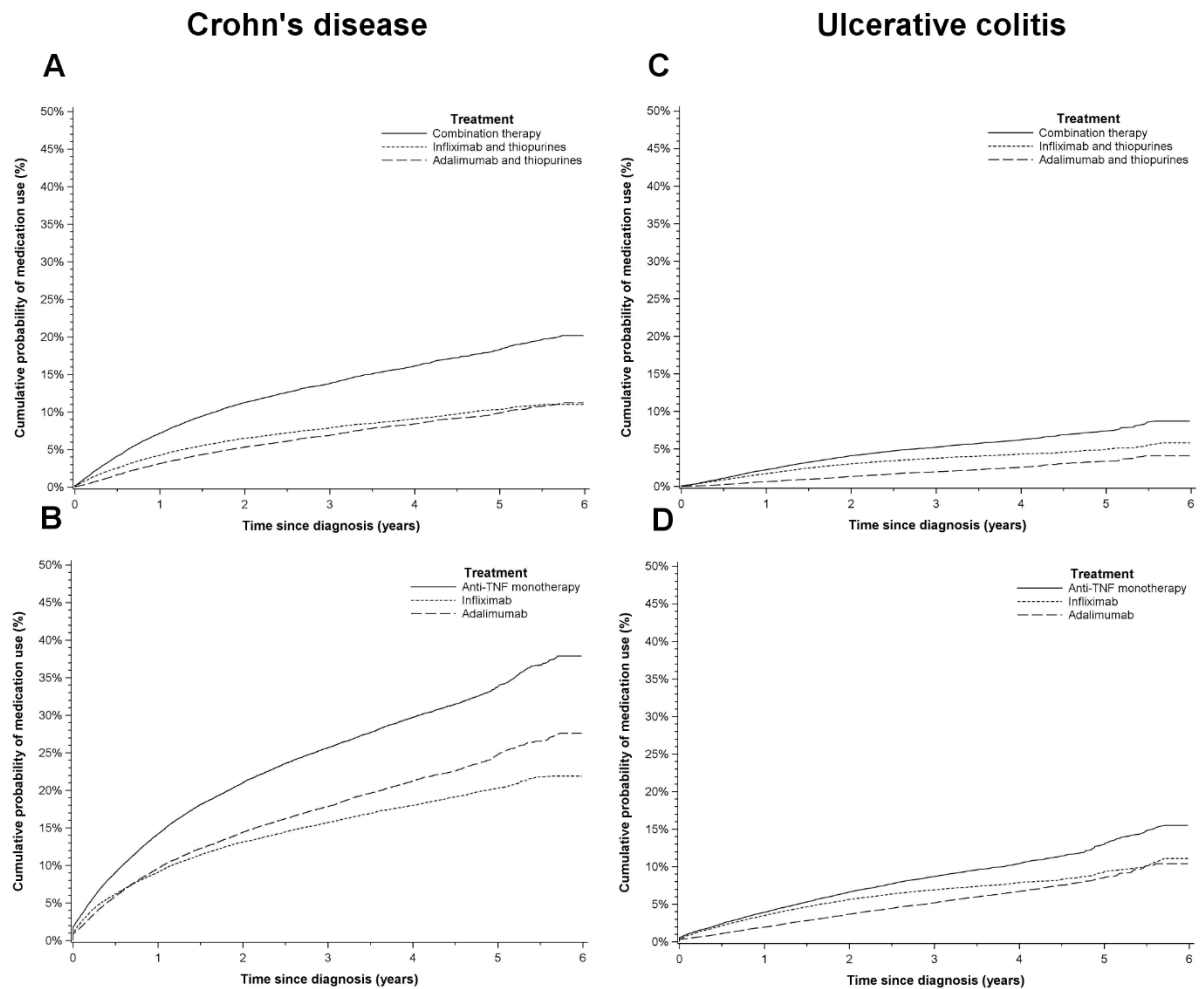
Supplementary table 6. IBD patients: hospitalization, surgery and drug exposure after anti-TNF and thiopurines withdrawal**Crohn's Disease**

First course of treatment before withdrawal	Anti-TNFs n=555				Thiopurines n=1873			
Second course of treatment after withdrawal	Combination therapy n=7	Anti-TNFs n=263	Thiopurines n=50	None n=235	Combination therapy n=19	Anti-TNFs n=199	Thiopurines n=901	None n=754
Drug exposure during withdrawal								
Methotrexate	0	23(8.7)	1(2)	27(11.5)	0	28(14.1)	3(0.3)	57(7.6)
Oral Corticosteroids	1(14.3)	76(28.9)	24(48)	99(42.1)	4(21.1)	93(46.7)	183(20.3)	293(38.9)
Only 5-aminosalicylates	1(14.3)	21(8)	6(12)	31(13.2)	4(21.1)	27(13.6)	77(8.5)	98(13)
Surgery related to IBD at withdrawal	0	30(11.4)	12(24)	32(13.6)	0	13(6.5)	23(2.6)	38(5)
Hospitalization at withdrawal, surgery excluded								
Related to IBD	0	13(4.9)	3(6)	12(5.1)	1(5.3)	7(3.5)	11(1.2)	26(3.4)
Any hospitalization	2(28.6)	34(12.9)	7(14)	31(13.2)	2(10.5)	15(7.5)	44(4.9)	59(7.8)
Patients without surgery or hospitalization at withdrawal occurrence and without IBD-related treatment* during withdrawal	4(57.1)	124 (47.1)	13(26)	72(30.6)	10 (52.6)	56 (28.1)	602 (66.8)	308 (40.8)
Adverse events during withdrawal								
Cancer	0	0	0	0	0	0	0	0
Serious infections	0	0	0	8(3.4)	0	0	0	22(2.9)

Ulcerative colitis

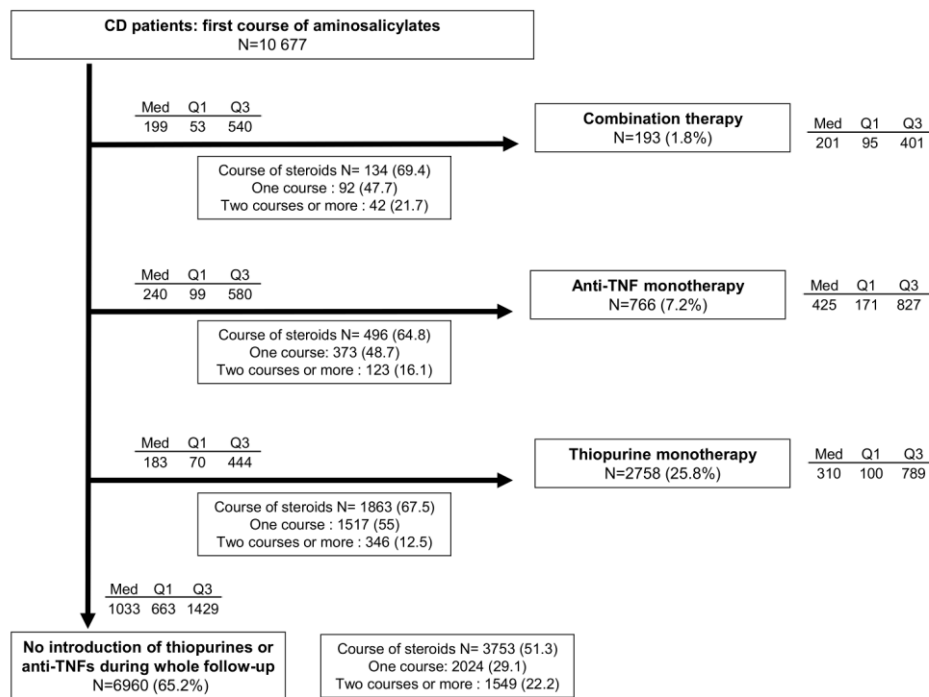
First course of treatment before withdrawal	Anti-TNFs n=148				Thiopurines n=924			
Second course of treatment after withdrawal	Combination therapy n=5	Anti-TNFs n=53	Thiopurines n=10	None n=80	Combination therapy n=9	Anti-TNFs n=104	Thiopurines n=373	None n=438
Drug exposure during withdrawal								
Methotrexate	0	6(11.3)	0	12(15)	1(11.1)	18(17.3)	8(2.1)	27(6.2)
Oral Corticosteroids	2(40)	19(35.8)	9(90)	43(53.8)	6(66.7)	80(76.9)	122(32.7)	202(46.1)
Only 5-aminosalicylates	2(40)	9(17)	1(10)	7(8.8)	1(11.1)	13(12.5)	44(11.8)	107(24.4)
Surgery related to IBD at withdrawal	0	0	0	13(16.3)	0	1(1)	2(0.5)	7(1.6)
Hospitalization at withdrawal, surgery excluded								
Related to IBD	1(20)	3(3.7)	2(20)	2(2.5)	0	6(5.8)	7(1.9)	10(2.3)
Any hospitalization	1(20)	5(9.4)	3(30)	9(11.3)	0	13(12.5)	16(4.3)	38(8.7)
Patients without surgery or hospitalization at withdrawal and without IBD-related treatment* during withdrawal	1(20)	19 (35.8)	0	25 (31.3)	2 (22.2)	9 (8.6)	201(53.9)	109(24.9)
Adverse events during withdrawal								
Cancer	0	0	0	0	0	0	0	0
Serious infections	0	0	0	7(8.8)	0	0	12 (2.7)	0

Results are expressed as median (interquartile range) or number (%); *IBD-related treatment includes 5-aminosalicylates, corticosteroids and methotrexate

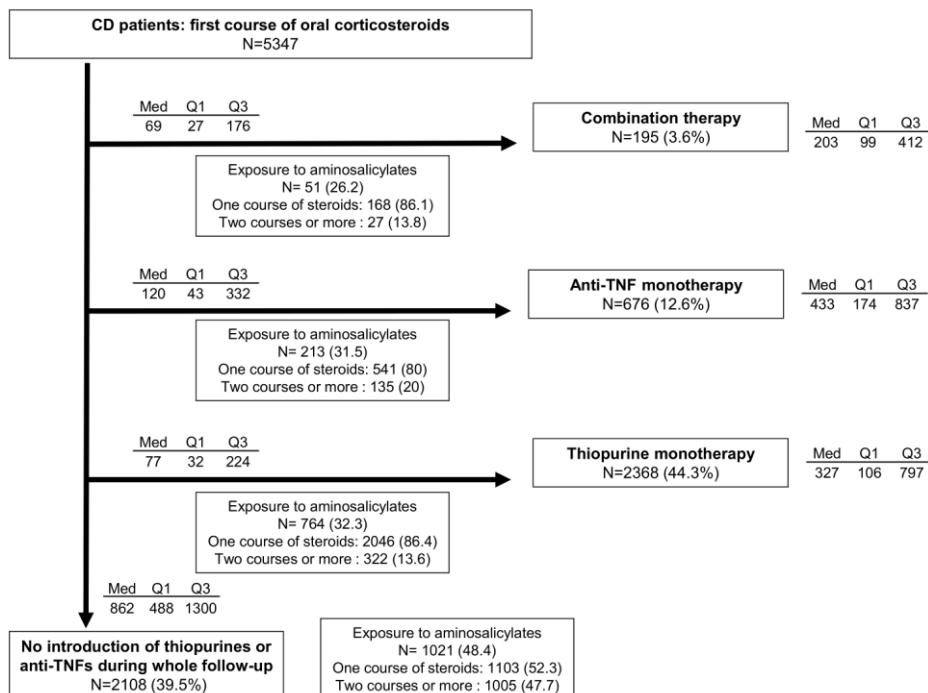


Supplementary Figure 1: (A-D) Cumulative probability (CP) of every drug use over time since diagnosis in Crohn's disease (left) and ulcerative colitis (right); CP of infliximab and adalimumab as combination therapy (A, C) and infliximab and adalimumab as monotherapies (B, D).

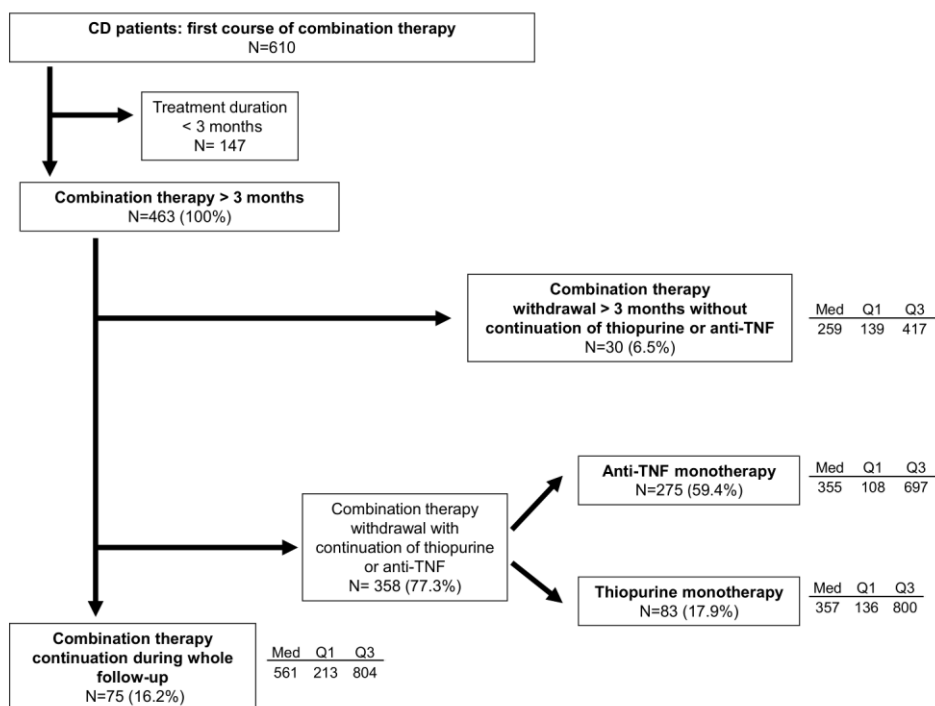
A



B

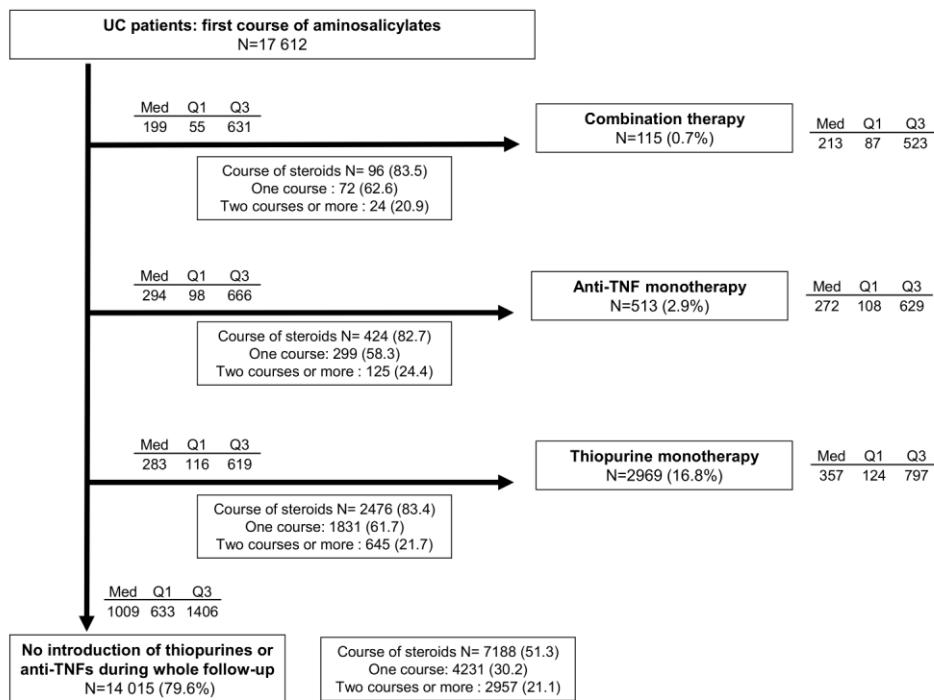


Supplementary Figure 2: Crohn's disease patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of aminosalicylates (A) and oral corticosteroids (B) (days). Legends: Med: median; Q1: 1st quartile; Q3: 3rd quartile.

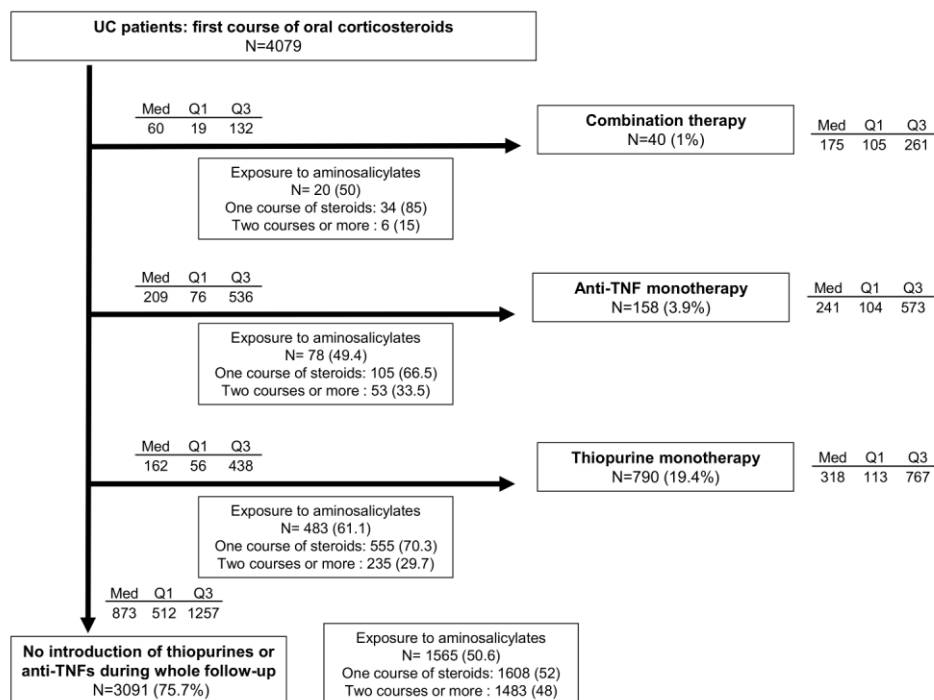


Supplementary Figure 3: Crohn's disease patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of combination therapy (days). Legends: Med: median; Q1: 1st quartile; Q3: 3rd quartile.

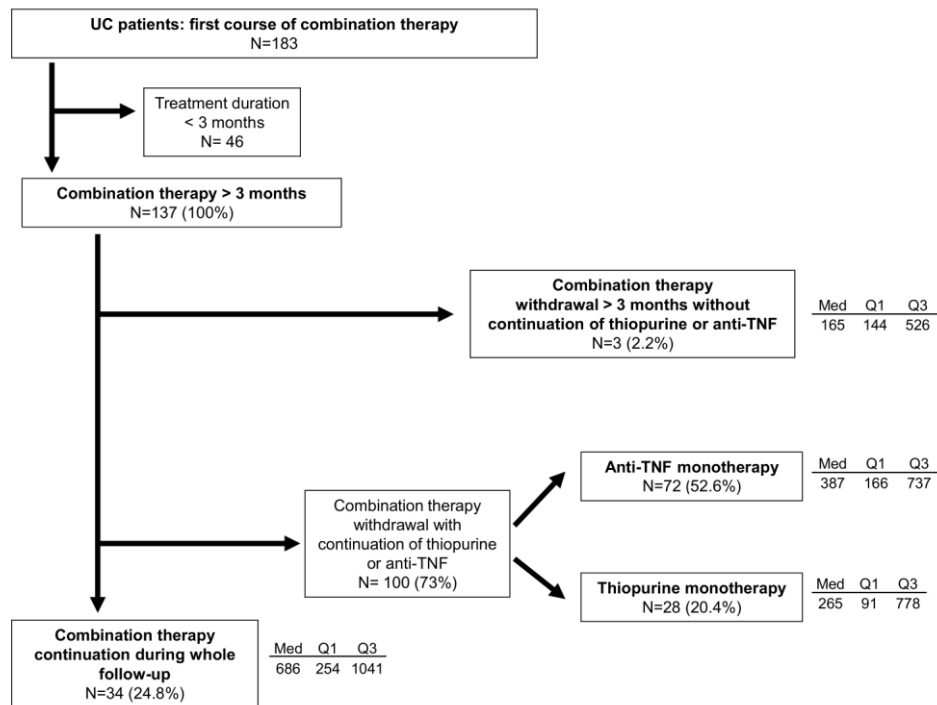
A



B



Supplementary Figure 4: Ulcerative colitis patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of aminosalicylates (A) and oral corticosteroids (B) (days). Legends: Med: median; Q1: 1st quartile; Q3: 3rd quartile.



Supplementary Figure 5: Ulcerative colitis patients naive to thiopurines and anti-TNFs at cohort inclusion. Therapeutic management and treatment duration after a first course of combination therapy (days). Legends: Med: median; Q1: 1st quartile; Q3: 3rd quartile.

2. Discussion

This study provides an indirect validation of IBD diagnosis in the SNIIRAM database, since we reported treatment exposure, hospitalisation, and surgery rates similar to current standard of care and incidence rates in the range of those reported in other populations.[22] It also provides several key messages regarding the therapeutic management of IBD in the current era in France.

Randomized controlled trials concluded that the combination therapy with infliximab and azathioprine was more effective than monotherapy with each drug in CD and UC patients.[5,6] However, despite its higher efficacy, the use of combination therapy as first-line treatment was low in real-life practice. Since the risk associated with combination therapy remains largely unexplored, this finding may be due to concerns on safety of combination therapy as compared with monotherapy, although further studies are needed to define the benefit-risk balance of these strategies.

We reported an unexpectedly high rate of thiopurines and anti-TNFs withdrawal after a first course of treatment. Maintenance treatment withdrawal can be due to several causes; it can precede the introduction of a new treatment after withdrawal; it can be due to sustained medically- or surgically-induced remission; it might also be due to loss of compliance. In the analysis assessing treatment withdrawal, patients were censored in case of cancer and serious infection occurrence or treatment duration shorter than three months, and withdrawal rates were similar between infliximab and adalimumab. Furthermore, treatment withdrawal was related to hospitalization or a surgical procedure in less than 30% of these patients. However, cause of treatment withdrawal may be difficult to assess in studies using administrative health databases.

Finally, this study provides large-scale, population-based data on trends in medication use, treatment withdrawal, surgery and hospitalizations in patients with IBD in the current era of anti-TNFs, and emphasizes the growing need for studies on de-escalation strategies in IBD. It also provides strong evidence on the validity of IBD diagnoses in the French administrative health databases.

RISK OF ACUTE ARTERIAL EVENTS IN PATIENTS WITH IBD COMPARED WITH THE GENERAL POPULATION, IMPACT OF AGE, SEX AND DISEASE ACTIVITY

The second objective was to assess the risk of acute arterial events among IBD patients compared with the general population, and the impact of age, sex and disease activity on the risk. This part relies on the analysis of data from the PMSI 2008-2013, including all French hospital discharges during this period, therefore IBD and non-IBD patients were included.

All patients, aged 15 years or older, identified with IBD between 2008 and 2013 from the PMSI, based on one hospitalisation discharge diagnosis both as primary or associated diagnosis related to CD or UC, were included. The general population at risk consisted in all adults (15 years or older) residing in France (National Vital Statistics in January of each year of the study period).

Occurrence of acute arterial events, cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, obesity, smoking behavior, and alcohol use disorder), surgical procedures, and hospitalizations related to IBD were assessed. Acute arterial events included ischemic heart disease, cerebrovascular disease and peripheral artery disease excluding acute mesenteric ischemia. Incidence of first acute arterial event in patients with IBD and expected incidence for each region-, sex-, and 5-year age-specific stratum based on observed incidence in the French general population were calculated. The impact of severe disease activity marker (recent hospitalization for uncontrolled IBD) was assessed among IBD patients by survival analysis adjusted for cardiovascular risk factors.

A total of 210 162 individuals with IBD (CD, 97 708; UC, 112 454) were included. During 595 202 person-years of follow-up, 5554 patients with IBD were diagnosed with incident acute arterial events, including 3177 ischemic heart diseases (57.2%), 1715 cerebrovascular diseases (30.9%) and 662 peripheral artery diseases (11.9%). Patients with CD (Standardized incidence ratio (SIR), 1.35; 95% confidence interval [95% CI] 1.30-1.41) and UC (SIR, 1.10; 95% CI, 1.06-1.13) had an increased risk of acute arterial events overall. Higher values of SIR were observed in patients aged less than 35 years, both in CD (SIR, 1.42; 95% CI 1.09-1.75) and UC (SIR, 1.65; 95% CI, 1.20-2.10). During follow-up, 22% and 13.3% of CD and UC patients were hospitalized for IBD-related symptoms. After adjustment for general cardiovascular risk factors, the 3-month periods before and after IBD-related hospitalization or surgery were associated with an increased risk of acute arterial events compared with other periods in patients with CD and UC (Hazard ratio [HR], 1.74; 95% CI, 1.44-2.09 and 1.87; 95% CI, 1.58-2.22, respectively).

1. Article: Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study

ORIGINAL ARTICLE

Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study

Julien Kirchgesner,^{1,2} Laurent Beaugerie,^{1,3} Fabrice Carrat,^{2,4} Nynne Nyboe Andersen,^{5,6} Tine Jess,^{5,6,7} Michaël Schwarzsinger,^{8,9} for the BERENICE study group

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¹Department of Gastroenterology, AP-HP, Hôpital Saint-Antoine, Paris, France

²UMRS 1136, INSERM, UPMC Univ Paris 06, Sorbonne Universités, Paris, France

³ERL 1057, INSERM/UMRS 7203 and GRC-UPMC 03, UPMC Univ Paris 06, Paris, France

⁴Department of Public Health, AP-HP, Hôpital Saint-Antoine, Paris, France

⁵Department of Epidemiology Research, Statens Serum Institute, Copenhagen, Denmark

⁶Department of Gastroenterology, Zealand University Hospital, Køge, Denmark

⁷Department of Clinical Epidemiology, Bispebjerg Hospital, Copenhagen, Denmark

⁸Translational Health Economics Network, Paris, France

⁹Infection Antimicrobials Modeling and Evolution, UMR 1137, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

Correspondence to

Dr Julien Kirchgesner, Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75571 Paris CEDEX 12, France; julien.kirchgesner@gmx.com

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ABSTRACT

Objective Magnitude and independent drivers of the risk of acute arterial events in IBD are still unclear. We addressed this question in patients with IBD compared with the general population at a nationwide level.

Design Using the French National Hospital Discharge Database from 2008 to 2013, all patients aged 15 years or older and diagnosed with IBD were identified and followed up until 31 December 2013. The rates of incident acute arterial events were calculated and the impact of time with active disease (period around hospitalisation for IBD flare or IBD-related surgery) on the risk was assessed by Cox regression adjusted for traditional cardiovascular risk factors.

Results Among 210 162 individuals with IBD (Crohn's disease (CD), n=97 708; UC, n=112 454), 5554 incident acute arterial events were identified. Both patients with CD and UC had a statistically significant overall increased risk of acute arterial events (standardised incidence ratio (SIR) 1.35; 95% CI 1.30 to 1.41 and SIR 1.10; 95% CI 1.06 to 1.13, respectively). The highest risk was observed in patients under the age of 55 years, both in CD and UC. The 3-month periods before and after IBD-related hospitalisation were associated with an increased risk of acute arterial events in both CD and UC (HR 1.74; 95% CI 1.44 to 2.09 and 1.87; 95% CI 1.58 to 2.22, respectively).

Conclusion Patients with IBD are at increased risk of acute arterial events, with the highest risk in young patients. Disease activity may also have an independent impact on the risk.

INTRODUCTION

IBD including Crohn's disease (CD) and UC are characterised by chronic intestinal and systemic inflammation. Chronic systemic inflammation is involved in the pathogenesis of atherosclerosis and associated with increased risk of acute arterial events.^{1,2} However, the risk of acute arterial events in patients with IBD remains unclear, in contrast with other chronic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus.^{3–5} In one meta-analysis,⁶ IBD was significantly associated with increased risks of ischaemic heart disease and cerebrovascular disease, but no significant association was found for peripheral artery disease. In another meta-analysis,⁷ no increased risk of acute arterial

Significance of this study

What is already known on this subject?

- Chronic systemic inflammation is associated with an increased risk of acute arterial events.
- Risk of acute arterial events in IBD remains debated, while risk differences between age categories and the impact of disease activity remain largely unexplored and may explain previous contradicting findings.

What are the new findings?

- Patients with IBD are at increased risk of acute arterial events, with the highest risk in younger patients for all arterial disease groups.
- Disease activity may be an independent risk factor of acute arterial events.

How might it impact on clinical practice in the foreseeable future?

- Our nationwide population-based cohort study suggests an increased risk of ischaemic heart disease, cerebrovascular disease and peripheral artery disease in patients with IBD, notably in younger patients and those with severely active disease. Strategies for optimising control of inflammation should be assessed to decrease the risk of acute arterial events in this patient population.

events was found in patients with IBD.⁶ Thus, the data are inconsistent and further generalisation of results is limited by the considerable heterogeneity found between studies.⁶

Several factors may explain the conflicting data on the association between IBD and acute arterial events, notably age and disease activity. Several studies reported an association between younger age and an increased risk of acute arterial events,^{8–10} while an increased risk of myocardial infarction was reported specifically in patients of older age.¹¹ Regarding disease activity, only one study reported the association between disease activity and the risk of myocardial infarction and stroke, but did not include peripheral artery disease.¹² Hence, the magnitude of the risk and the independent risk factors of acute arterial events in patients with IBD remain unclear and need further investigation.

Inflammatory bowel disease

Our aim was to assess the risk of acute arterial events, including ischaemic heart disease, cerebrovascular disease and peripheral artery disease in patients with IBD as compared with the general population, and to assess the impact of age and IBD activity on the risk of acute arterial events, at a nationwide level.

MATERIALS AND METHODS

Data source

The French National Hospital Discharge Database (Programme de Médicalisation des Systèmes d'Information (PMSI)) covers all public and private hospitals in France. The standardised discharge summary includes: patient's demographics; primary and associated discharge diagnosis codes (WHO International Classification of Diseases, 10th revision (ICD-10)¹³; medical and surgical procedures performed (French Medical Common Procedure Coding System); length of stay, entry and in-hospital mortality, which accounted for 57.4% of all adult deaths recorded in France between 2008 and 2013.¹⁴ A unique anonymous identifier allows linking all hospital claims of the patient since January 2008 and tracking the occurrence and progression of chronic conditions over time.

Study population

All patients, aged 15 years or older, identified with IBD between 2008 and 2013 from the PMSI were included. Identification of IBD cases was based on one hospitalisation discharge diagnosis both as primary or associated diagnosis related to CD (K50) or UC (K51). The ICD-10 code for indeterminate colitis (K52.3) was not considered in this study. Detailed individual-level information regarding hospitalisations was available from 1 January 2008. Date of cohort inclusion was 1 January 2010 for patients diagnosed with IBD before 1 January 2010 and the date of first hospital claim related to IBD for patients identified after 1 January 2010. In case of multiple hospitalisations related to both UC and CD, the most recent diagnosis at cohort inclusion was retained. All subjects were followed until occurrence of any outcome, in-hospital death or end of the study, 31 December 2013, whichever came first.

The general population at risk consisted in all adults (15 years or older) residing in France (National Vital Statistics in January of each year of the study period), hence including IBD and non-IBD individuals. Incident acute arterial events among non-IBD individuals were assessed from the PMSI between 1 January 2008 and 31 December 2013. Individuals diagnosed with IBD after 1 January 2010 contributed person-time as non-IBD individuals until the date of IBD diagnosis.

The same exclusion criteria were applied in the IBD population and the general population and were identified between 1 January 2008 and date of cohort inclusion (ie, at least during 2 years of follow-up for every patient). Individuals with a history of an acute arterial event or related cardiovascular disease, primary or associated discharge diagnosis of atrial fibrillation, heart failure or cardiomyopathy, procedures related to cardiac electronic device, cardiac valve prosthesis, angiography, coronary catheterisation or coronary artery bypass grafting were excluded (see online supplementary table 1).

Outcomes

Study outcome was the first occurring acute arterial event following cohort entry, defined by a primary discharge diagnosis or procedures specifically related to: (1) ischaemic heart disease (including myocardial infarction); (2) cerebrovascular disease (including stroke); (3) peripheral artery disease, excluding acute

mesenteric ischaemia. We did not include acute mesenteric ischaemia, since local intestinal rather than systemic inflammation may be associated with acute mesenteric ischaemia in patients with IBD^{15 16} (see online supplementary table 1 for the ICD-10 codes and procedure codes).

Covariates

Traditional cardiovascular risk factors including hypertension, hyperlipidaemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders were assessed during each hospitalisation between 1 January 2008 and end of follow-up (see online supplementary table 2). Since assessment during hospitalisation may underestimate the prevalence of cardiovascular risk factors, which additionally may be undiagnosed although already present until the occurrence of an acute arterial event, cardiovascular risk factors were considered present at cohort entry in the main analysis if recorded at any time during follow-up. Disease activity prior to cohort entry for patients diagnosed with IBD before 1 January 2010 or at cohort entry for patients identified after 1 January 2010 was assessed by three mutually exclusive categories: (1) hospitalisation not related to IBD with an associated diagnosis of IBD (without day hospitalisation for IBD-related endoscopy or hospitalisation related to IBD activity or surgery); (2) day hospitalisation for IBD-related endoscopy (without hospitalisation related to IBD activity or surgery); (3) hospitalisation related to IBD activity or surgery.

Statistical analysis

Continuous data are expressed as median (IQR), while discrete data are given as percentages, and comparisons were made with Pearson's χ^2 test.

The incidence rate of acute arterial events was assessed for patients with IBD and for the French general population, between 2010 and 2013. The expected number of cases of acute arterial events in the general population was obtained by multiplying person-years at risk in each 5-year age group by the corresponding sex, age and region-specific incidence rate for each year between 2010 and 2013. The reported number of cases of acute arterial events was divided by the expected number to obtain standardised incidence ratios (SIRs). CIs were calculated with an exact method based on the Poisson distribution. Lastly, subgroups analyses were performed by age groups (15–34; 35–54; 55–74; 75 years or older), sex and number of traditional cardiovascular risk factors in patients with IBD (compared with the general population and irrespective of the number of cardiovascular risk factors in the general population).

To assess the impact of disease activity on the risk of acute arterial events among patients with IBD, hospitalisations or surgery related to IBD were used as surrogate markers for disease activity. Active disease was defined as the 3 months before and after an IBD-related hospitalisation or surgery. In case of readmission related to IBD in the 3 months following an IBD-related hospitalisation, period of disease activity was extended to coincide with the date of the readmission. The 3 months after cohort inclusion were likewise defined as a period of IBD activity in patients hospitalised for IBD activity at cohort entry. A Cox regression analysis was performed separately for each IBD subtype and adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry and traditional cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders). IBD activity was fitted as time-varying covariate, and periods of disease activity were compared with periods of no disease activity.

All other covariates were included as time-fixed covariates. Results were reported as HRs with 95% CI. The proportionality of hazards was evaluated using plots of Schoenfeld residuals, and no violation of the proportional hazard assumption was detected.

Since data on out-of-hospital deaths, which may mostly affect elderly people, are not available in the database, subgroups analyses were stratified on age groups (patients aged 18–54 and 55 years or older) to assess the impact of these lacking mortality data. Additionally, we performed several sensitivity analyses to test the robustness of our results. We varied the length of time patients were regarded as having active disease, reducing it to 1 month and extending it to 6 months before and after an IBD-related hospitalisation or surgery. Since cardiovascular risk factors were considered present in the main analysis if recorded at any time during follow-up, we only considered cardiovascular risk factors present at cohort entry in a sensitivity analysis. Furthermore, data on hospitalisations was available until 31 December 2013 and acute arterial events occurring between October and December 2013 may thus not be associated with IBD-related hospitalisations occurring in 2014 in our study. A sensitivity analysis was therefore performed by censoring follow-up to 30 September 2013. Lastly, we performed a sensitivity analysis excluding the postoperative period, since non-cardiac surgery is associated with a postoperative morbidity related to cardiac complications.¹⁷

Patients with a concomitant date of first IBD claim in the database and occurrence of acute arterial event were excluded from this analysis.

The study was approved by the French Data Protection Agency (CNIL DE-2015-025). All data used in this study only contained anonymous patient records. The statistical analyses were performed with SAS V.9.4 statistical software.

RESULTS

Overall, 210 162 patients identified with IBD in the 2008–2013 French National Hospital Discharge Database were included (figure 1): 97 708 with CD (46.5%) and 112 454 with UC (53.5%). The median follow-up was 3.4 years (IQR:1.8–4.0). Patients' characteristics are shown in table 1.

The majority of patients with IBD were women (53.8%), with significantly higher proportions in patients with CD (57.7%) as compared with UC (50.5%) ($p<0.0001$). Patients with CD were younger than patients with UC at cohort entry (median age at cohort entry (IQR): 40 years (28–53) and 49 years (36–62), respectively). The proportion of patients with active disease prior to cohort entry was higher in patients with CD (25.9%) compared with patients with UC (14.6%). The majority of patients (66.3%) were identified at cohort entry by IBD-related endoscopy. At least one cardiovascular factor was recorded in 24.8% of patients with IBD, with higher rates of tobacco smokers recorded among patients with CD (9.6%) than patients with UC (4.4%) ($p<0.0001$). A total of 5232 of patients (2.5%) died in hospital during follow-up.

Risk of any acute arterial event

A total of 5554 acute arterial events occurred in patients with IBD during 595 202 person-years of follow-up, including 3177 (57.2%) ischaemic heart diseases, 1715 (30.9%) cerebrovascular diseases and 662 (11.9%) peripheral artery diseases. Crude incidence rates per 1000 person-years were: 9.3 (95% CI 9.1 to 9.6) for all acute arterial event; 5.3 (95% CI 5.1 to 5.5) for ischaemic heart disease; 2.9 (95% CI 2.7 to 3) for cerebrovascular disease and 1.1 (95% CI 1 to 1.2) for peripheral artery disease. Crude incidence rates according to IBD subtype are provided in online supplementary figure 1.

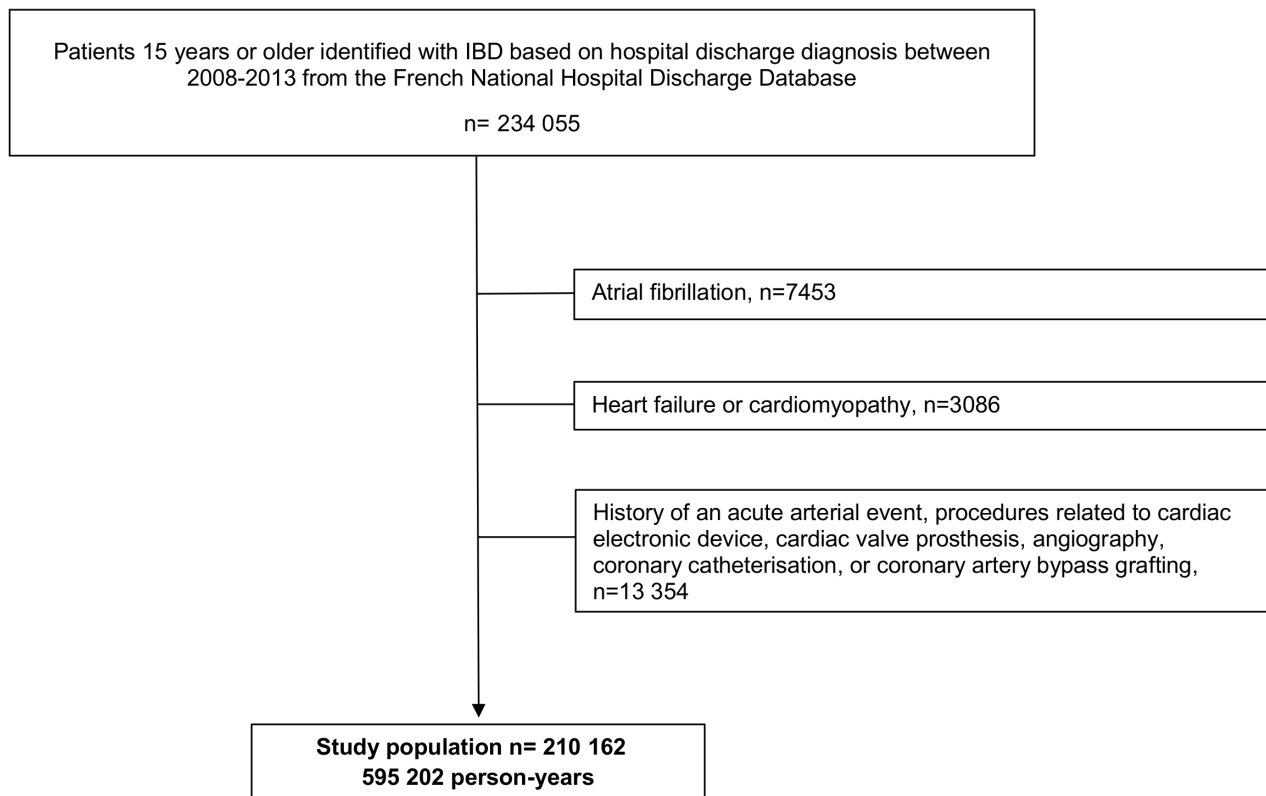


Figure 1 Study population flowchart.

Inflammatory bowel disease

Table 1 Characteristics of patients with IBD

	CD (n=97 708)	UC (n=1 12 454)	Total (n=210 162)
Male sex	41 369 (42.3)	55 636 (49.5)	97 005 (46.2)
Age at cohort entry (years)	40 (28–53)	49 (36–62)	45 (32–59)
Follow-up (years)	3.7 (1.9–4.0)	3.2 (1.6–4.0)	3.4 (1.8–4.0)
Disease activity prior to cohort entry			
Hospitalisation not related to IBD activity	17 695 (18.1)	11 532 (10.2)	29 227 (13.9)
Day hospitalisation for IBD-related endoscopy	54 746 (56.0)	84 532 (75.2)	139 278 (66.3)
Hospitalisation related to IBD activity or surgery	25 267 (25.9)	16 390 (14.6)	41 657 (19.8)
Cardiovascular risk factors recorded			
Hypertension	10 477 (10.7)	16 906 (15.0)	27 383 (13.0)
Hyperlipidaemia	3512 (3.6)	6757 (6.0)	10 269 (4.9)
Diabetes mellitus	3706 (3.8)	6205 (5.5)	9911 (4.7)
Obesity	5210 (5.3)	6464 (5.7)	11 674 (5.6)
Tobacco smoking	9349 (9.6)	4900 (4.4)	14 249 (6.8)
Alcohol use disorders	2383 (2.4)	2469 (2.2)	4852 (2.3)

Results are expressed as median (IQR) or number (%).

During the study period, 1 555 959 French adults of the general population were hospitalised for an incident acute arterial event with a similar distribution of acute arterial events at first hospitalisation compared with patients with IBD (see online supplementary table 3). Crude incidence rates are provided by age groups for patients with IBD and the general population in online supplementary figure 2.

The risk of acute arterial events was significantly increased in patients with IBD compared with the general population (SIR, 1.19; 95% CI 1.16 to 1.22) (table 2). Similar findings were found for ischaemic heart disease (SIR, 1.17; 95% CI 1.13 to 1.21), cerebrovascular disease (SIR, 1.19; 95% CI 1.13 to 1.24) and peripheral artery disease (SIR, 1.27; 95% CI 1.17 to 1.37).

The risk of acute arterial events was higher in patients with CD as compared with patients with UC (SIR 1.35; 95% CI 1.30 to 1.41 vs 1.10; 95% CI 1.06 to 1.13, respectively). The risk estimates were statistically significant for all arterial disease groups, except for peripheral artery disease in patients with UC (SIR 1.07; 95% CI 0.96 to 1.18). In patients with CD, the highest risk was observed for peripheral artery disease (SIR 1.65; 95% CI 1.46 to 1.83), while the risks of ischaemic heart disease and cerebrovascular disease were comparable. In patients with UC,

risk of ischaemic heart disease and cerebrovascular disease were also comparable (table 2). SIRs for arterial disease subgroups according to IBD subtype are provided in online supplementary table 4.

Subgroup analyses according to age, sex and cardiovascular risk factors

SIRs of acute arterial events are provided by age groups and IBD subtype in figure 2 and online supplementary table 5. In patients with CD, the highest risk was observed in patients aged from 15 to 34 years (SIR, 1.42; 95% CI 1.09 to 1.75) and patients aged from 35 to 54 years (SIR, 1.58; 95% CI 1.45 to 1.70). The risk decreased for later age, while remaining statistically significant (SIR of patients aged from 55 to 74 years and aged of more than 75 years, 1.38; 95% CI 1.30 to 1.47 and 1.13; 95% CI 1.03 to 1.22, respectively). In patients with UC, the highest risk was observed in patients aged from 15 to 34 years (SIR, 1.65; 95% CI 1.20 to 2.10). Conversely, the risk of acute arterial events was not increased in patients aged from 35 to 54 years (SIR, 1.02; 95% CI 0.93 to 1.11) nor in patients older than 75 years (SIR, 1.05; 95% CI 0.99 to 1.11), whereas

Table 2 SIRs of acute arterial events according to IBD subtype

	Person-years	Reported cases	Expected cases	SIR (95% CI)	p Value
All patients with IBD	595 202				
All acute arterial events		5554	4679	1.19 (1.16 to 1.22)	<0.0001
Ischaemic heart disease		3177	2706	1.17 (1.13 to 1.21)	<0.0001
Cerebrovascular disease		1715	1446	1.19 (1.13 to 1.24)	<0.0001
Peripheral artery disease		662	521	1.27 (1.17 to 1.37)	<0.0001
Patients with CD	287 134				
All acute arterial events		2244	1658	1.35 (1.30 to 1.41)	<0.0001
Ischaemic heart disease		1253	956	1.31 (1.24 to 1.38)	<0.0001
Cerebrovascular disease		694	523	1.33 (1.23 to 1.43)	<0.0001
Peripheral artery disease		297	180	1.65 (1.46 to 1.83)	<0.0001
Patients with UC	308 068				
All acute arterial events		3310	3021	1.10 (1.06 to 1.13)	<0.0001
Ischaemic heart disease		1924	1750	1.10 (1.05 to 1.15)	<0.0001
Cerebrovascular disease		1021	923	1.11 (1.04 to 1.17)	<0.01
Peripheral artery disease		365	341	1.07 (0.96 to 1.18)	0.21

SIR, standardised incidence ratio.

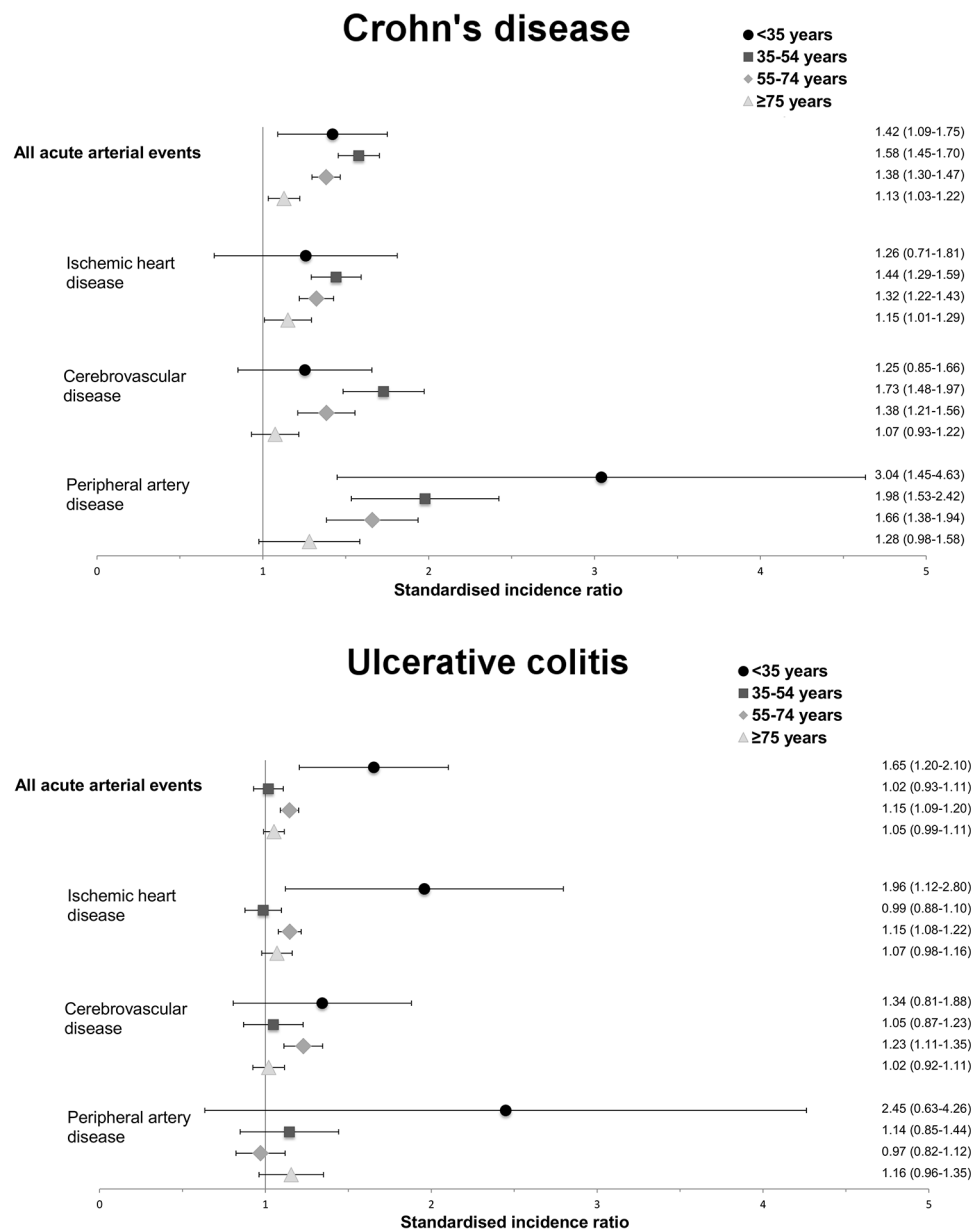


Figure 2 Standardised incidence ratios of all acute arterial events according to IBD subtype and age groups.

patients aged from 55 to 74 years were at increased risk (SIR, 1.15; 95% CI 1.09 to 1.20).

Compared with the general population, women with IBD were at higher risk than men with IBD for all arterial disease groups in both CD and UC, with the highest risk in women with CD (see online supplementary figure 3). Among patients without any identified cardiovascular risk factors, an increased risk of acute arterial events was maintained in patients with CD (SIR, 1.26; 95% CI 1.19 to 1.34), whereas no increased risk was observed in patients with UC (SIR, 0.96; 95% CI 0.92 to 1.01). The risk increased progressively with an increasing number of cardiovascular risk factors (see online supplementary figure 4).

Impact of IBD activity on the risk of acute arterial events

Among 97 348 patients with CD and 112 181 patients with UC included in this analysis, 22 700 patients with CD (23.3%) and 15 747 patients with UC (14%) were hospitalised for IBD

activity during follow-up. Median (IQR) duration of active disease period in patients with CD and UC was 180 (90–205) and 92 (90–180) days, accounting for 4% and 2.1% of total follow-up, respectively. Among patients hospitalised for IBD activity, period of active disease accounted for 24.8% of total follow-up, while 7857 patients with CD (34.6%) and 3967 patients with UC (24.7%) were hospitalised more than once. Surgical procedures for IBD were performed in 24.9% of active disease periods.

In patients with CD, disease activity was associated with an increased risk of acute arterial events (HR, 1.74; 95% CI 1.44 to 2.09). This increased risk remained statistically significant for all arterial disease groups and the magnitude of risk was highest for peripheral artery disease (figure 3). In patients with UC, disease activity was also associated with an increased risk of acute arterial events (HR, 1.87; 95% CI 1.58 to 2.22); however, the risk of cerebrovascular disease was not statistically significant (figure 3).

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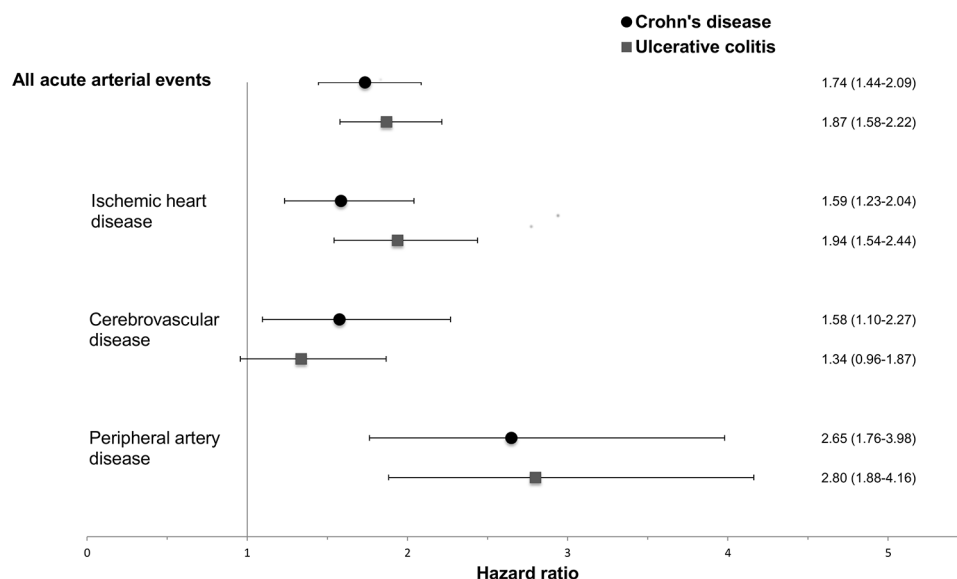


Figure 3 Impact of disease activity (3-month periods before and after IBD-related hospitalisation or surgery) on the risk of acute arterial events according to IBD subtype. Legend: adjusted for age at cohort entry, sex, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidaemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders.

Regarding other predictive factors, male sex and all traditional cardiovascular risk factors except obesity were, as expected, associated with an increased risk of acute arterial events (table 3).

Sensitivity analyses confirmed the robustness of the main results (see online supplementary table 6). Results were consistent across age groups. When the definition of duration of active disease was reduced to 1 month before and after an IBD-related hospitalisation, the HR for acute arterial event at the time of active disease increased in both patients with CD and UC to 1.91 (95% CI 1.48 to 2.48) and 2.03 (95% CI 1.59 to 2.59), respectively. When the definition of the duration of active disease was increased to 6 months before and after an IBD-related hospitalisation, the HR for acute arterial event at the time of active disease was reduced in patients with CD and UC to 1.46 (95% CI 1.25 to 1.71) and 1.69 (95% CI 1.46 to 1.95), respectively. Similar results were observed in the sensitivity analyses considering only cardiovascular risk factors present at cohort entry,

censoring follow-up to 30 September 2013 and excluding the postoperative period from the active disease definition.

DISCUSSION

Our study demonstrated that the overall risk of acute arterial events is increased in patients with IBD compared with the general population. The risk was higher in patients with CD compared with patients with UC. In patients with CD, the increased risk was more prominent for younger patients with the highest risk in those aged from 35 to 54 years. For older patients, the SIRs appeared lower but the risk still remained increased compared with the general population. In patients with UC, the risk was increased in patients younger than 35 years and in those aged from 55 to 74 years. Similarly to the observation in patients with CD, the highest risk was observed in younger patients. Lastly, we demonstrated that the disease activity was independently associated with an increased risk of acute arterial events in both CD and UC.

With this study, we have provided new evidence on the association between acute arterial events and inflammatory bowel diseases. The magnitude of the risk observed in our study for ischaemic heart disease and cerebrovascular disease was similar to previous findings published in a recent meta-analysis.⁶ Conversely, to the data published in the latter meta-analysis, we revealed an increased risk of peripheral artery disease in patients with IBD. However, the meta-analysis only included 148 patients with peripheral artery disease, thus power limitations might explain the different findings. Moreover, systemic inflammation may be higher in peripheral artery disease than in coronary artery disease,¹⁸ suggesting that the impact of inflammation may be higher in peripheral artery disease.

Several pathophysiological mechanisms, including structural and functional vascular changes, as well as biochemical and genetic changes may be involved in the risk of acute arterial events in patients with IBD.¹⁹ Besides an increased carotid intima-media thickness and arterial stiffness,^{20 21} microvascular endothelial dysfunction was observed in patients with IBD.²²

Table 3 Predictive factors of acute arterial events according to IBD subtype: Cox multivariate analysis

	HR (95% CI)	
	CD	UC
Male sex	1.71 (1.56 to 1.87)	2.08 (1.93 to 2.24)
Disease activity (3-month periods before and after IBD-related hospitalisation or surgery)	1.74 (1.44 to 2.09)	1.87 (1.58 to 2.22)
Cardiovascular risk factors		
Hypertension	1.18 (1.05 to 1.32)	1.24 (1.14 to 1.35)
Hyperlipidaemia	1.34 (1.16 to 1.56)	1.16 (1.05 to 1.30)
Diabetes mellitus	1.32 (1.14 to 1.52)	1.48 (1.33 to 1.64)
Obesity	1.02 (0.86 to 1.20)	1.01 (0.89 to 1.15)
Tobacco smoking	1.82 (1.58 to 2.09)	1.49 (1.28 to 1.74)
Alcohol use disorders	1.52 (1.26 to 1.84)	1.51 (1.27 to 1.79)

Adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidaemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders.

These pathophysiological mechanisms may also support the hypothesis of a more pronounced increased risk of overall acute arterial events in CD as compared with UC. Patients with CD are more prone to a higher degree of systemic inflammation compared with patients with UC, among others evidenced by higher level of C-reactive protein production^{23–25} and serum concentration of interleukin 6.²⁶ Interestingly, these markers of inflammation are increased in both IBD and atherosclerosis.¹⁶ The difference in risk estimates between patients with CD and patients with UC could also be linked to the prothrombotic effect of hyperhomocysteinaemia and low vitamin B6 plasma level, which may be related to malabsorption in patients with CD.^{27 28} Lastly, polymorphisms in NOD2/CARD15 have been associated with both coronary atherosclerosis and IBD with a stronger link with CD.²⁹ NOD2/CARD15 variants may predispose to CD.³⁰

Higher risk of acute arterial events observed in younger patients with IBD may reflect the different impact of inflammation across age groups. Indeed, patients diagnosed with CD at young age are more likely to have a severe disease course³¹ and age ranges associated with an increased risk in patients with UC correspond to peak ages for UC onset.^{32 33} Moreover, disease activity tends to decrease over time.³⁴ Traditional cardiovascular risk factors in older patients may also potentially outweigh the risk related to systemic inflammation owing to IBD.

Compared with the general population of similar sex and age, women were at higher risk of acute arterial events than men, whereas male sex was, as would be expected, an independent predictive factor of acute arterial event in patients with IBD after adjustment of all cardiovascular risk factors. It suggests that the risk differences compared with the general population between men and women may be related to the higher prevalence of traditional cardiovascular risk factors in men compared with women.

This study has several strengths. Using nationwide register-based data on the entire French population provided a large sample size allowing for sufficient power to perform comprehensive and multiple subgroups analyses on the risk of acute arterial events, identify its independent drivers and thus, strengthen our findings. Additionally, several studies have found the reliability, validity and accuracy of medical coding in the PMSI database for various diseases to be good.^{35–39} In particular, stroke as a primary discharge diagnosis code was associated with a positive predictive value of about 90%.⁴⁰ Regarding ischaemic heart disease, the annual incidence rate observed in the general population was in the range of those recently reported in three French regional registries, thus supporting a high validity of the data.⁴¹

This study also has some limitations that need to be discussed. Cardiovascular risk factors were identified during hospitalisation. Rates of cardiovascular risk factors, including tobacco smoking, may be therefore underestimated,⁴² while tobacco smoking may partly account in differences between CD and UC. However, the increased risk of acute arterial events was maintained in patients with CD without traditional cardiovascular risk factors compared with the general population. Disease activity was also associated with an increased risk of acute arterial events in both CD and UC after adjustment of all cardiovascular risk factors recorded. Furthermore, patients with CD had a nearly twofold increase in periods of disease activity compared with patients with UC. Despite the underestimation of tobacco smoking, it may highlight the fact that systemic inflammation is one of the trigger of acute arterial events in patients with IBD and the increased inflammatory burden in patients with CD may account for differences between CD and UC. Furthermore, adjustment for region of residence may to some extent have captured the effect of tobacco smoking, since the prevalence

of tobacco smoking in France differs according to the region of residence.⁴³

The definition of active disease was based on IBD-related hospitalisation. Thus, it excludes mild and moderate flares managed in an outpatient setting and treated with regimens such as aminosaliclates. Hence, the risks assessed in our study relate to flares severe enough to require hospitalisation. These flares may be associated with high systemic inflammation, and further studies are needed to assess the risk related to mild and moderate flares managed in an outpatient setting. However, surgical procedures were performed in a minority of hospitalisations and we reported consistent findings after exclusion of the postoperative period from the active disease definition, which may exclude the most severe flares. Additionally, active disease was arbitrarily defined as the 3 months before and after an IBD-related hospitalisation or surgery, while the true duration of risk would vary between individuals. However, we reported consistent findings in sensitivity analyses varying active disease duration.

Data on treatment modalities were not included in the analysis. Therefore, we were not able to use corticosteroids exposure as a surrogate marker of active disease nor to adjust or stratify on the different treatment options. Antitumour necrosis factor (TNF) agents reduce systemic inflammation and could decrease cardiovascular events and related mortality in patients with IBD, which has been suggested in patients with rheumatoid arthritis.⁵ Further studies are therefore required to assess the impact of treatment on the risk of acute arterial events in patients with IBD.

Until now, there has been no validation study of the ICD-10 codes related to IBD in the PMSI. However, a similar cohort from the same inpatient database and including outpatient database has been extensively described and provides evidence on the validity of IBD diagnoses in these databases.⁴⁴

In conclusion, this nationwide population-based cohort study including more than 200 000 patients diagnosed with IBD reported an increased risk of acute arterial events in patients with IBD. We determined that the risk was the highest in patients with CD and in young patients compared with the corresponding persons of the general population. We also established a clear link between IBD activity and the risk of acute arterial events. Overall, this study supports the increasing concept that a tight control of inflammation is crucial in patients with IBD to avoid IBD-related systemic complications. For arterial diseases and IBD, the impact of therapies, including anti-TNFs, still has to be addressed.

Collaborators Collaborators of the BERENICE study group are the following: Laurent Beaugerie, Anne-Marie Bouvier, Anne Buisson, Franck Carbonnel, Fabrice Carrat, Jacques Cosnes, Corinne Gower-Rousseau, Julien Kirchgesner, Alain Olympie, Laurent Peyrin-Biroulet, Jean-François Rahier, Frank Ruemmele, Michaël Schwarzingier, Tabassome Simon, Yazdan Yazdanpanah.

Contributors JK: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis. LB: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. FC: analysis and interpretation of data, critical revision of the manuscript for important intellectual content. NNA: analysis and interpretation of data, critical revision of the manuscript for important intellectual content. TJ: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. MS: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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Competing interests LB has received lecture fees from Abbott, Abbvie, MSD, Ferring Pharmaceuticals, Janssen, and research support from Abbott, Biocodex and Ferring Pharmaceuticals. NNA has received lecture fees from MSD and Ferring. MS is an employee of Translational Health Economics Network (THEN), Paris, France that received research grants of Abbvie, Gilead, Merck and co, Novartis, outside and unrelated to the submitted work.

Patient consent All data used in this study only contained anonymous patient records.

Ethics approval The French Data Protection Agency (CNIL)

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All analyses are included in the main manuscript or online supplementary material.

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Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study

Julien Kirchgesner, Laurent Beaugerie, Fabrice Carrat, Nynne Nyboe Andersen, Tine Jess and Michaël Schwarzingen

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Supplementary material

Supplementary Table 1. Exclusion criteria and outcomes

Comorbidities prior to cohort entry	ICD-10 codes	French Medical Common Procedure Coding System
Exclusion criteria		
Ischemic heart disease	I20-I25, T820, T822, T823, T826, T827 Z45.0, Z86.71, Z95 (except Z95.8, Z95.9)	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	I60-I66, G45, G460-G462, I670, I671, I68, I69, Z86.60, Z86.70	Cerebral angiography with arterial dilation or embolization Angiography (excluding coronary catheterization, cerebral and mesenteric angiography) with arterial dilation; Peripheral artery bypass
Peripheral artery disease	I74	
Heart Failure	I50	-
Atrial fibrillation	I48	-
Cardiomyopathies	I42-I43	-
Outcomes		
Ischemic heart disease	I20-I25	Coronary catheterization; CABG
Myocardial infarction	I21-I22	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	I60-I64, G45	Cerebral angiography with arterial dilation or embolization
Stroke	I60-I64 (except I63.6)	Cerebral angiography with arterial dilation or embolization Angiography (excluding coronary catheterization, cerebral and mesenteric angiography) with arterial dilation; Peripheral artery bypass
Peripheral artery disease	I74	

Supplementary Table 2. Cardiovascular risk factors and variables related to IBD activity

Covariates	ICD-10 codes	French Medical Common Procedure Coding System
Cardiovascular risk factors		
Hypertension	I10-I13, I15	-
Hyperlipidemia	E78.0-E78.5	-
Diabetes mellitus	E10-E14, M14.2, M14.6, N08.3, H28.0, H36.0, G59.0, G63.2, G73.0, G99.0, I79.2	-
Obesity	E66	-
Tobacco smoking	F17, Z71.6, Z72.0, T65.2	-
Alcohol use disorders	F10.1, F10.24, F10.25, F10.26, F10.3, F10.4, Z50.2, Z71.4, Z72.1, E24.4, E51.1, K70x, G31.2, G62.1, G72.1, I42.6, K29.2, K85.2, K86.0, F10.5, F10.6, F10.7, F10.8, F10.9, F10.20, F10.21, F10.22, F10.23	-
Digestive endoscopy	-	Colonoscopy, Upper GI endoscopy, Capsule Endoscopy
Hospitalisation related to IBD		
IBD	K50, K51	-
Occlusion	K56	-
Fistula, perforation	K63.1, K63.2	-
Abscess	K63.0	-
Perianal complications	K60, K61	-
Surgery related to IBD	-	Colectomy, Intestinal resection, Abscess drainage, Surgical procedure related to anal abscess or fistula

Supplementary Table 3.Characteristics of patients with acute arterial events among patients with IBD and the French general population

	Crohn's disease n = 2244	Ulcerative colitis n = 3310	IBD Total N = 5554	French general population n= 1,555,959
Male sex	1208 (53.8)	2137 (64.6)	3310 (59.6)	945,396 (60.8)
Age at event (years)	61 (50-73)	67 (57-77)	65 (55-75)	68 (57-78)
Acute arterial event subtype				
Ischemic heart disease	1253 (55.9)	1924 (58.1)	3177 (57.2)	884,457 (56.9)
Myocardial infraction	410 (18.3)	680 (20.5)	1090 (19.6)	326,115 (21.0)
Cerebrovascular disease	694 (30.9)	1021 (30.9)	1715 (30.9)	500,138 (32.1)
Stroke	626 (27.9)	915 (27.6)	1541 (27.7)	452,544 (29.1)
Peripheral artery disease	297 (13.2)	365 (11.0)	662 (11.9)	171,364 (11.0)
Cardiovascular risk factors recorded precluding acute arterial events				
Hypertension	688 (30.7)	1202 (36.3)	1890 (34.0)	361,622 (23.2)
Hyperlipidemia	244 (10.9)	452 (13.7)	696 (12.5)	129,389 (8.3)
Diabetes mellitus	258 (11.5)	509 (15.4)	767 (13.8)	160,061 (10.3)
Obesity	175 (7.8)	279 (8.4)	454 (8.2)	81,370 (5.2)
Tobacco smoking	279 (12.4)	200 (6.0)	479 (8.6)	67,111 (4.3)
Alcohol use disorders	133 (5.9)	159 (4.8)	292 (5.3)	51,707 (3.3)
Results are expressed as median (interquartile range) or number (%)				

Supplementary Table 4. Standardised incidence ratios of arterial events according to IBD subtype

	Person-years	Reported cases	Expected cases	SIR (CI 95%)	P value
All IBD patients	595,202				
All acute arterial events		5554	4679	1.19 (1.16-1.22)	<.0001
Ischemic heart disease		3177	2706	1.17 (1.13-1.21)	<.0001
Myocardial infraction		1090	1004	1.09 (1.02-1.15)	<0.01
Cerebrovascular disease		1715	1446	1.19 (1.13-1.24)	<.0001
Stroke		1541	1302	1.18 (1.12-1.24)	<.0001
Peripheral artery disease		662	521	1.27 (1.17-1.37)	<.0001
Crohn's disease patients	287,134				
All acute arterial events		2244	1658	1.35 (1.30-1.41)	<.0001
Ischemic heart disease		1253	956	1.31 (1.24-1.38)	<.0001
Myocardial infraction		410	351	1.17 (1.05-1.28)	<0.01
Cerebrovascular disease		694	523	1.33 (1.23-1.43)	<.0001
Stroke		626	470	1.33 (1.23-1.44)	<.0001
Peripheral artery disease		297	180	1.65 (1.46-1.83)	<.0001
Ulcerative colitis patients	308,068				
All acute arterial events		3310	3021	1.10 (1.06-1.13)	<.0001
Ischemic heart disease		1924	1750	1.10 (1.05-1.15)	<.0001
Myocardial infraction		680	653	1.04 (0.96-1.12)	0.30
Cerebrovascular disease		1021	923	1.11 (1.04-1.17)	<0.01
Stroke		915	832	1.10 (1.03-1.17)	<0.01
Peripheral artery disease		365	341	1.07 (0.96-1.18)	0.21

Supplementary Table 5. Standardised incidence ratios of all arterial events according to IBD subtype and age category

	Person-years	Reported cases	Expected cases	SIR (CI 95%)	P value
Crohn's disease patients					
< 35 years	104,721				
All acute arterial events		71	50	1.42 (1.09-1.75)	0.01
Ischemic heart disease		20	16	1.26 (0.71-1.81)	0.36
Myocardial infraction		6	5	1.31 (0.26-2.35)	0.56
Cerebrovascular disease		37	30	1.25 (0.85-1.66)	0.22
Stroke		30	25	1.22 (0.78-1.66)	0.32
Peripheral artery disease		14	5	3.04 (1.45-4.63)	0.01
35-54 years	114,833				
All acute arterial events		621	394	1.58 (1.45-1.70)	<.0001
Ischemic heart disease		353	245	1.44 (1.29-1.59)	<.0001
Myocardial infraction		127	96	1.32 (1.09-1.55)	<0.01
Cerebrovascular disease		192	111	1.72 (1.48-1.97)	<.0001
Stroke		174	98	1.77 (1.51-2.03)	<.0001
Peripheral artery disease		76	39	1.97 (1.53-2.42)	<.0001
55-74 years	53,816				
All acute arterial events		1013	735	1.38 (1.29-1.46)	<.0001
Ischemic heart disease		627	475	1.32 (1.22-1.42)	<.0001
Myocardial infraction		182	166	1.10 (0.94-1.26)	0.22
Cerebrovascular disease		247	179	1.38 (1.21-1.55)	<.0001
Stroke		219	155	1.41 (1.22-1.60)	<.0001
Peripheral artery disease		139	84	1.66 (1.38-1.93)	<.0001
≥ 75 years	13,765				
All acute arterial events		539	479	1.13 (1.03-1.22)	0.01
Ischemic heart disease		253	220	1.15 (1.01-1.29)	0.04
Myocardial infraction		95	85	1.12 (0.89-1.34)	0.31
Cerebrovascular disease		218	203	1.07 (0.93-1.22)	0.32
Stroke		203	191	1.06 (0.91-1.21)	0.41
Peripheral artery disease		68	53	1.28 (0.97-1.58)	0.07
Ulcerative colitis patients					
< 35 years	61,942				
All acute arterial events		52	31	1.65 (1.20-2.10)	<0.01
Ischemic heart disease		21	11	1.96 (1.12-2.79)	0.03
Myocardial infraction		7	3	2.22 (0.57-3.86)	0.15
Cerebrovascular disease		24	18	1.34 (0.80-1.88)	0.21
Stroke		16	15	1.08 (0.55-1.60)	0.78
Peripheral artery disease		7	3	2.44 (0.63-4.26)	0.12

35-54 years	119,822				
All acute arterial events	497	489	1.02 (0.93-1.11)	0.72	
Ischemic heart disease	309	314	0.98 (0.88-1.09)	0.79	
Myocardial infraction	101	127	0.79 (0.64-0.95)	<0.01	
Cerebrovascular disease	131	125	1.05 (0.87-1.23)	0.62	
Stroke	118	111	1.06 (0.87-1.25)	0.52	
Peripheral artery disease	57	50	1.14 (0.85-1.44)	0.35	
55-74 years	96,526				
All acute arterial events	1660	1452	1.14 (1.09-1.20)	<.0001	
Ischemic heart disease	1071	936	1.14 (1.08-1.21)	<.0001	
Myocardial infraction	371	333	1.11 (1.00-1.23)	0.05	
Cerebrovascular disease	424	346	1.23 (1.11-1.34)	<.0001	
Stroke	369	299	1.23 (1.11-1.36)	<.0001	
Peripheral artery disease	165	170	0.97 (0.82-1.12)	0.68	
≥ 75 years	29,778				
All acute arterial events	1101	1049	1.05 (0.99-1.11)	0.12	
Ischemic heart disease	523	490	1.07 (0.98-1.16)	0.15	
Myocardial infraction	201	189	1.06 (0.92-1.21)	0.40	
Cerebrovascular disease	442	434	1.02 (0.92-1.11)	0.71	
Stroke	412	407	1.01 (0.92-1.11)	0.79	
Peripheral artery disease	136	118	1.15 (0.96-1.35)	0.12	

Supplementary Table 6. Sensitivity analyses on the hazard ratios for acute arterial events according to IBD subtype.

Disease activity (3-month periods before and after IBD-related Hospitalisation discharge or surgery)		
	HR (95% CI)	
	Crohn's disease	Ulcerative colitis
All acute arterial events		
Main analysis	1.74 (1.44-2.09)	1.87 (1.58-2.22)
Age at cohort entry		
18-54 years	2.22 (1.67-2.96)	1.87 (1.23-2.84)
≥ 55 years	1.52 (1.20-1.93)	1.88 (1.56-2.26)
Assessment of cardiovascular risk factors at cohort entry	1.83 (1.52-2.20)	1.95 (1.65-2.31)
Exclusion of postoperative period as period of disease activity	1.65 (1.36-2.00)	1.78 (1.49-2.13)
Follow-up censored at 30 September 2013	1.78 (1.47-2.15)	1.92 (1.62-2.29)
Abbreviation: HR, hazard ratio.* Adjusted for age at cohort entry, sex, region of residence, year of cohort entry, disease activity prior to cohort entry, hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders.		

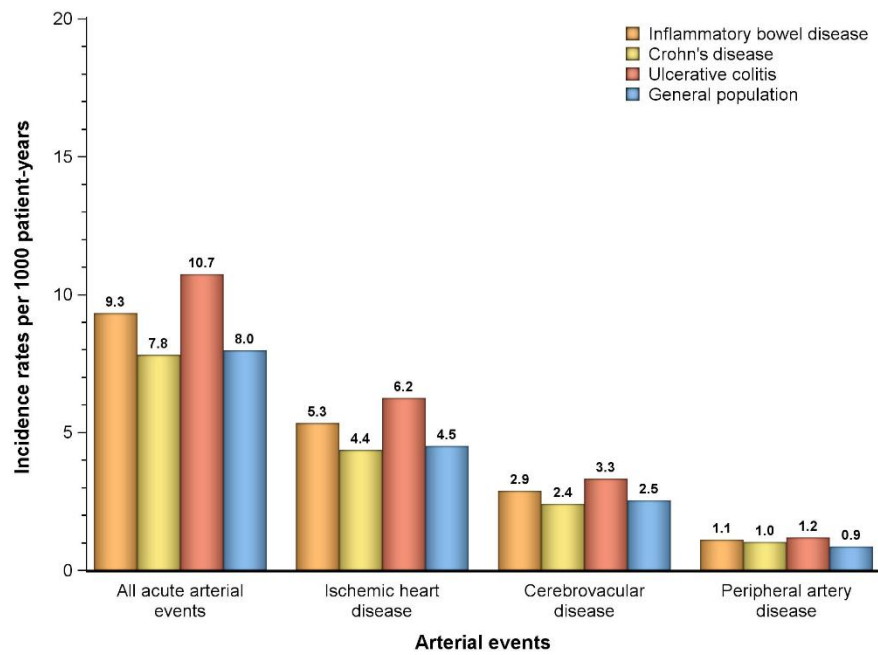
Figure Legends :

Supplementary figure 1: Crude incidence rates of acute arterial events in patients with IBD and the general population

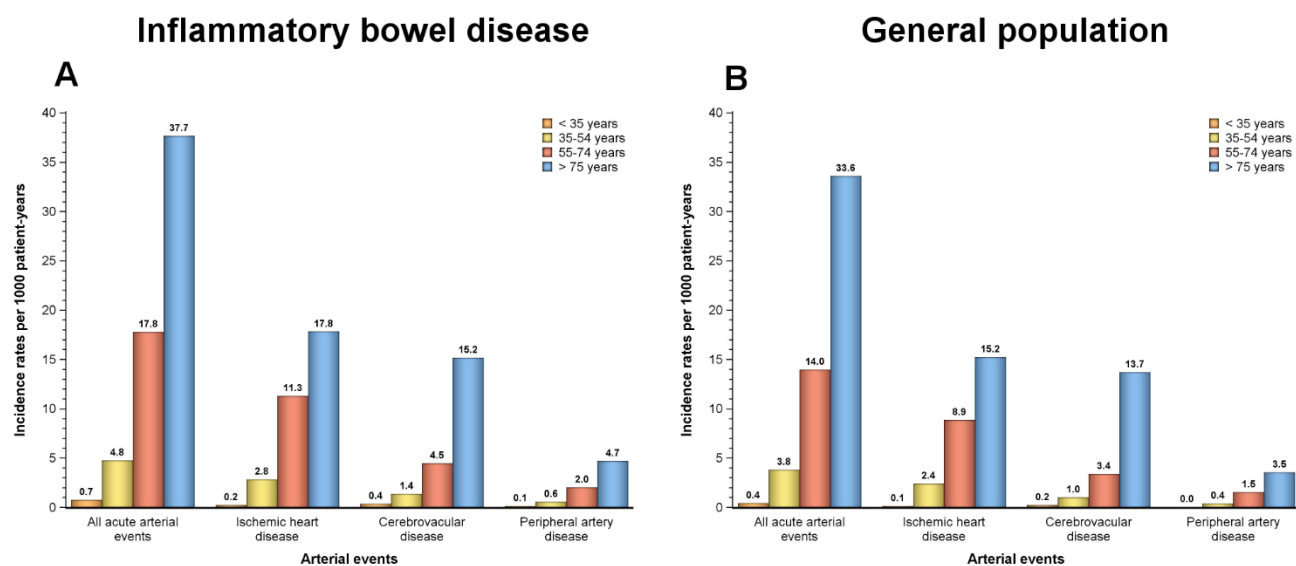
Supplementary figure 2: Crude incidence rates of acute arterial events according to age in patients with IBD (A) and the general population (B)

Supplementary figure 3: Standardised incidence ratios of all acute arterial events according to IBD subtype and sex

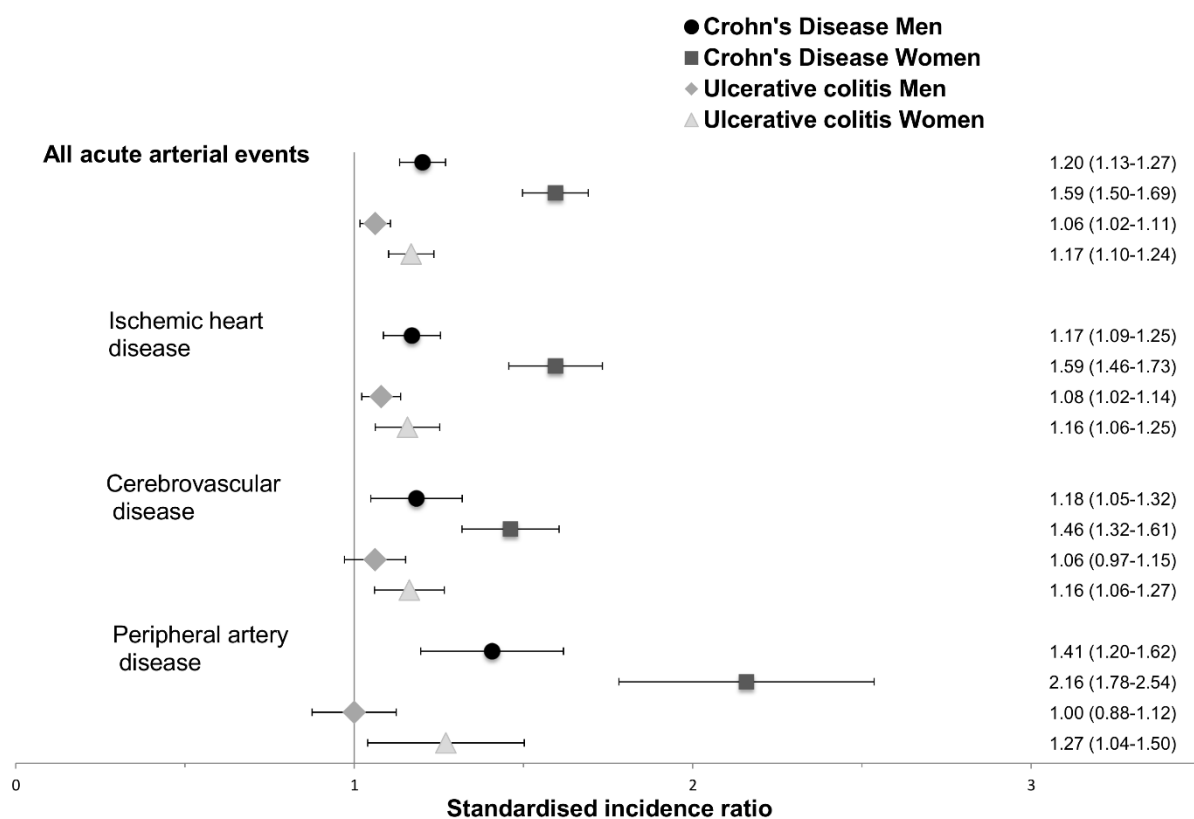
Supplementary figure 4: Standardised incidence ratios of all acute arterial events according to IBD subtype and number of traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders)



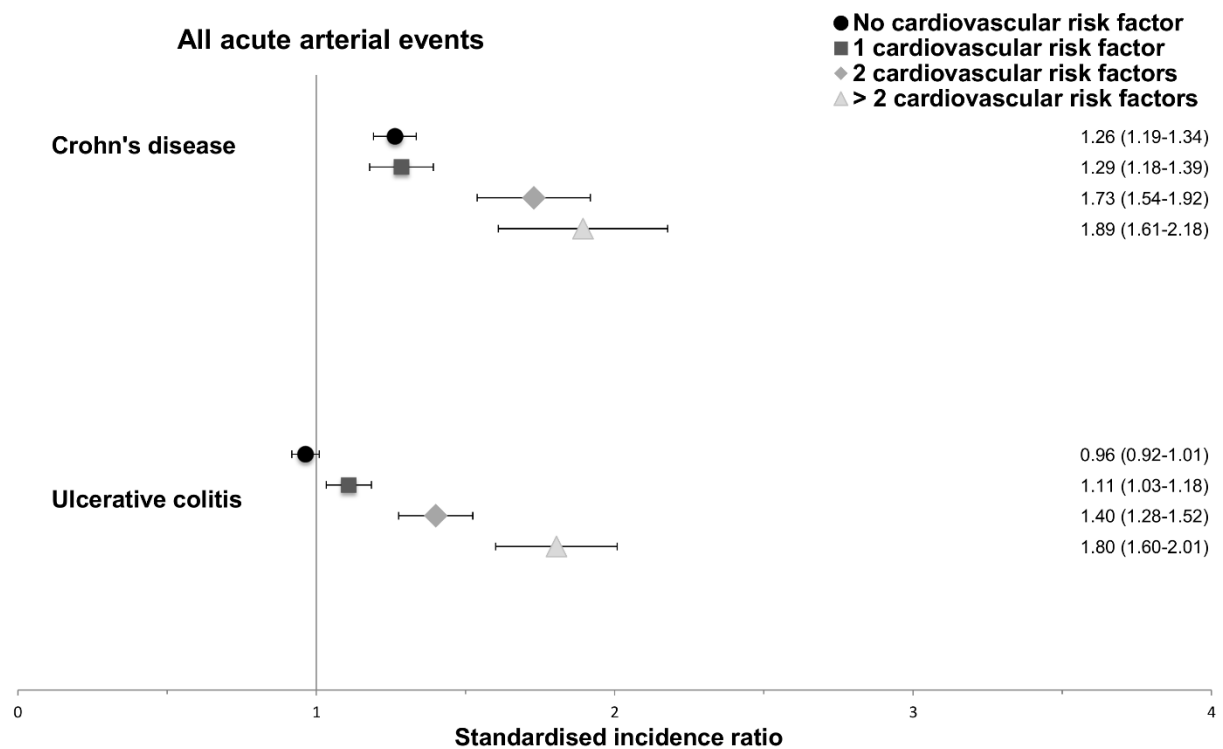
Supplementary figure 1: Crude incidence rates of acute arterial events in patients with IBD and the general population



Supplementary figure 2: Crude incidence rates of acute arterial events according to age in patients with IBD (A) and the general population (B)



Supplementary figure 3: Standardised incidence ratios of all acute arterial events according to IBD subtype and sex



Supplementary figure 4: Standardised incidence ratios of all acute arterial events according to IBD subtype and number of traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking and alcohol use disorders)

2. Discussion

This study provides new evidence of an increased risk of acute arterial events in IBD, and further analyzes the impact of key factors for risk stratification, such as age, sex, IBD subtype and disease activity.

The impact of systemic inflammation and traditional cardiovascular risk factors may drive the differences observed in subgroups analyses. The increased risk in patients with CD compared to patients with UC may be related to a higher degree of systemic inflammation, despite the underestimation of tobacco smoking in this population. Similarly, differences observed in SIR between sex and age categories may be related to the distribution of traditional cardiovascular risk factors, more prominent in men and older ages, since the addition of traditional cardiovascular risk factors may potentially outweigh the risk related to systemic inflammation owing to IBD. Disease activity leading to systemic inflammation may be also higher during the first years after diagnosis in UC and patients with CD diagnosed at young age.

Identification criteria of IBD diagnosis differed from the first study based on the SNIIRAM database, since the PMSI database did not include neither information on LTD, nor pharmacy claims. It notably explains differences observed in IBD subtype between the two studies, since a higher proportion of patients with uncertain diagnosis of IBD may be coded as a diagnosis of UC. However, all subgroups and sensitivity analyses were consistent, suggesting that the inclusion of a minor proportion of false IBD diagnoses may not alter the association observed.

We demonstrated that disease activity may be an independent risk factor of acute arterial events, in both UC and CD. Since non-cardiac surgery is associated with a postoperative morbidity related to cardiac complications, we performed a sensitivity

analysis excluding the postoperative period from the active disease definition and the results were similar.

Finally, strategies for optimizing control of inflammation should be assessed to decrease the risk of acute arterial events in this patient population.

IMPACT OF TREATMENT ON THE RISK OF ACUTE ARTERIAL EVENTS

Having concluded that patients with IBD are at increased risk of acute arterial events compared with the general population, the last objective of the thesis was to assess the impact of immunosuppressive treatment on the risk of acute arterial events in patients with IBD. This part relies on the analysis of the SNIIRAM 2010-2014.

All patients affiliated to the French national health insurance diagnosed with IBD were included from 2010 to 2011 and followed up until 31 December 2014. Patients with a single hospital discharge diagnosis of IBD and no pharmacy claim for any IBD medication (aminosalicylates, enteral budesonide, thiopurines, and anti-TNFs), were considered to have a non-confirmed diagnosis of IBD and therefore excluded from the main analysis. Exclusion criteria were similar as the previous study, but were identified not only through hospitalisation discharge summaries, but also through notification of LTDs. Outcomes were also similar as the previous study, identified through hospitalisation, procedures and LTDs. Risks of acute arterial events were compared between thiopurines and anti-TNFs exposed and unexposed patients with marginal structural Cox proportional hazard models adjusting for baseline and time-varying demographics, medications, and comorbidities, including IBD disease activity.[188]

A total of 178 360 IBD patients were included (54% females, mean age at cohort entry 46.3 years, 50.7% Crohn's disease). Among them, 22.8%, 13.5% and 5.7% were exposed to thiopurine monotherapy, anti-TNF monotherapy and combination therapy during follow-up, respectively. Overall, 4376 incident acute arterial events occurred (incidence rates: 5.6 per 1000 PY, person-years), including 2204 (50.4%) ischemic heart diseases, 1476 (33.7%) cerebrovascular diseases, and 696 (15.9%) peripheral

artery diseases. Exposure to thiopurine monotherapy, anti-TNF monotherapy and combination therapy were all numerically associated with a decreased risk of acute arterial event compared to unexposed patients, but the difference was only statistically significant in patients exposed to combination therapy (HR, 0.91; 95% CI, 0.81-1.02; HR, 0.89; 95% CI, 0.76-1.04; HR, 0.81; 95% CI, 0.66-0.99, respectively). The magnitude in risk reduction was highest in men with CD exposed to combination therapy (HR, 0.58; 95% CI, 0.40-0.83).

1. Article: Exposure to combination therapy with thiopurines and anti-TNF agents is associated with reduced incidence of acute arterial events in patients with inflammatory bowel disease (IBD): a nationwide French cohort study.

Exposure to combination therapy with thiopurines and anti-TNF agents is associated with reduced incidence of acute arterial events in patients with inflammatory bowel disease (IBD): a nationwide French cohort study

Julien Kirchgesner (1,2), Nynne Nyboe Andersen (3,4), Fabrice Carrat (2,5), Michaël Schwarzingen (6,7), Tine Jess (3,8), Laurent Beaugerie (1,9) for the BERENICE study group^A

Short title: Acute arterial events and inflammatory bowel disease related treatment

(1) Department of Gastroenterology, AP-HP, Hôpital Saint-Antoine, Paris, France

(2) UMRS 1136, INSERM, UPMC Univ Paris 06, Sorbonne Universités, Paris, France

(3) Department of Epidemiology Research, Statens Serum Institute, Copenhagen, Denmark

(4) Department of Gastroenterology, Zealand University Hospital, Køge, Denmark

(5) Department of Public Health, AP-HP, Hôpital Saint-Antoine, Paris, France

(6) ERL 1057 INSERM/UMRS 7203 and GRC-UPMC 03, UPMC Univ Paris 06, Paris, France

(7) THEN, Translational Health Economics Network, Paris, France

(8) Department of Clinical Epidemiology, Bispebjerg Hospital, Copenhagen, Denmark

(9) Infection Antimicrobials Modeling & Evolution (IAME), UMR 1137, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Paris, France.

^A Collaborators of the BERENICE Study Group are listed at the end of the manuscript

Corresponding author: Julien Kirchgesner, Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75571 Paris CEDEX 12, France. Tel: +33 1 49 28 31 72, Fax: +33 1 49 28 31 88. E-mail: julien.kirchgesner@aphp.fr

Author Contributions:

Julien Kirchgesner: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis.

Nynne Nyboe Andersen: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

Fabrice Carrat: analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

Michael Schwarzingner: analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Tine Jess: study concept and design; analysis and interpretation of data; critical revision of the manuscript for important intellectual content

Laurent Beaugerie: study concept and design; analysis and interpretation of data; drafting of the manuscript; study supervision.

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Abstract

Introduction: Patients with inflammatory bowel disease (IBD) are at increased risk of acute arterial events, probably due to systemic inflammation leading to atherosclerosis. Anti-tumor necrosis factor agents (anti-TNFs) and thiopurines may, due to their anti-inflammatory properties, lower the risk of acute arterial events. The aim of this study was to assess the impact of thiopurines and anti-TNFs on the risk of acute arterial event in IBD patients.

Methods: Patients aged 18 years or older and affiliated to the French national health insurance with a diagnosis of IBD were followed from Jan 1, 2010 until Dec 31, 2014. The risks of acute arterial event were compared between thiopurines and anti-TNFs exposed and unexposed patients with marginal structural Cox proportional hazard models adjusting for baseline and time-varying demographics, medications, traditional cardiovascular risk factors, and comorbidities, including IBD disease activity.

Results: Among 178 360 patients with IBD (96 373 [54%] women; mean age at cohort entry 46.3 years [SD 16.4]; 90 423 [50.7%] with Crohn's disease), 4376 incident acute arterial events occurred (incidence rates: 5.6 per 1000 person-years), including 2204 (50.4%) ischemic heart diseases, 1476 (33.7%) cerebrovascular diseases, and 696 (15.9%) peripheral artery diseases. Compared to unexposed patients, exposure to thiopurine monotherapy, anti-TNF monotherapy and combination therapy were all numerically associated with a decreased risk of acute arterial events, but the difference was only statistically significant in patients exposed to combination therapy (hazard ratio [HR] 0.91; confidence interval 95% [0.81-1.02]; HR95%: 0.89 [0.76-1.04]; HR95%: 0.81 [0.66-0.99], respectively). The magnitude in risk reduction was highest in men with Crohn's disease exposed to combination therapy (HR95%: 0.58 [0.40-0.83]).

Conclusion: Exposure to combination therapy is associated with a decreased risk of acute arterial events in patients with IBD, particularly in men with Crohn's disease. Prevention of acute arterial events should be considered in the benefit-risk balance assessment of thiopurines and anti-TNFs in IBD patients.

Keywords: Inflammatory bowel disease, cardiovascular disease, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, thiopurines, anti-TNFs, combination therapy.

Abbreviations used in this paper: IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; PMSI: Programme de Médicalisation des Systèmes d'Information; ICD-10: WHO International Classification of Diseases, 10th revision.

INTRODUCTION

Patients with inflammatory bowel disease (IBD) are at increased risk of acute arterial events,[1,2] and disease activity was reported as an independent risk factor after adjustment for traditional cardiovascular risk factors.[2] This increased risk may be driven by systemic inflammation, known to be involved in atherosclerosis pathogenesis and associated to cardiovascular events.[3] Notably, the risk of cardiovascular disease is well established in other chronic inflammatory disorders such as rheumatoid arthritis (RA) in which systemic inflammation and disease activity were associated with cardiovascular events.[4,5] Anti-tumor necrosis factor agents (anti-TNFs) and thiopurines are effective in the treatment of patients with IBD and may lower the risk of acute arterial event due to their anti-inflammatory properties, as it is increasingly suggested with anti-TNFs in patients with RA.[6] Additionally, anti-TNFs may have a specific effect on atherosclerosis independently of their anti-inflammatory effect, since TNF- α is directly involved in atherosclerogenesis.[7] However, the impact of anti-TNFs and thiopurines on the risk of acute arterial events in patients with IBD remains largely unexplored, potentially due to a lack of statistical power in most IBD populations, as seen in previous studies.[8] As long as the potential protective effect of IBD related treatment is not well-established, efficient prevention strategy cannot be elaborated, whereas recommendations for cardiovascular risk management in patients with RA, ankylosing spondylitis and psoriatic arthritis have been published since 2010.[5] The aim of this study was to assess the impact of thiopurines and anti-TNFs on the risk of acute arterial events including ischemic heart disease, cerebrovascular disease and peripheral artery disease in patients with IBD.

MATERIALS AND METHODS

Data source

This cohort study was based on the French National Health Insurance database (*Système National d'Information Inter-Régimes de l'Assurance Maladie*, SNIIRAM),[9] which covers 95% of the French population with different insurance schemes based on employment situation. The general health insurance scheme covers employees in the industry, business and service sectors, public service employees and students, accounting for approximately 88% of the French population. Due to data availability and quality, only individuals insured by the general scheme were considered. Excluded insurance schemes cover specific professions and do not depend on comorbidities or medical conditions.

The SNIIRAM provides individual data on all drug reimbursements and outpatient medical care prescribed by healthcare professionals as well as individuals' status with respect to full reimbursement of care for severe long-term diseases (LTD),[9] including Crohn's disease (CD) and ulcerative colitis (UC). Using a unique anonymous identifier, information from the SNIIRAM is linked to the French national hospital discharge database which provides individual medical information on all hospital admissions in France, including discharge diagnoses (International Classification of Diseases, 10th edition [ICD-10]) and medical procedures performed. These databases have been used previously for large pharmacoepidemiological studies.[10–12]

Study population

The source population included all patients aged 18 years or older identified with IBD before 2014 from the French administrative health databases. Identification of IBD cases was based upon LTDs and/or hospitalization discharges including ICD-10 codes

of CD or UC. Patients with a single hospital discharge diagnosis of IBD and no pharmacy claim for any IBD medication (5-aminosalicylates, enteral budesonide, thiopurines [azathioprine and mercaptopurine], and anti-TNFs), were considered to have a non-confirmed diagnosis of IBD. We did not include corticosteroids except enteral budesonide in this definition, since they are widely prescribed apart from IBD. In case of multiple hospitalizations with ICD-10 codes related to both CD and UC, the most recent diagnosis at cohort entry was retained. Date of diagnosis was the first date of IBD-related in- or outpatient care. Patients diagnosed with IBD before January 1, 2010 were referred to as prevalent cases of IBD while patients identified between January 1, 2010 and December 31, 2011 accounted for incident cases of IBD. This cohort has been extensively described elsewhere.[12]

Patients with a history of acute arterial event or related cardiovascular disease, atrial fibrillation, heart failure, or cardiomyopathy, procedures related to cardiac electronic device, cardiac valve prosthesis, angiography, coronary catheterization, or coronary artery bypass grafting were excluded (based on data from hospitalization discharges, LTDs, and specific procedures, see details in supplementary Table 1).

Follow-up

Date of inclusion in the cohort was January 1, 2010 for prevalent cases and the date of IBD diagnosis for incident cases. Patients were followed until December 31, 2014, death, and occurrence of acute arterial event, whichever occurred first.

Drug exposure

In France, infliximab, adalimumab, and golimumab are dispensed in hospitals or private clinics. Adalimumab, golimumab, and thiopurines are dispensed by pharmacies for one month.[13] Patients who received infliximab were considered exposed for two months following the infusion, those who received adalimumab, golimumab or

thiopurines were considered exposed for one month following delivery. Combination therapy was defined as concomitant exposure to anti-TNFs and thiopurines.

Outcomes

Study outcome was the first occurring acute arterial event following cohort entry, defined by a primary discharge diagnosis or procedures specifically related to: (1) ischemic heart disease (including myocardial infarction); (2) cerebrovascular disease (including stroke); (3) peripheral artery disease, excluding acute mesenteric ischemia. We did not include acute mesenteric ischemia, since local intestinal rather than systemic inflammation may be associated with acute mesenteric ischemia in patients with IBD.[14,15] In case of full reimbursement of care for acute arterial event introduced before the first hospitalization or procedure related to acute arterial event, the date of disease onset specified for full reimbursement was defined as the date of acute arterial event occurrence. See Supplementary Table 2 for the according ICD-10 codes and procedure codes.

Covariates

Two groups of covariates were considered. Time-fixed covariates were measured at cohort entry and included sex, age, disease duration (≥ 10 years, 0-10 years, incident patients), exposure to methotrexate, aminosalicylates and antiplatelet drugs in the preceding 3 months, comorbidities (based on data from hospitalization discharges, LTDs, and specific procedures or treatments, see details in supplementary Table 1) including: history of respiratory chronic disease, chronic kidney disease, cirrhosis and portal hypertension, rheumatic disease, cancer, venous thromboembolism, HIV, and atherosclerosis, and traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco smoking, and alcohol use disorders). Time-varying covariates, including IBD activity as measured by exposure

to corticosteroids and occurrence of IBD-related hospitalization or surgery, were updated every six months during follow-up.

Statistical analysis

We used marginal structural Cox proportional hazard models[16] adjusted for the time-fixed and time-varying covariates listed above to compare the risks of acute arterial events in patients of each exposure group (thiopurine monotherapy, anti-TNF monotherapy, or combination therapy) to unexposed patients (either never exposed or past-exposed). Marginal structural models are appropriate in the presence of time-dependent covariates (such as exposure to corticosteroids and IBD activity) that might be associated with both exposure and outcomes[17,18] (time-dependent confounders) and could also be affected by past exposure to thiopurines and anti-TNFs. Weights calculation was performed as suggested by Cole and Hernan.[19] Detailed statistical method is provided in the supplementary appendix.

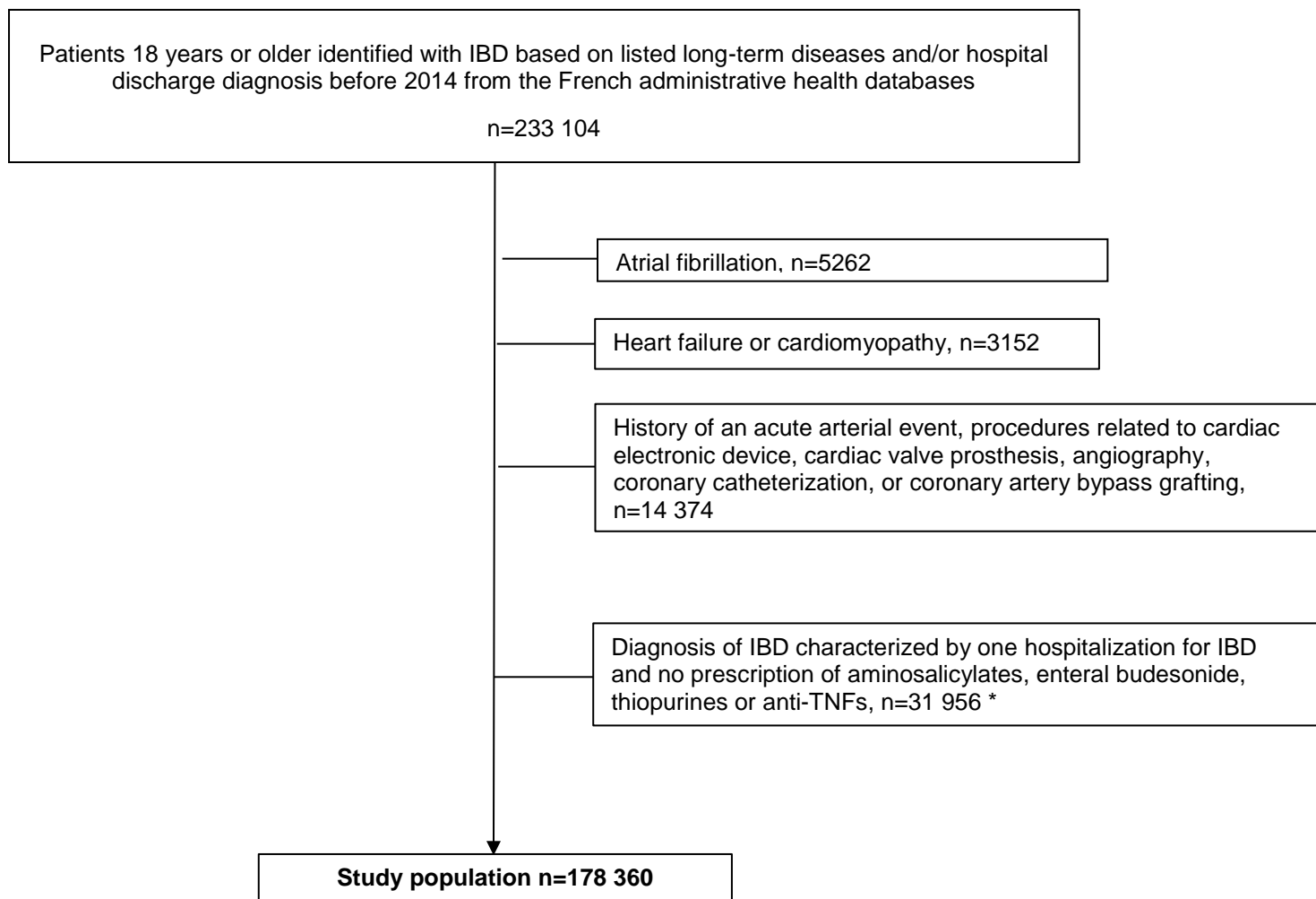
The main analysis was restricted to patients with a confirmed diagnosis of IBD. Additional analyses included subgroups analyses stratified on IBD phenotype, sex and age (18-54; 55 years or older), and sensitivity analyses restricting to incident patients and including patients with a non-confirmed IBD diagnosis.

The study was approved by the French Data Protection Agency. All data used in this study only contained anonymous patient records. The statistical analyses were performed with SAS (version 9.4) statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the cohort

Among the 233 104 individuals aged 18 years or older identified with IBD before 2014, 178 360 were included in the main analysis (Figure 1). During follow-up, 121 471 (67.3%) had never been exposed to thiopurines and anti-TNFs, while 40 728 (24.9%), 24 147 (13.8%), and 10 091 (6.3%) had ever been exposed to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, respectively, accounting for 93 207, 55 503, and 10 228 person-years (PY) of follow-up.



*Considered in sensitivity analyses

Figure 1: Study Population Flowchart

Overall, patients were predominantly female (54.0%) with a mean age of 46.3 (SD, 16.4) years at cohort entry. Half had a diagnosis of CD (50.7%) and half UC (49.3%). Incident cases accounted for 16% of the cohort, while 55.6% had been diagnosed for at least 10 years. IBD-related complications had occurred within the 6 months preceding cohort entry in 3.7%. These characteristics differed according to subsequent treatment exposure during follow-up (Table 1). Patients unexposed to thiopurines and anti-TNFs had a mean age of 49 years, a majority of them had a longstanding, uncomplicated UC. Those exposed to thiopurines and/or anti-TNFs, were mostly younger than 40 years and recently diagnosed with CD, and had substantial rates of IBD-related hospitalization or surgery at cohort entry.

Table 1. Patients characteristics at cohort entry according to subsequent treatment exposure during follow-up^a

Characteristic	Unexposed to thiopurines or anti-TNFs (n=121 471)	Exposed to thiopurine monotherapy (n=40 728)	Exposed to anti-TNF monotherapy (n=24 147)	Exposed to combination therapy (n=10 091)
Total treatment duration (days), mean (SD)	-	519 (545)	586 (542)	277 (314)
Age at cohort inclusion, mean (SD)	49.0 (16.4)	40.7 (14.8)	38.2 (13.8)	35.4 (12.5)
Male sex, n (%)	55 847 (46.0)	18 913 (46.4)	10 716 (44.4)	4667 (46.2)
Complementary universal health insurance, n (%) ^a	9822 (8.1)	4600 (11.3)	3212 (13.3)	1458 (14.4)
Inflammatory bowel disease subtype, n (%)				
Crohn's disease	52 103 (42.9)	25 985 (63.8)	18 092 (74.9)	7258 (71.9)
Ulcerative colitis	69 368 (57.1)	14 743 (36.2)	6055 (25.1)	2833 (28.1)
Age at IBD diagnosis, mean (SD)	41.6 (16.3)	34.4 (14.4)	32.0 (13.5)	30.0 (12.2)
Disease duration at cohort entry, n (%)				
≥ 10 years	37 034 (30.5)	9574 (23.5)	5419 (22.4)	1915 (19.0)
0-10 years	65 774 (54.1)	23 519 (57.7)	14 412 (59.7)	5926 (58.7)
Incident patients	18 663 (15.4)	7635 (18.7)	4316 (17.9)	2250 (22.3)
Inflammatory bowel disease drugs, n (%) ^b				
Corticosteroids	3093 (2.5)	1896 (4.7)	1185 (4.9)	533 (5.3)
Methotrexate	1171 (1.0)	148 (0.4)	1097 (4.5)	96 (1.0)
Aminosalicylates	34 951 (28.8)	9808 (24.1)	4640 (19.2)	2100 (20.8)
Complications related to IBD before cohort entry ^b				
Surgery related to IBD	768 (0.6)	725 (1.8)	778 (3.2)	378 (3.7)
Hospitalization related to IBD >24h	1367 (1.1)	2094 (5.1)	1818 (7.5)	968 (9.6)
Comorbidities, n (%)				
Chronic pulmonary disease	2099 (1.7)	430 (1.1)	283 (1.2)	74 (0.7)
Chronic kidney disease	744 (0.6)	233 (0.6)	150 (0.6)	40 (0.4)
Cirrhosis	599 (0.5)	163 (0.4)	176 (0.7)	40 (0.4)
Rheumatic disease	3366 (2.8)	1018 (2.5)	2950 (12.2)	470 (4.7)
HIV	291 (0.2)	39 (0.1)	26 (0.1)	11 (0.1)
Cancer	7342 (6.0)	1241 (3.0)	1001 (4.1)	279 (2.8)
Venus thromboembolism	1153 (0.9)	388 (1.0)	298 (1.2)	87 (0.9)
Atherosclerosis	837 (0.7)	134 (0.3)	68 (0.3)	15 (0.1)
Cardiovascular risk factors, n (%)				
Hypertension	22 166 (18.2)	4257 (10.5)	2231 (9.2)	662 (6.6)
Diabetes	6156 (5.1)	1287 (3.2)	659 (2.7)	225 (2.2)
Dyslipidemia	12 781 (10.5)	2487 (6.1)	1179 (4.9)	372 (3.7)
Obesity	1547 (1.3)	446 (1.1)	364 (1.5)	126 (1.2)
Smoking behavior	3616 (3.0)	1712 (4.2)	1454 (6.0)	502 (5.0)
Alcohol use disorder	1179 (1.0)	275 (0.7)	221 (0.9)	72 (0.7)
Exposure to Antiplatelet Drugs, n (%) ^b	3442 (2.8)	535 (1.3)	219 (0.9)	59 (0.6)

^a Patients exposed to more than one exposure group during follow-up were considered in each corresponding group. ^b Free access to healthcare for people with an annual income <50% of poverty threshold. ^c As registered within three months before cohort entry

Risk of acute arterial events according to treatment exposure

Overall, 4376 acute arterial events occurred, 2204 (50.4%) ischemic heart diseases, 1476 (33.7%) cerebrovascular diseases, and 696 (15.9%) peripheral artery diseases. Patients with an acute arterial event during follow-up were predominantly males (63.8%) and diagnosed with UC (55.1%), with a mean age of 64.4 years (SD, 14.0) at acute arterial events occurrence. Prevalence of traditional cardiovascular risk factors was expectedly higher compared to patients without acute arterial event during follow-up. (Supplementary Table 3)

Incidence rates per 1000 person-years (PY) were 5.6 for all acute arterial event, 2.8 for ischemic heart disease, 1.9 for cerebrovascular disease and 0.9 for peripheral artery disease. Among patients younger than 55 years with CD and UC, incidence rates of all acute arterial event were 3.3 and 2.8 per 1000 PY, respectively. Incidence rates increased expectedly with age, with 16.7 and 15.4 acute arterial events per 1000 PY in patients aged 55 years or older with CD and UC, respectively. Incidence rates according to treatment exposure are provided in Table 2.

Table 2. Incidence of acute arterial events according to medication exposure

	Total	Unexposed to thiopurines or anti-TNFs 624 436 PY	Exposed to thiopurine monotherapy 93 207 PY	Exposed to anti-TNF monotherapy 55 503 PY	Exposed to combination therapy 10 228 PY
All acute arterial events	4376 (5.6)	3812 (6.1)	358 (3.8)	181 (3.3)	25 (2.4)
Ischemic heart disease	2204 (2.8)	1925 (3.1)	181 (1.9)	86 (1.6)	12 (1.1)
Myocardial infarction	777 (1.0)	673 (1.1)	62 (0.7)	36 (0.6)	6 (0.5)
Cerebrovascular disease	1476 (1.9)	1287 (2.1)	112 (1.2)	67 (1.2)	10 (0.9)
Stroke	1077 (1.4)	943 (1.5)	83 (0.9)	43 (0.8)	8 (0.8)
Peripheral artery disease	696 (0.9)	600 (1.0)	65 (0.7)	28 (0.5)	3 (0.3)

Abbreviation: PY, person-years. Numbers are n (incidence rates/1000 person-years)

Exposures to thiopurine monotherapy, anti-TNF monotherapy and combination therapy were all numerically associated with a decreased risk of acute arterial event compared to no thiopurines and anti-TNFs exposure (hazard ratio [HR], 0.91; 95% CI 0.81-1.02; HR, 0.89; 95% CI 0.76-1.04; HR, 0.81; 95% CI 0.66-0.99, respectively). This risk reduction was only statistically significant in patients exposed to combination therapy.

Among specific arterial disease groups, the hazard ratio was below 0.90 for several subgroups, including ischemic heart disease in patients exposed to anti-TNF monotherapy and combination therapy (HR, 0.83; 95% CI 0.65-1.04; HR, 0.74; 95% CI 0.55-0.99, respectively), cerebrovascular disease in patients exposed to thiopurine monotherapy and combination therapy (HR, 0.85 95% CI 0.70-1.04; HR, 0.85; 95% CI 0.61-1.20, respectively), and peripheral artery disease in patients exposed to anti-TNF monotherapy (HR, 0.84 95% CI 0.56-1.28), but only reached statistical significance for ischemic heart disease in patients exposed to combination therapy. HRs for arterial disease subgroups according to treatment exposure are provided in Table 3.

Table 3. Multivariable Adjusted hazard ratios for any acute arterial events according to medication exposure between exposed and non-exposed patients ^a

	Exposed to thiopurine monotherapy versus unexposed to thiopurines or anti-TNFs	Exposed to anti-TNF monotherapy versus unexposed to thiopurines or anti-TNFs	Exposed to combination therapy versus unexposed to thiopurines or anti-TNFs
	HR (95% CI)	HR (95% CI)	HR (95% CI)
All acute arterial events	0.91 (0.81-1.02)	0.89 (0.76-1.04)	0.81 (0.66-0.99)
Ischemic heart disease	0.89 (0.76-1.05)	0.83 (0.65-1.04)	0.74 (0.55-0.99)
Myocardial infarction	0.91 (0.69-1.20)	0.95 (0.66-1.37)	0.86 (0.53-1.39)
Cerebrovascular disease	0.85 (0.70-1.04)	1.00 (0.77-1.31)	0.85 (0.61-1.20)
Stroke	0.87 (0.69-1.09)	0.89 (0.64-1.24)	0.77 (0.51-1.17)
Peripheral artery disease	1.08 (0.82-1.43)	0.84 (0.56-1.28)	0.91 (0.54-1.54)

Abbreviation: HR, hazard ratio. ^a For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.

The magnitude of risk reduction was higher in men exposed to anti-TNFs compared to women exposed to anti-TNFs, and higher in patients with CD as compared with patients with UC in all treatment exposure groups. Among patients with CD, exposure to thiopurine monotherapy and combination therapy were associated with a decreased risk of acute arterial event (HR, 0.84; 95% CI 0.71-0.98; HR, 0.71; 95% CI 0.54-0.93, respectively). The highest magnitude in risk reduction was observed in men with CD exposed to combination therapy (HR, 0.58; 95% CI 0.40-0.83).

Results remained unchanged after inclusion of patients with a non-confirmed IBD diagnosis. Corresponding HRs were of similar magnitude when the analysis was restricted to incident patients. (Supplementary Table 4)

Table 4. Multivariable Adjusted hazard ratios for any acute arterial events according to medication exposure between exposed and non-exposed patients ^a

	Exposed to thiopurine monotherapy versus unexposed to thiopurines or anti-TNFs	Exposed to anti-TNFs monotherapy versus unexposed to thiopurines or anti-TNFs	Exposed to combination therapy versus unexposed to thiopurines or anti-TNFs
	HR (95% CI)	HR (95% CI)	HR (95% CI)
All acute arterial events			
Overall (main analysis)	0.91 (0.81-1.02)	0.89 (0.76-1.04)	0.81 (0.66-0.99)
Male	0.91 (0.79-1.04)	0.78 (0.63-0.97)	0.71 (0.55-0.92)
Female	0.91 (0.75-1.12)	1.07 (0.84-1.38)	0.98 (0.70-1.37)
Age at cohort entry			
18-54	0.95 (0.80-1.12)	0.98 (0.80-1.21)	0.93 (0.71-1.22)
>55 years	0.89 (0.77-1.02)	0.89 (0.71-1.10)	0.79 (0.61-1.02)
Crohn's disease			
Overall	0.84 (0.71-0.98)	0.85 (0.70-1.03)	0.71 (0.54-0.93)
Male	0.84 (0.68-1.04)	0.69 (0.53-0.90)	0.58 (0.40-0.83)
Female	0.84 (0.65-1.08)	1.06 (0.81-1.40)	0.89 (0.60-1.32)
Ulcerative colitis			
Overall	0.99 (0.84-1.16)	0.97 (0.72-1.29)	0.96 (0.68-1.34)
Male	0.97 (0.81-1.16)	1.00 (0.72-1.39)	0.96 (0.66-1.42)
Female	1.06 (0.76-1.48)	0.90 (0.49-1.66)	0.95 (0.47-1.94)

Abbreviation: HR, hazard ratio. ^a For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.

DISCUSSION

Our study demonstrated that exposure to combination therapy is associated with a decreased risk of acute arterial event in patients with IBD, while exposures to anti-TNFs and thiopurines monotherapies are numerically but not significantly associated with a decreased risk of acute arterial event. The risk reduction is higher in men and patients with CD as compared respectively with women and patients with UC, while the risk reduction is the highest in men with CD.

Whereas the impact of immunosuppressive treatment has been extensively reported among patients with RA, this study is the first nationwide population based cohort study assessing the risk of acute arterial events associated with thiopurines and anti-TNFs exposure in patients with IBD. Indeed, conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), as well as biologics, such as anti-TNFs have been associated with a decreased risk of acute arterial events in patients with RA. A recent meta-analysis reported a risk of ischemic heart disease and cerebrovascular disease 30% lower in patients exposed to the two treatment regimens compared to unexposed patients.[20] The underlying mechanisms of this risk reduction associated with immunosuppressive treatment in RA and IBD may be notably related to shared pathogenic processes between atherosclerosis and these inflammatory chronic diseases. Disease activity, associated with an increased risk of acute arterial event in patients with RA[21,22] and IBD,[2] leads to systemic inflammation,[23] while atherosclerosis is now defined as a chronic inflammatory condition of the vessel wall. Indeed, recent findings revealed that the inflammatory response in atherosclerosis involves elements of both the innate and adaptive immunity.[3] Additionally, several studies concluded that C-reactive protein (CRP) level predicts ischemic heart disease,

cerebrovascular disease, and cardiovascular death after adjustment for traditional cardiovascular risk factors.[24]

We reported differences regarding risk reduction between combination therapy and thiopurines and anti-TNFs monotherapies. This may be related to the higher proportion of clinical and mucosal healing obtained with combination therapy,[25] while mucosal healing was associated with low CRP levels and sustained clinical remission.[26] However, risk reductions associated with thiopurines and anti-TNF monotherapies were at the limits of statistical significance, suggesting that the protective effect observed may be noticeably related to the reduction of systemic inflammation, irrespective of the treatment regimen.

Differences of risk across IBD phenotype, sex and age categories may be related to the different distributions of systemic inflammation and traditional cardiovascular risk factors across these groups. Patients with CD are at increased risk of acute arterial events compared to UC patients, and patients with CD are more prone to a higher degree of systemic inflammation compared to UC patients, amongst others evidenced by higher level CRP production[23,27] and serum concentration of interleukin-6.[28] Hyperhomocysteinemia and low vitamin B6 plasma level, [29,30] related to malabsorption in CD patients, and polymorphisms in NOD2/CARD15[31,32] may also be involved in the pathogenesis of atherosclerosis in patients with CD. Additionally, traditional cardiovascular risk factors are more prominent in men and older patients. The highest risk reduction associated with anti-TNFs was observed in the population with the highest absolute risk of acute arterial event, namely men, older patients, and CD patients, while differences in risk reduction across sex and age categories were predominantly observed in patients exposed to anti-TNFs. These findings may highlight the specific impact of anti-TNFs by reversing preexisting atherosclerosis, as suggested in several studies.[33]

This study has several strengths. Using nationwide register-based data on the entire French population provided a large sample size allowing for sufficient power to perform comprehensive and multiple subgroups analyses on the risk of acute arterial events. Additionally, several studies have found the reliability, validity, and accuracy of medical coding in the French administrative database for various diseases to be good.[34–38] The identification of acute arterial event was also similar as in the study based on the same inpatient database, and reporting an increased risk of acute arterial events in patients with IBD compared to the general population.[2]

We previously reported that disease activity was one of the strongest significant predictor of acute arterial events,[2] while corticosteroids exposure has been associated with an increased risk of acute arterial events.[39] Disease activity and use of steroids may have an impact on treatment modification and occurrence of acute arterial events, whereas these time-varying covariates may also impact the future treatment assignment. Under the assumption of no unmeasured confounders, we used therefore marginal structural Cox proportional hazard models to account for time dependent confounding in treatment assignment.

This study also has some limitations that need to be discussed. Environmental factors are not accurately reported in the French administrative databases. Rates of tobacco smoking, may be therefore underestimated,[40] Yet, tobacco smoking is a cardiovascular risk factor and smoking reduces the risk of UC occurrence, while increasing the risk of CD occurrence.[41–43] Furthermore, tobacco smoking increased disease activity in patients with CD,[44] and patients treated with thiopurines and anti-TNFs are more prone to be smokers compared to patients not exposed to these drugs.[40] A potential bias related to an underestimation of tobacco smoking may tend to underestimate the risk reduction of acute arterial event associated with combination

therapy, suggesting that such a bias, if any, did not alter the association between immunosuppressive treatment and the protective effect observed.

Until now, there has been no validation study of the ICD-10 codes related to IBD in the French administrative health databases. However, a descriptive study on the same cohort[12] reported treatment exposure, hospitalization and surgery rates similar to current standard of care and incidence rates in the range of those reported in the literature.[45]

Finally, these findings added to the previous conclusions regarding the risk of acute arterial events in patients with IBD compared to the general population [2] underscores the fact that the magnitude of risk associated with IBD and the impact of treatment should be stratified according to key parameters, such as age, sex, and IBD subtype, in order to be included in clinical decision-making.

In conclusion, this nationwide population-based cohort study including more than 170 000 patients diagnosed with IBD reported a decreased risk of acute arterial events associated with exposure to combination therapy, while risk reductions associated with thiopurine and anti-TNF monotherapies were at the limits of statistical significance. This risk reduction was notably the highest in men with CD. Prevention of acute arterial events should be considered in the benefit-risk balance assessment of thiopurines and anti-TNFs in patients with IBD.

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SUPPORTING INFORMATION

Supplementary Table 1. Codes used to define exclusion criteria and covariates

Comorbidity	ICD-10 codes	Anatomical Therapeutic Chemical (ATC) classification system code*	French Medical Common Procedure Coding System
Exclusion criteria			
Ischemic heart disease	I20-I25, T820, T822,T823, T826, T827 Z45.0, Z86.71, Z95 (except Z95.8,Z95.9)	-	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	I60-I66, G45, G460- G462, I670 , I671, I68, I69	-	Cerebral angiography with arterial dilation or embolization
Peripheral artery disease	I74	-	Angiography (excluding coronary catheterization and cerebral angiography) with arterial dilation; Peripheral artery bypass
Heart failure	I50	-	-
Atrial fibrillation	I48	-	-
Cardiomyopathies	I42-I43	-	-
Covariates			
Cancer	C0-C9, E88.3, G53.3, G55.0, G63.1, G73.2, G94.1, J70.0, J70.1, K52.0, K62.7, L58.0, L58.1, L59.8, D63.0, L59.9, M36.0, M36.1, M90.6, M90.7, M96.2, M96.5, N30.4, O35.6, Z08, Z51.1, Z54.2, Z85 I85; I86.4; I98.2; I98.3; K70.0; K70.3-K70.4; K71.1; K71.7; K72; K74.4- K74.6; K76.6; K76.7;	-	Chemotherapy and radiotherapy
Cirrhosis and portal hypertension	J40-J44, J47, J96.1 K71.1; K71.7; K72; K74.4- K74.6; K76.6; K76.7;	-	-
Respiratory chronic disease	J40-J44, J47, J96.1	R03AC, R03B	-
Chronic kidney disease	I12, N18, N19, Z49, I13.0, I13.1, Y84.1	-	-
Venous thromboembolism	I26, I80-I82, O22.3, O22.9, O87.1, O88.2	-	-
HIV	B20-B24, C46, R75, Z21, F02.4, O98.7		
Rheumatic disease	M05-M09, M45, M35.1, M35.3		
Atherosclerosis	I70		

Cardiovascular risk factors

Diabetes	E10-E14, M14.2 , M14.6, N08.3, H28.0, H36.0, G59.0, G63.2, G73.0, G99.0, I79.2	A10	-
Dyslipidemia	E78.0-E78.5 E244, F100, F101, F10.20-F10.26, F10.3- F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, O35.4, T51, X45, X65, Y15, Z50.2	C10	-
Alcohol use disorder		-	-
Hypertension	I10-I13, I15	C02 C03 C07 C08 C09	-
Smoking behavior	F17, Z71.6, Z72.0, T65.2	-	-
Obesity	E66	-	-
Markers of IBD severity			
IBD-related hospitalization	K50; K51; K56; K60; K61	-	-
IBD-related surgery			
Colectomy	-	-	HHFA002, HHFA004, HHFA005, HHFA006, HHFA008, HHFA009, HHFA010, HHFA014, HHFA017, HHFA018, HHFA021, HHFA022, HHFA023, HHFA024, HHFA026, HHFA028, HHFA029, HHFA030, HHFA031
Intestinal resection	-	-	HGCA005, HGCC015, HGFA003, HGFA004, HGFA005, HGFA007, HGFC014, HGFC016, HGFC021 HKPA004, HKPA005, HKPA006, HKPA007, HKPA008, HGCA008, HGCC026, HGLA001, HHCA003, HHCC011, HPPA002, HPPC003, ZCJA002, ZCJA004
Perineal surgery and minor digestive surgery	-	-	

Supplementary Table 2: Outcomes

Outcomes	ICD-10 codes	French Medical Common Procedure Coding System
Ischemic heart disease	I20-I25	Coronary catheterization with arterial dilation; CABG
Myocardial infarction	I21-I22	Coronary catheterization with arterial dilation; CABG
Cerebrovascular disease	I60-I64 (except I63.6) , G45	Cerebral angiography with arterial dilation or embolization
Stroke	I60-I64 (except I63.6)	Cerebral angiography with arterial dilation or embolization
Peripheral artery disease	I74	Angiography (excluding coronary catheterization and cerebral angiography and mesenteric angiography) with arterial dilation; Peripheral artery bypass

Supplementary Table 3. Patients characteristics at cohort entry according to subsequent treatment exposure during follow-up^a

Characteristic	Total n=178 360	Acute arterial event during follow-up n=4376	No acute arterial event during follow-up n=173 984
Age at cohort inclusion, mean (SD)	46.3 (16.4)	62.3 (14.0)	45.8 (16.2)
Male sex, n (%)	81987 (46.0)	2793 (63.8)	79194 (45.5)
Complementary universal health insurance, n (%) ^a	16473 (9.2)	321 (7.3)	16152 (9.3)
Inflammatory bowel disease subtype, n (%)			
Crohn's disease	90423 (50.7)	1965 (44.9)	88458 (50.8)
Ulcerative colitis	87937 (49.3)	2411 (55.1)	85526 (49.2)
Age at IBD diagnosis, mean (SD)	39.1 (16.1)	54.0 (15.4)	38.8 (15.9)
Disease duration at cohort entry, n (%)			
≥ 10 years	50630 (28.4)	1558 (35.6)	49072 (28.2)
0-10 years	99152 (55.6)	2203 (50.3)	96949 (55.7)
Incident patients	28578 (16.0)	615 (14.1)	27963 (16.1)
Inflammatory bowel disease drugs, n (%) ^b			
Corticosteroids	5736 (3.2)	127 (2.9)	5609 (3.2)
Methotrexate	2336 (1.3)	55 (1.3)	2281 (1.3)
Aminosalicylates	47648 (26.7)	1391 (31.8)	46257 (26.6)
Complications related to IBD before cohort entry ^b			
Surgery related to IBD	2031 (1.1)	34 (0.8)	1997 (1.1)
Hospitalization related to IBD >24h	5882 (3.3)	106 (2.4)	4482 (2.6)
Comorbidities, n (%)			
Chronic pulmonary disease	2756 (1.5)	185 (4.2)	2571 (1.5)
Chronic kidney disease	1101 (0.6)	109 (2.5)	992 (0.6)
Cirrhosis	914 (0.5)	43 (1.0)	871 (0.5)
Rheumatic disease	7033 (3.9)	218 (5.0)	6815 (3.9)
HIV	350 (0.2)	10 (0.2)	340 (0.2)
Cancer	9394 (5.3)	514 (11.7)	8880 (5.1)
Venus thromboembolism	755 (0.4)	92 (2.1)	1667 (1.0)
Atherosclerosis	1018 (0.6)	238 (5.4)	780 (0.4)
Cardiovascular risk factors, n (%)			
Hypertension	28089 (15.7)	1995 (45.6)	26094 (15.0)
Diabetes	7932 (4.4)	635 (14.5)	7297 (4.2)
Dyslipidemia	16119 (9.0)	1175 (26.9)	14944 (8.6)
Obesity	2283 (1.3)	91 (2.1)	2192 (1.3)
Smoking behavior	6378 (3.6)	215 (4.9)	6163 (3.5)
Alcohol use disorder	1633 (0.9)	97 (2.2)	1536 (0.9)
Exposure to Antiplatelet Drugs, n (%) ^b	4141 (2.3)	564 (12.9)	3577 (2.1)

^a Patients exposed to more than one exposure group during follow-up were considered in each corresponding group. ^b Free access to healthcare for people with an annual income <50% of poverty threshold. ^c As registered within three months before cohort entry

Supplementary Table 4. Multivariable Adjusted hazard ratios (and 95% confidence interval) of any acute arterial events according to medication exposure between exposed and non-exposed patients in sensitivity analyses ^a

	Exposed to thiopurine monotherapy versus unexposed to thiopurines or anti- TNFs	Exposed to anti-TNF monotherapy versus unexposed to thiopurines or anti- TNFs	Exposed to combination therapy versus unexposed to thiopurines or anti- TNFs
	HR (95% CI)	HR (95% CI)	HR (95% CI)
All acute arterial events			
Main analysis	0.91 (0.82-1.02)	0.90 (0.77-1.04)	0.82 (0.68-0.99)
Analysis restricted to incident patients	0.99 (0.73-1.34)	0.84 (0.53-1.33)	0.83 (0.47-1.47)
Analysis including patients with a non-confirmed IBD diagnosis ^b	0.91 (0.81-1.01)	0.87 (0.75-1.03)	0.79 (0.65-0.97)

Abbreviation: HR, hazard ratio. ^a For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section. ^b Patients with only one single hospital discharge IBD diagnosis and no pharmacy claim for any of the following IBD medications: aminosalicylates, enteral budesonide, thiopurines and anti-TNFs were considered to have a non-confirmed diagnosis of IBD

Appendix: Methods

Under the assumption of no unmeasured confounders, we used marginal structural models to estimate causal effects of thiopurines and anti-TNFs on the risk of acute arterial events.[1] These models, adjusted for time-dependent covariates with inverse probability treatment weights, are appropriate in the presence of time-dependent covariates (such as exposure to corticosteroids and IBD activity) that might be associated with both prescription of thiopurines or anti-TNFs and outcomes (time-dependent confounders) and could also be affected by past exposure to thiopurines and anti-TNFs.

The conditional probability of receiving observed treatment was estimated using multinomial logistic regression with generalised logit link. Covariates included were the baseline and time-dependent covariates (listed in Supplementary Table 1) and past treatment history.

Weights from the exposure selection model were calculated as follows: the numerator was the probability of receiving the treatment actually received after treatment modification conditional on baseline covariates and past treatment history. The denominator was the predicted probability of receiving the treatment actually received after treatment modification conditional on baseline covariates, past treatment history and time-varying covariates (measured in the prior six months).

To adjust for potential selection bias from loss to follow-up, we similarly modeled the propensity to be censored. Binary logistic regression was used for the censoring model. Weights from the censoring model were calculated as follows: the numerator was the probability of being censored conditional on baseline covariates and past treatment history. The denominator was the predicted probability of being censored conditional on baseline covariates, past treatment history and time-varying covariates (measured in the prior six months).

The stabilised weights were the product of the weights from the exposure selection and the censoring models, updated at each time interval. After calculation, the weights were truncated at 1st and 99th percentiles to minimise the impact of extreme weights and improve precision. [2,3]

In the main analysis, stabilised weights using inverse probability of treatment and inverse probability of censoring were calculated at each treatment modification, since treatment assignment was continuously recorded rather than during scheduled follow-up visits.

After truncation at the 1st percentile (0.50) and 99th percentile (3.67), Mean (SD) of the weights were 1.00 (0.23). There was no tendency for the mean to deviate from 1 after a long period of follow-up.

The outcome analysis model was adjusted for baseline covariates. Robust variance estimators were used to estimate conservative 95% confidence intervals.

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2. Discussion

This study is the first reporting a protective effect associated with immunosuppressive treatment exposure on the risk of acute arterial events in patients with IBD. While conventional synthetic DMARDs as well as anti-TNFs were shown to reduce the risk of acute arterial event in patients with rheumatoid arthritis, we reported differences regarding risk reduction between combination therapy, thiopurines and anti-TNFs monotherapies. It may be related to the higher proportion of clinical and mucosal healing obtained with combination therapy,[189] while mucosal healing is associated with low CRP levels and sustained clinical remission.[190] However, risk reductions associated with thiopurines and anti-TNF monotherapies were at the limits of statistical significance, suggesting that one of the underlying mechanism is the reduction of systemic inflammation, irrespective of the treatment regimen. Additionally, several studies suggest that anti-TNFs may also reverse atherosclerosis. [140] It may explain the highest impact of risk reduction in the population most at risk, that is the one with preexisting atherosclerosis before introduction of anti-TNFs.

We reported disease activity as one of the strongest significant predictor of acute arterial events, while corticosteroids exposure was associated with an increased risk of acute arterial events.[191] Disease activity and use of steroids may have an impact on treatment modification and occurrence of acute arterial events, whereas these time-varying covariates may also impact the future treatment assignment. Under the assumption of no unmeasured confounders, we used therefore marginal structural Cox proportional hazard models to account for time dependent confounding in treatment assignment.

Differences in incidence rates of acute arterial events were observed between the two studies. A lower rate was observed in the study based on the SNIIRAM database, while diagnosis codes and surgical procedures used for acute arterial events identification were similar between the two studies. This difference may be related to the notification of a medical history of acute arterial events through LTDs in the SNIIRAM database, which was not reported in the PMSI database. Thus, some patients with a medical history of acute arterial event may have been included in the study assessing the risk compared with the general population. However, similar criteria were applied in the general population and all analyses were consistent.

Finally, exposure to combination therapy with thiopurines and anti-TNFs was associated with a decreased risk of acute arterial events in patients with IBD, while risk reductions associated with thiopurines and anti-TNF monotherapies were at the limits of statistical significance. This risk reduction was the highest in men with CD. Prevention of acute arterial events should be considered in the benefit-risk balance assessment of thiopurines and anti-TNFs treatment in patients with IBD.

REFLECTION AND CONCLUSIONS

1. Acute arterial event as a frequent outcome in patients with IBD

Cardiovascular disease is a leading cause of disability and death in the world.[89] Indeed, incidence rates of all acute arterial were above 5 per 1000 person years in both studies, while the absolute risk was expectedly the highest among older men. The incidence rate of acute arterial events was almost five-fold higher than that of colorectal advanced neoplasia (colorectal high-grade dysplasia and cancer), based on the CESAME cohort, a nationwide prospective observational cohort designed to assess the risk of cancer in IBD patients.[192]

Compared with the general population, we observed a 35% and 10% increase of risk of acute arterial events in patients with CD and UC, respectively. This magnitude of risk is consistent with previous findings published in a recent meta-analysis.[169] It may be mostly related to systemic inflammation, since disease activity was one of the strongest significant predictor of acute arterial events, after adjustment of all traditional cardiovascular risk factors recorded. This is consistent with many studies concluding that the relative impact of CRP is at least as large as that individually of hyperlipidemia, hypertension, or smoking.[126]

We reported an overall relative risk reduction between 10 and 20%, which seems small compared to the potential chemopreventive effect of thiopurines on colorectal advanced neoplasia in patients with long-standing extensive colitis, which was above 60% in the CESAME cohort.[192] However, assuming that the efficacy of combination therapy remained consistent with time, the estimated number needed to treat[193] for combination therapy use to prevent one acute arterial event over 1 year fell from 645

for patients younger than 55 years, to 45 for patients aged 55 years or older. In men with CD aged 55 years or older, this number was 14. It highlights the fact that, although the relative risk reduction of acute arterial event associated with immunosuppressive treatment may be small, the impact may be major in specific populations among whom the absolute risk is high.

2. Assessment of disease activity and traditional cardiovascular risk factors

All analyses were based on administrative health databases. Hence, some variables may be not accurately reported, notably environmental factors, such as tobacco smoking. Yet, tobacco smoking is a cardiovascular risk factor and smoking reduces the risk of UC occurrence, while increasing the risk of CD occurrence.[39–41] Regarding the risk of acute arterial events in IBD patients compared with the general population, the risk was increased in both IBD subtypes. Additionally, the increased risk of acute arterial events was maintained in patients with CD without traditional cardiovascular risk factors. Disease activity was also associated with an increased risk of acute arterial events in both CD and UC after adjustment of all cardiovascular risk factors recorded. Furthermore, patients with CD had a nearly two-fold increase in periods of disease activity compared with UC patients. Despite the underestimation of tobacco smoking, it may highlight the fact that systemic inflammation is one of the trigger of acute arterial events in patients with IBD and the increased inflammatory burden in patients with CD may account for differences between CD and UC. Adjustment for region of residence may to some extent have also captured the effect of tobacco smoking, since the prevalence of tobacco smoking in France differs according to the region of residence.[194]

Furthermore, tobacco smoking increased disease activity in patients with CD, and patients treated with thiopurines and anti-TNFs are more prone to be smokers compared to patients not exposed to these drugs.[195] In the study assessing the impact of immunosuppressive treatment on the risk of acute arterial event, a potential bias related to an underestimation of tobacco smoking may tend to underestimate the risk reduction associated with combination therapy, suggesting that such a bias, if any, did not alter the association between immunosuppressive treatment and the protective effect observed.

Disease activity was assessed through hospitalisations, surgery and exposure to corticosteroids. It excludes mild and moderate flares managed in an outpatient setting and treated with regimens such as aminosalicylates. Hence, the risks assessed in our studies relate to flares severe enough to require hospitalisation and corticosteroids. These flares may be associated with high systemic inflammation, and further studies are needed to assess the risk related to mild and moderate flares managed in an outpatient setting.

While CRP has been identified as an independent cardiovascular risk factor, [126] CRP level is not recorded in the French administrative health databases. Although CRP level is correlated with clinical activity, [34–36] which was included in all our analyses, some patients with IBD may have high CRP level without symptoms. The risk associated with high CRP level independently of clinical activity should be assessed in future studies.

3. Risk stratification

The therapeutic management of IBD has radically changed in the last decades, with patients exposed to immunosuppressive treatment early after diagnosis and for prolonged periods. In our cohort, the 5-year cumulative probabilities of combination therapy, anti-TNF monotherapy and thiopurine monotherapy prescriptions were 18.3%, 33.8%, 43.6% in CD patients, and 7.4%, 12.9%, and 24.9% in UC patients, respectively. In this era of early and more aggressive treatment strategy, an issue of growing concern today is the increasing proportion of IBD patients exposed to prolonged immunosuppressive therapy with unknown risk-benefit balance over lifetime. Major parameters, such as sex, age and IBD subtype may greatly impact the benefit risk balance of thiopurines and anti-TNFs, and very few studies assessed the benefit risk-balance of therapeutic strategies in patients with IBD.[196]

Thus, we stratified all analyses on sex, age and IBD subtype. These subgroups analyses allowed us to underline the different impact of systemic inflammation and immunosuppressive treatment according to each patient's characteristics.

The study assessing the risk of acute arterial events compared with the general population and calculating SIRs highlights the impact of systemic inflammation compared to all other traditional cardiovascular risk factors. Indeed, SIRs were the highest in specific subgroups with few traditional cardiovascular risk factors. Compared with the general population of similar sex and age, women and young patients were at higher risk of acute arterial events than men and old patients, respectively. It suggests that the risk differences in SIRs between sex and age categories may be related to the higher prevalence of traditional cardiovascular risk factors in men and older patients.

Traditional cardiovascular risk factors in these populations may potentially outweigh the risk related to systemic inflammation owing to IBD.

Conversely, the study assessing the effect of thiopurines and anti-TNFs highlights the underlying mechanisms by which these treatments may be protective on the risk of acute arterial events. Firstly, we reported differences regarding overall risk reduction between combination therapy and monotherapies. This may be notably related to the higher proportion of clinical and mucosal healing obtained with combination therapy,[189] while mucosal healing is associated with low CRP levels and sustained clinical remission.[190] However, risk reductions associated with thiopurines and anti-TNF monotherapies were at the limits of statistical significance, suggesting that one of the underlying mechanism is the reduction of systemic inflammation, irrespective of the treatment regimen. Secondly, the highest risk reduction associated with thiopurines and anti-TNFs was observed in the population with the highest absolute risk of acute arterial event, namely men, older patients, and CD patients, since CD is associated with higher systemic inflammation as compared with UC. Moreover, differences in risk reduction across sex and age categories were predominantly observed in patients exposed to anti-TNFs. These findings may highlight the specific impact of anti-TNFs by reversing preexisting atherosclerosis.

In the era of personalized medicine, this risk stratification provides key elements to assess the risk of acute arterial events and the potential benefit of thiopurines and anti-TNFs for each patient. Further studies are required to construct and validate score algorithms predicting the risk of acute arterial events in patients with IBD, as it is already developed in rheumatoid arthritis.[146,147]

CONCLUSION

The work conducted in the context of this thesis underscores the impact of systemic inflammation on the risk of acute arterial event and the protective effect of immunosuppressive treatment, in addition to its impact on intestinal inflammation, in patients with IBD. Overall, this study supports the increasing concept that a tight control of inflammation is crucial in patients with IBD to avoid IBD-related systemic complications. Prevention of acute arterial events should be considered in the benefit-risk balance assessment of thiopurines and anti-TNFs treatment in patients with IBD, according to age, sex and IBD subtype for each individual.

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