Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Position Paper

Preventing and managing cardiovascular events in patients with inflammatory bowel diseases treated with small-molecule drugs, an international Delphi consensus

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ARTICLE INFO

Article history:
Received 11 November 2023
Accepted 17 March 2024
Available online xxx

Keywords:
Cardiovascular events
Inflammatory bowel disease
Prevention
Small molecule drugs

ABSTRACT

Janus kinase (JAK) inhibitors and sphingosine 1 phosphate (S1P) receptor modulators are small molecule drugs (SMDs) approved for IBD treatment. Their use in clinical practice might be limited due to cardiovascular concerns. We aimed to provide guidance on risk assessment, monitoring, and management strategies, aiming to minimize potential cardiovascular risks of SMDs and to facilitate an adequate shared decision-making.

A systematic literature search was conducted, and proposed statements were prepared. A virtual consensus meeting was held, in which eleven IBD physicians and two cardiovascular specialists from ten countries attended. Proposed statements were voted upon in an anonymous manner. Agreement was defined as at least 75 % of participants voting as 'agree' with each statement.

Consensus was reached for eighteen statements. Available evidence does not show a higher risk of cardiovascular events with JAK inhibitors in the overall IBD population, although it might be increased in patients with an unfavorable cardiovascular profile. S1P receptor modulators may be associated with a

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https://doi.org/10.1016/j.dld.2024.03.010

risk of bradycardia, atrioventricular blocks, and hypertension. Cardiovascular risk stratification should be done before initiation of SMDs. Although the risk of cardiovascular events in patients with IBD on SMDs appears to be low overall, caution should still be taken in certain scenarios.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two primary forms of inflammatory bowel diseases (IBD), which are characterized by periods of flare and remission and could lead to bowel tissue damage and complications [1,2].

The current therapeutic armamentarium in IBD includes conventional therapies such as corticosteroids, immunomodulators, and aminosalicylates, as well as advanced therapies like biologic agents and targeted small molecule drugs (SMDs) [3]. Biologic agents have been the cornerstone of the treatment paradigm of moderate-to-severe IBD over the past two decades. However, due to certain inherent limitations of biologics (such as moderate effectiveness, potential immunogenicity, and the need for parenteral administration), recent drug research and development in IBD have focused on SMDs [4]. Janus kinase (JAK) inhibitors and sphingosine 1 phosphate (S1P) receptor modulators are classes of SMDs that have been approved by the Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for IBD treatment [5,6]. Despite their potential benefits, JAK inhibitors and S1P modulators may be associated with cardiovascular safety concerns, which may limit their use in clinical practice.

Evidence from rheumatoid arthritis literature suggests that the JAK inhibitor tofacitinib may increase the risk of major adverse cardiovascular events (MACE), particularly in patients with pre-existing cardiovascular risk factors, as well as venous thromboembolic events (VTE), infections, and malignancy [7,8]. In response, the FDA included a boxed warning on tofacitinib and other JAK inhibitors, such as upadacitinib and baricitinib, and limited their use in cases of history of failure or intolerance to anti-tumor necrosis factor (TNF) inhibitors [9,10]. The EMA has also recently issued guidelines to reduce the risk of serious adverse events associated with the use of JAK inhibitors in immune-mediated inflammatory diseases (IMIDs) [11]. Moreover, S1P modulators have been associated with cardiovascular events in clinical trials, especially cardiac conduction abnormalities and bradyarrhythmia [12].

As a result, patients and gastroenterologists might be reluctant to use SMDs in patients with IBD, given cardiovascular safety concerns. In the current landscape of ever-expanding treatment options, the process of shared decision-making in IBD has become more relevant than ever [13]. A fundamental premise of a shared decision-making process is to aid physicians in conveying evidence-based information in a manner that patients can readily comprehend and engage them in treatment decisions, thereby facilitating a decision that aligns with their preferences [14]. Hence, there is a need to develop strategies to mitigate cardiovascular risks and ensure the safe use of SMDs in IBD while allowing an adequate physician-patient interaction around the decision to use these therapies. To address this issue, an international group of experts in IBD and cardiology convened to develop practical position statements for preventing and managing cardiovascular events in patients with IBD treated with SMDs. These consensus statements provide clinicians with guidance, aiming to minimize the potential cardiovascular risks in patients treated with SMDs.

2. Materials and methods

A systematic literature search was conducted to identify studies assessing the risk of cardiovascular events with the use of JAK inhibitors and S1P receptor modulators in patients with IBD. Published studies without language restrictions were identified using MEDLINE, Embase, and Cochrane CENTRAL from inception until December 20, 2022. Major congresses databases (European Crohn's and Colitis Organization, Digestive Disease Week, and United European Gastroenterology Week) in the period 2012–2022 were also reviewed manually. Search strategies are provided in Supplementary Table 1. Results from the literature search were recently published. Proposed statements were prepared prior to the meeting by two authors (PAO and LPB) based on the systematic literature search results (Supplementary Table 2).

On January 25th, 2023, a virtual consensus meeting was held to define the cardiovascular risk in patients with IBD treated with SMDs and to give recommendations regarding management and mitigation strategies.

Eleven physicians with expertise in the field of IBD (PAO, AD, MCD, PGK, ID, TK, SG, FM, BS, SD, LPB) and two cardiovascular specialists (PG, JRFN) from ten countries worldwide (Argentina, Brazil, France, Germany, Ireland, Israel, Italy, Japan, Portugal, and the United States) attended the meeting.

During the meeting, the literature review results were presented, followed by the presentation of the proposed statements. Each proposed statement was voted upon anonymously. An agreement was defined as at least 75 % of participants voting as 'agree' with each proposed statement. If a 75 % agreement was not achieved, further discussion ensued, which might have included amendment of voting statements when required, followed by a second round of voting using the same approach as before if the statement remained controversial. If an agreement could not be reached after two rounds of voting, then the statement was excluded. For each statement, the level of evidence was graded according to the Oxford Centre for Evidence-based Medicine 2011 (Table 1) [15].

3. Results

1. **JAK inhibitors are associated with mild increases in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), with the LDL-C to HDL-C ratio usually stable. These lipid changes are reversible with statin treatment. (Level of Evidence: 1. Agreement: 100 %).**

Treatment with tofacitinib has been associated with lipid profile abnormalities in both IBD and other IMIDs [16–20], with similar effects observed with other JAK inhibitors such as upadacitinib [21,22]. A pooled analysis of the tofacitinib programme in UC evaluated lipid profile changes in 1157 patients exposed to tofacitinib [20]. Following an 8-week induction period, patients receiving a twice-daily dose of tofacitinib 10 mg demonstrated significant increases in total cholesterol, HDL-C, and LDL-C levels, which were

Table 1
Accepted statements.

#	Statement	Level of evidence	Agreement
1	JAK inhibitors are associated with mild increases in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), with the LDL-C to HDL-C ratio usually stable. These lipid changes are reversible with statin treatment.	Level of Evidence: 1	100 %
2	Available evidence from the overall IBD population does not indicate a higher risk of cardiovascular events with JAK inhibitors.	Level of Evidence: 3	100 %
3	The role of isoform selectivity of JAK inhibitors in the cardiovascular safety profile in IBD is unclear.	Level of Evidence: 5	100 %
4	Cardiovascular risk factors and previous history of atherosclerotic cardiovascular events influence the risk of cardiovascular events in patients with IBD exposed to JAK inhibitors.	Level of Evidence: 3	100 %
5	The potential risk of cardiovascular events associated with JAK inhibitors should be weighed versus that of uncontrolled inflammation.	Level of Evidence: 5	100 %
6	S1P receptor modulators may be associated with a dose-dependent, transient risk of bradycardia and atrioventricular blocks.	Level of Evidence: 1	100 %
7	S1P receptor modulators may be associated with new-onset hypertension.	Level of Evidence: 1	92 %
8	Screening of cardiovascular risk factors and risk stratification should be done in all patients with IBD.	Level of Evidence: 5	79 %
9	Screening of cardiovascular risk factors and risk stratification should be done before initiation of JAK inhibitors or S1P receptor modulators.	Level of Evidence: 5	100 %
10	Management of cardiovascular risk factors should follow recommendations used in the general population in collaboration with cardiologists and primary care physicians.	Level of Evidence: 5	100 %
11	Counselling and education regarding cardiovascular risk should be done in patients with IBD. Healthy lifestyle modifications should be encouraged.	Level of Evidence: 5	100 %
12	In patients with IBD with history of atherosclerotic cardiovascular disease or at a significant risk, treatment with JAK inhibitors should be considered if there are no suitable therapeutic alternatives.	Level of Evidence: 5	100 %
13	When starting a JAK inhibitor, the lipid profile (including total cholesterol, LDL-C, HDL-C, and triglycerides) should be measured at baseline, after induction, and routinely every 6 months. Management of dyslipidaemia should follow current guidelines.	Level of Evidence: 5	82 %
14	During the maintenance phase, the lowest effective dose to maintain remission with JAK inhibitors should be aimed. The higher maintenance dose should be avoided in patients with IBD and known cardiovascular risk factors.	Level of Evidence: 5	92 %
15	When considering treatment with an S1P receptor modulator, concomitant medications and symptoms suggestive of cardiac conduction abnormalities should be reviewed.	Level of Evidence: 5	90 %
16	Holter monitoring should be considered in patients with IBD and a history of symptoms suggestive of cardiac conduction abnormalities when treatment with an S1P receptor modulator is considered.	Level of Evidence: 5	83 %
17	A cardiology consultation should be considered before starting an S1P receptor modulator in patients with IBD and risk factors for cardiac conduction abnormalities or uncontrolled hypertension.	Level of Evidence: 5	77 %
18	Blood pressure of patients with IBD treated with an S1P receptor modulator should be routinely checked.	Level of Evidence: 5	100 %

inversely correlated with C-reactive protein levels. In the maintenance phase, patients receiving tofacitinib 5 or 10 mg twice daily also showed elevated total cholesterol, HDL-C, and LDL-C levels compared to placebo, with generally higher levels observed in the tofacitinib 10 mg group versus the 5 mg group. Throughout the maintenance phase, lipid levels remained relatively stable with tofacitinib compared to placebo and tended to return to baseline levels observed during induction. These findings suggest that changes in lipid profiles are dose-dependent and reversible [20]. Also, the ratios of LDL-C to HDL-C and total cholesterol to HDL-C did not exhibit significant changes.

SMDs have the potential for drug-drug interactions [4], which could be problematic with the concomitant use of lipid-lowering medications, such as statins [23]. Notwithstanding, JAK inhibitors have been shown to have no clinically relevant effect on the pharmacokinetics of commonly used statins, such as rosuvastatin and atorvastatin [24,25].

Importantly, a previous randomized controlled trial (RCT) conducted on patients with rheumatoid arthritis revealed that the lipid elevation observed in individuals receiving tofacitinib could be effectively attenuated with atorvastatin treatment [26].

2. **Available evidence from the overall IBD population does not indicate a higher risk of cardiovascular events with JAK inhibitors. (Level of Evidence: 3. Agreement: 100 %).**

In clinical trials of JAK inhibitors in IBD, overall case reports of cardiovascular events are limited [27]. The most extensive evidence comes from studies of tofacitinib, where data are available from long-term extension studies and pooled analyses of trials. The most recent pooled safety analysis from the tofacitinib development programme included 1157 patients with UC who received at least one dose of tofacitinib and were followed for up to 7.8 yrs, with a total exposure of 2999.7 patient-years [28]. The majority of patients (955/1157; 82.5 %) received a predominant dose of tofacitinib 10 mg twice daily. Multivariable analysis revealed that advanced age was a risk factor for MACE [28]. The incidence rate (IR) of MACE across all doses of tofacitinib in the overall population was 0.29 (95 % CI 0.13–0.55), a rate comparable to that observed with the use of anti-TNF agents in patients with UC (IR 0.51, 95 % CI 0.31–0.79) [29].

Newer JAK inhibitors, such as upadacitinib and filgotinib, have been tested in induction and maintenance trials for IBD with a promising safety profile. However, due to the low incidence of cardiovascular events in the IBD population and the limited duration of these trials, it is important to gather more data from long-term extension studies and real-world registries to gain a full understanding of the cardiovascular safety profile of these compounds. The phase 3 program for upadacitinib in UC included two induction 8-week trials and one 52-week maintenance trial [30]. No cases of MACE were reported in the induction trials. In the maintenance trial, one patient who was receiving placebo experienced acute myocardial infarction but none in the upadacitinib arms [30]. In the phase 3 programme of upadacitinib in CD, only one cardiovascular event was reported during the 12-week induction trial in a patient who received placebo. However, there were no cases of cardiovascular events in the upadacitinib arm. Furthermore, no cases of cardiovascular events were reported during the 52-week maintenance trial [31].

In the phase 2b/3 development programme of filgotinib in UC, there was only one case of a cerebrovascular event in a patient

receiving placebo in one of the two 11-week induction trials. In the maintenance study, there was one transient ischemic attack event in a patient receiving filgotinib 200 twice daily, and there was one death due to left ventricular heart failure in a patient older than 65 yrs of age [32].

Moreover, previous systematic reviews and meta-analyses of clinical trials have not identified a significantly increased risk of MACE between JAK inhibitors and placebo or active comparators in IBD and other IMIDs [33,34].

Many observational studies have been conducted to evaluate the safety of tofacitinib in real-world settings [35–45]. However, most of these studies have small sample sizes and short follow-up periods, with the majority of these studies reporting no cases of MACE [46].

3. **The role of isoform selectivity of JAK inhibitors in the cardiovascular safety profile in IBD is unclear. (Level of Evidence: 5. Agreement: 100 %).**

Several JAK inhibitors have been developed with different affinities to the four intracellular isoforms of JAKs: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) [47–50]. There are theoretical advantages to selectively targeting specific JAK isoforms: by selectively inhibiting specific isoforms, JAK inhibitors have the potential to modulate more precisely immune responses and inflammatory pathways, thereby minimizing off-target effects and improving the overall risk-benefit ratio [51,52]. For example, selective targeting of JAK1 may be beneficial in the treatment of IBD as it is primarily involved in pro-inflammatory cytokine signaling, which plays a critical role in the pathogenesis of the disease. By selectively inhibiting JAK1, it may be possible to dampen the excessive immune response while minimizing the impact on other isoforms involved in key physiological processes [53]. However, while isoform selectivity is promising, its impact on cardiovascular safety needs to be carefully assessed [54], and to date, there is no evidence that selective JAK inhibitors are safer for the cardiovascular standpoint than non-selective inhibitors in IBD. Further long-term data with the use of selective JAK inhibitors, such as upadacitinib and filgotinib, are necessary.

4. **Cardiovascular risk factors and previous history of atherosclerotic cardiovascular events influence the risk of cardiovascular events in patients with IBD exposed to JAK inhibitors. (Level of Evidence: 3. Agreement: 100 %).**

Although the number of cases of MACE in clinical trials of JAK inhibitors in IBD was low, they were consistently seen in patients with pre-existing atherosclerotic cardiovascular disease or risk factors [30,32,55–61]. In the tofacitinib programme in UC, there were a total of nine cases of MACE, all of which occurred in patients with at least one cardiovascular risk factor, such as older age, smoking status, dyslipidemia, hypertension, diabetes mellitus, or obesity [28].

A recent post-hoc analysis examined the risk of MACE in patients treated with tofacitinib for UC based on their baseline cardiovascular risk [62]. The study used the pooled cohort equations (ASCVD-PCE) for atherosclerotic cardiovascular disease to estimate 10-year risk of the MACE, considering various factors such as age, sex, race, cholesterol levels, blood pressure, history of diabetes, hypertension treatment, and smoking status [63,64]. Out of 1157 patients, 4 % had a prior history of ACVD, while the majority (83 %) had a low or borderline 10-year risk of MACE. Patients with a previous history of cardiovascular disease (IR 0.95; 95 % CI 0.02–5.27), intermediate (IR 1.54, 95 % CI 0.42–3.95), or high (IR 1.81, 95 % CI 0.05–10.07) baseline cardiovascular risk as assessed by the ASCVD-PCE had significantly higher incidence rates of MACE, whereas those with low or borderline risk had almost negligible incidence rates (IR 0 and 0.09, respectively) [62].

5. **The potential risk of cardiovascular events associated with JAK inhibitors should be weighed versus that of uncontrolled inflammation. (Level of Evidence: 5. Agreement: 100 %).**

Systemic inflammation is a well-recognized risk factor for atherosclerotic cardiovascular events, even in the general population [65]. Moreover, inflammatory conditions such as rheumatoid arthritis and IBD are associated with systemic inflammation, which itself contributes to cardiovascular risk [66,67]. Indeed, patients with IBD have a slightly higher risk of arterial thrombotic events, even though traditional risk factors for ACVD are not overrepresented in the IBD population. Several studies have confirmed this increased risk [68–72], and importantly, active disease may further increase the likelihood of cardiovascular events, including myocardial infarction and stroke. A Danish cohort study found that patients with IBD had an increased risk of myocardial infarction, stroke, and cardiovascular death, which increased further during periods of disease activity [73]. Similarly, a French population-based study reported a significant increase in the risk of acute arterial thrombotic events in patients with IBD compared with the general population. The risk was higher in patients with CD than in those with UC, although periods of active disease were independently associated with an increased risk of arterial events in both patient groups [74]. Another cohort study involving 31,175 patients with IBD found an increased risk of myocardial infarction in patients with acute or chronic disease activity [75]. Also, a nested case-control study from France also found that diabetes and clinical disease activity were independently associated with acute arterial thrombotic events in patients with IBD [76]. These findings highlight the importance of recognizing active inflammation as a potentially modifiable cardiovascular risk factor faced in patients with IBD. In this context, when evaluating the risk-benefit profile of JAK inhibitors, it becomes crucial to weigh the potential cardiovascular risks associated with these medications against the risks posed by uncontrolled inflammation and other factors (Fig. 1).

6. **S1P receptor modulators may be associated with a dose-dependent, transient risk of bradycardia and atrioventricular blocks. (Level of Evidence: 1. Agreement: 100 %).**

Sinus bradycardia, characterized by a slow heart rate (< 60 beats per minute), has been reported as an adverse event associated with S1P receptor modulators [12]. This effect is more pronounced shortly after the initiation of treatment, particularly with the first dose, and tends to normalize over time [77]. Monitoring of heart rate before and after initiation of therapy is essential, especially during the titration phase. In addition to bradycardia, S1P receptor modulators have also been associated with atrioventricular (AV) block [78]. AV block is characterized by impaired conduction between the atria and ventricles, resulting in a delay or complete block of electrical signals [79]. Similar to sinus bradycardia, AV block is more likely to occur within the first few hours of treatment initiation, warranting close monitoring during this period. Most AV blocks associated with S1P receptor modulators are of first- and second-degree types, with complete heart blocks being rare.

Ozanimod, a selective S1P1 and S1P5 modulator, demonstrated some cases of cardiac conduction abnormalities in phase 2 and phase 3 RCTs for UC [80,81]. In a phase 2 trial, a single patient in the 0.5 mg group experienced asymptomatic first-degree AV block and sinus bradycardia. However, no second- or third-degree AV blocks were observed [80]. Similarly, in a phase 3 RCT of 796 ozanimod-exposed patients, five cases of bradycardia were reported during the induction period, but none occurred during the maintenance period [81]. The mean decrease in heart rate after the first dose was marginal and returned to baseline within

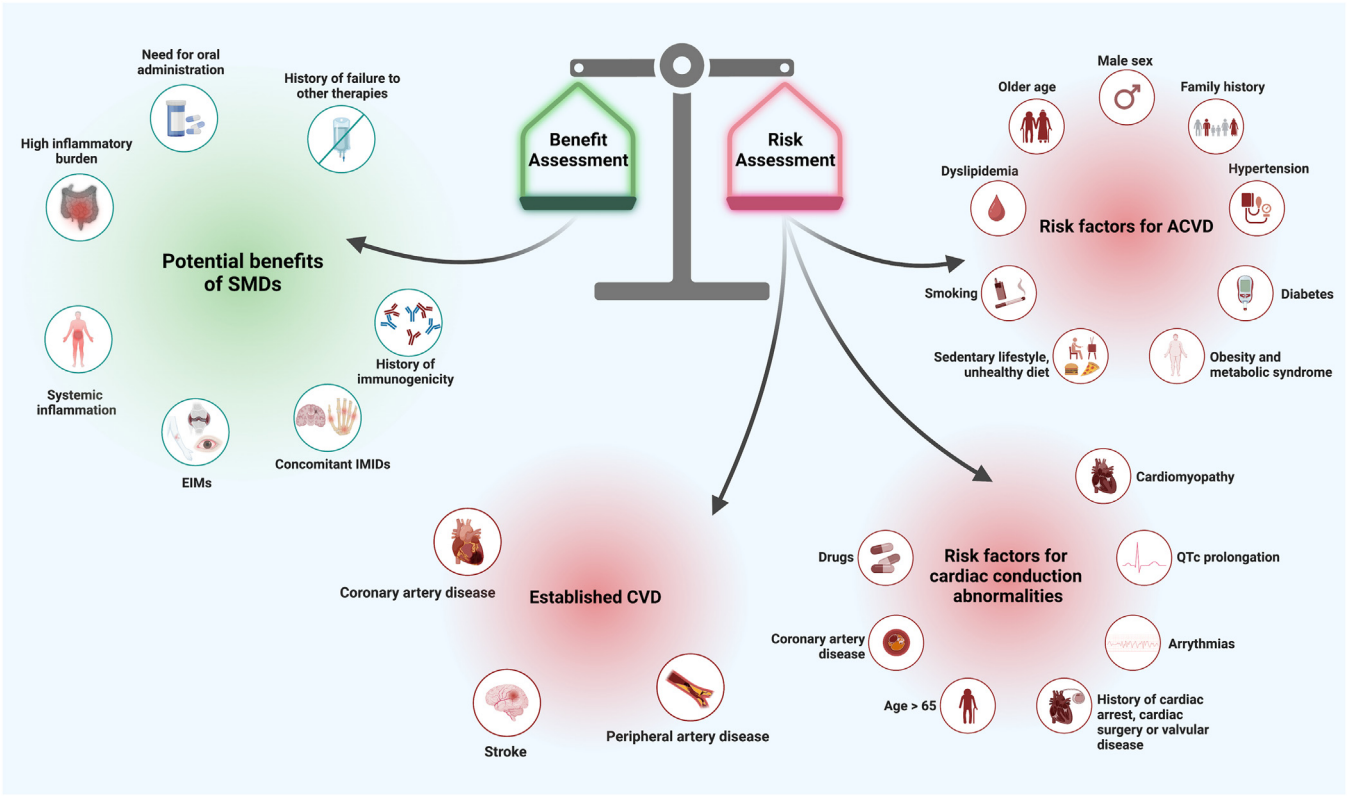

Fig. 1. Balancing potential benefits and cardiovascular risks when considering prescribing small molecule drugs (SMDs) in inflammatory bowel disease. CVD: cardiovascular disease. ACVD: atherosclerotic cardiovascular disease. IMIDs: immune-mediated inflammatory diseases. EIMs: extraintestinal manifestations. Created with BioRender.com.

six hours. Pooled data from phase 3 RCTs suggested a low risk of bradycardia with ozanimod, primarily during the induction period [82]. Long-term data from the TOUCHSTONE extension study reported no cases of bradycardia or AV block in patients receiving 1 mg ozanimod daily for 44 weeks [83].

Etrasimod, a selective S1P1, S1P4, and S1P5 receptor modulator, showed some cardiovascular effects in the phase 2 OASIS study in UC [84]. Among patients receiving etrasimod, one patient experienced second-degree AV block, and two patients experienced first-degree AV block, all of which were detected prior to exposure to etrasimod. During the open-label extension study, no patients discontinued treatment due to cardiac conduction abnormalities, and only one patient experienced a decrease in heart rate [85].

In phase 3 trials (ELEVATE UC 52 and ELEVATE UC 12) involving etrasimod in UC, a total of nine bradycardia events were observed, all occurring in patients receiving etrasimod [86]. Most of these events were reported on day 1 of treatment, and none were reported after day 2. The majority of events were asymptomatic and resolved without intervention. Three events of AV block were also reported, all of which were non-serious, asymptomatic, and resolved spontaneously. Baseline characteristics did not appear to be associated with the development of bradycardia or AV block [87]. Long-term follow-up data from the ongoing 5-year open-label extension study will provide further insight into the cardiovascular safety profile of etrasimod.

Of note, cases of delayed AV blocks requiring pacemaker implantation have been described with the use of fingolimod in multiple sclerosis [88], but to the best of our knowledge, none with ozanimod or etrasimod.

7. **S1P receptor modulators may be associated with new-onset hypertension. (Level of Evidence: 1. Agreement: 92 %).**

New-onset hypertension, including cases of hypertensive crisis, has been reported as a potential adverse effect associated with S1P receptor modulators in multiple sclerosis and IBD [81,83,86,89]. The mechanism by which S1P receptor modulators may contribute to new-onset hypertension is not fully understood, as some studies have suggested an anti-hypertensive effect of S1P [90]. However, it is thought to involve the modulation of S1P receptors in vascular smooth muscle cells and T-cell mobilization, leading to vasoconstriction and increased peripheral resistance [91–93]. Also, consumption of foods high in tyramine (i.e., more than 150 mg) should be avoided, as ozanimod has been associated with increased sensitivity to tyramine, which may lead to the development of hypertension [94,95].

A systematic review and meta-analysis included 17 RCTs in multiple sclerosis (12 for fingolimod; 3 for ozanimod; 2 for siponimod) involving 13,295 patients, demonstrated a 2-fold higher risk of hypertension with the use of S1P receptor modulators in multiple sclerosis (RR 2.00, 95 %CI 1.49–2.67). In a subgroup analysis of studies with ozanimod, the association remained significant (RR 1.76, 95 %CI 1.10–2.82) [89].

In the TRUE NORTH phase 3 trial of ozanimod for UC, 1.6 % (13 out of 796) of patients in the ozanimod group experienced hypertension during the induction phase, compared to none in the placebo group. In the maintenance phase, 1.7 % (4 out of 230) of the ozanimod group had hypertension, compared to 1.6 % (3 out of 227) in the placebo group. One patient in the ozanimod group experienced a hypertensive crisis on the first day of induction, while one patient in the ozanimod group and one in the placebo group experienced hypertensive crises during the maintenance phase [81]. In the open-label extension study of the TOUCHSTONE phase 2 trial, 5.9 % (10 out of 170) of patients receiving ozanimod reported hypertension, which was the second most common adverse event after UC worsening [83]. A study conducted by Cohen et al. evaluated the effects of ozanimod in 30 patients (27 with UC) in a real-world setting. After 26 weeks of treatment, one patient adherent to a low tyramine diet experi-

enced a hypertensive crisis, which led to the discontinuation of therapy [96].

In the ELEVATE UC 12 study, one patient out of 116 in the placebo arm (0.9 %) experienced hypertension compared to three patients out of 239 (1.3 %) in the etrasimod arm. In the ELEVATE UC 52 study, 1 out of 144 patients (0.7 %) who received placebo experienced hypertension, compared to 8 out of 289 patients (2.8 %). However, none of these events led to an interruption or discontinuation of the studies [86].

8. **Screening of cardiovascular risk factors and risk stratification should be done in all patients with IBD. (Level of Evidence: 5. Agreement: 79 %).**

As the overall IBD population ages, cardiovascular disease has become a significant comorbidity in individuals with IBD [27,97–99]. Proactive assessment of cardiovascular risk factors and risk stratification in this population has become necessary due to the growing recognition of the association between IBD and cardiovascular disease [100]. Several studies have linked IBD and cardiovascular disease, with chronic inflammation being an important driving factor (statement 5) [68,69,71,73–76,101].

Patients with IBD may have classic cardiovascular risk factors such as smoking, diabetes, dyslipidemia, obesity, and a sedentary lifestyle, although these are not often overrepresented compared with the general population [70,102,103]. These factors may act synergistically to further increase the risk of cardiovascular events, together with the chronic inflammatory state that characterizes IBD. Additionally, drugs used to treat IBD may further increase cardiovascular risk even higher [27,100]. In particular, corticosteroids have been associated with increased risk due to changes in lipid profiles and glucose metabolism [104–108].

Implementing regular screening for cardiovascular risk factors at age-appropriate levels is crucial and should be assessed in collaboration with primary care physicians. This includes assessment of body mass index, fasting glucose levels, lipid profiles, and blood pressure. Evaluation of smoking habits and family history of cardiovascular disease is important. By incorporating these screenings into routine clinical care, the risk of cardiovascular events can be reduced through early detection and prompt referral to a cardiovascular specialist for appropriate intervention.

A key component of ASCVD prevention is the identification of individuals who will benefit most from risk factor therapy. In that regard, the risk of cardiovascular disease risk in apparently healthy, asymptomatic individuals can be estimated using various models, including the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations CV Risk Calculator [63,64], the European Society of Cardiology (ESC) Systemic Coronary Risk Estimation (SCORE2) algorithm [109,110], or the NICE (National Institute for Health and Care Excellence) QRISK3 calculator [111,112]. Also, the World Health Organisation developed a validated model for cardiovascular disease risk prediction calibrated for various world regions, including low-income and middle-income countries [113].

9. **Screening of cardiovascular risk factors and risk stratification should be done before initiation of JAK inhibitors or S1P receptor modulators. (Level of Evidence: 5. Agreement: 100 %).**

Given the potential cardiovascular effects of S1P receptor modulators and JAK inhibitors, screening for cardiovascular risk factors and conducting risk stratification prior to initiating this class of medications in IBD patients is of particular importance. Risk stratification based on individual cardiovascular risk profiles allows for a personalized approach [27].

High-risk patients may require closer monitoring or an alternative treatment. Careful screening and risk stratification can help physicians optimize the risk-benefit profile of initiating JAK inhibitors or S1P receptor modulators in IBD [114]. Other IBD-related factors to consider include a history of previous treatment failures, availability of alternative treatment options, extraintestinal manifestations, or concomitant IMIDs (Fig. 1).

10. **Management of cardiovascular risk factors should follow recommendations used in the general population in collaboration with cardiologists and primary care physicians. (Level of Evidence: 5. Agreement: 100 %).**

In patients with IBD with established cardiovascular disease or known risk factors, it is essential to establish appropriate management strategies that include both lifestyle modifications and pharmacological interventions to effectively reduce cardiovascular events. The need for lifestyle modification or pharmacological interventions, such as antihypertensive or lipid-lowering agents, should be evaluated on the basis of each individual's specific profile based on guidelines for the non-IBD population [115]. Collaborative efforts among primary care physicians, cardiologists, and gastroenterologists through a multidisciplinary approach are pivotal components for achieving comprehensive management plans.

11. **Counselling and education regarding cardiovascular risk should be done in patients with IBD. Healthy lifestyle modifications should be encouraged. (Level of Evidence: 5. Agreement: 100 %).**

Promoting healthy lifestyle modifications is a crucial component of patient counseling and education. Patients with IBD can reduce their cardiovascular risk profile by being encouraged to adopt and maintain a healthy lifestyle. Key elements of lifestyle modification include encouraging regular physical activity, smoking cessation, and adopting a balanced diet [115]. Healthy lifestyle changes have also been associated with improvements in the overall quality of life [116]. To enable patients to make informed choices about their lifestyle choices and actively participate in the management of their cardiovascular health, counseling and education, are of paramount importance.

12. **In patients with IBD with a history of atherosclerotic cardiovascular disease or at significant risk, treatment with JAK inhibitors should be considered if there are no suitable therapeutic alternatives. (Level of Evidence: 5. Agreement: 100 %).**

According to current labeling and regulatory recommendations, JAK inhibitors should be avoided in the presence of established ASCVD or in patients at significant cardiovascular risk unless there are no suitable therapeutic alternatives [9–11]. JAK inhibitors have proven to be one of the most effective therapies in patients who already failed other mechanisms of action [117–119]. Therefore, in biologic-experienced patients, especially those with a high inflammatory burden, the benefits of JAK inhibitors may outweigh the risks even in the presence of cardiovascular risk factors (Fig. 1). Notwithstanding, the decision to treat patients with a less favorable cardiovascular profile with JAK inhibitors should be individualized by effectively communicating the potential risk in a shared decision-making process [114].

Patients with established ASCVD are always considered at a very high cardiovascular risk; for the other patients, there are several calculators available to estimate the risk of future cardiovascular events (statement 8). In most of these risk calculators, age is the main factor, meaning that male patients younger than 40 yrs of age and female patients younger than 50 years are almost always at low risk, whereas those older than 65 yrs of age (75 yrs for women) are almost invariably at high risk [109]. However, younger patients may have modifiable risk factors that significantly increase their lifetime cardiovascular risk, and physicians should assess for

these and the overall cardiovascular risk before prescribing JAK inhibitors (statement 9).

13. **When starting a JAK inhibitor, the lipid profile (including total cholesterol, LDL-C, HDL-C, and triglycerides) should be measured at baseline, after induction, and routinely every 6 months. Management of dyslipidemia should follow current guidelines. (Level of Evidence: 5. Agreement: 82 %).**

Tofacitinib and other JAK inhibitors have been associated with changes in the lipid profile (statement 1). A reduction in cholesterol ester catabolism has been implicated in the increase in lipid levels [17,19,47]. The prescribing information for tofacitinib recommends that lipid concentrations should be monitored for 4–8 weeks after initiation of therapy. A prospective study analyzed the lipid profile after induction therapy with systemic therapies and found that relative increases in total cholesterol, HDL-C, and LDL-C were significant with prednisone (+ 26 %, + 31 %, + 12 %) and tofacitinib therapy (+ 20 %, +25 %, + 26 %), but not with other drug classes [120]. These results have been seen in other real-world cohorts and, along with data from clinical trials, support the notion of monitoring lipid abnormalities after induction.

A pooled analysis of six phase 3 trials and two long-term extension studies in rheumatoid arthritis found 52 cases of MACE in 4076 patients over 12,873 patient-years of exposure (incidence rate 0.4 per 100 patient-years). Interestingly, after 24 weeks of therapy, increased HDL-C, but not increased LDL-C or total cholesterol, appeared to be associated with a lower risk of future MACE after adjustment for age, baseline risk factors, and time-varying tofacitinib dose [18]. These results suggest that routine monitoring of the lipid profile may be warranted, as variable lipid levels may affect the risk of future MACE.

14. **During the maintenance phase, the lowest effective dose to maintain remission with JAK inhibitors should be aimed. The higher maintenance dose should be avoided in patients with IBD and known cardiovascular risk factors. (Level of Evidence: 5. Agreement: 92 %).**

Given the dose-dependent effect on the safety profile of JAK inhibitors, the lowest dose that is effective in maintaining remission should be sought [27]. However, clinical trials and real-world data suggest that a higher maintenance dose of JAK inhibitors may be required in certain scenarios (e.g., previous failure of multiple lines of therapy, high inflammatory burden). In patients with established cardiovascular disease or in those with an unfavorable cardiovascular risk profile, the highest maintenance dose of JAK inhibitors (e.g., tofacitinib 10 mg twice daily or upadacitinib 30 mg daily) should be avoided if possible [114]. In patients with IBD at increased cardiovascular risk who are unable to maintain remission on the lower dose, the use of the higher dose should be considered with extreme caution in patients without therapeutic alternatives and under close cardiological monitoring.

15. **When considering treatment with an S1P receptor modulator, concomitant medications and symptoms suggestive of cardiac conduction abnormalities should be reviewed. (Level of Evidence: 5. Agreement: 90 %).**

When considering treatment with an S1P receptor modulator, it is important to review concomitant medications that could potentially interact with these drugs [27]. An active metabolite of ozanimod inhibits monoaminoxidase-B in vitro; hence, there is a potential risk of serious adverse reactions, including hypertensive crisis, with concomitant use of ozanimod with drugs that can increase norepinephrine or serotonin (e.g., opioid drugs, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressants) [121].

Antiarrhythmic drugs are commonly prescribed to treat heart rhythm disorders, and their concomitant use with S1P receptor modulators may lead to additive effects on cardiac conduction, paradoxically increasing the risk of arrhythmias and conduction disturbances [122].

Drugs that prolong the QT interval can predispose individuals to a specific type of polymorphic ventricular arrhythmia known as *torsades de pointes* [122]. Drugs that are known to prolong the QT interval include antiarrhythmics, some antidepressants, antimicrobials such as macrolide and fluoroquinolone antibiotics, and azole antifungals [123]. When used concurrently with S1P receptor modulators, there is a possibility of additive QT prolongation, potentially increasing the risk of arrhythmias.

Additionally, medications that reduce the heart rate should be reviewed. S1P receptor modulators have the potential to cause a transient decrease in heart rate and should, therefore, be carefully monitored in combination with drugs with a negative chronotropic effect (e.g., beta-blockers and calcium channel blockers) should be carefully monitored to avoid sinus bradycardia or AV blocks [121].

If S1P receptor modulators are being considered in patients requiring antiarrhythmics or medications that may prolong the QT interval or reduce the heart rate, cardiac assessment is required before initiation.

16. **Holter monitoring should be considered in patients with IBD and a history of symptoms suggestive of cardiac conduction abnormalities when treatment with an S1P receptor modulator is considered. (Level of Evidence: 5. Agreement: 83 %).**

According to the drug label, baseline electrocardiograms (ECGs) should be performed routinely in patients initiating S1P receptor modulators to identify asymptomatic cardiac conduction abnormalities, such as atrioventricular block [121]. Holter ECG monitoring with 24-hour or longer recording should be considered in conjunction with a thorough cardiovascular assessment by a general practitioner or cardiologist, depending on local practice and availability, in patients with symptoms suggestive of cardiac arrhythmia or conduction abnormalities (e.g., syncope, dizziness, palpitations) and in patients with known or suspected risk factors for such conditions [124,125].

17. **A cardiology consultation should be considered before starting an S1P receptor modulator in patients with IBD and risk factors for cardiac conduction abnormalities or uncontrolled hypertension. (Level of Evidence: 5. Agreement: 77 %).**

Clinicians should exercise caution when prescribing S1P receptor modulators to patients with known pre-existing cardiac conduction disorders (e.g., AV block, sick sinus syndrome, or sinoatrial heart block) or risk factors for these, such as a history of cardiovascular disease (e.g., ischemic heart disease, cardiomyopathy, cardiac arrest, cardiac surgery, surgical/percutaneous treatment of valvular disease), increasing age, QT prolongation, or uncontrolled hypertension [27]. These individuals may be at higher risk of developing sinus bradycardia or AV block. Close monitoring of cardiac function and careful evaluation of the risk-benefit ratio are essential in such cases.

18. **Blood pressure of patients with IBD treated with an S1P receptor modulator should be routinely checked. (Level of Evidence: 5. Agreement: 100 %).**

S1P receptor modulators have been associated with cardiovascular effects, including new-onset hypertension (statement 7). Regular blood pressure monitoring allows for early detection and timely intervention to prevent complications [126]. It helps to identify patients who may be more prone to developing hypertension or experiencing abnormal blood pressure changes [127]. As S1P receptor modulators are often prescribed for the long-term

management of IBD, routine blood pressure monitoring provides valuable information on the ongoing effects of the medication.

Given the potential effects of ozanimod on tyramine sensitivity and hypertension, a low tyramine diet should be advised during ozanimod treatment. If hypertension develops, it should be treated according to current guidelines [121].

4. Conclusions and future directions

While JAK inhibitors and S1P receptor modulators have been shown to be effective in IBD, some clinicians may be cautious about prescribing them because of the perceived cardiovascular risk profiles associated with these drugs.

Patients, too, may be reluctant about medications carrying boxed warnings. However, it is crucial to recognize that individual patients assess risks and benefits differently, and their treatment preferences are influenced by a unique set of factors that weigh what is more important to them [128]. Physicians tend to underestimate the risks patients are willing to accept in order to achieve better disease control and avoid complications [129], especially when a dedicated shared decision-making process is implemented [130]. Therefore, every therapeutic decision in every clinical scenario in IBD should take these factors into consideration.

Evidence of these risks has largely been extrapolated from other IMIDs, such as the ORAL surveillance study in rheumatoid arthritis or the use of fingolimod in multiple sclerosis [7,89]. Although the overall risk of MACE and cardiac conduction abnormalities in patients with IBD appears to be low overall, caution is warranted in certain clinical scenarios. The aim of this consensus is to provide practical advice, based on the available evidence, to help clinicians minimize the cardiovascular risk of SMDs while communicating information to patients in a way that enables adequate informed decisions. Specific management of established cardiovascular disease and risk factors is outside the scope of this consensus, and gastroenterologists should consult primary care physicians and cardiovascular specialists for support in these cases. Although the current evidence is reassuring, additional long-term extension trials of newer compounds, such as selective JAK1 inhibitors and real-world observational studies, are still needed to fully understand the safety profile of these drugs.

Funding statement

Independent Medical Education Grant from Pfizer

Authorship statement

LPB was the guarantor of the article. All authors approved the final version of the manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used Grammarly® to improve grammar and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Conflict of Interest

PAO declares no conflict of interest. AD reports fees for participation in clinical trials, review activities such as data monitoring boards, statistical analysis, and end point committees from Abivax, AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb/Celgene, Dr Falk Foundation, Galapagos, Gilead, Janssen, and Pfizer; consultancy fees from AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Boehringer Ingelheim, Bristol Myers Squibb/Celgene, Celltrion, Dr Falk Foundation, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos, Janssen, Lilly, MSD, Pfizer, Pharmacosmos, Roche/Genentech, Sandoz/Hexal, Takeda, Tillotts, and Vifor Pharma; payment from lectures including service on speakers bureaus from AbbVie, Biogen, CED Service GmbH, Celltrion, Falk Foundation, Ferring, Galapagos, Gilead, High5MD, Janssen, Materia Prima, MedToday, MSD, Pfizer, Streamed-Up, Takeda, Tillotts, and Vifor Pharma; payment for manuscript preparation from Falk Foundation, Takeda, Thieme, and UniMed Verlag. MCD has received consulting fees from AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, Pfizer Inc, Prometheus Laboratories, Takeda, and UCB. GP declares no conflict of interest. PGK: speaking and consultancy honorarium from Abbvie, Janssen, Pfizer and Takeda; Scientific grants from Pfizer and Takeda. ID has served as a speaker, consultant, or advisory board member for Takeda, Janssen, AbbVie, Pfizer, Eli-Lilly, Ferring, Roche/Genentech, Cambridge Healthcare, Celgene/BMS, Falk Pharma, Ierative Scopes, Rafa Laboratories, Neopharm, Arena, Gilead, Galapagos, Celltrion, Sublimity, Sandoz, Abbott, and Athos Therapeutics. TK has served as a speaker, a consultant or an advisory board member for AbbVie, Alfresa Pharma, Bristol Myers Squibb, Celltrion, Covidien, EA Pharma, Eisai, Eli Lilly, Ferring Pharmaceuticals, Gilead Sciences, Janssen, JIMRO, Kyorin Pharmaceutical, Kissei, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Sekisui Medical, Takeda Pharmaceutical, Zeria Pharmaceutical, and received research funding from AbbVie, Alfresa Pharma, EA Pharma, Gilead, Kyorin Pharmaceutical, Mochida Pharmaceutical, Nippon Kayaku, Otsuka Holdings, Pfizer, Sekisui Medical, Takeda Pharmaceutical, Zeria Pharmaceutical. SG reports research grants from GSK, Abbvie; Drug Monitoring Committee from Janssen, Steering Committees from BMS, Receptos, Janssen, Abbvie, Gilead, Galapagos; Lecture fees from Takeda, Pfizer, Janssen, Abbvie, BMS, Galapagos, Gilead, Celltrion and consulting fees from Abbvie, Janssen, Takeda, Pfizer, Galapagos, Celltrion, Ferring. FM has served as a speaker and received honoraria from Abbvie, Arena, Biogen, Bristol-Myers Squibb, Falk, Ferring, Hospira, Janssen, Laboratórios Vitoria, Pfizer, Lilly, Merck Sharp & Dohme, Sandoz, Takeda, UCB, and Vifor. JRFN declares no conflict of interest. BS has consulted for AbbVie, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Endpoint Health, Falk Pharma, Galapagos, Janssen, Landos, Lilly, Pfizer, Prometheus, and Takeda; has received speaker fees from AbbVie, CED Service GmbH, Falk Pharma, Ferring, Janssen, Novartis, Pfizer, and Takeda, and has received funding from Pfizer. SD has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson & Johnson, Millenium Takeda, MSD, NikkisoEurope GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma, and Vifor. LPB reports personal fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Celltrion, Takeda, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Inotrem, Al-lergan, MSD, Roche, Arena, Gilead, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, OSE Immunotherapeutics, Enthera, Theravance, Pandion Therapeutics, Gossamer Bio, Viatris, Thermo Fisher; grants from AbbVie, MSD, Takeda, Fresenius Kabi; and has stock options in CTMA.

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ing. **Paulo G. Kotze:** Supervision, Writing – review & editing. **Iris Dotan:** Supervision, Writing – review & editing. **Taku Kobayashi:** Supervision, Writing – review & editing. **Subrata Ghosh:** Supervision, Writing – review & editing. **Fernando Magro:** Supervision, Writing – review & editing. **Jose Rocha Faria-Neto:** Supervision, Writing – review & editing. **Britta Siegmund:** Supervision, Writing – review & editing. **Silvio Danese:** Supervision, Writing – review & editing. **Laurent Peyrin-Biroulet:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.03.010.

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