



ICT 2023

28th International
Congress on Thrombosis

Risk of thrombosis in pediatric patients with inflammatory bowel disease

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Declaration of Conflict Of Interest

✓ I have no potential conflict of interest to report

Thrombotic Risk factors in PIBD

Severe disease

Surgery

Smoking

Oral contraceptive pill

Complete immobilisation

Central venous catheters or PICC
lines

Obesity

Concurrent significant infection

Known thrombotic disorder

Previous VTE

Family history of VTE

Systemic steroids

Parenteral nutrition

Risk of Venous Thromboembolism in Children: A Population-Based Matched Cohort Study

- 5-year incidence of VTE among 3593 children with IBD:
 - 31.2 [95% CI 23.7–41.0] /10 000 person-years vs 0.8 [0.4–1.7] in 16289 controls [adjusted **HR 22.91**, 95% CI 11.50–45.63].
- VTE was less common in Crohn's disease than ulcerative colitis
- Uncontrolled active inflammation could play a significant etiological role

Venous thromboembolisms (VTE) in paediatric-onset inflammatory bowel disease (PIBD)

Rare and severe complications in PIBD patients

Large coverage of PIBD patients in Europe



Countries

30



Monthly reporting of VTE occurrence



PIBD-SETQ
Safety registry

International prospective registry

129

Participating centers



53,762 PIBD patient-years

VTE incidence

per 10 000 patient-years (95% CI)



Higher incidence



0.27 (0.18 – 0.38)

General paediatric population

3.72 (2.27 – 5.74)

Paediatric IBD population

VTE types



Cerebral sinus venous thrombosis



Deep vein thrombosis



Pulmonary embolism

IBD-specific risk factors



Active disease
19/20 cases



Ulcerative colitis/IBD-U
14/20 cases



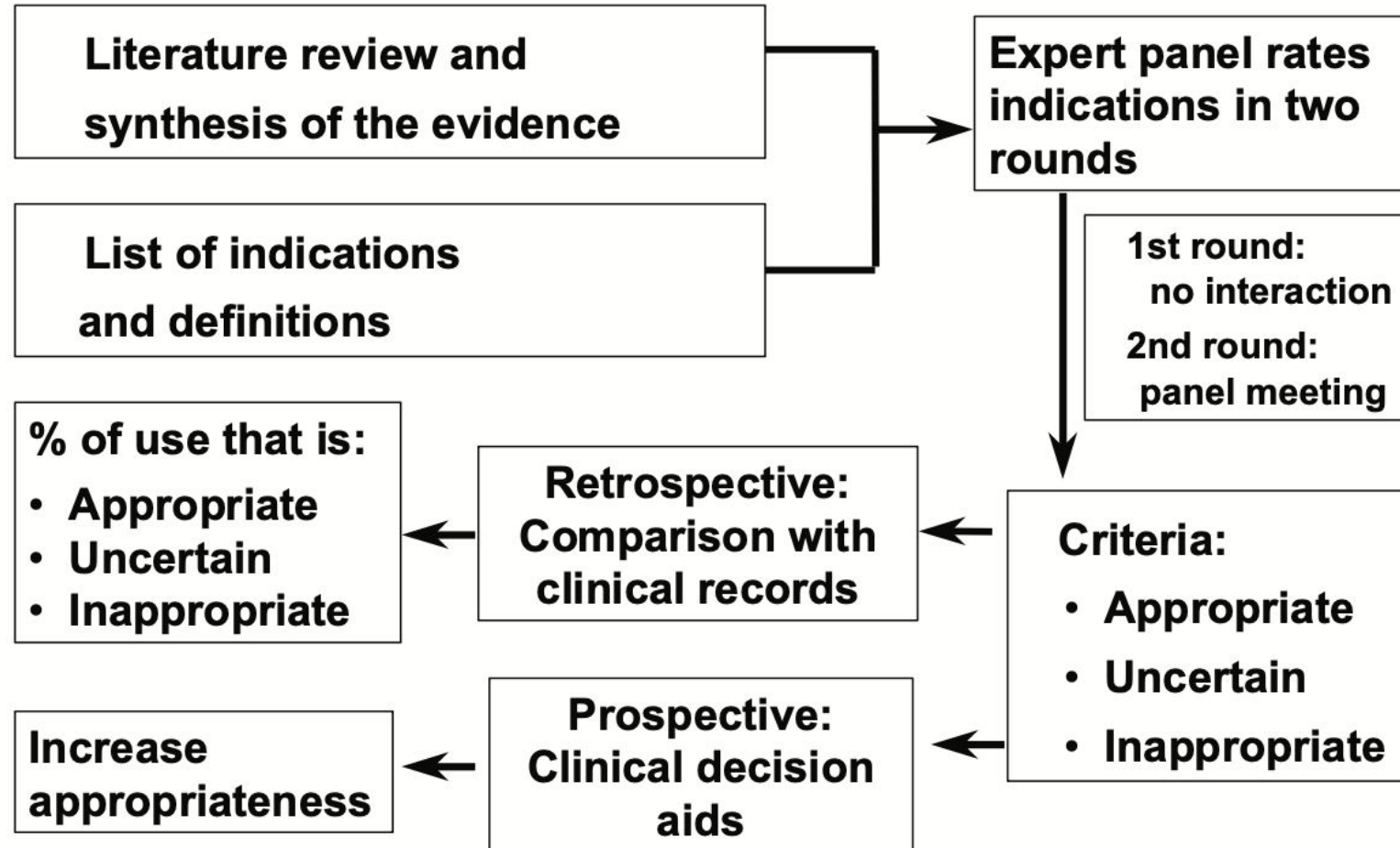
Hospital admission
RR 559 (231 – 1348)

The Incidence and Characteristics of Venous Thromboembolisms in Paediatric-Onset Inflammatory Bowel Disease: A Prospective International Cohort Study Based on the PIBD-SETQuality Safety Registry

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- 129 PIBD Centres (24802 patients)
- 20 episodes of VTE (30% Crohn's Disease)
- The incidence of VTEs was 3.72 (95% confidence interval [CI] 2.27–5.74) per 10 000 person-years
 - 14-fold higher than in the general population
- No patient received thromboprophylaxis
 - according to current PIBD guidelines, this was recommended in 4/20 patients

RAND/UCLA Appropriateness method



Method

- Panel of 12 pediatric gastroenterologists
- Literature search performed and provided
- Members of the panel were asked to rate the appropriateness of prescribing thromboprophylaxis in hospitalised patients with IBD in specific clinical scenarios:
 - new-onset acute severe colitis
 - known Crohn's disease with a severe flare requiring hospitalization
 - known ulcerative colitis with a severe flare requiring hospitalization
- Online meeting that included four experts (pediatric and adult colorectal surgeon, pediatric haematologist, pediatric clinical nurse specialist) and two moderators.

New onset acute severe colitis

| Management | Offer no thromboprophylaxis | Offer thromboprophylaxis until discharged home | Offer thromboprophylaxis until clinical remission |
|--|-----------------------------|--|---|
| 9-year-old Pre-pubertal | Inappropriate | Appropriate | Uncertain |
| 15-year-old Female Post-pubertal | Inappropriate | Appropriate | Uncertain |
| 15-year-old Male Post-pubertal | Inappropriate | Appropriate | Uncertain |

Known ulcerative colitis requiring admission

| Thrombosis risk | | No risk factors | | | ≥ 1 Risk factor | |
|----------------------------------|-----------------------------|--|---|-----------------------------|--|---|
| Management | Offer no thromboprophylaxis | Offer thromboprophylaxis until discharged home | Offer thromboprophylaxis until clinical remission | Offer no thromboprophylaxis | Offer thromboprophylaxis until discharged home | Offer thromboprophylaxis until clinical remission |
| 9-year-old Pre-pubertal | Uncertain | Appropriate | Uncertain | Inappropriate | Appropriate | Uncertain |
| 15-year-old Female Post-pubertal | Inappropriate | Appropriate | Uncertain | Inappropriate | Appropriate | Uncertain |
| 15-year-old Male Post-pubertal | Inappropriate | Appropriate | Uncertain | Inappropriate | Appropriate | Uncertain |

Flaring patients with known UC requiring admission

| Thrombosis risk | No risk factors | | | ≥ 1 Risk factor | | |
|--------------------------------------|-----------------------------|--|---|-----------------------------|--|---|
| Management | Offer no thromboprophylaxis | Offer thromboprophylaxis until discharged home | Offer thromboprophylaxis until clinical remission | Offer no thromboprophylaxis | Offer thromboprophylaxis until discharged home | Offer thromboprophylaxis until clinical remission |
| 9-year-old Pre-pubertal | Inappropriate | Appropriate | Uncertain | Inappropriate | Appropriate | Uncertain |
| 15-year-old Female | Inappropriate | Appropriate | Uncertain | Inappropriate | Appropriate | Uncertain |
| Post-pubertal 15-year-old Male | Inappropriate | Appropriate | Uncertain | Inappropriate | Appropriate | Uncertain |
| Post-pubertal | | | | | | |

Flaring patients severe Crohn's disease requiring admission, despite adequate first line immunosuppression

In a 9-year-old (pre-pubescent) patient with known Crohn's disease with severe active disease in an "ileal" distribution (Paris L1, B1) despite adequate first line immunosuppression and **no associated risk factors for venous thrombosis**

| | | | | | |
|---|-----|------|------|-----|------------------|
| Offer no thromboprophylaxis | 4.5 | 0.97 | 2.39 | 3.0 | Uncertain |
| Offer thromboprophylaxis until discharged home | 5.5 | 0.77 | 2.34 | 2.4 | Uncertain |
| Offer thromboprophylaxis until clinical remission | 3.5 | 0.46 | 1.62 | 2.7 | Uncertain |

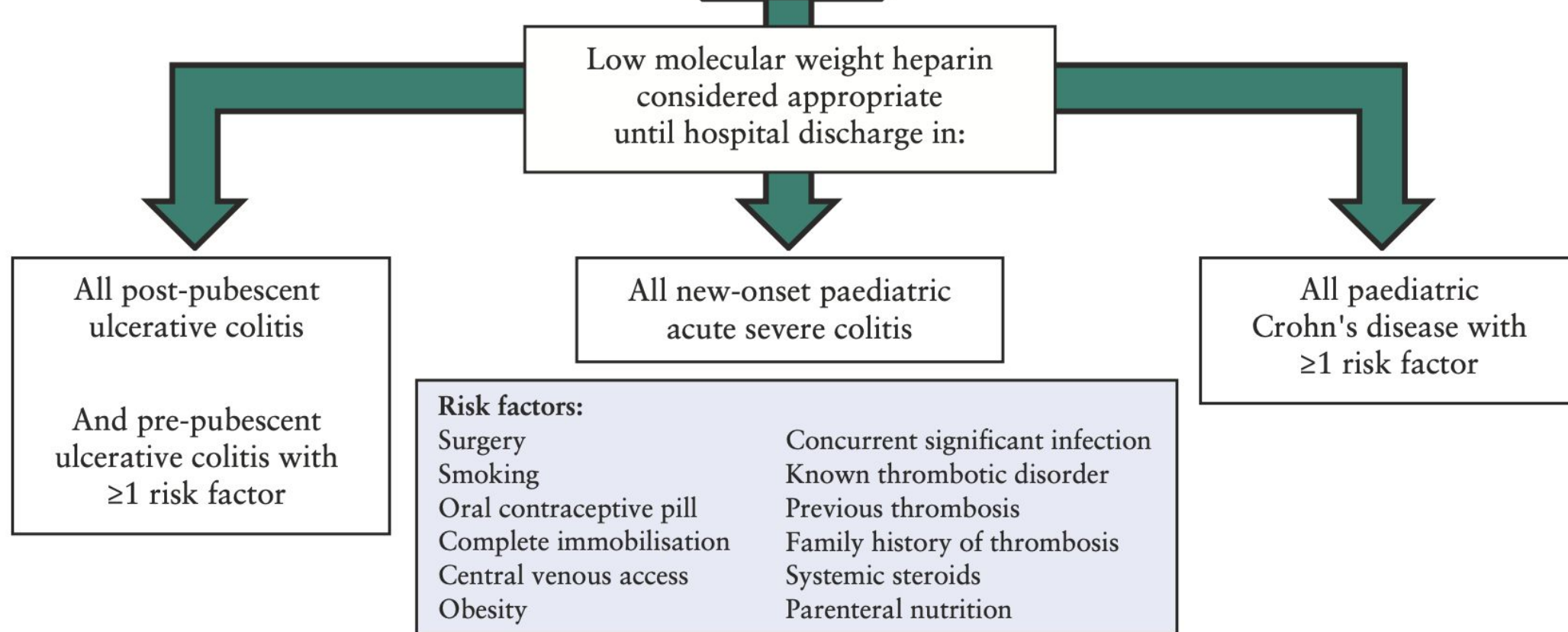
Flaring patients severe Crohn's disease requiring admission, despite adequate first line immunosuppression

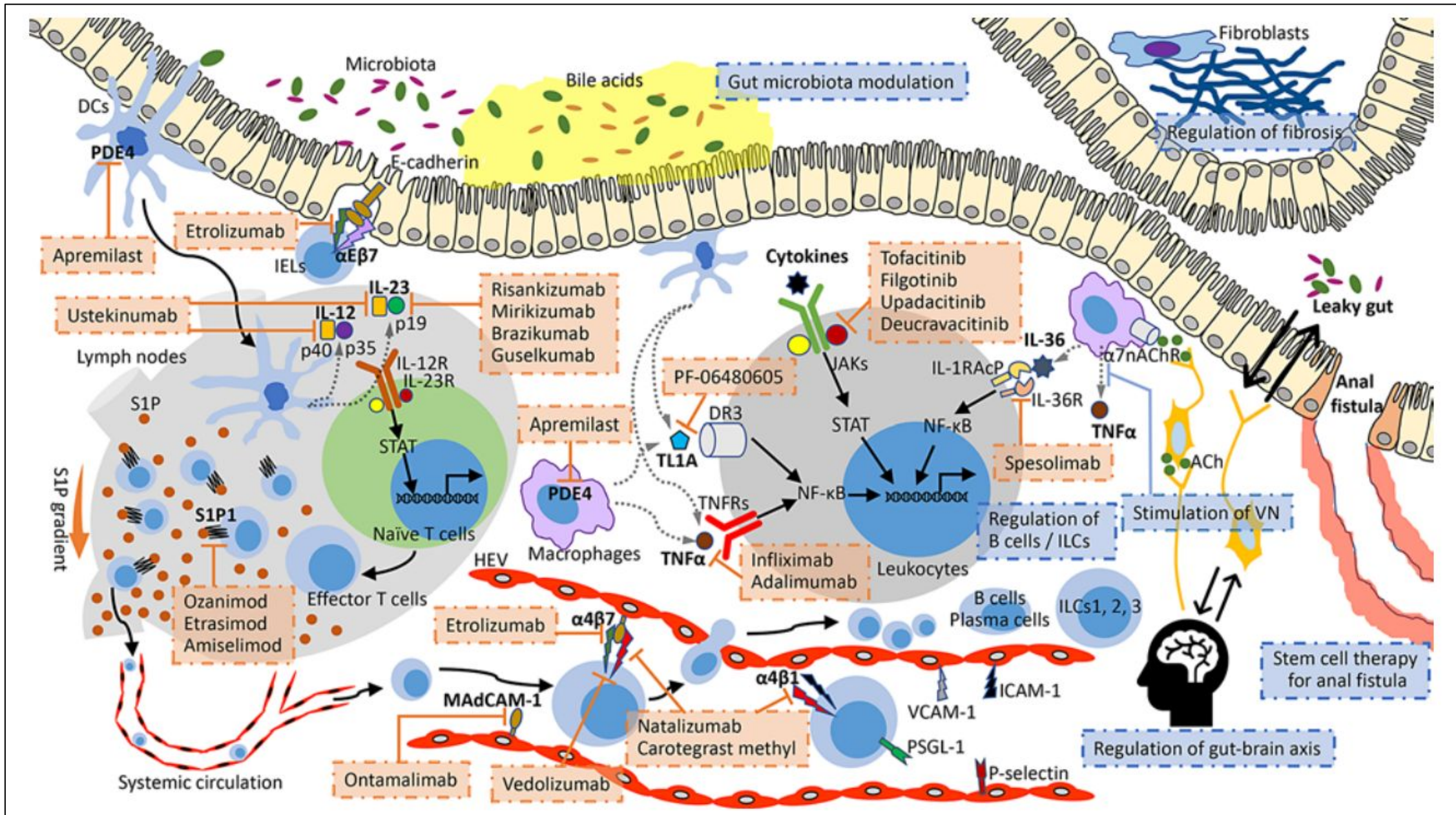
| In a 9-year-old (pre-pubescent) patient with known Crohn's disease with severe active disease in an "ileal" distribution (Paris L1, B1) despite adequate first line immunosuppression and one or more associated risk factors for venous thrombosis | | | | | |
|---|-----|------|------|-----|---------------|
| Offer no thromboprophylaxis | 3.0 | 0.22 | 1.50 | 1.0 | Inappropriate |
| Offer thromboprophylaxis until discharged home | 7.0 | 0.26 | 1.82 | 1.4 | Appropriate |
| Offer thromboprophylaxis until clinical remission | 4.0 | 0.52 | 1.65 | 2.0 | Uncertain |

Thromboprophylaxis Use in Paediatric Inflammatory Bowel Disease: An International RAND Appropriateness Panel

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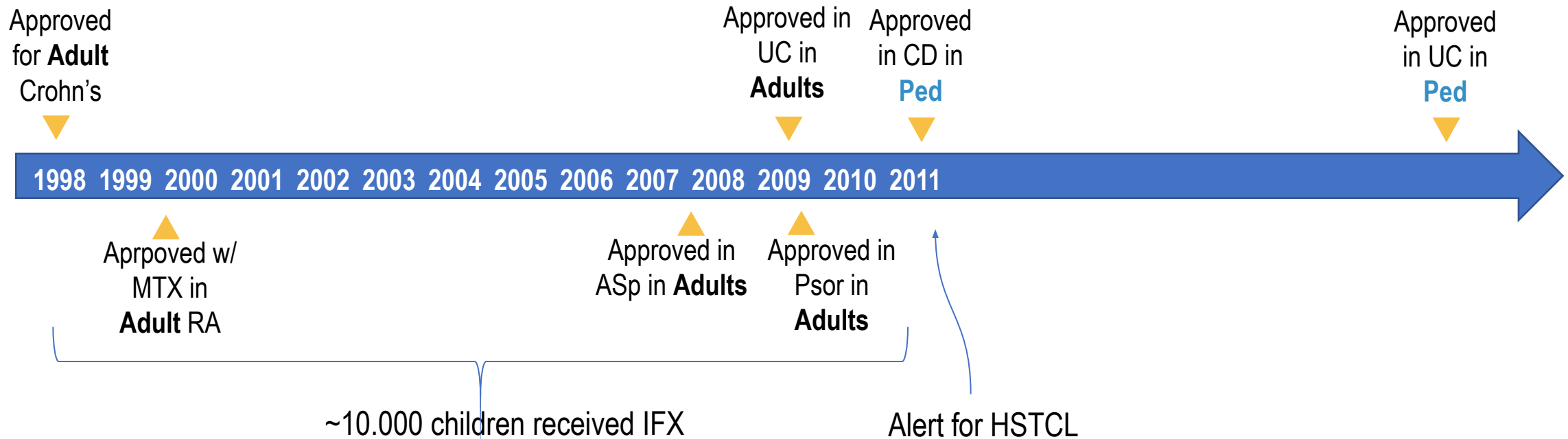




Increasing treatment options

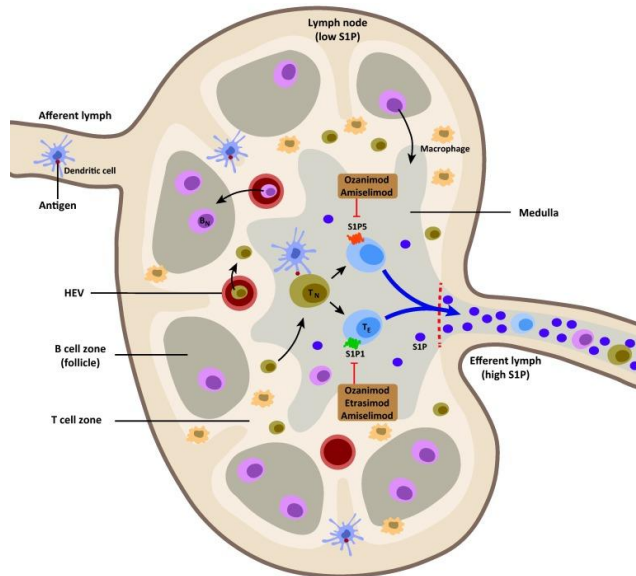
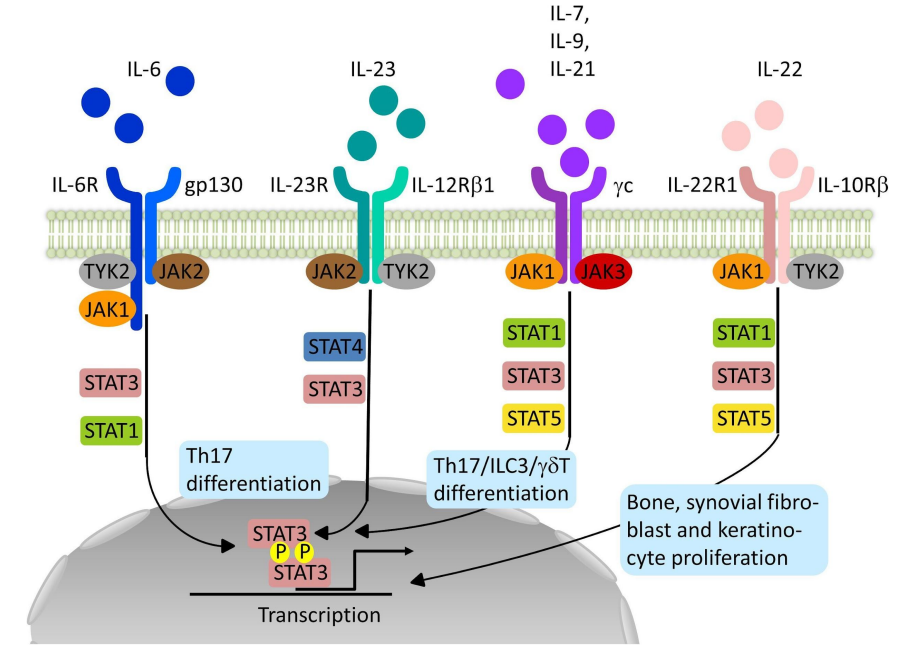
Long time from adult and pediatric approval of new drugs

Time of approval of Infliximab



New drugs for IBD

- Targeting downstream cytokine signaling with Janus kinase (JAK) inhibitors.



- Blocking lymphocytic traffic with sphingosine-1-phosphate receptor (S1P) modulators.

Tofacitinib Therapy in Children and Young Adults With Pediatric-onset Medically Refractory Inflammatory Bowel Disease

^{*†}Hillary Moore, ^{*}Lucie Dubes, ^{*†}Steven Fusillo, ^{*†}Robert Baldassano, and ^{*†}Ronen Stein

Systematic Review With Meta-analysis: Safety and Effectiveness of Combining Biologics and Small Molecules in Inflammatory Bowel Disease

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LETTERS TO THE EDITORS

AP&T Alimentary Pharmacology & Therapeutics

WILEY

Letter: tofacitinib use for biologic-refractory paediatric inflammatory bowel disease

Dual Biologic and Small Molecule Therapy for the Treatment of Refractory Pediatric Inflammatory Bowel Disease

Michael T. Dolinger, MD, MBA, Elizabeth A. Spencer, MD^o, Joanne Lai, MD, David Dunkin, MD, and Marla C. Dubinsky, MD

JAK inhibitors – FDA and EMA recommendations

FDA

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with tofacitinib, baricitinib or upadacitinib, particularly in:

- Current or past smokers
- Presence of CV risk factors
- History or risk of malignancy, other than a successfully treated non-melanoma skin cancer

Reserve JAK inhibitors for patients who have had an inadequate response or intolerance to one or more anti-TNF agents

Inform patients about the symptoms of serious CV events and to seek emergency medical attention if they occur

EMA

JAK inhibitors (tofacitinib, upadacitinib, filgotinib, baricitinib, abrocitinib) should only be used if no suitable treatment alternatives are available in the following:

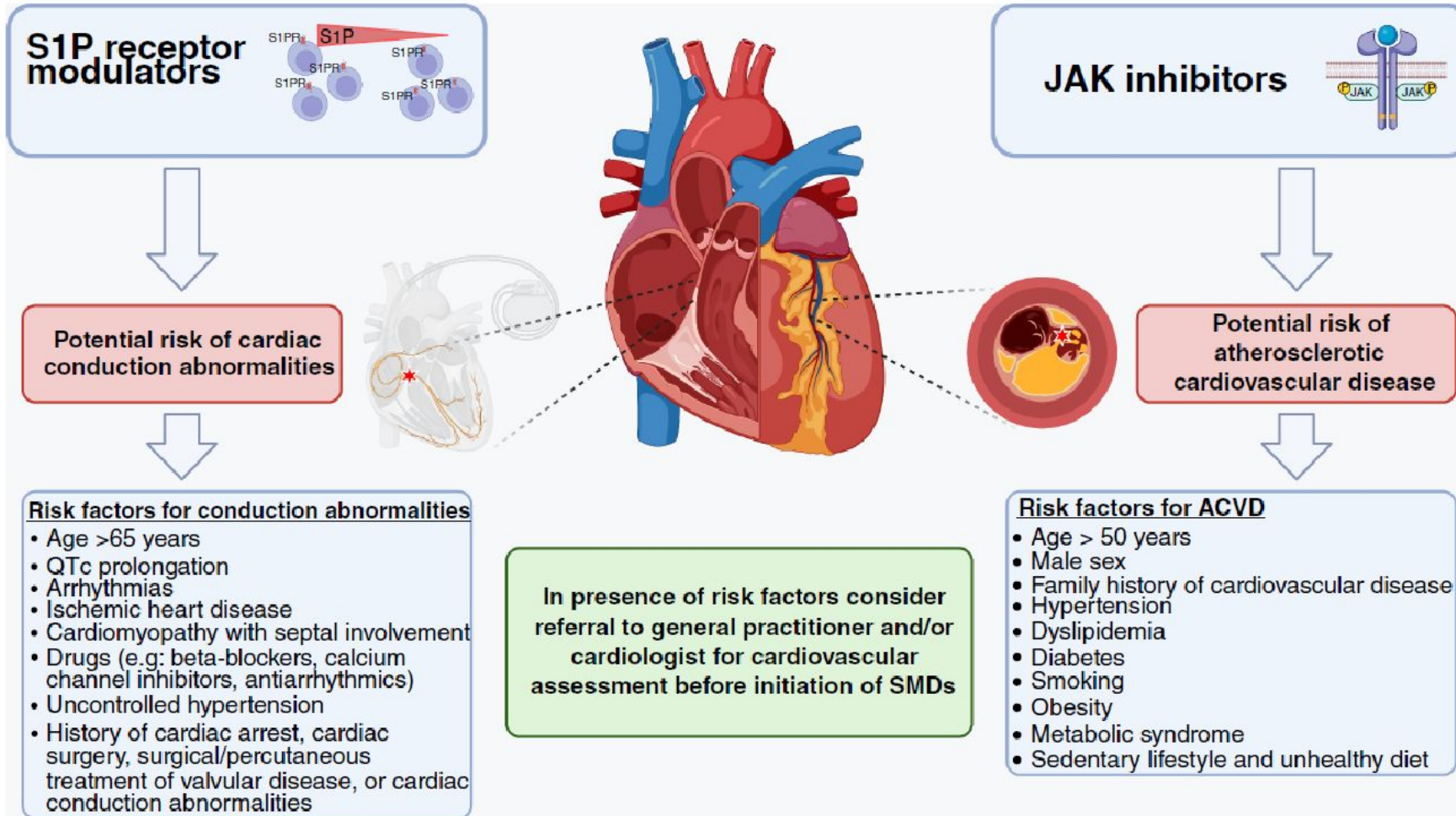
- Age ≥ 65 years
- Current or past long-time smokers
- History of atherosclerotic CV disease or other CV risk factors
- Malignancy risk factors.

Cautious use is also recommended in patients with known risk factors for VTE

If JAK inhibitors are needed in patients with these risk factors, a lower dose may be recommended

HCPs should discuss the risks associated with JAK inhibitors with their patients

New small molecules in IBD



P. A. Olivera *et al.* Aliment Pharmacol Ther 2023

Conclusions

- P-IBD carries a significant risk of thromboembolic events.
- Risk factors need to be carefully identified.
- Thrombo-prophylaxis with Low Molecular Subcutaneous Heparin must be applied to most patients that need hospital admittance.
- New treatments with small molecules may further increase thrombotic risk.
 - Preliminary experience has not shown this risk in pediatric patients
 - **Awareness is essential.**