What's New in GI

Positioning therapies for IBD in 2025

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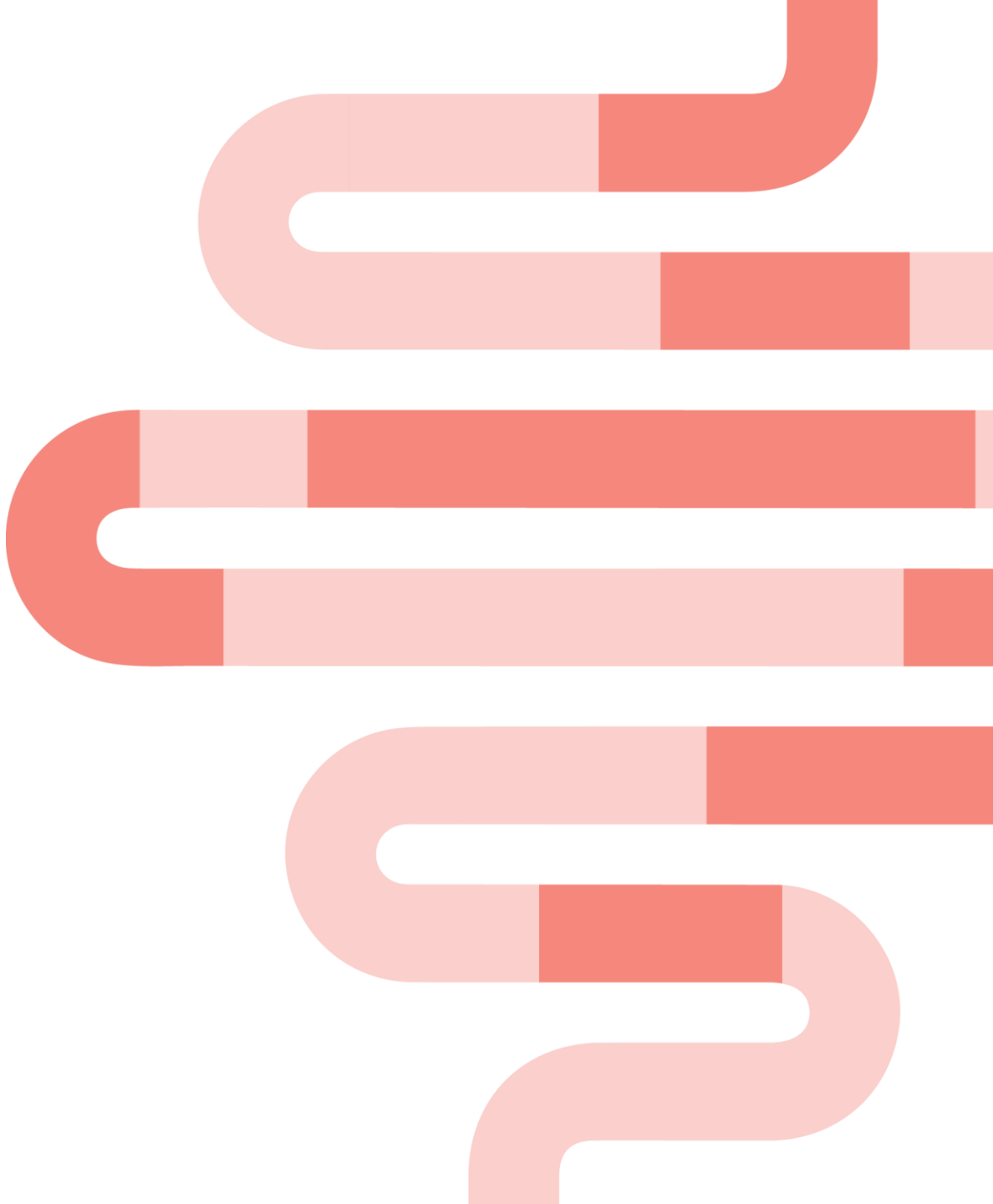


Disclosures

- Consulting/advisory boards for Pfizer, Fresenius Kabi, Janssen
- Off-label use will be discussed

Key questions on positioning advanced therapies

Advanced therapy for whom?

Which advanced therapy?

Drug factors	Patient factors	Other factors
•Effectiveness of drug •Safety of drug	•Individual risk of disease •Individual risk of treatment	•Comorbid IMIDs •External factors (logistics, payors)

Advanced therapy: delays and underuse

- **Patients starting biologic or small molecule 2017-2021** (claims data)

	Crohn's	UC
Years before biologic, mean (SD)	**6 years** (3)	**6 years** (3)
***Steroid episodes* before biologic** (among steroid users), mean (SD)	***5 episodes*** (4)	***6 episodes*** (5)
Days on conventional therapy, mean	420 days	685 days

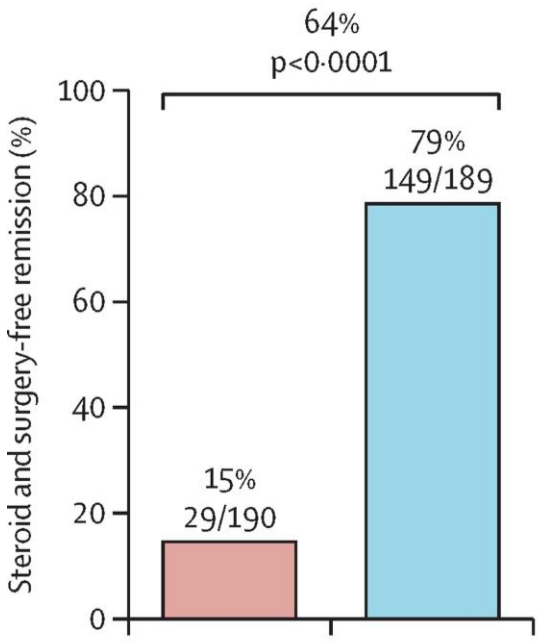
Siegel et al. Sa1814 DDW 2023

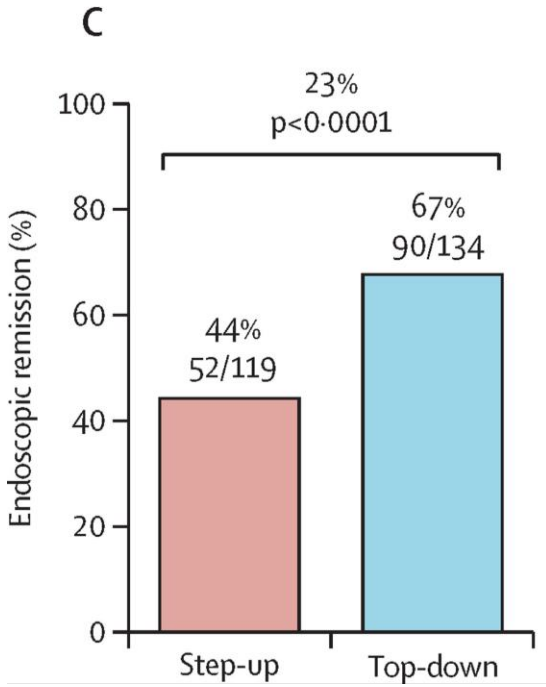
Early effective therapy in CD

- Numerous studies: better outcomes in Crohn's with top-down rather than step-up therapy

- **PROFILE study**:
  - 1:1 randomized top-down versus accelerated step-up treatment in newly diagnosed CD
  - **Top-down: infliximab plus immunomodulator**
  - Accelerated step-up: steroids and immunomodulator for 1st flare, add infliximab if 2nd flare
  - Median time from diagnosis to enrollment: 12 days (range 0–191)

- **Top-down:** >5x more patients in steroid- and surgery-free remission at 48wk
- **Top-down:** Fewer adverse events at 48wk





The Lancet Gastroenterology & Hepatology 2024
9415-427DOI: (10.1016/S2468-1253(24)00034-7)

In (very) brief:
Advanced therapy for whom?

Crohn's

- 75% or more of patients

Ulcerative colitis

- After rapid step-up from 5ASA (4-8wk max)
- At diagnosis

Which advanced therapy?

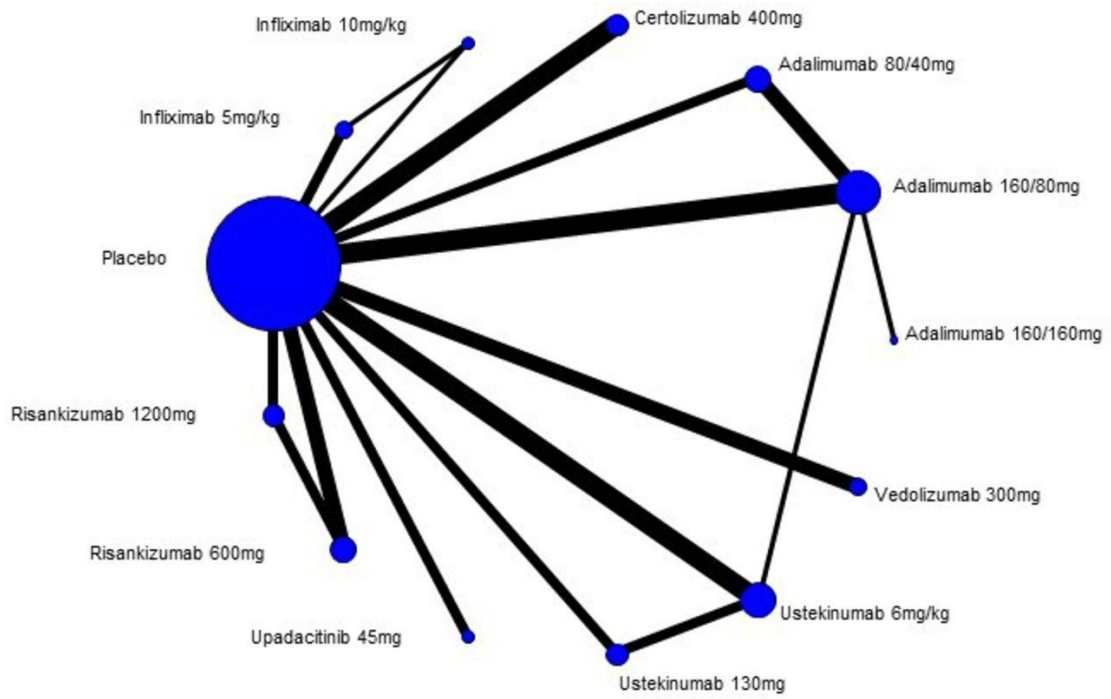
Drug factors	Patient factors	Other factors
•Effectiveness of drug •Safety of drug	•Individual risk of disease •Individual risk of treatment	•Comorbid IMIDs •External factors (logistics, payors)

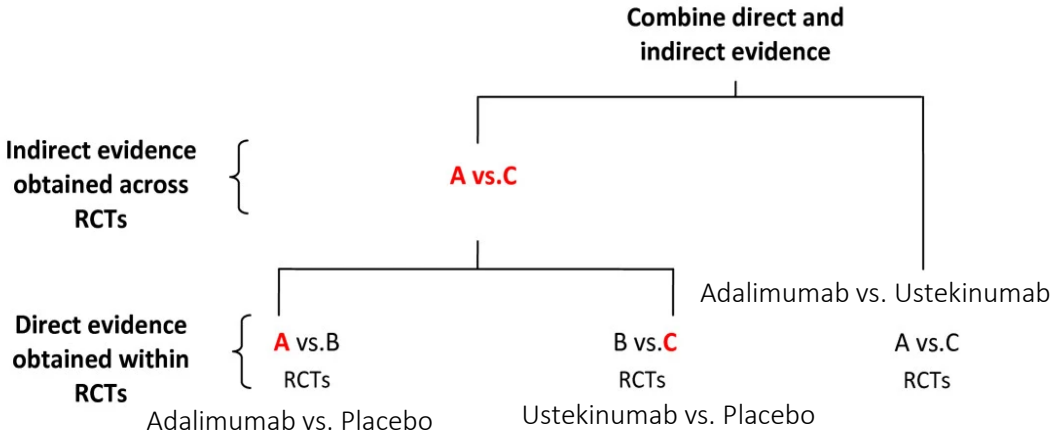
Comparative effectiveness in **Crohn's**: RCTs and observational data

Drug	Question	Result	Data source
Ustekinumab	vs **adalimumab** in bionaive	**Comparable**	**RCT** (SEAVUE)
Ustekinumab	vs **risankizumab** in aTNF-exposed	**Risankizumab** superior	**RCT** (SEQUENCE)
Ustekinumab	vs **guselkumab**	**Guselkumab** superior	**RCT** (GALAXI2/3)
Ustekinumab	vs **mirikizumab**	Mirikizumab non-inferior	**RCT** (VIVID1)
Ustekinumab	vs **vedolizumab** in aTNF failure	**Ustekinumab** superior	*Observational* data
Risankizumab	after failure of ustekinumab q8w	**Risankizumab** effective	*Observational* data

Comparative effectiveness: “Network meta-analyses”

- Compare multiple treatments using both direct comparisons of interventions and indirect comparisons across trials between a common comparator
- Significant limitations, especially study heterogeneity

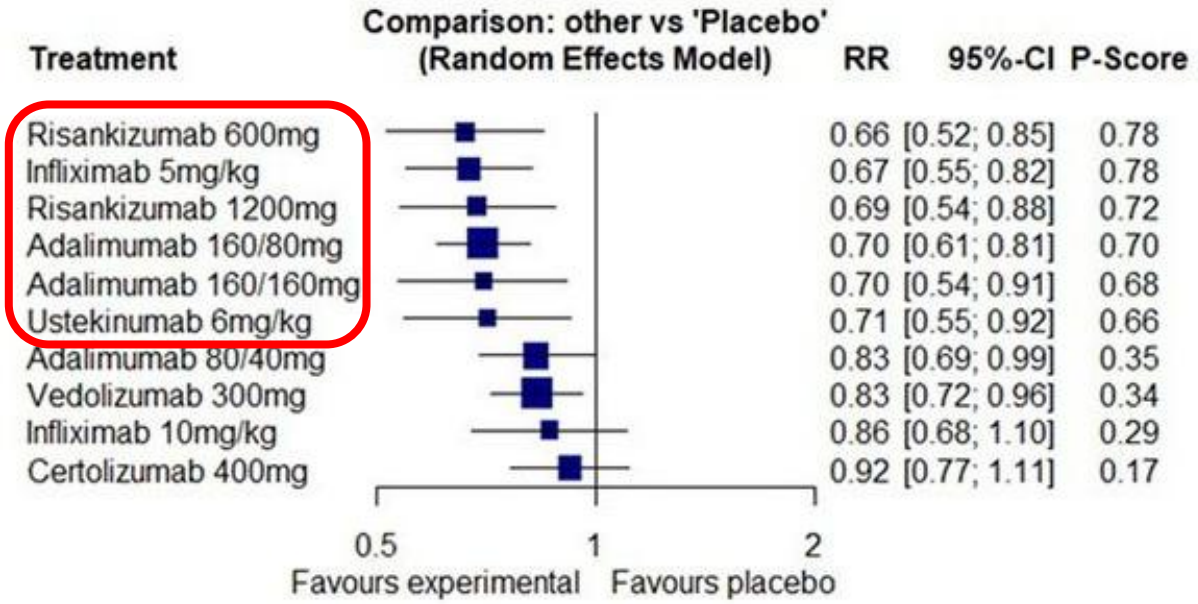




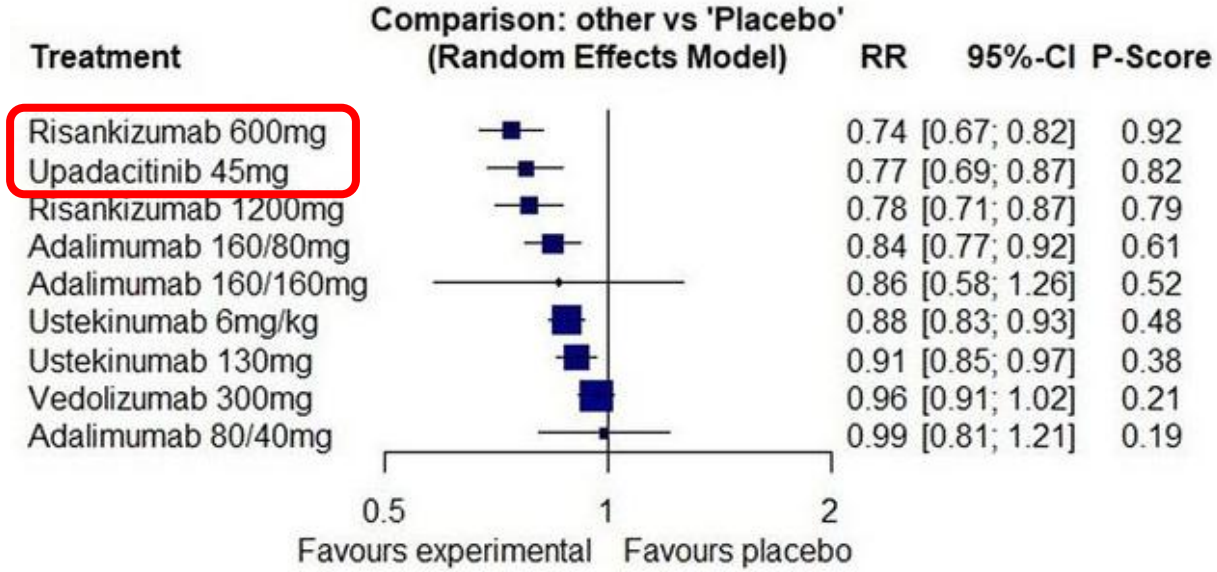
Brigida Barberio et al. Gut 2023;72:264-274

NMA for CD: Failure to induce clinical remission

Biologic Naïve



Biologic Experienced



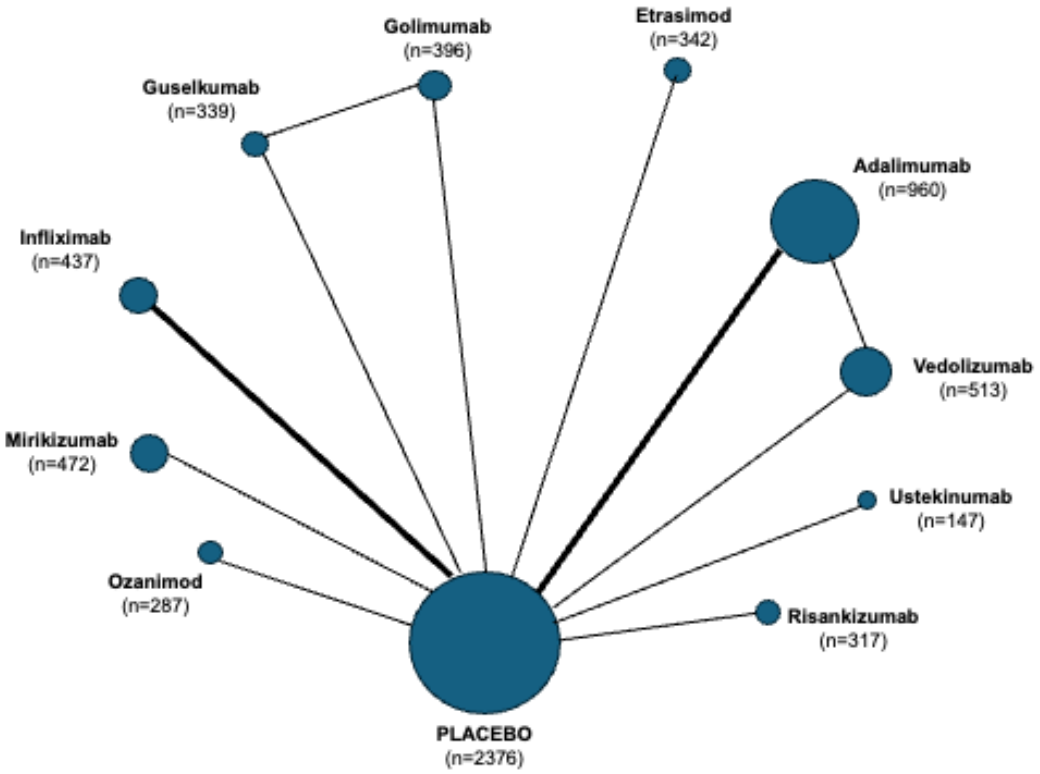
Brigida Barberio et al. Gut 2023;72:264-274

Comparative effectiveness in UC: RCTs and Observational Data

Question	Result	Data source
Vedolizumab vs **adalimumab**	**Vedolizumab** superior	**RCT** (VARSITY)
Ustekinumab vs **vedolizumab** after aTNF	**Ustekinumab** superior	*Observational* data
Tofacitinib vs **vedolizumab** after aTNF	**Tofacitinib** superior	*Observational* data
Upadacitinib vs **tofacitinib**	**Upadacitinib** superior	*Observational* data

AGA UC Living Guideline: Pharmacological Management of Moderate-to-Severe UC (2024)

- Based on NMA
- Groups meds by efficacy buckets:
  - higher, intermediate, lower
- Recommends higher or intermediate efficacy meds
  - Conditional recommendations, low/low-moderate certainty of evidence



2024 AGA UC Guideline: Efficacy buckets

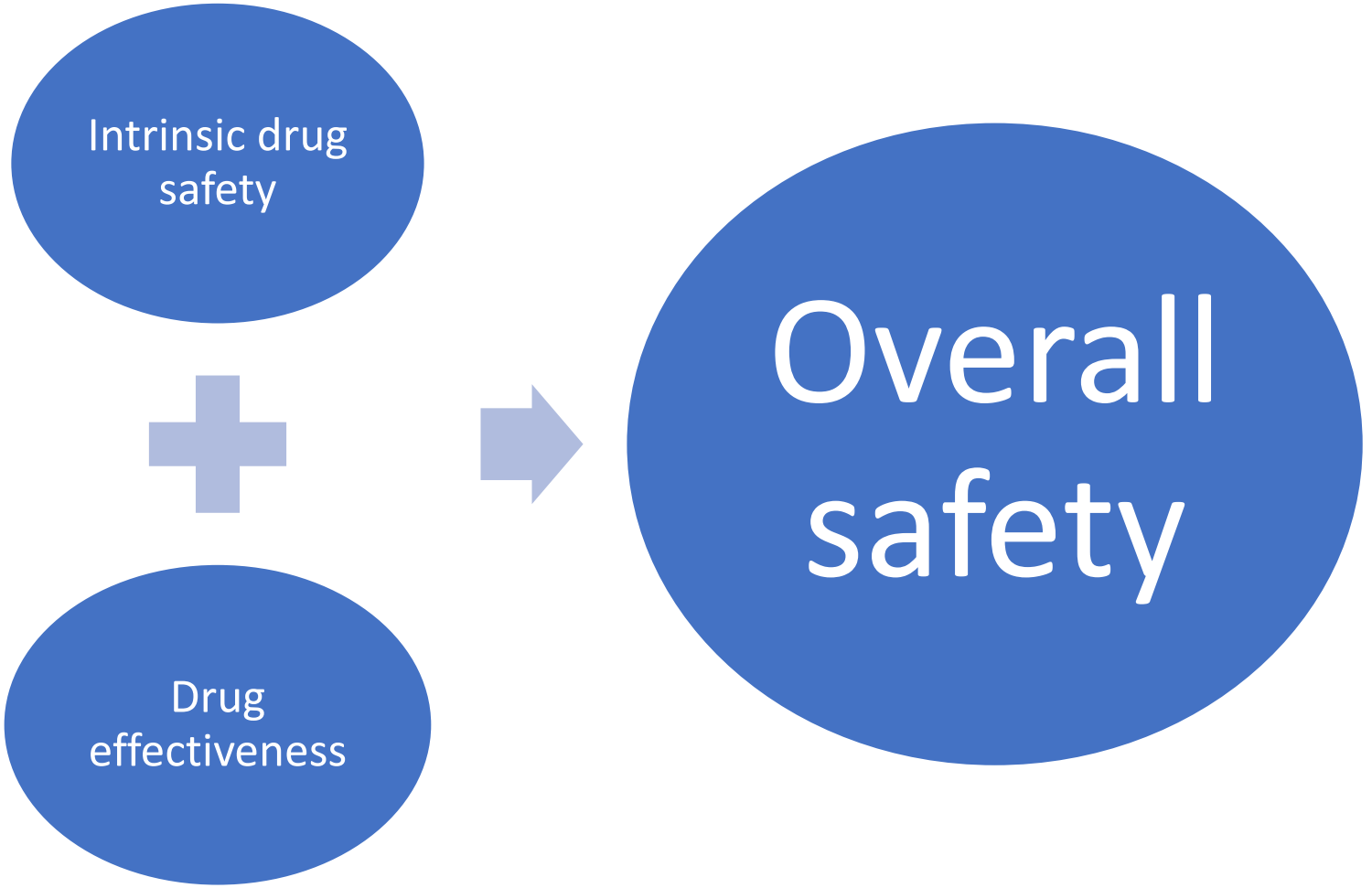
	Higher efficacy	Intermediate efficacy	Lower efficacy
Bio-naïve	• Infliximab • Vedolizumab • Ozanimod, etrasimod • Upadacitinib* • Risankizumab	• Ustekinumab • Mirikizumab • Tofacitiinib* • Golimumab	• Adalimumab
aTNF/bio-exposed	• Upadacitinib, tofacitinib • Ustekinumab	• Mirikizumab • Risankizumab	• Adalimumab • Vedolizumab • Ozanimod, etrasimod

***FDA: JAKi after aTNF**

Drug safety is two-pronged

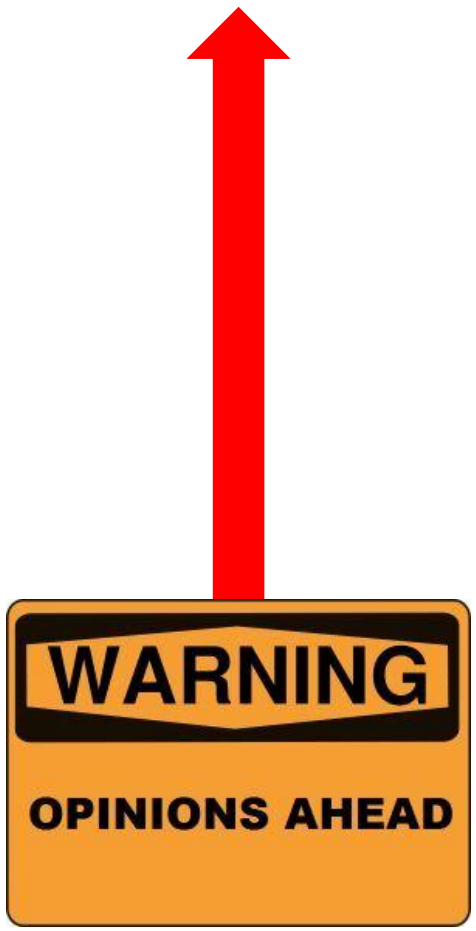
- **“Intrinsic” safety** of medication
  - Most influential on long-term risks

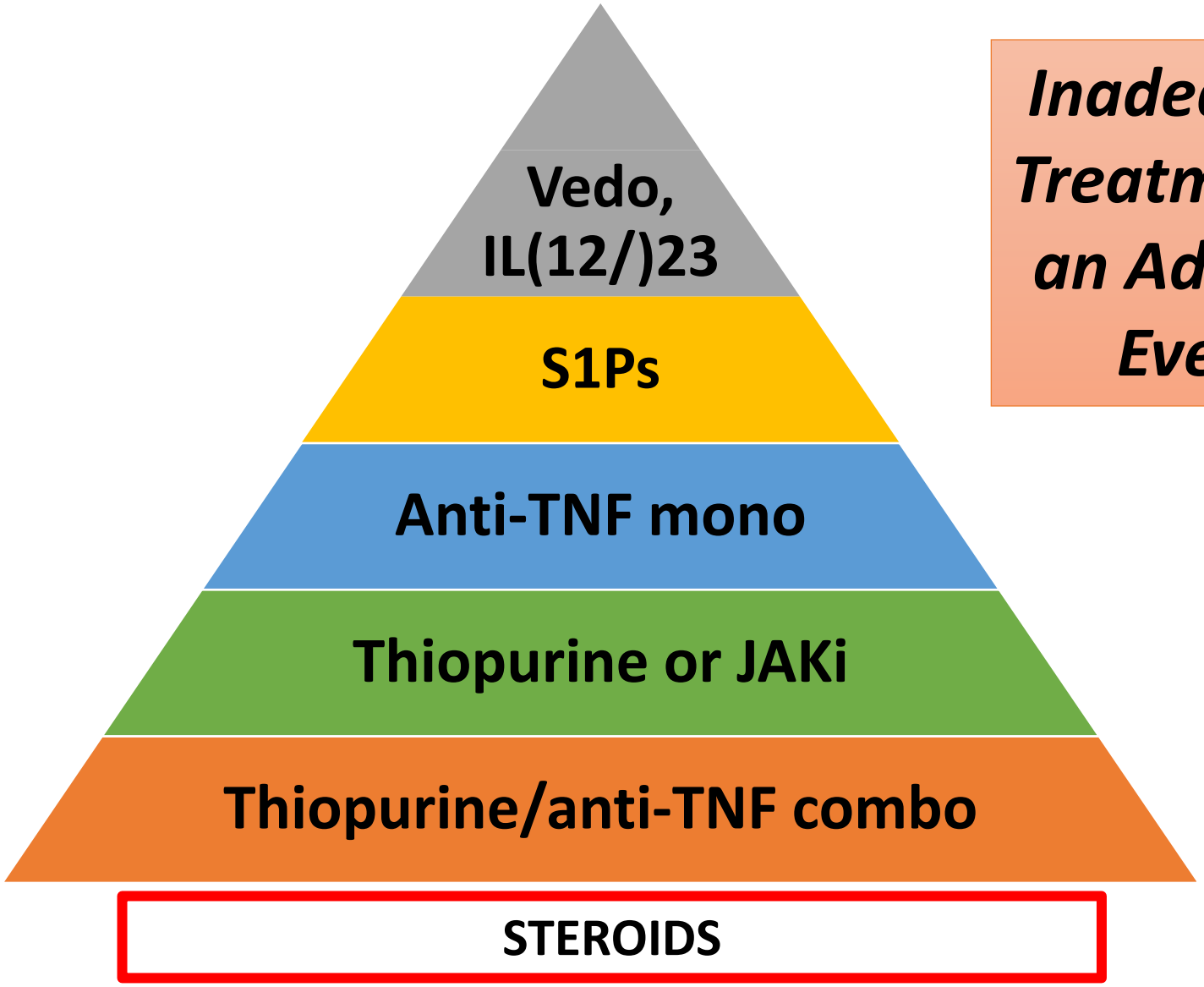
- **Effectiveness in controlling disease**
  - Most influential on short-term risks
  - More effective med generally safer than less effective



“Intrinsic” Safety Pyramid

“Safest”
(if effectiveness were equal)





Inadequate Treatment is an Adverse Event

Adapted/altered from Queiroz NSF, Regueiro, M. Curr Opin Gastroenterol. 2019

Risk of serious infections with advanced therapies for IBD

Meta-analysis of 20 head-to-head studies

Ustekinumab vs. TNFα antagonists
(5 cohorts; 23,232 patients)

- **CD**: **51% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Vedolizumab vs. TNFα antagonists
(17 cohorts; 51,596 patients)

- **CD**: **No difference** in risk of serious infections (OR, 1.03)
- **UC**: **32% lower risk** of serious infections with vedolizumab

Ustekinumab vs. vedolizumab
(5 cohorts; 1,420 patients)

- **CD**: **60% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Safety profile of advanced therapies for IBD varies, and is influenced by treatment effectiveness and intrinsic immune suppression

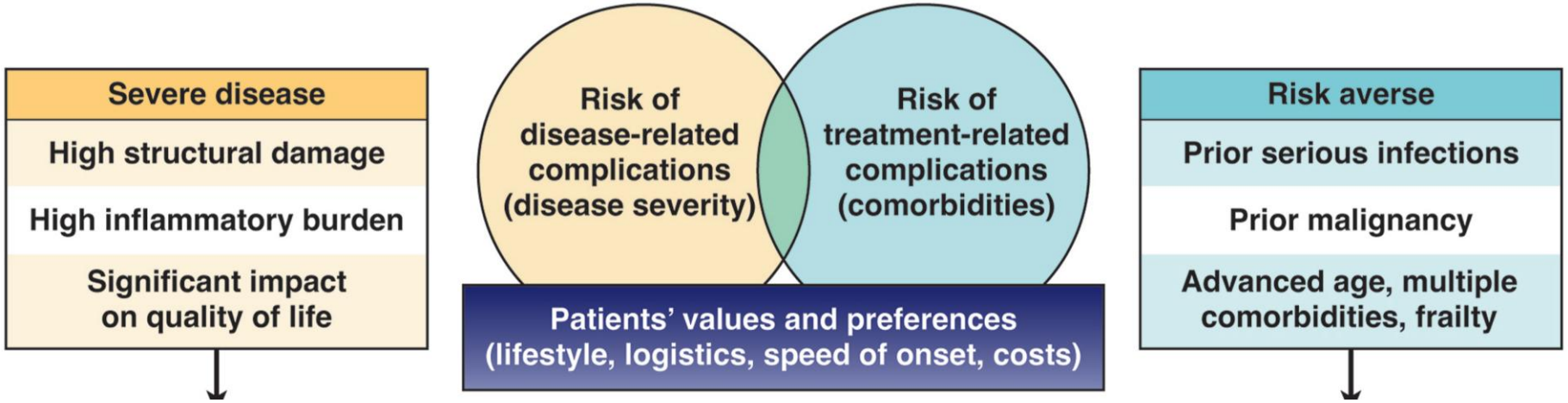
Slide: S Singh

Solitano, …, Singh. *Clin Gastroenterol Hepatol* 2022

Not just efficacy and adverse events!

Patient preferences	Safety in select populations	Coexisting IMIDs	Speed, clearance	Insurance barriers
• Mode and frequency of delivery • Perceptions of disease-related vs medication-related risks	• **Pregnancy** (avoid JAKi/S1P) • **Cardiac disease** • **Malignancy**	• **Arthritis, especially axial:** aTNF or JAKi • **Psoriasis/PsA**: aTNF or IL23 • **MS**: Ozanimod (and natalizumab)	• **Fastest acting**: aTNF and JAKi • **Most immunogenic:** aTNF (IFX>ADA) • **Clearance:** favors small molecules (ie JAKi)	• Medical (IV) or pharmacy (SC, oral) benefit, or both • Commercial vs governmental insurance (assistance programs) • On vs off-label dosing

Crohn's disease



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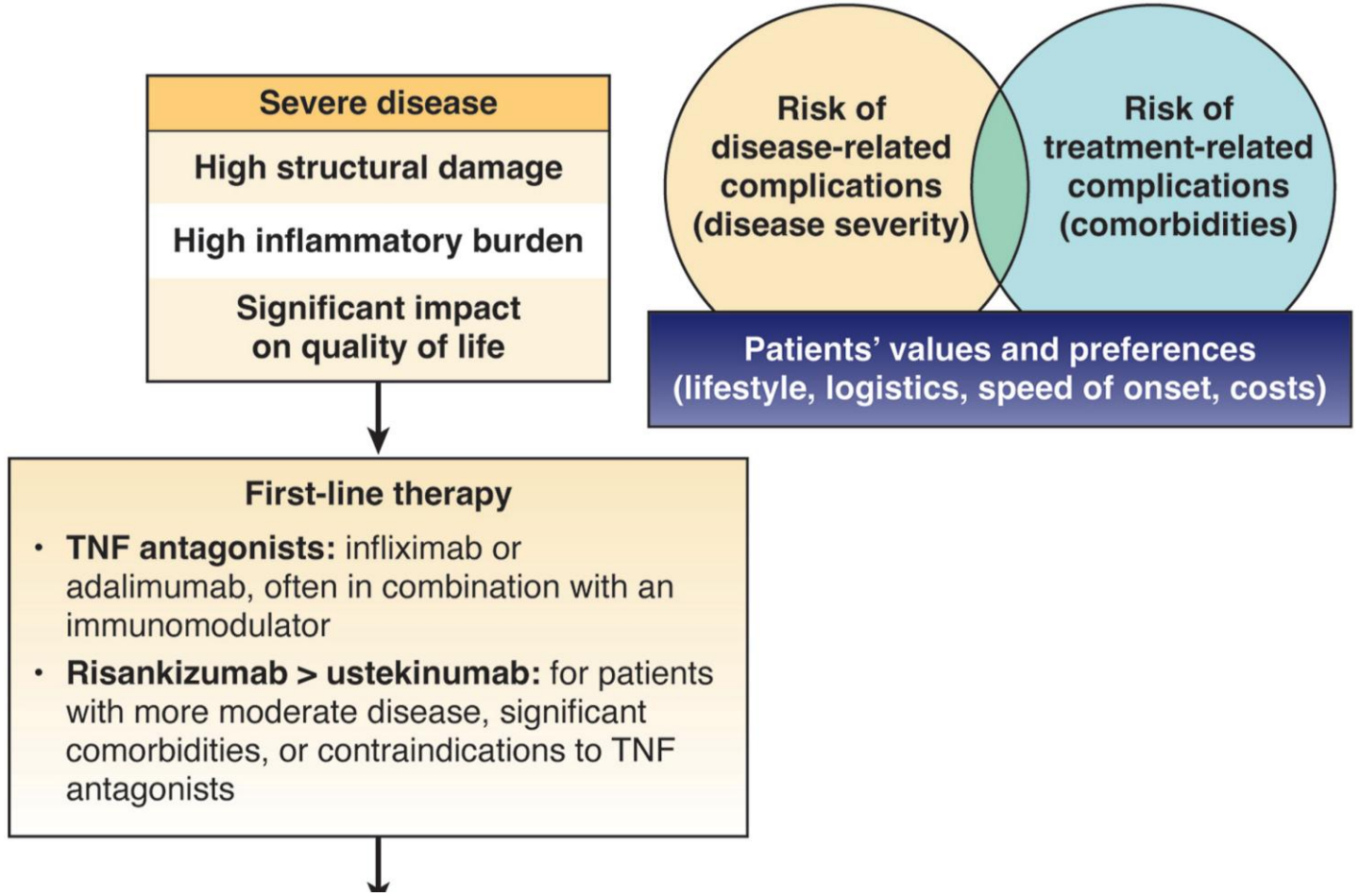
Crohn's disease



aTNF

IL23

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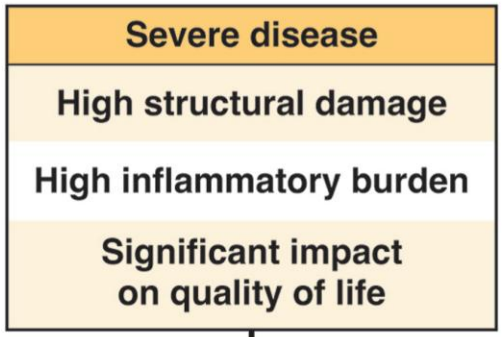
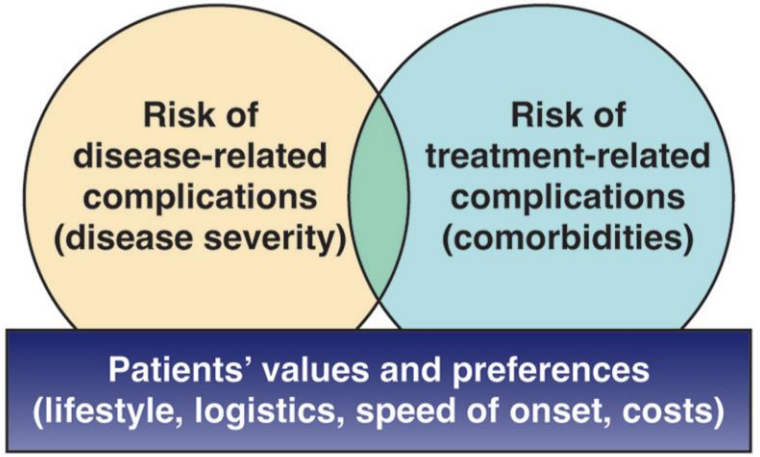
Crohn's disease





First-line therapy

aTNF

- **TNF antagonists:** infliximab or adalimumab, often in combination with an immunomodulator

IL23

- **Risankizumab > ustekinumab:** for patients with more moderate disease, significant comorbidities, or contraindications to TNF antagonists

Second-line therapy

(in patients with prior exposure to infliximab or adalimumab)

IL23

- **Risankizumab > ustekinumab**

Upa

- **Upadacitinib:** if high drug clearance or colonic disease
- **2nd TNF antagonist:** in patients with loss of response due to immunogenicity to first TNF antagonist; use with immunomodulator

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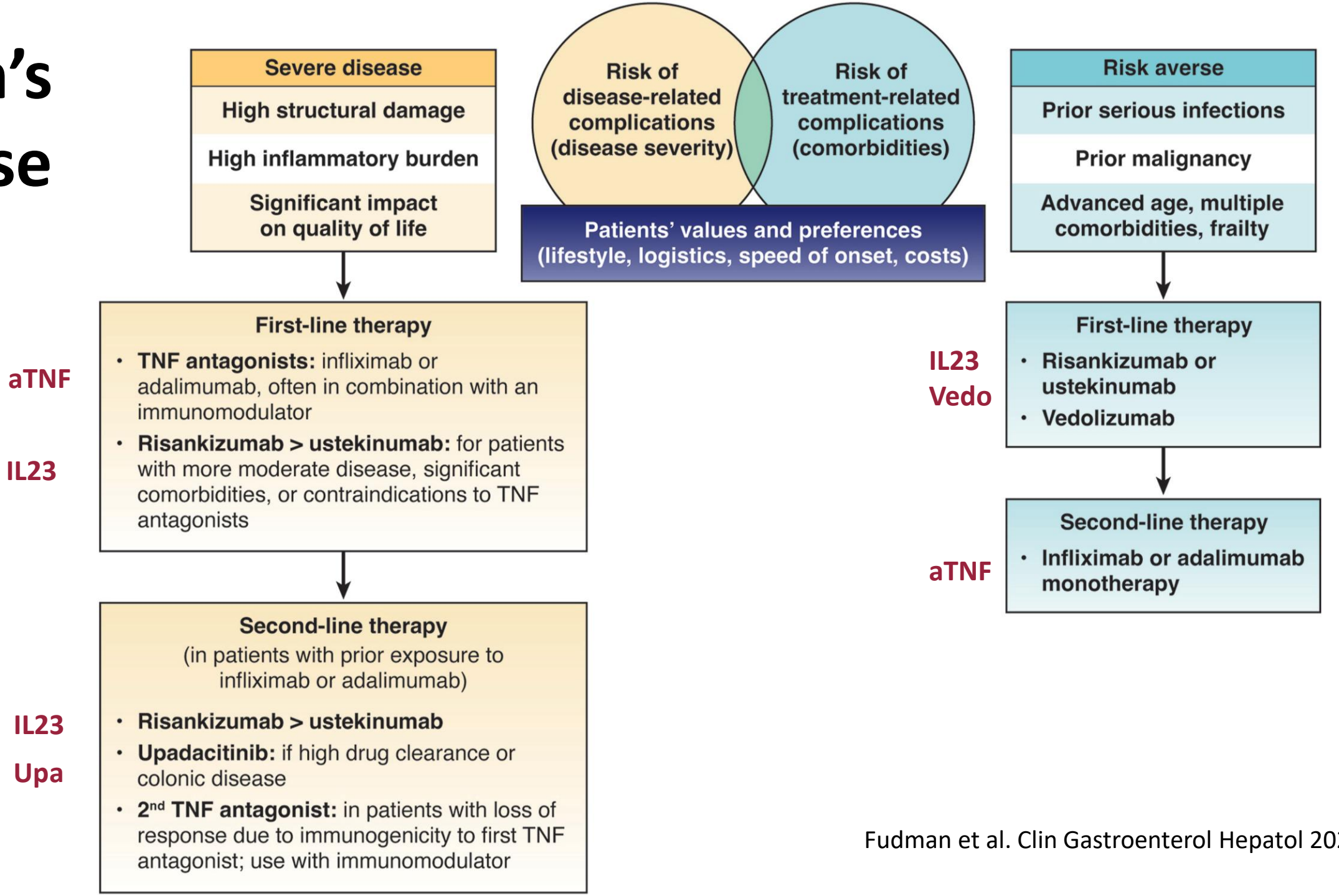
Crohn's disease



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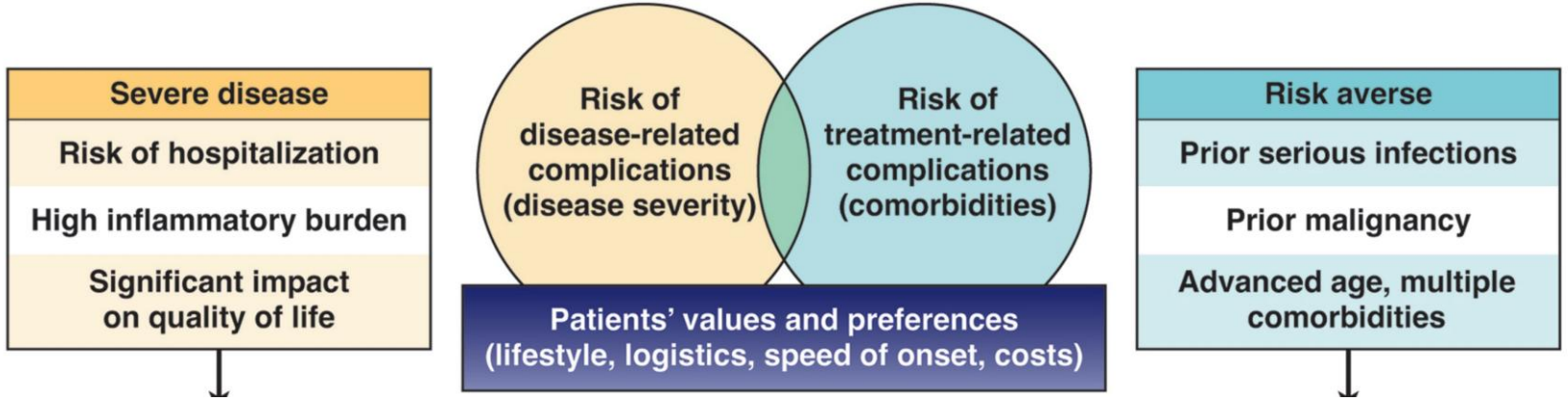
Ulcerative colitis



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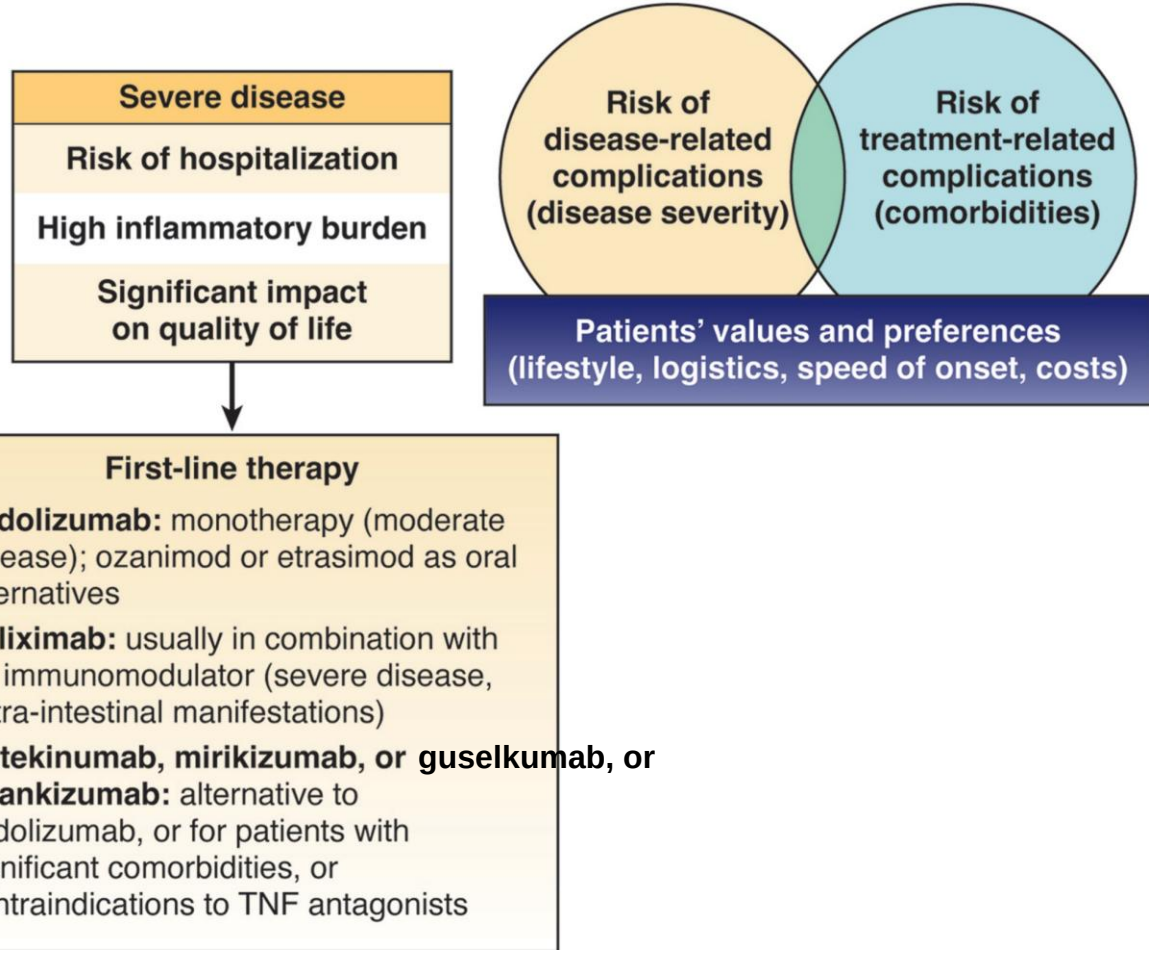
Ulcerative colitis



Vedo
S1P
IFX
IL23

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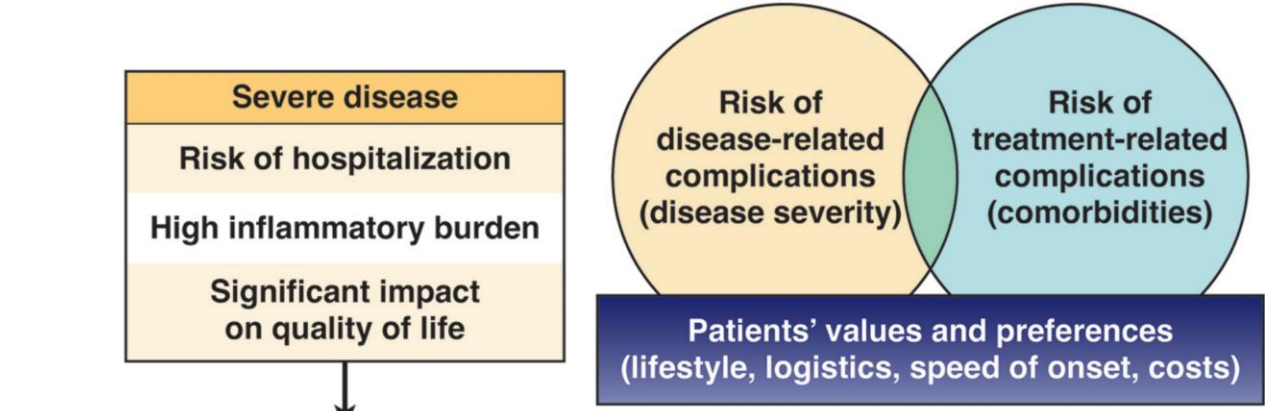
Ulcerative colitis



First-line therapy

- **Vedolizumab:** monotherapy (moderate disease); ozanimod or etrasimod as oral alternatives
- **Infliximab:** usually in combination with an immunomodulator (severe disease, extra-intestinal manifestations)
- **Ustekinumab, mirikizumab, or risankizumab:** alternative to vedolizumab, or for patients with significant comorbidities, or contraindications to TNF antagonists

guselkumab, or

Vedo
S1P
IFX
IL23

Second-line therapy

- **Prior failure of infliximab:** upadacitinib > tofacitinib > ustekinumab, mirikizumab, or risankizumab or guselkumab
- **Prior failure of vedolizumab:** infliximab > ustekinumab, mirikizumab, or risankizumab
- **Prior intolerance to infliximab:** vedolizumab

After infliximab, upa or IL23

After vedo, infliximab > IL23

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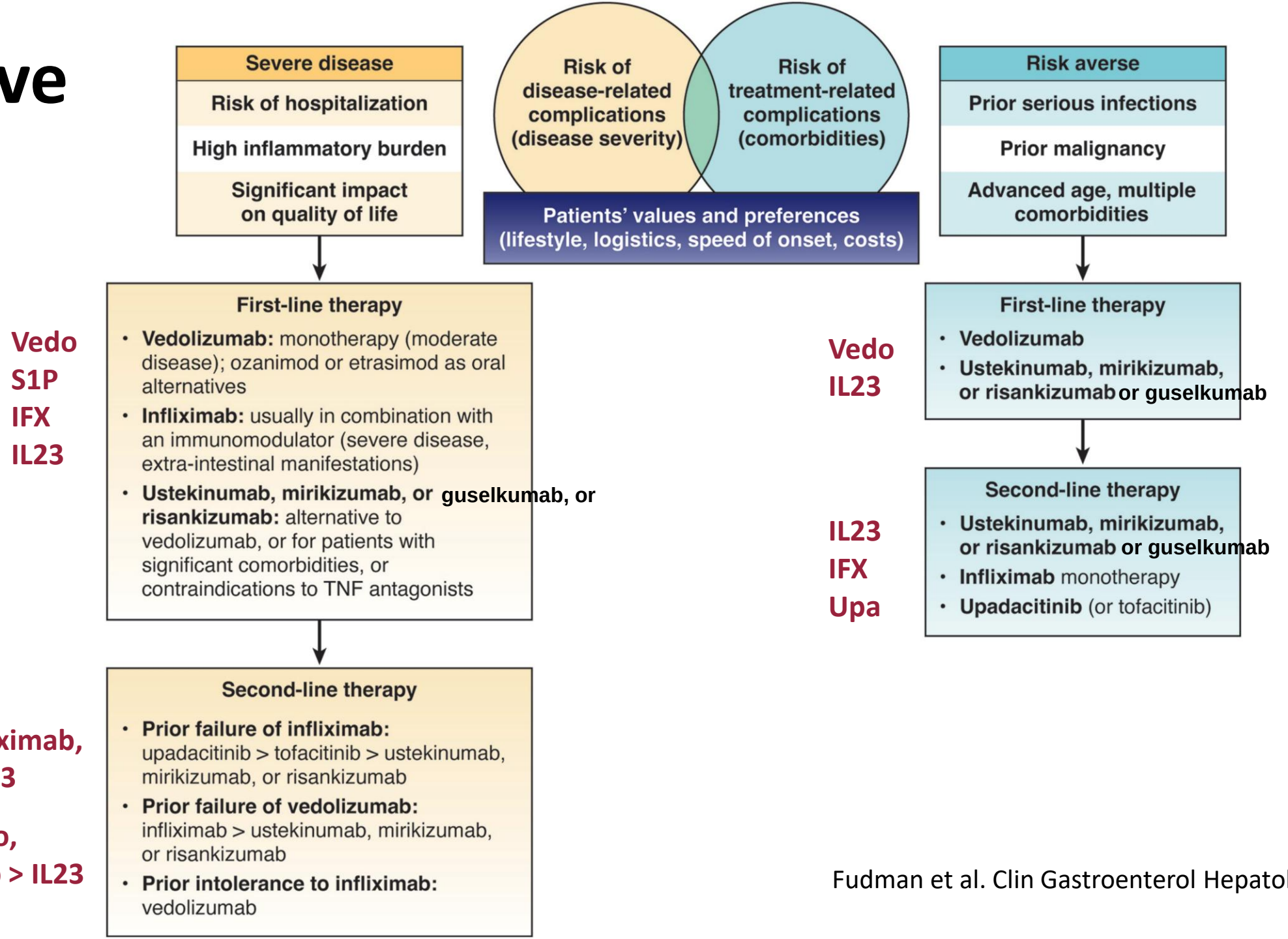
Ulcerative colitis



Vedo
S1P
IFX
IL23

Vedo
IL23

IL23
IFX
Upa

After infliximab, upa or IL23

After vedo, infliximab > IL23

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Wrap up: Positioning therapies in 2025

- **Identify who needs advanced therapies**, then treat early and effectively
- Multiple considerations when **selecting therapy**
  - Patient-specific disease activity and severity
  - Patient-specific drug-related risks
  - Drug comparative effectiveness (in view of prior therapies)
  - Concurrent EIMs/IMIDs
  - Logistics and patient preferences
- **Drug safety** is dictated by TWO factors
  - Medication's inherent safety
  - Effectiveness at preventing disease-related complications
- **Sequencing pearls:**
  - Anti-trafficking agents (vedolizumab, S1Ps) work best if 1st line; less well in bio-failure
  - After aTNF for Crohn's, IL23 >> ustekinumab

Thank you!