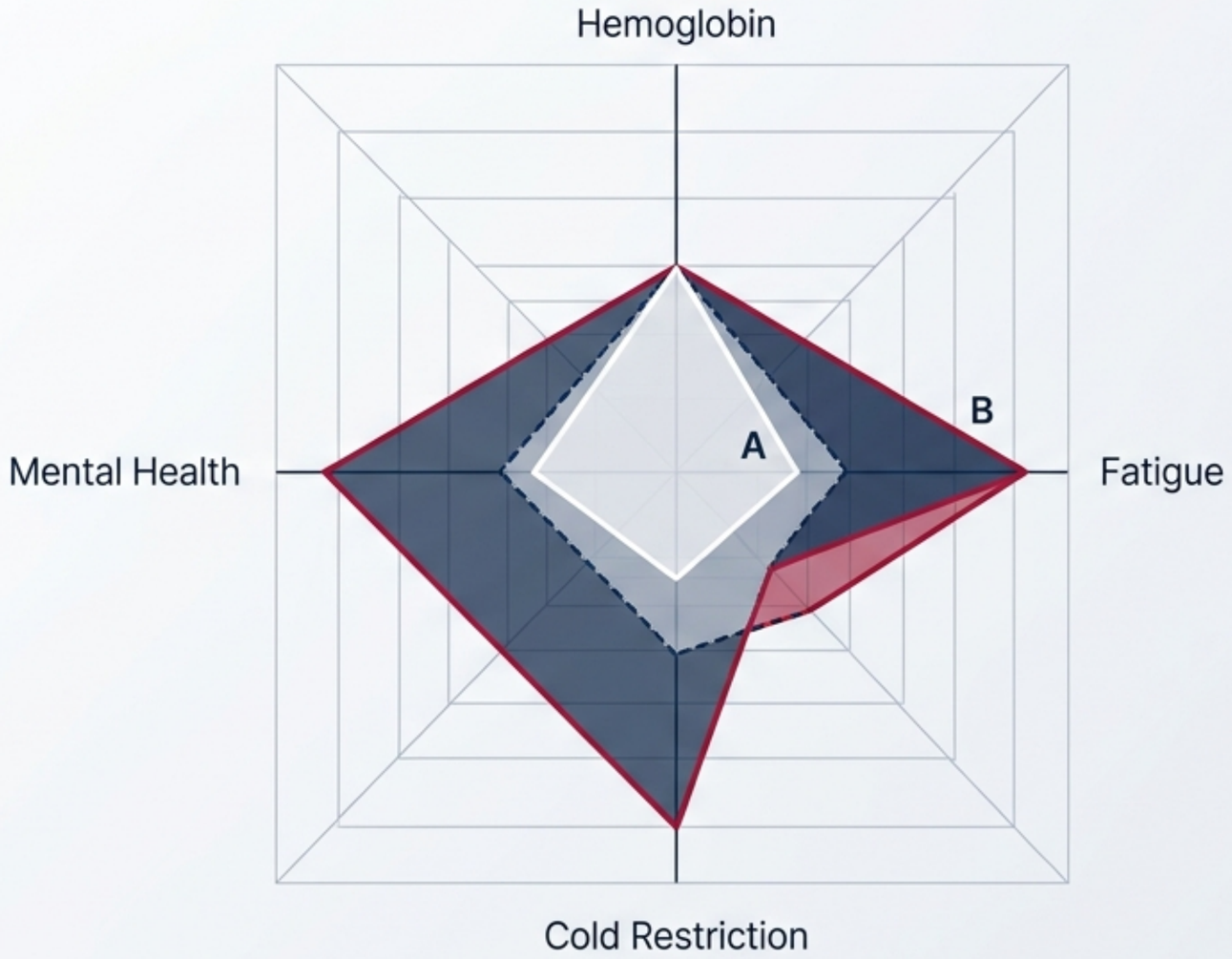
Beyond Hemoglobin: The Lived Reality of Cold Agglutinin Disease

Why lab values fail to capture the disease, and how quality of life must drive clinical strategy.

A Stable Hemoglobin Does Not Guarantee a Stable Life



Hemoglobin is a useful measure of anemia. It is not a complete measure of disease.

Two patients with the same hemoglobin may have very different lives.

The Illusion of Mild Disease

Waterline

THE LIVED EXPERIENCE

Debilitating Fatigue

Acrocyanosis Travel restriction

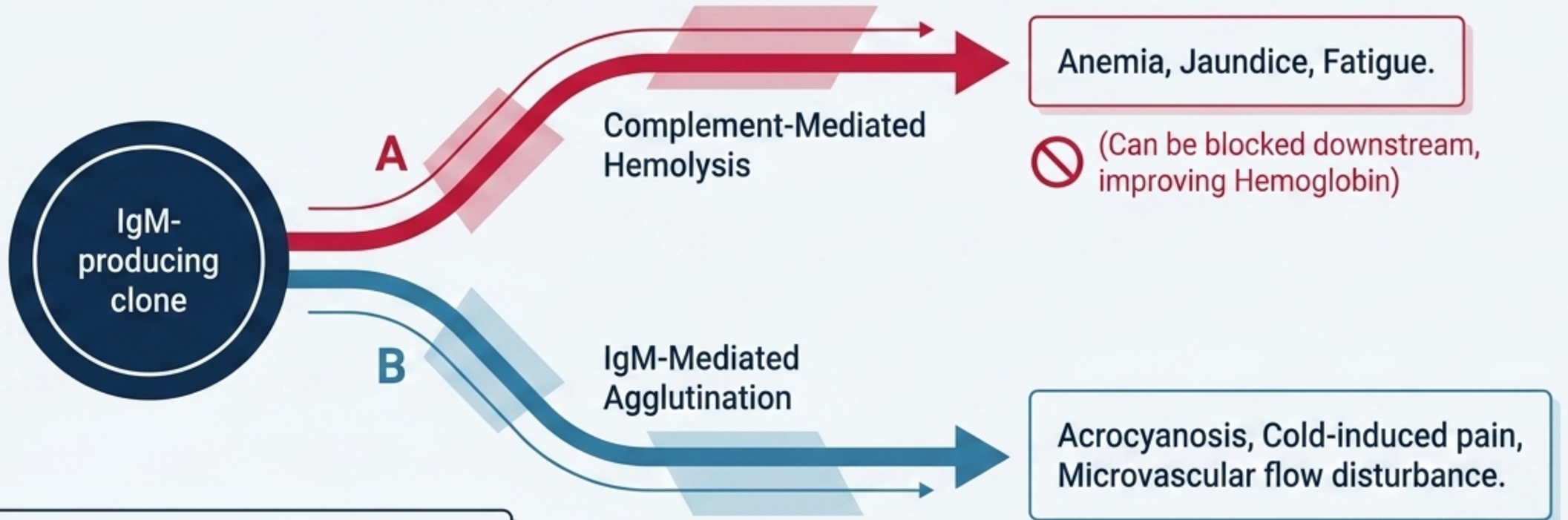
Raynaud-like symptoms Cold avoidance

Travel restriction Treatment burden

Anxiety Dyspnea

CAD burden is not measured by hemoglobin alone. It is a disease of adaptation.

One Disease, Two Distinct Pathways



This dual biology explains a central clinical dissociation: hemolysis can improve while debilitating circulatory symptoms persist.

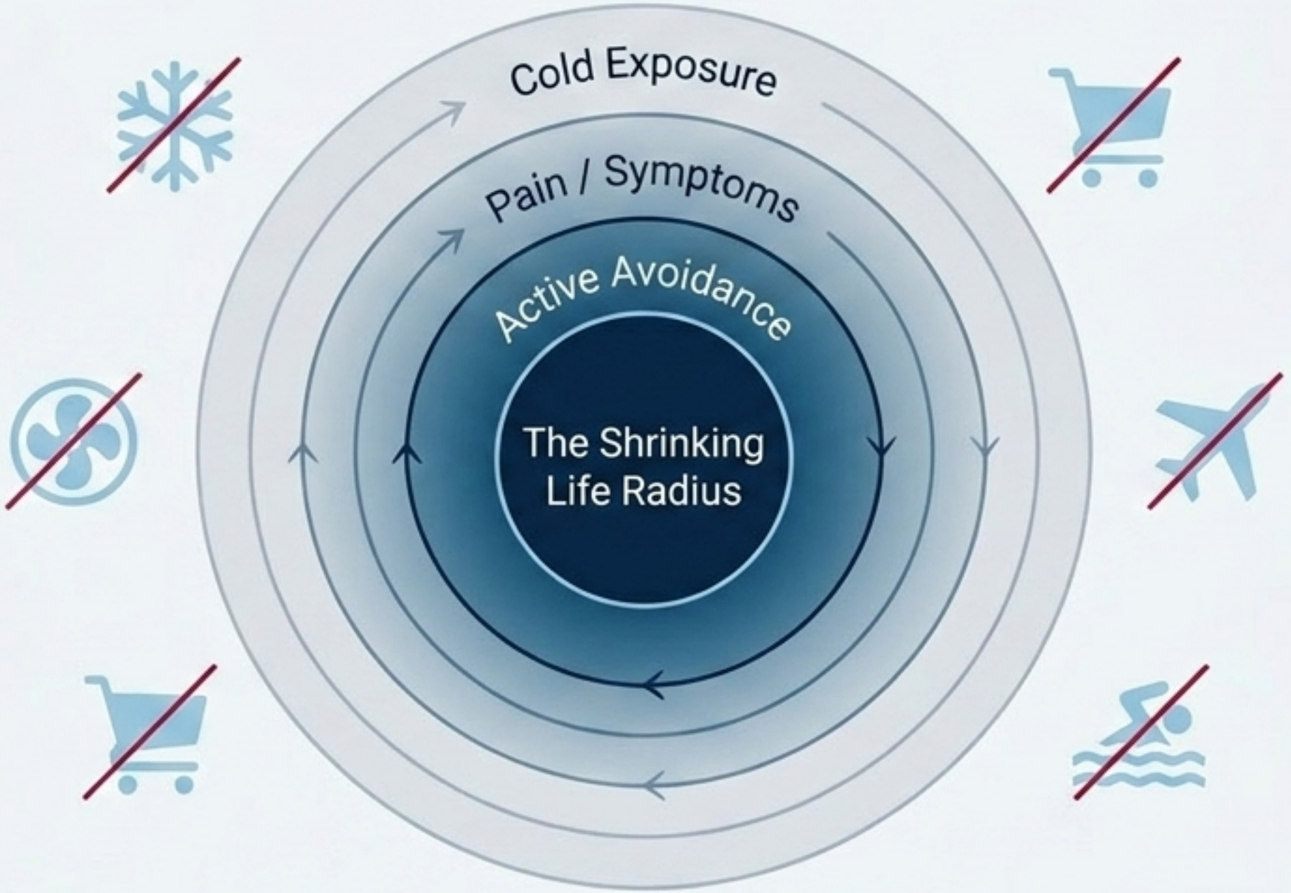
Fatigue: The Central Patient Experience

>90%
of patients report fatigue (often daily).

Reported by
93.8%
of CAD-SIQ concept elicitation participants.

Fatigue should not be dismissed simply because the patient's anemia is deemed "not severe enough" to explain it.

The Invisible Cost of ‘Manageable’ Symptoms



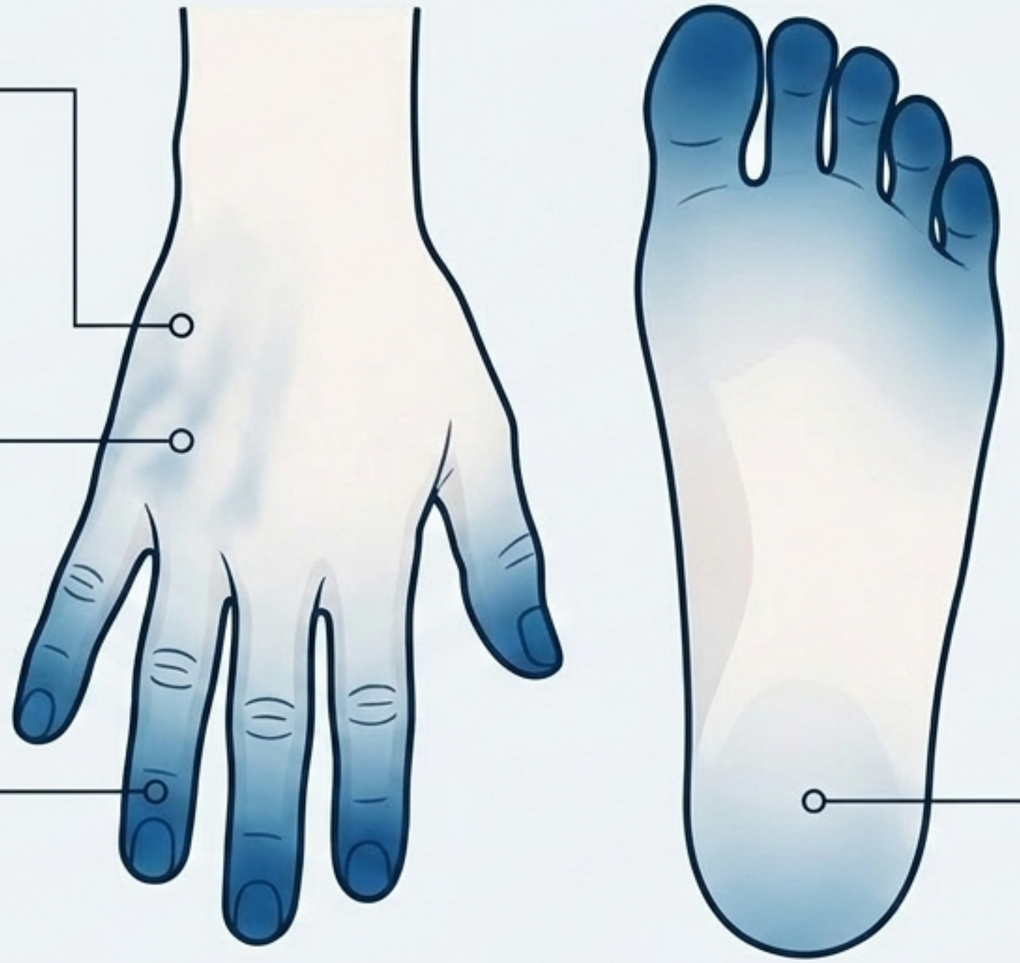
CAD burden can become invisible when patients adapt. The clinician’s task is not only to ask whether symptoms occur, but to ask what life has become in order to keep those symptoms from occurring.

When the Dominant Burden is Flow, Not Hemoglobin

Acrocyanosis & Raynaud-like color changes

Livedo-like skin changes

Impaired manual function in cold conditions, cold-induced pain/numbness

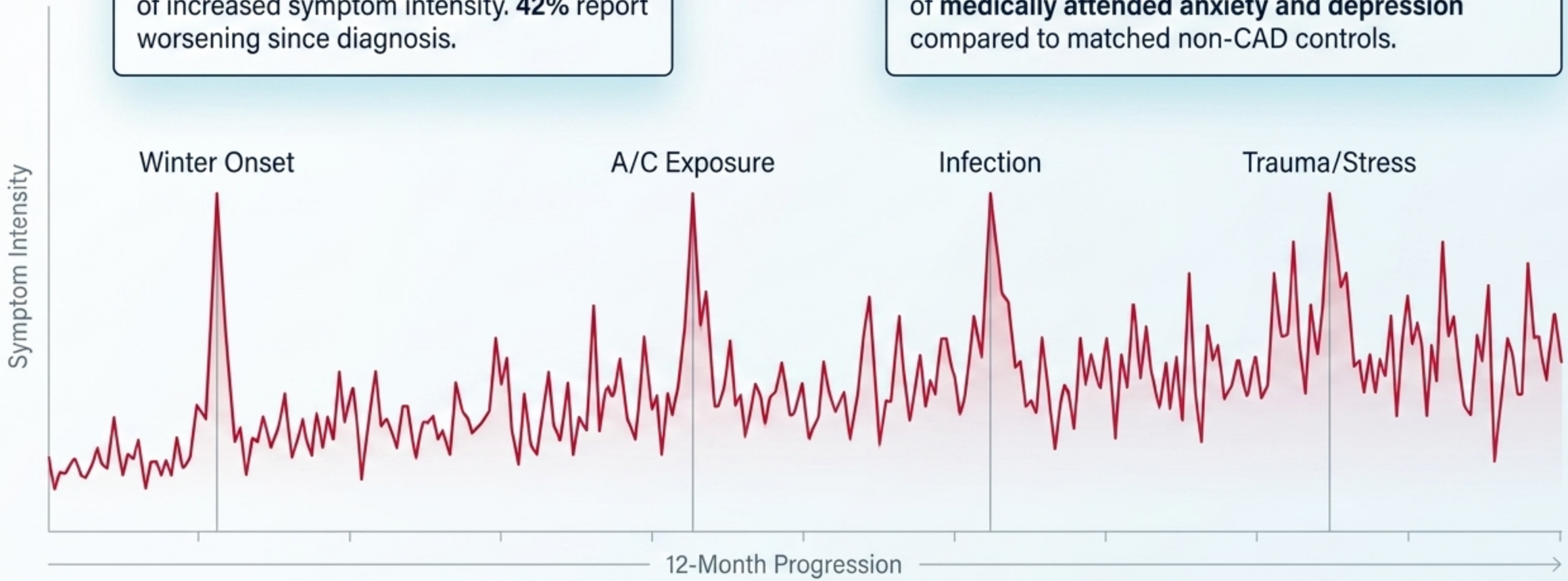


These symptoms reflect agglutination in cooled vascular beds. They do not track with Hemoglobin, Bilirubin, or LDH.

Unpredictability Becomes Part of the Disease

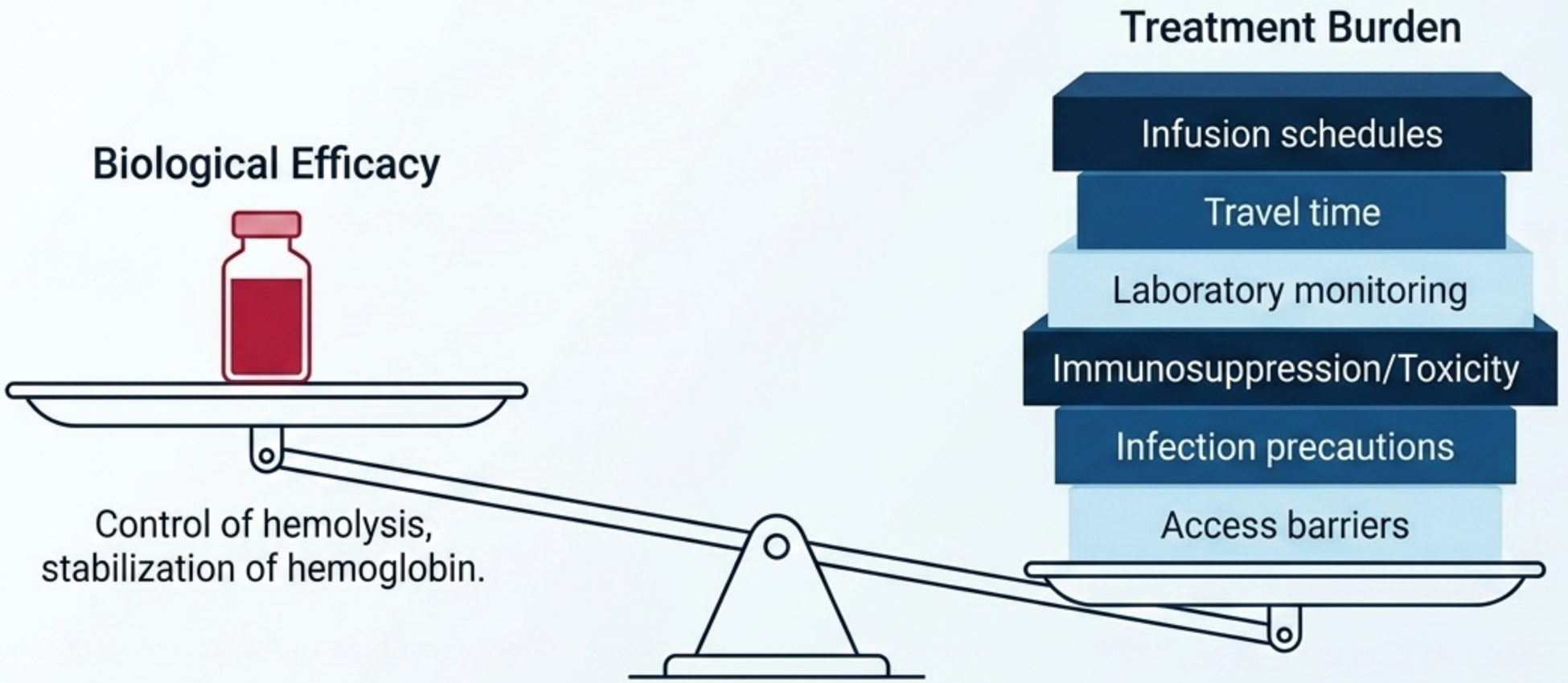
88% of surveyed patients report episodes of increased symptom intensity. **42%** report worsening since diagnosis.

Claims-clinical data shows significantly **higher rates** of **medically attended anxiety and depression** compared to matched non-CAD controls.



Fear of the ‘next flare’ dominates. Mental health belongs in the clinical landscape, not outside of it.

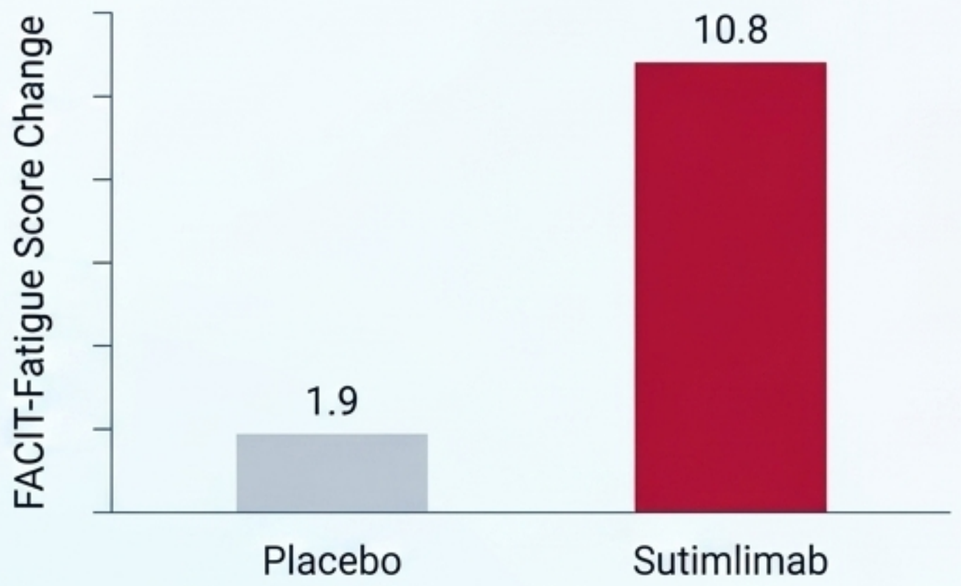
The Heavy Logistics of a ‘Rare’ Disease



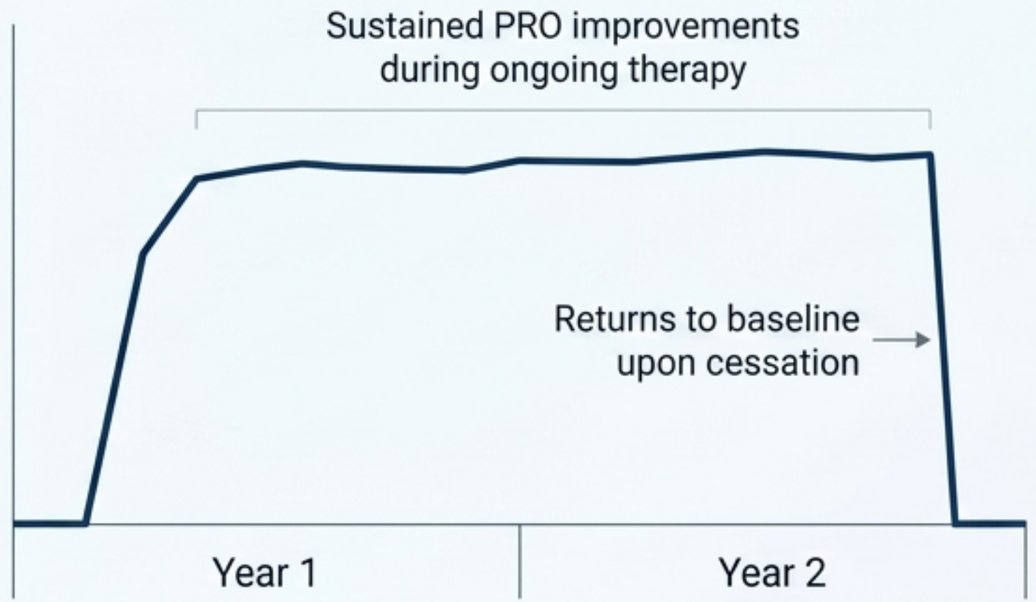
Stanford and Optum longitudinal cohorts reveal persistent severe anemia events and high transfusion reliance. However, a treatment can be biologically effective and still poorly aligned with a patient’s life.

Patient-Reported Outcomes (PROs) Are Clinical Data

CADENZA Trial (26 Weeks)



CARDINAL Trial (2 Years)



Treatment success is shifting from isolated biochemical control to measurable improvement in how patients feel and function.

Aligning Strategy with the Dominant Burden

Dominant Burden	Likely Clinical Question	Strategy to Consider
Stable mild anemia	Can we observe safely?	Observation / supportive management
Active hemolysis, transfusion need	Can we control hemolysis now?	Complement-directed therapy / transfusion
Persistent IgM circulatory symptoms	Can we reduce pathogenic antibody production?	Clone-directed therapy
High burden from continuous therapy	Can we reduce treatment dependence?	Reassessment / shared decision-making
Fluctuating symptoms	What mechanism is dominant?	Reassess hemolysis vs. agglutination vs. triggers

Ask About Adaptation, Not Just Symptoms

THE ROUTINE CHECKLIST

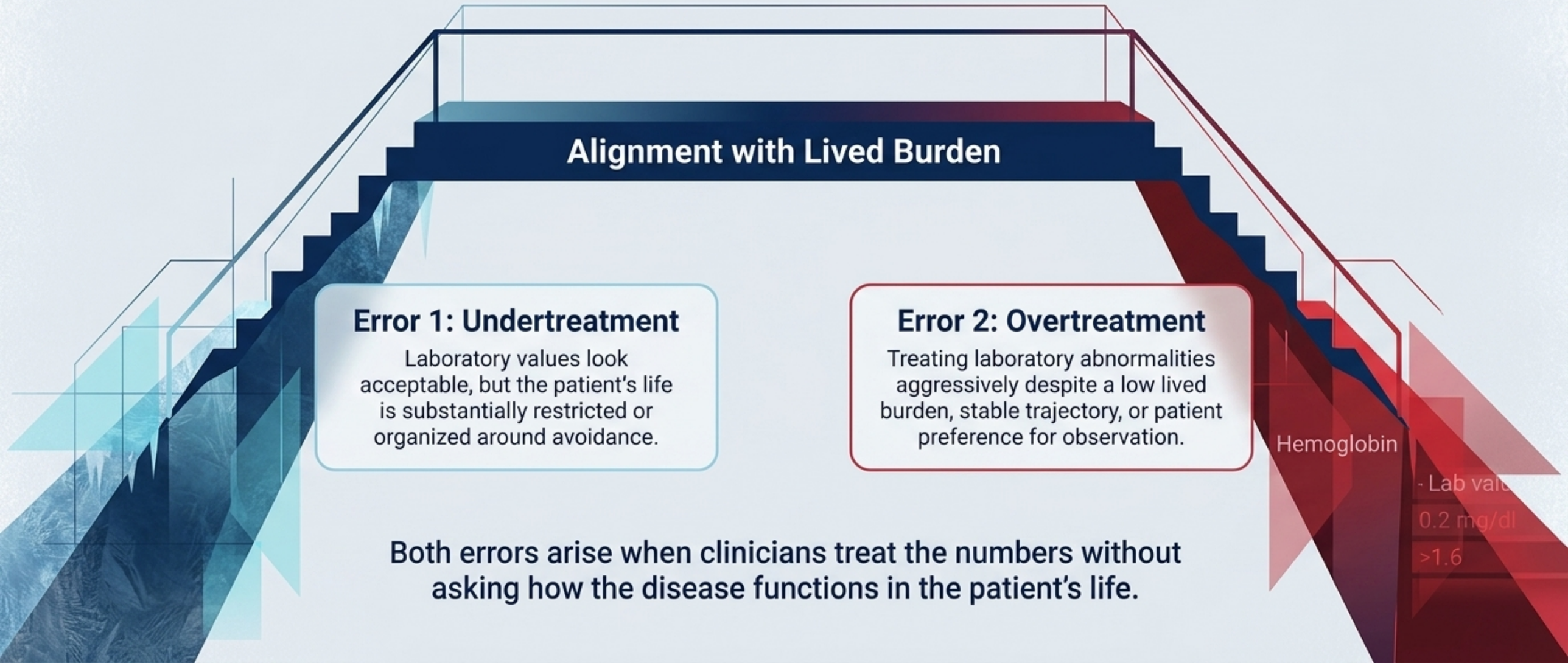
- ✕ Do you feel tired?
- ✕ Are you in pain?
- ✕ What is your Hemoglobin?

THE ADAPTATION INTERVIEW

- ✓ What do you avoid because of cold sensitivity?
- ✓ How has CAD changed your travel or work?
- ✓ Do you plan your day around temperature exposure?
- ✓ Which bothers you more: anemia, cold symptoms, or treatment burden?

Clinicians often ask about symptoms.
CAD requires asking about adaptation.

The Dual Risks of Number-Focused Care



Error 1: Undertreatment

Laboratory values look acceptable, but the patient's life is substantially restricted or organized around avoidance.

Error 2: Overtreatment

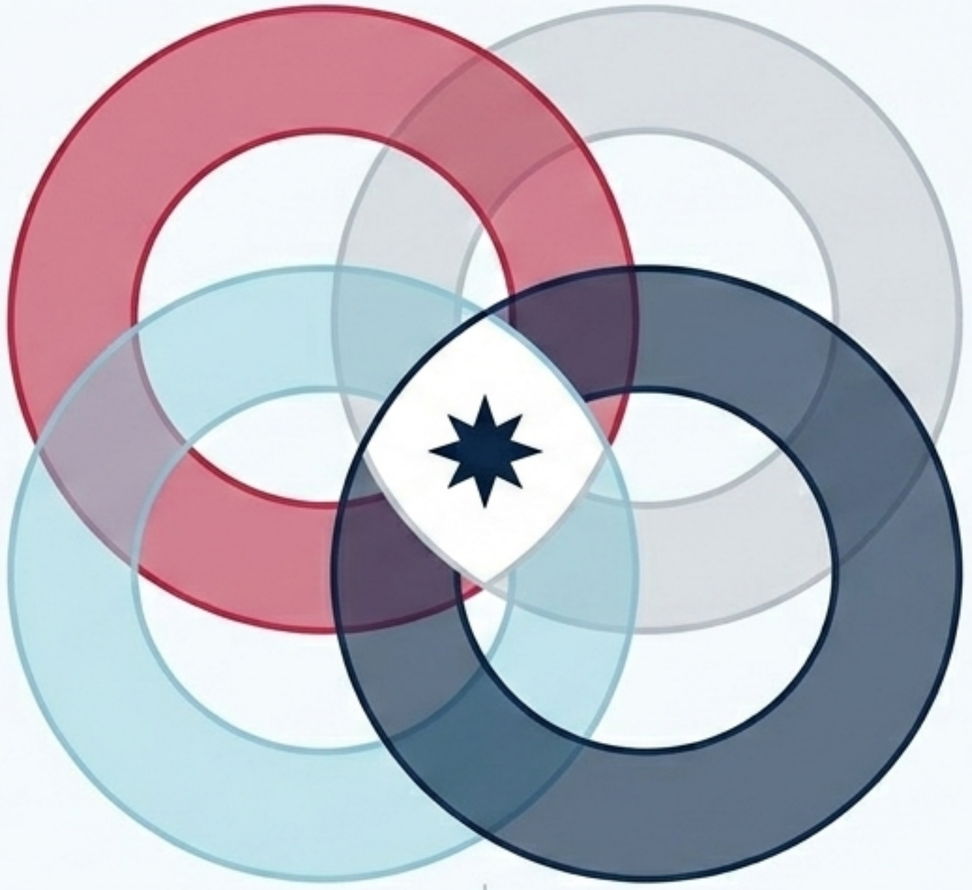
Treating laboratory abnormalities aggressively despite a low lived burden, stable trajectory, or patient preference for observation.

Both errors arise when clinicians treat the numbers without asking how the disease functions in the patient's life.

The New Standard of CAD Care

Blood
(Hemoglobin / Anemia)

Complement
(Hemolysis)



Temperature
(Agglutination / Flow)

Adaptation
(Lived Experience / QoL)

Expert care requires all four. Quality-of-life burden does not replace laboratory assessment—it changes how laboratory results are interpreted.

Reflect & Apply

"Think of a patient with CAD whose hemoglobin seemed "acceptable." Ask yourself:

What parts of life had they quietly given up? Were their symptoms driven by hemolysis, cold, or the burden of treatment?

The key question is not 'How low is the hemoglobin?'**, but 'How much of this patient's life is being organized around CAD?'**