Understanding the immunopathogenesis of CAD: What are the implications of new and emerging therapies?

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Agenda

- Understanding the immunopathogenesis of cold agglutinin disease
- Navigating the evolving treatment landscape in cold agglutinin disease
- Individualizing cold agglutinin disease management in the clinic

Understanding the immunopathogenesis of cold agglutinin disease

Prof. Morie Gertz

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CAD and autoimmune haemolytic anaemias

AIHAs include several distinct forms[1,2]

Warm-antibody type	Cold-antibody type
Primary	**Primary CAD**
Secondary	**Secondary CAS** Associated with underlying malignant disease or acute infection
	Paroxysmal cold haemoglobinuria

Mixed cold- and warm-antibody type

Adapted from Berentsen and Barcellini, 2021; Jäger, 2020.

Primary CAD accounts for ~15–25% of all AIHAs[2,3]

CAD is traditionally defined as AIHA mediated by CAs. Patients may have evidence of a B-cell lymphoproliferative disorder, but no evidence of malignancy[2]

CAs are autoantibodies that react optimally at cold temperature (4°C), but can react at other temperatures depending on the thermal amplitude[3]

AIHA, autoimmune haemolytic anaemia; CA, cold agglutinin; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome.

1. Berentsen S, Barcellini W. *N Engl J Med.* 2021;385:1407–19; 2. Jäger U, et al. *Blood Rev*. 2020;41:100648; 3. Gabbard A, Booth G. *Clin Hematol Int*. 2020;2:95–100.

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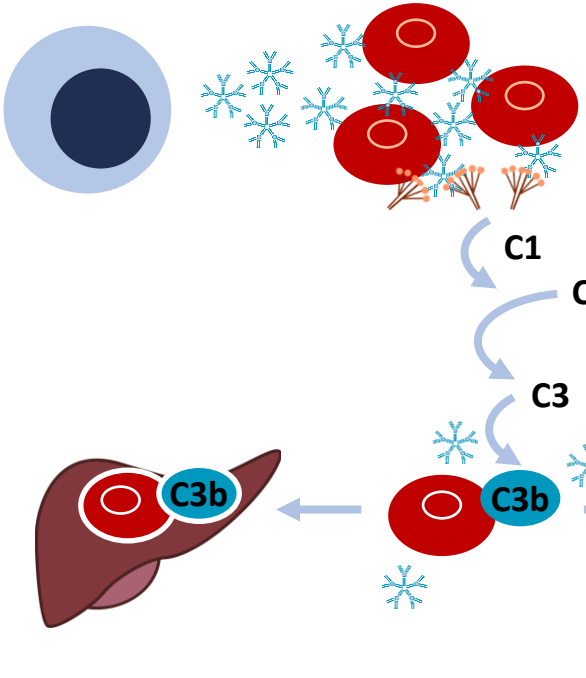
Pathophysiology of CAD

Monoclonal B cells produce IgM CAs that target RBCs



CA binding causes RBC agglutination and C1 activates the classical complement pathway

Cold agglutinin
Complement protein
Red blood cell

Extravascular haemolysis

C3b-opsonized RBCs are phagocytosed, mainly in the liver

Intravascular haemolysis

Formation of MAC in severe disease may also result in intravascular haemolysis

Adapted from Berentsen, 2020.

C, serum complement protein; CA, cold agglutinin; CAD, cold agglutinin disease; IgM, immunoglobulin M; MAC, membrane attack complex; RBC, red blood cell.

Berentsen S. *Front Immunol*. 2020;11:590.

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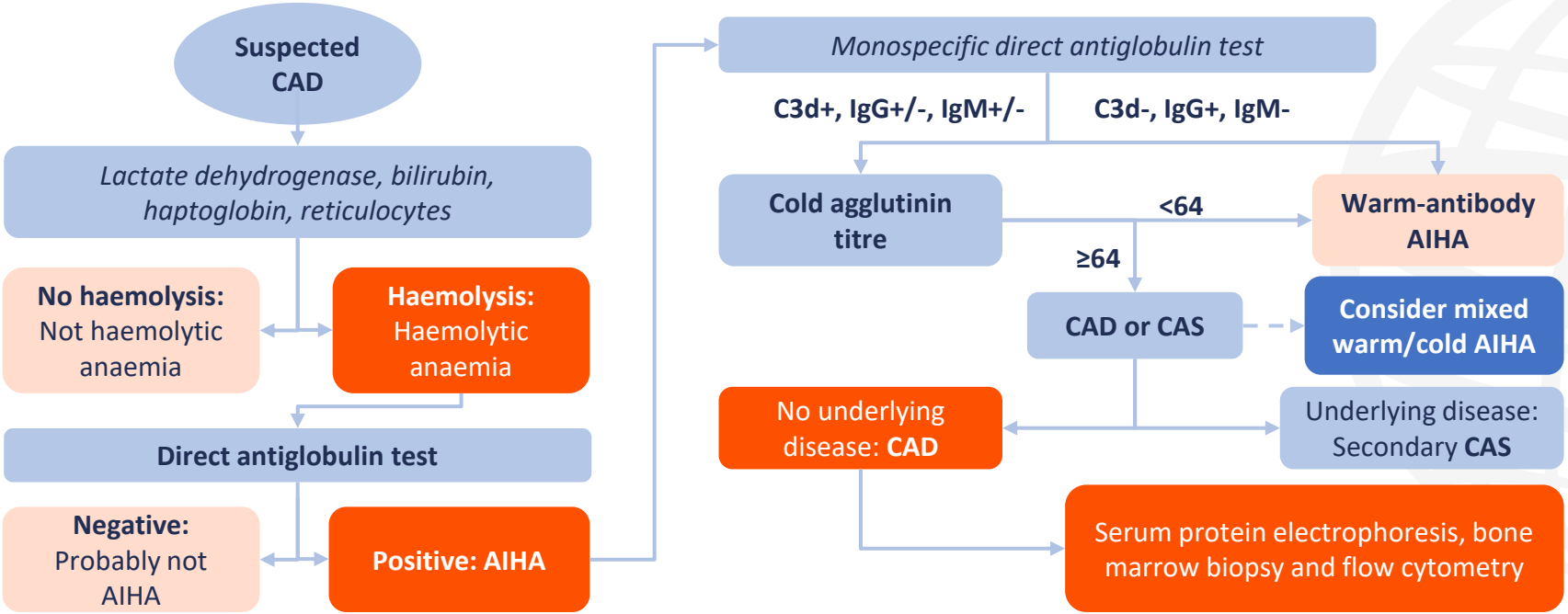
Diagnosis algorithm

- **CAD diagnosis relies on exclusion of secondary diseases or other causes**



Adapted from Berentsen and Barcellini, 2021.

AIHA, autoimmune haemolytic anaemia; C, serum complement protein; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; IgG/M, immunoglobin G/M.

Berentsen S, Barcellini W. *N Engl J Med.* 2021;385:1407–19.

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Navigating the evolving treatment landscape in cold agglutinin disease

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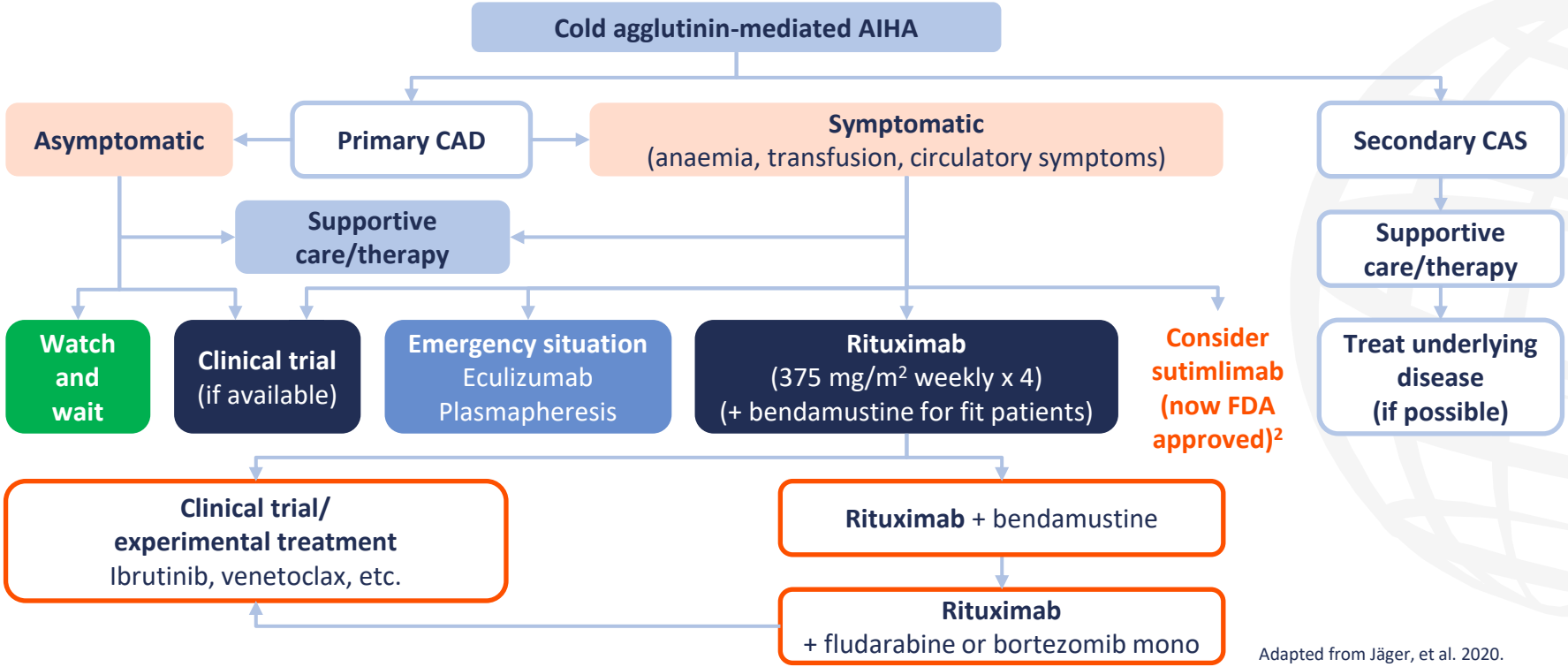
Evolving treatment algorithm for CAD[1]



Adapted from Jäger, et al. 2020.

AIHA, autoimmune haemolytic anaemia; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; FDA, Food and Drug Administration; mono, monotherapy.

1. Jäger U, et al. *Blood Rev*. 2020;41:100648; 2. FDA. Sutimlimab PI. 2022. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2022/761164s000lbl.pdf (accessed 23 August 2022).

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Novel agents currently under investigation for CAD

Intervention	Mode of action	Trial	Results
Sutimlimab	mAb targeting C1	CARDINAL (Phase III; NCT03347396)[1]	At 26 weeks, the mean haemoglobin level >11g/dL was maintained from week 3, with rapid inhibition of the complement pathway and decreased bilirubin levels
		CADENZA (Phase III; NCT03347422)[2]	Sutimlimab increased mean haemoglobin at assessed timepoint (mean of weeks 23, 25, 26), and normalized bilirubin by week 1. Improvements correlated with near-complete inhibition of classical complement pathway (2.3% mean activity at week 1)
		Phase III (NCT05132127)[3]	*[Ongoing: Using ongoing sutimlimab in patients who have already benefited from sutimlimab in the CARDINAL/CADENZA trials]*
Pegcetacoplan (APL-2)	Complement C3 inhibitor	Phase II (NCT03226678)[4]	Increased mean haemoglobin in CAD and wAIHA; sustained benefit with longer exposure
		Phase III (NCT05096403)[5]	*[Ongoing: pegcetacoplan in patients with primary CAD]*
Iptacopan	Complement factor B inhibitor[6]	Phase II (NCT05086744)[7]	*[Ongoing: assess efficacy, safety and PK in CAD and ITP]*
BIVV020	mAb targeting C1[8]	Phase I (NCT04269551)[9]	*[Ongoing: assess the safety and tolerability in CAD after single dose]*

C, serum complement protein; CAD, cold agglutinin disease; ITP, immune thrombocytopenia; mAb, monoclonal antibody; PK, pharmacokinetics; wAIHA, warm autoimmune haemolytic anaemia.

1. Röth A, et al. *N Engl J Med.* 2021;384:1323–34; 2. Röth A, et al. *Blood.* 2022;140:980–91; 3. ClinicalTrials.gov. NCT05132127. Available at: https://clinicaltrials.gov/ct2/show/NCT05132127 (accessed 23 August 2022); 4. Gertz M, et al. *Hemasphere.* 2019;3(Suppl. 1):405; 5. ClinicalTrials.gov. NCT05096403. Available at: https://clinicaltrials.gov/ct2/show/NCT05096403 (accessed 23 August 2022); 6. Jang J, et al. *Blood Adv*. 2022;6:4450–60; 7. ClinicalTrials.gov. NCT05086744. Available at: https://clinicaltrials.gov/ct2/show/NCT05086744 (accessed 23 August 2022); 8. Berentsen S. *Blood*. 2021;137:1295–03; 9. ClinicalTrials.gov. NCT04269551. Available at: https://clinicaltrials.gov/ct2/show/NCT04269551 (accessed 23 August 2022).

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Individualizing cold agglutinin disease management in the clinic

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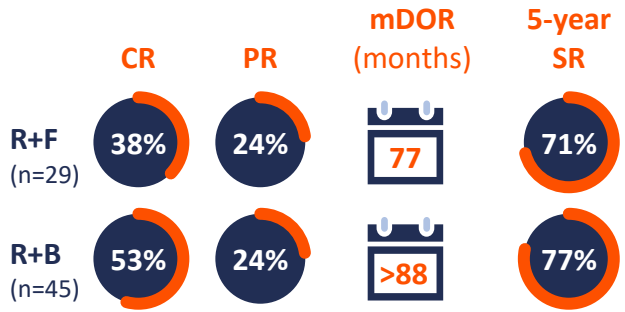
Unmet treatment needs in CAD

Experience with conventional therapy and impact on patients with CAD

Retrospective analysis of CAD outcomes in 232 patients[1]

24% no prior treatment	**45%** received R-monotherapy	**59%** responded at least once

- **Deeper responses over time with both R+F and R+B**



- **Higher risk of late-occurring malignancies with R-F vs R-B**
- **Increased risk of thromboembolic events**

Retrospective observational cohort study with 60 months' follow-up[2]

High burden on healthcare system: transfusions, hospitalizations, outpatients and emergency room visits

of patients hospitalized in first year

of patients hospitalized over entire follow-up

Higher burden with moderate and severe anaemia or with haemolysis

Patients still experience moderate to severe anaemia and haemolysis 5 years after diagnosis

B, bendamustine; CAD, cold agglutinin disease; CR, complete response; F, fludarabine; mDOR, median duration of response; PR, partial response; R, rituximab; SR, sustained remission.

1. Berentsen S. *Blood.* 2020;136:480–8; 2. Wilson A, et al. *ASH 2020.* Abstract 151.

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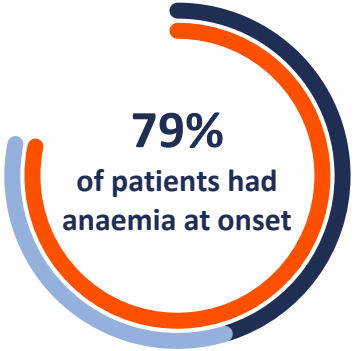
STRIDE cohort: Anaemia

In a retrospective analysis of CAD patients from a large US database:



45% had severe anaemia

34% had moderate anaemia

72% of the patients had ≥1 severe anaemia event within the first year of follow-up

Mean and median haemoglobin were similar

Mean: 8.3 g/dL
Median: 8.2 g/dL
Range: 4.7–11.6 g/dL

During the follow-up period, there were:

- **7.1 severe anaemia events per patient-year** (787 events per 110.5 patient-years)
- **10.8 moderate events per patient-year** (1,196 events per 110.5 patient-years)
- **8.0 mild events per patient-year** (888 events per 110.5 patient-years)

- The severity of anaemia varied for each patient over time
- Many patients remained severely anaemic despite receiving multiple therapies

The degree of anaemia can be associated with substantial impairment in quality of life

CAD, cold agglutinin disease; STRIDE, Stanford Translational Research Integrated Database Environment.
Mullins M, et al. *Blood Adv*. 2017;1:839–48.

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Optum retrospective analysis of the largest CAD cohort to date: Thromboembolic events

In a matched cohort comparison study evaluating the risk of TEs in patients with and without CAD over a 10-year period:

- Of 608 patients with CAD, **29.6% had TE** (n=180/608 patients) compared with **17.6% of patients without CAD** (n=1,033/5,873 patients; adjusted HR 1.94 [95% CI 1.64–2.30])

TE type	Patients with CAD (N=608)	Patients without CAD (N=5,873)	Adjusted HR (95% CI)
Venous TE	14.6%	5.2%	2.95 (2.28–3.82)
Arterial TE	7.6%	3.7%	1.93 (1.37–2.72)
Cerebral TE	14.0%	11.6%	1.26 (1.00–1.60)

There is a

1.9 ×

higher overall risk of having a TE in patients with CAD versus patients without CAD

(HR 1.94 [95% CI 1.64, 2.30])

- **Patients with CAD have an increased risk of TEs when compared with a matched non-CAD population**

CAD, cold agglutinin disease; CI, confidence interval; HR, hazard ratio; TE, thromboembolic event.

Broome C, et al. *Res Pract Thromb Haemost*. 2020;4:628–35.

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