Cold Agglutinin Disease is about more than avoiding the cold, CHRONIC HEMOLYSIS CAN HAVE SEVERE CONSEQUENCES

CAD is a rare type of autoimmune hemolytic anemia

Know the disease and risks. UnderstandingCAD.com
Patients are burdened by more than just anemia

CAD is a serious hemolytic disease with systemic acute and chronic repercussions\(^2\)

- Vulnerable to hemolytic crisis
- Increased transfusion burden
- Afflicted with a lifelong condition

In a retrospective review of a healthcare system database in patients with CAD (n=29):

- 72% experienced a hemolytic crisis
- 65% needed a transfusion
- 53% required emergency room visits*

*Driven by severe anemia events in the 15 patients who were followed for 1 year.

The disease course is unpredictable with events ranging in occurrence and severity\(^1\)\(^3\)

For patients, CAD is not just a benign condition

CAD=Cold Agglutinin Disease.
Patients may face a significant thromboembolic threat\textsuperscript{3}.

In the largest retrospective claims-database study of patients with CAD (n=814) vs a matched cohort without CAD (n=7960),\textsuperscript{*} there was a:

55\% increased risk of thromboembolic events

- 31\% experienced a thromboembolic event vs 20\% in the comparison cohort (P<0.0001)

Patients are at a significant increased risk for:

- \textbf{STROKE} (P<0.0001)\textsuperscript{5}
- \textbf{MI} (P=0.002)\textsuperscript{5}
- \textbf{DVT} (P=0.003)\textsuperscript{5}
- \textbf{PE} (P<0.0001)\textsuperscript{5}

\begin{itemize}
  \item Anemia is not the only predictor of risk—markers of hemolysis may be signs of thromboembolic risk
  \item 90\% of patients who experienced thromboembolic events had evidence of active hemolysis\textsuperscript{†} while only 23\% had hemoglobin of ≤8 g/dL
\end{itemize}

\textsuperscript{*}Patients were matched 1:10 on sex, ethnicity, region, follow-up, age, and entry date.

\textsuperscript{†}Elevated bilirubin and LDH.

In the first and only population-based study comparing patients with CAD (n=72) vs a general population cohort (n=720),\textsuperscript{1} there was:

Increased mortality seen \textbf{as early as year 1} after diagnosis\textsuperscript{4}.

- This study assessed mortality in CAD and measured survival using the Kaplan-Meier method
- Patients were identified in the Danish National Patient Registry, Civil Registration System, and National Health Service Prescription Database from 1999 to 2013
- Each patient was matched 1:10 based on age, sex, region, and adjusted based on Charlson Comorbidity Index score, including cancer and other conditions\textsuperscript{5}

Additional studies are needed to further understand the risks associated with CAD.

\textbf{Survival probability in patients with CAD from diagnosis at study entry}

\begin{itemize}
  \item Only 61\% of patients with CAD were likely to be alive at year 5 vs 82\% of the matched cohort
\end{itemize}

\textsuperscript{1}Sponsored by Bioverativ Therapeutics Inc., an affiliate of Sanofi.

DVT=deep vein thrombosis; LDH=lactate dehydrogenase; MI=myocardial infarction; PE=pulmonary embolism.
On the surface of RBCs, bound cold agglutinins recruit and activate C1.

In patients with CAD, a clonal expansion of B cells produces IgM antibodies, also known as cold agglutinins, which bind to RBCs.

Activated C1 initiates the classical complement pathway triggering a cascade that results in both extravascular and intravascular hemolysis.

Downstream of C1, activated C3 leads to extravascular hemolysis.

Downstream of C1 and C3, activated C5 leads to intravascular hemolysis.

This C1-activated hemolysis leaves patients chronically compromised by an unstable hemolytic state.

IgM=immunoglobulin M; RBC=red blood cell.
Confirming a diagnosis of Cold Agglutinin Disease

If CAD is suspected, a blood sample must be kept at 37°C to 38°C from the time it is drawn until it is tested to avoid potential false-negatives. Refrigeration must be avoided.⁷,⁸

To diagnose CAD¹,⁹

**TWO main criteria must be met**

1. Positive Coombs test results (direct antibody test)
2. Presence of an IgM autoantibody

Currently, there are no FDA-approved treatments.² Inhibiting chronic hemolysis is key to the potential treatment of CAD³

Sanofi Genzyme is committed to CAD research

If you have any patients with CAD who are looking for educational resources, please give them the card attached or direct them to:

- **Call our patient support lines**
  - Inside the US: 1-833-CAD-CHAT (1-833-223-2428)
  - Outside the US: 1-781-902-0355
- **Or visit CADunraveled.com**