ACCADEMIA di FORMAZIONE

SIMTI

Malattia emolitica da anticorpi freddi: documento di consenso per la gestione diagnostica immunoematologica

CAD: definizione, fisiopatologia del complemento e strategie di terapia anti-complemento

Gianluca Ubezio

Ospedale Policlinico di Genova

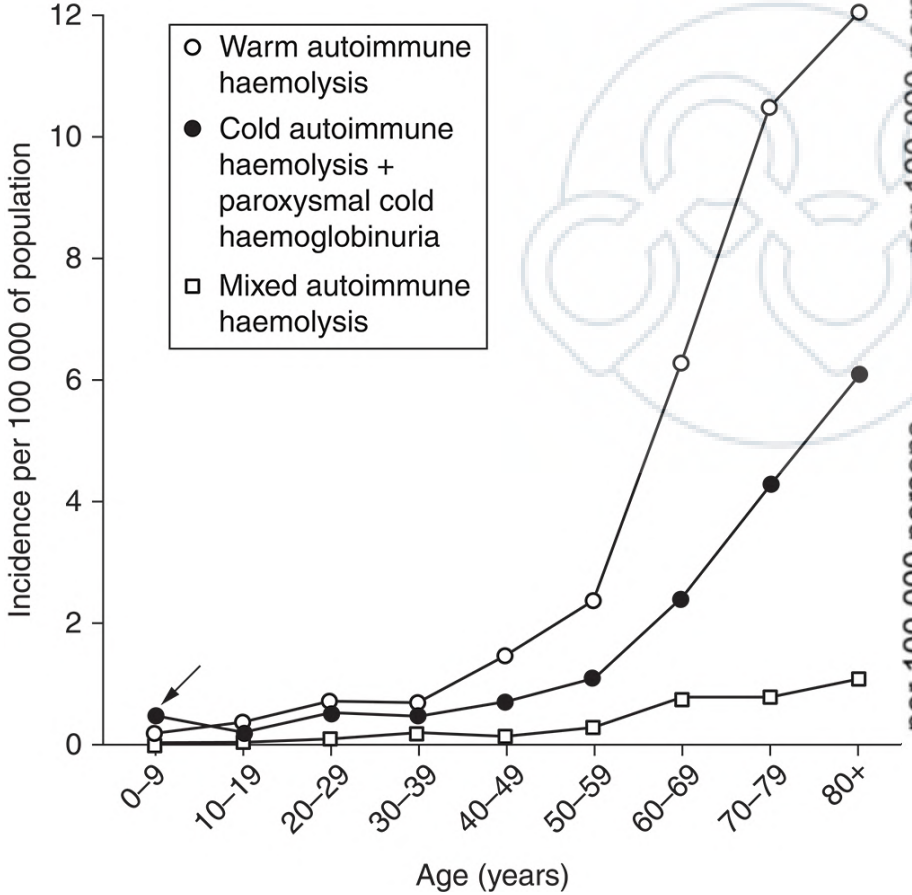
Il sottoscritto, in qualità di Relatore
dichiara che

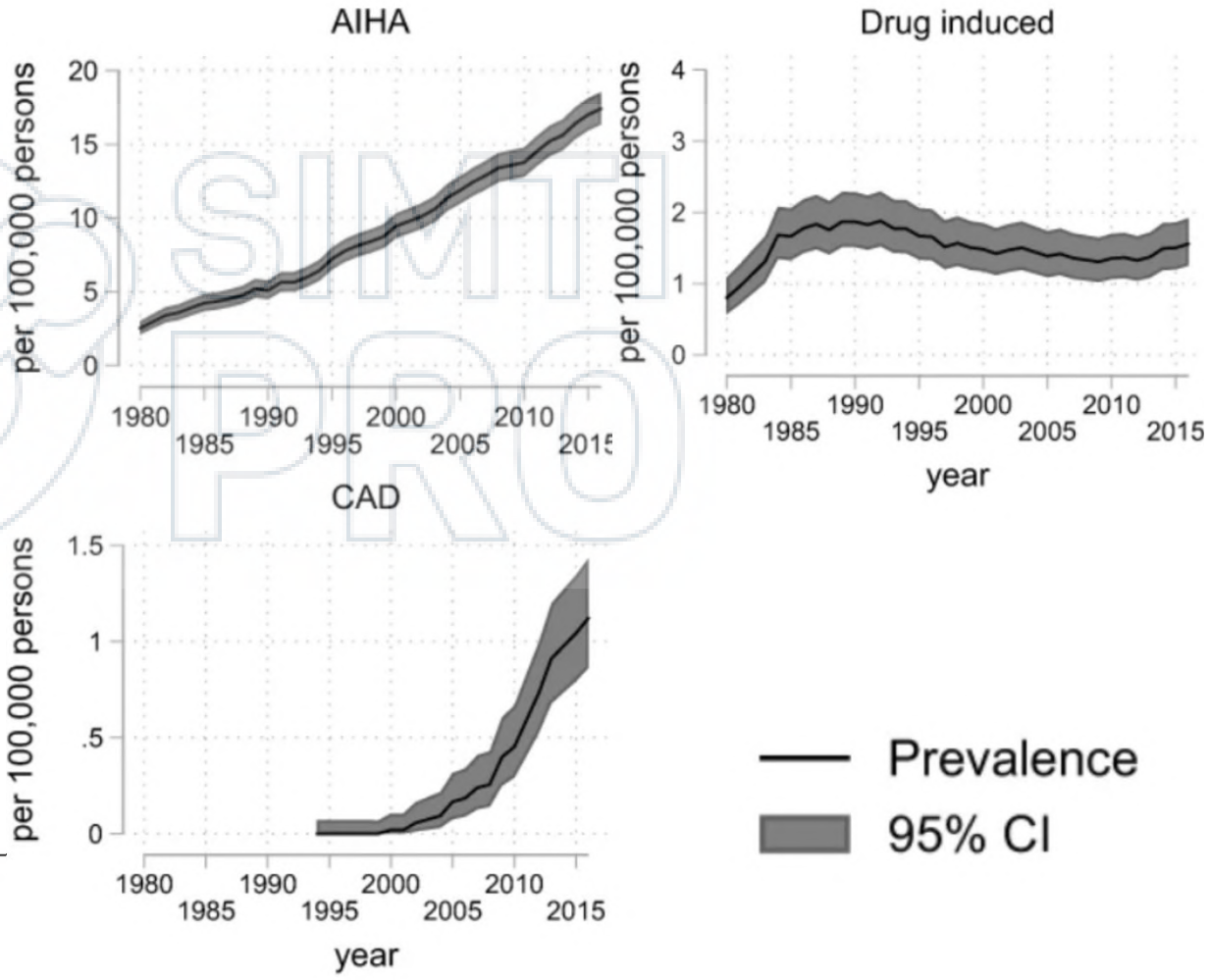
nell'esercizio della Sua funzione e per l'evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

EPIDEMIOLOGIA

Incidenza: 1-3 casi / 100’000 / anno
Prevalenza: 17 / 100’000

50% idiopatica,
20% sec. a m. linfoproliferative,
20% sec. a m. autoimmuni,
10% sec. a neoplasie o infezioni.





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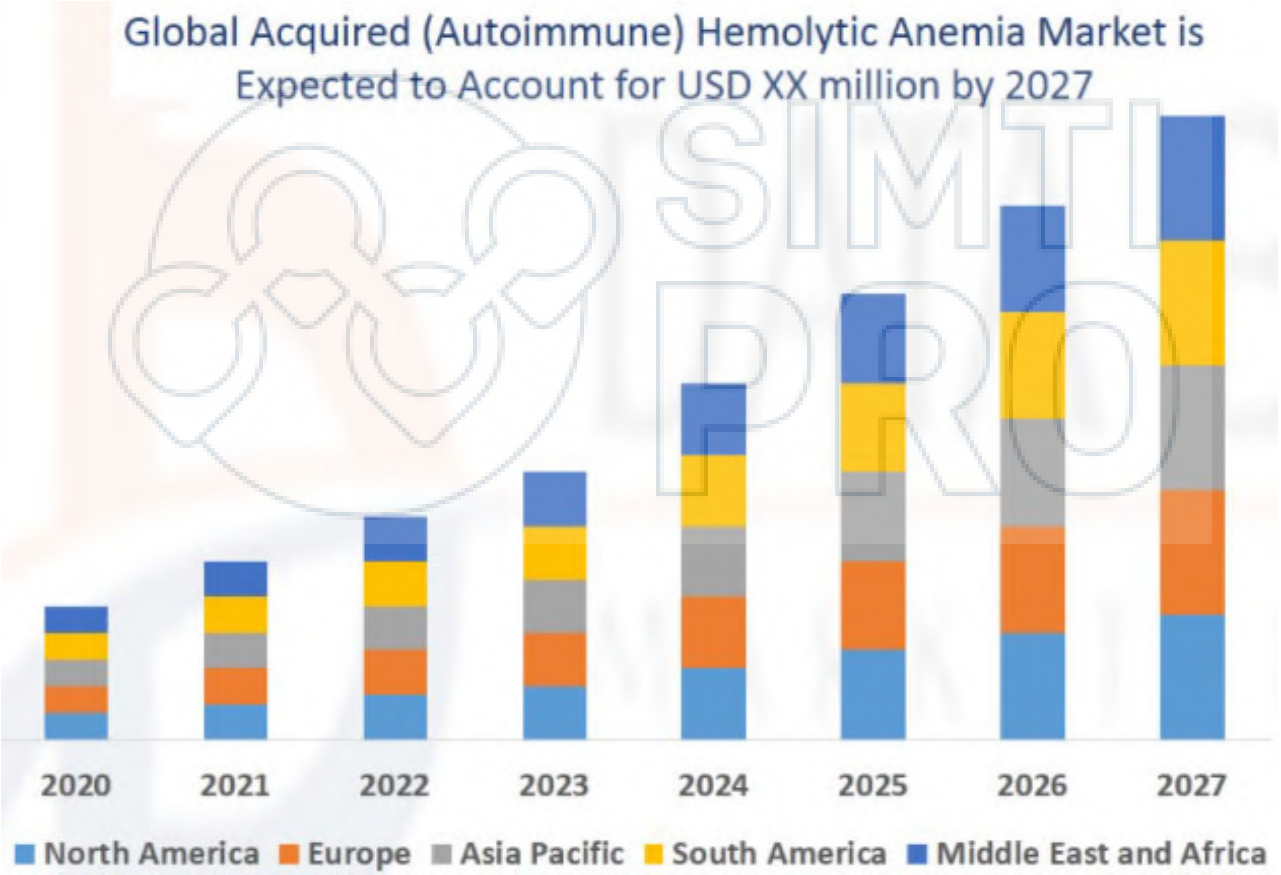


ANEMIE EMOLITICHE AUTOIMMUNI da anticorpi FREDDI (IgM)

MALATTIA DA CRIOAGGLUTININE

Principalmente mediata da **IgM** (raramente IgA o IgG).

- Temperatura ottimale di legame compresa tra 0 e 4°C.
- Frequentemente travate **a basso titolo** in adulti sani.
- Aumento del titolo in corso di patologia:
    1. **Oligoclonale**: infezioni;
    2. **Monoclonale**: processi neoplastici o paraneoplastici.

ANEMIE EMOLITICHE AUTOIMMUNI da anticorpi FREDDI (IgM)

MALATTIA DA CRIOAGGLUTININE

FISIOPATOLOGIA

- Emolisi principalmente **extravascolare** (intravascolare nelle fasi acute di malattia)
- Colpisce più frequentemente **soggetti anziani** ed in minor misura bambini
- **Anemizzazione cronica**, soprattutto nelle forme primarie

FATTORI CONDIZIONANTI LA GRAVITA' DELL'EMOLISI

- Policlonalità vs oligo/monoclonalità
- Range termico
- Titolo (il titolo è influenzato dalla temperatura in cui si effettua la valutazione)

Le crioagglutinine che mantengono la loro reattività fino a 25-30°C sono in grado di determinare attivazione del complemento in vivo e distruzione eritrocitaria.

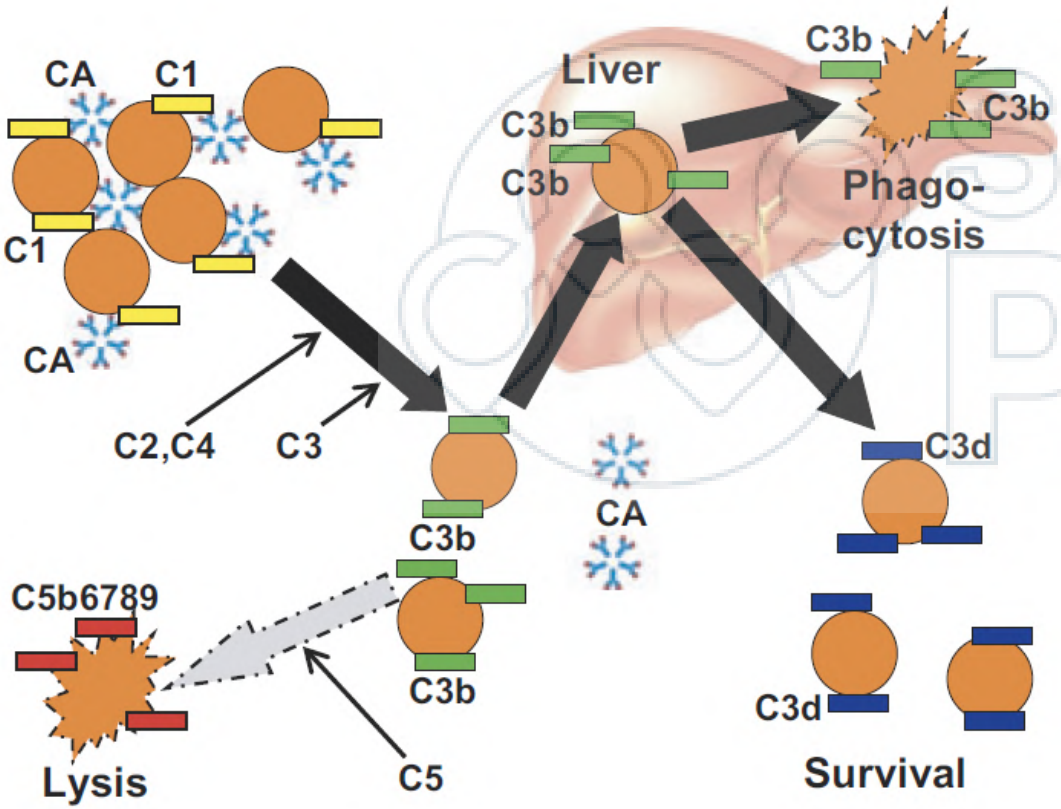
Alti titoli a range termico inferiore possono comunque causare microagglutinazione intravascolare dei capillari periferici.

ANEMIE EMOLITICHE AUTOIMMUNI da anticorpi FREDDI (IgM)

MALATTIA DA CRIOAGGLUTININE

Temperatura ottimale di legame compresa tra 0 e 4°C

- Emolisi principalmente **extravascolare**.



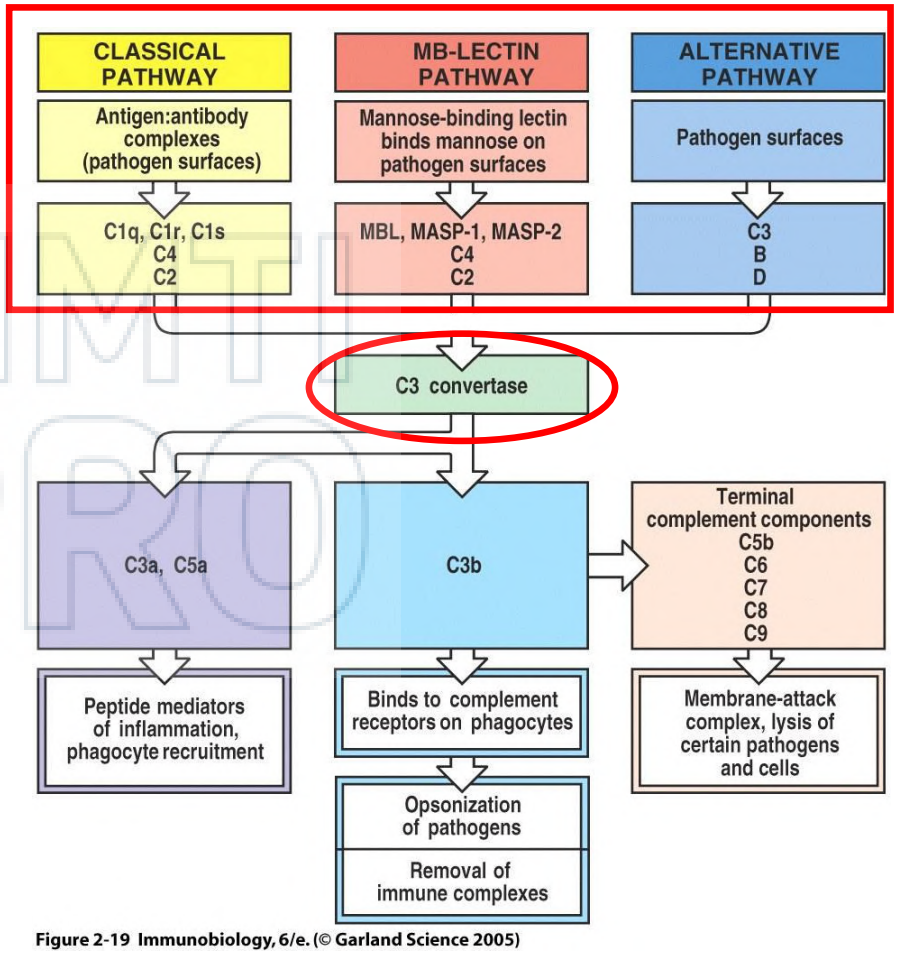


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

ELEMENTI CLASSIFICATIVI

Cold Agglutinin Disease
(previously, "*Primary CAD*")

- Malattia linfoproliferativa B a basso grado, evidenziabile nel sangue periferico o nel midollo
- Mancanza di segni evidenti di altre neoplasie

Cold Agglutinin Syndrome
(previously, "*Secondary CAD*")

Patologia secondaria a:

- Malattia linfoproliferativa B, con segni di presenza radiologica e sintomatologia
- Infezione acuta, più frequentemente da Mycomplasma pneumoniae o EBV o SARS-Cov-2
- Malattie autoimmunitarie (per es. LES)

TEMPERATURA AMBIENTALE E RISCHIO DI MALATTIA

COLD AGGLUTININ DISEASE REVISITED; A MULTINATIONAL, OBSERVATIONAL STUDY OF 232 PATIENTS

	Population, 10^6	Prevalence, cases/10^6 inhabitants	Incidence, cases/10^6 inhabitants/y	Outdoor temperature, °C, yearly-average
Norway	5.32	20.5	1.9	6.0*
Lombardy, Italy	7.0†	5.0	0.48	13.1

Calculation of prevalence was based on the number of patients still alive at the end of the study period. The yearly number of newly diagnosed cases was approximately constant from 2007 and was used to estimate incidence.

*Heterogeneous. Estimate based on yearly-average in Oslo, Bergen, and Trondheim.

†Refers to the relevant part of the region.

SISTEMA DEL COMPLEMENTO

MECCANISMI DI ATTIVAZIONE

1. VIA CLASSICA

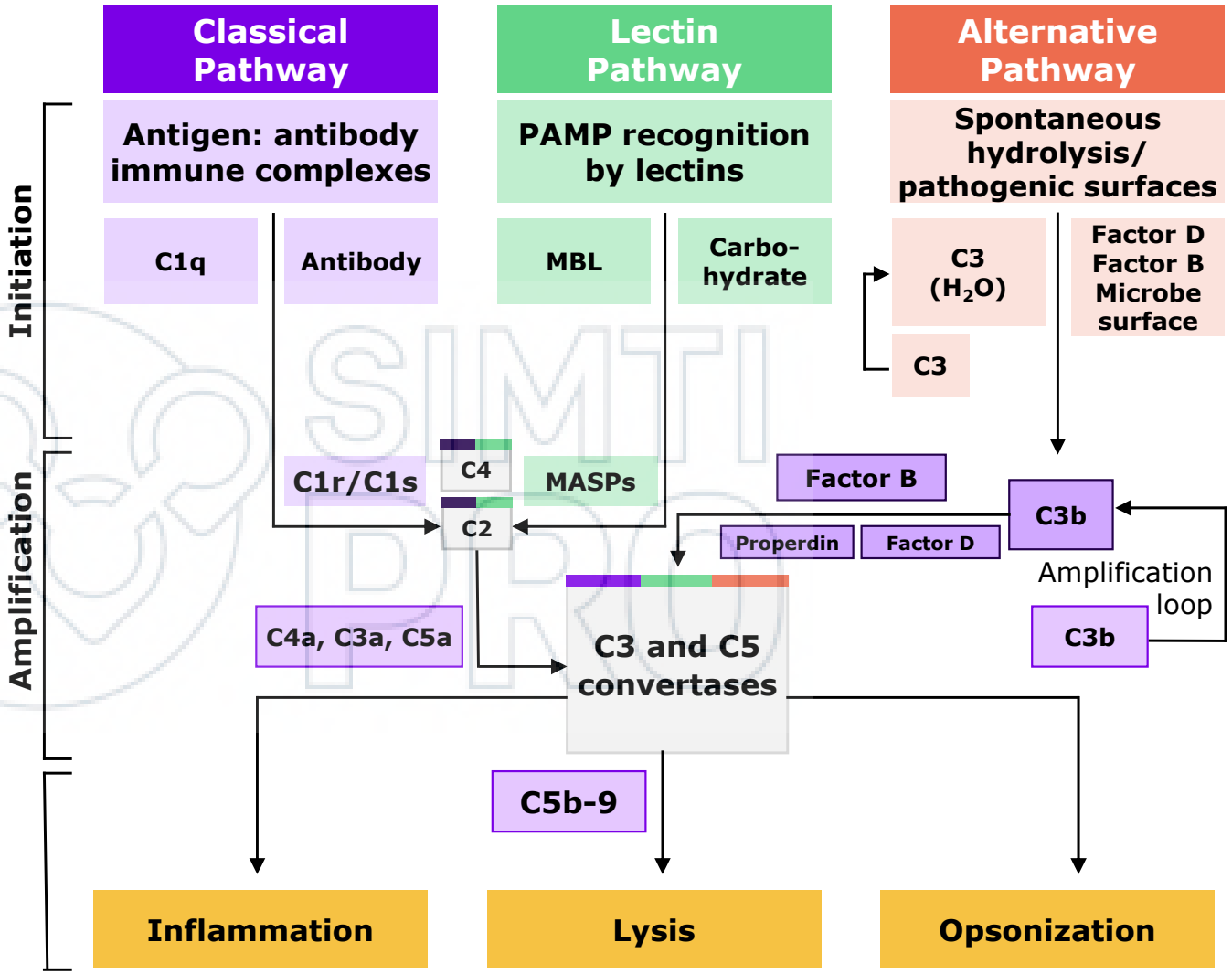
Attivazione mediate dal legame tra Ag-Abe attivazione di C1

2. VIA LECTINICA

Le MBL legano residui di mannosio, presenti sulla superficie dei patogeni

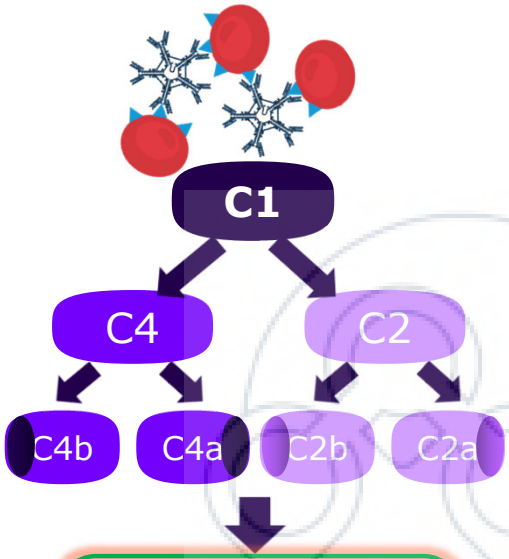
3. VIA ALTERNATIVA

Derivata dal fenomeno di attivazione spontanea (*tick-over*), in presenza di H2O, indipendentemente dalla presenza di anticorpi



SISTEMA DEL COMPLEMENTO

VIA CLASSICA



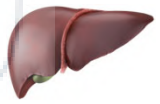
C3 CONVERTASI

C3a espleta una azione pro-infiammatoria, mentre **C3b** si deposita sulle emazie e rappresenta in segnale necessario ad indurre emolisi extra-vascolare.

In alcuni casi, l'attività di C3 convertasi è tale da indurre l'attivazione della fase terminale del complemento (**MAC** – emolisi intra-vascolare).

CITOLISI & OPSONIZZAZIONE

Emolisi extravascolare
(predominante in CAD)



Emolisi intravascolare

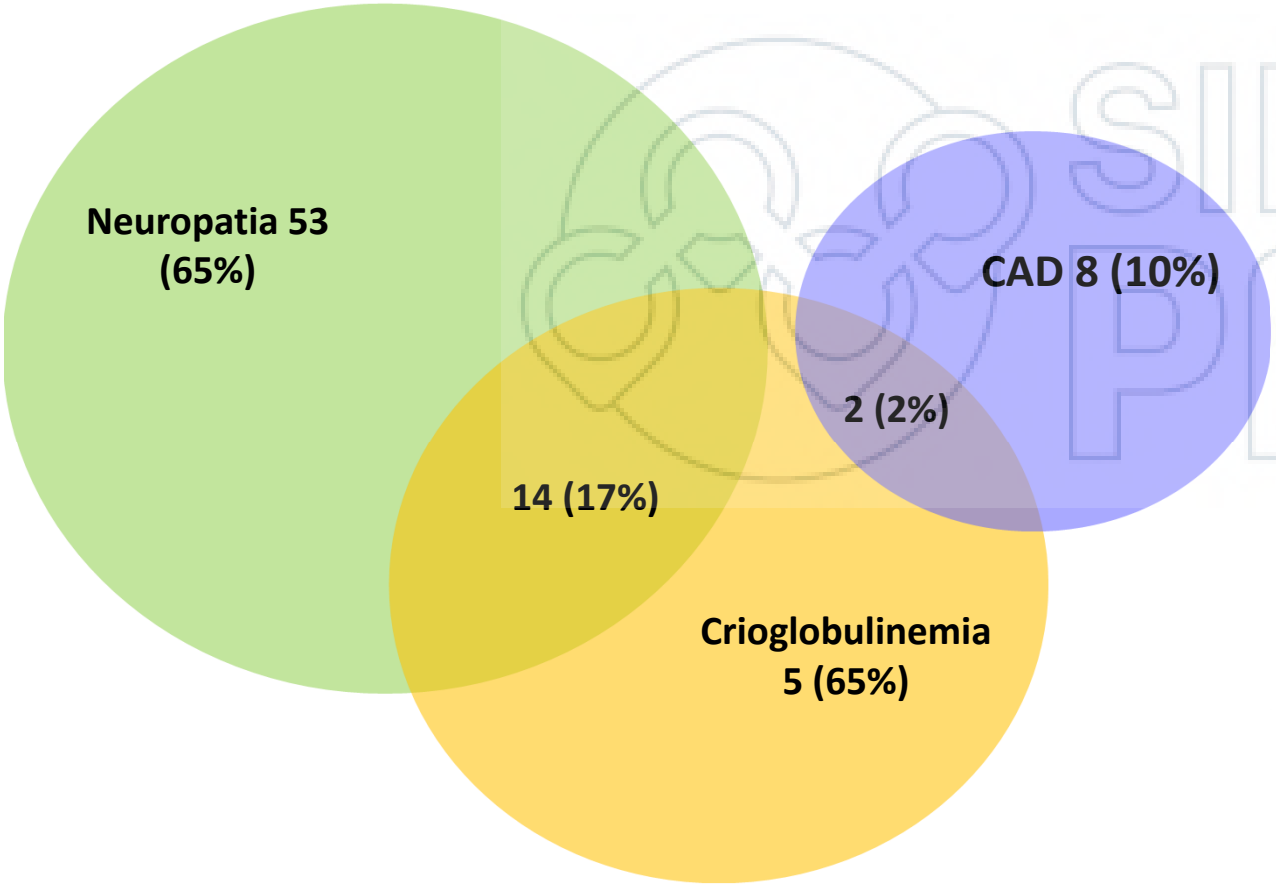
INFIAMMAZIONE

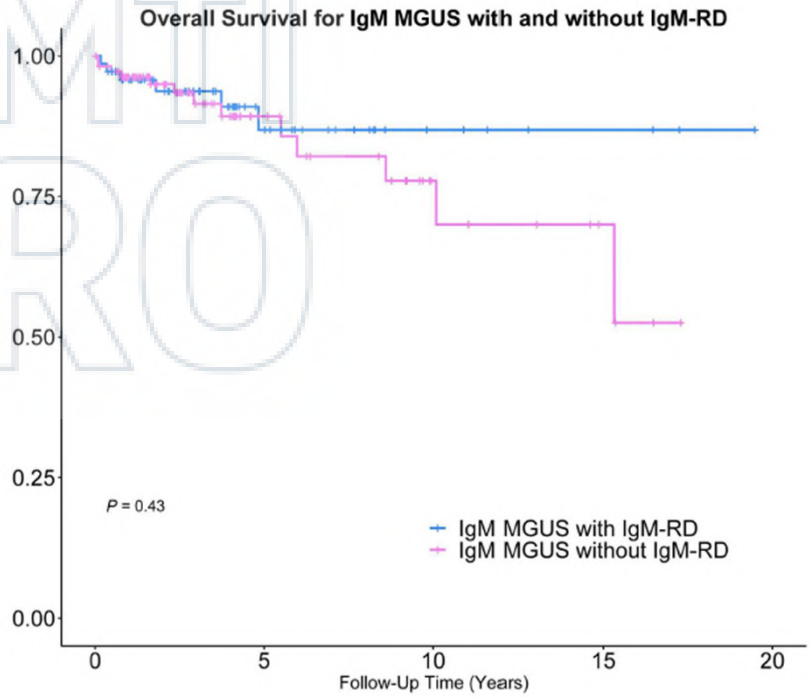
CAD vs MGUS IgM

Recentemente, sono state descritte caratteristiche genetiche ricorrenti in CAD che permettono di distinguerla da LPL/IgM MGUS. Tra queste, l'assenza di mutazione **MYD88 L265P** ed il frequente riscontro di trisomy 3, 12 e 18.

In una coorte di 191 soggetti con IgM MGUS, solo 10 (5%) avevano CAD.

Rispetto ai soggetti che presentano mutazione MYD88 L265P , i soggetti con CAD hanno evidenziato anemia di maggiore gravità (*p* 0.007).



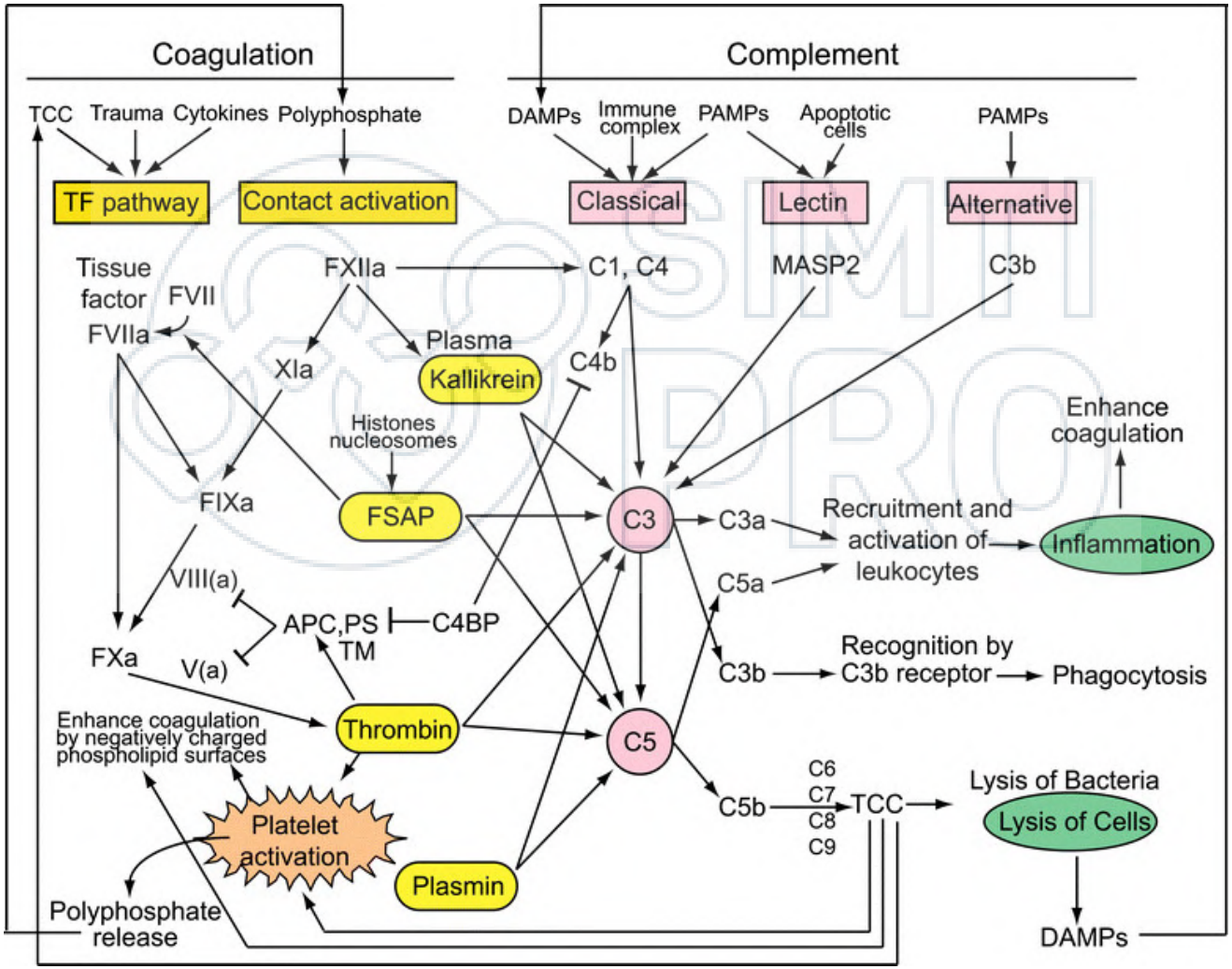


CAD vs MGUS IgM

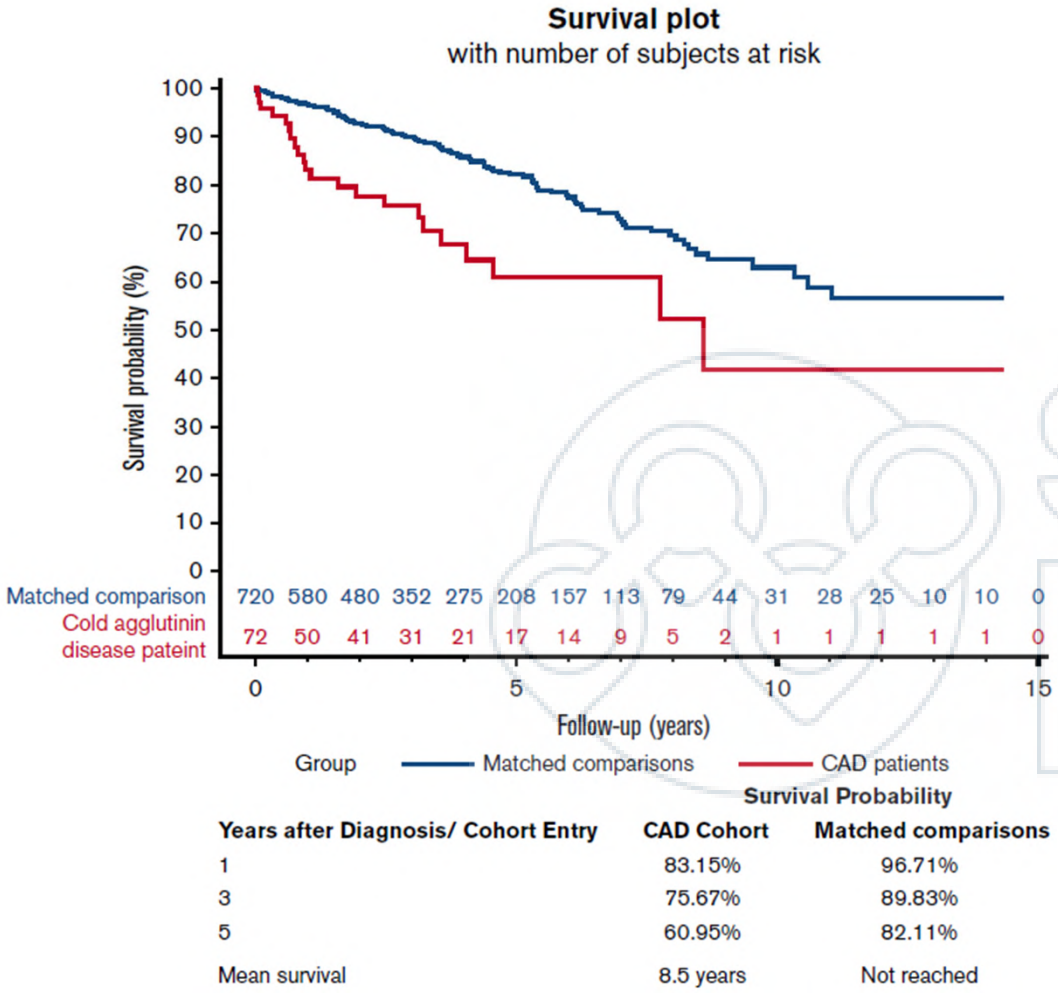
		All IgM MGUS	IgM MGUS w/o CAD	IgM MGUS with CAD	*P*
Total, N (%)		191 (100)	181 (95)	10 (5)	-
Sex, N (%)	Male	115 (60)	109 (60.2)	6 (60)	1.000
	Female	76 (40)	72 (39.8)	4 (40)	
Age at Bmbx in years, mean (median, SD)		69.6 (70.4-9.8)	69.6 (70.3-9.8)	69.6 (72.5-9.9)	0.992
IgM mg/dL mean (median, SD)		469 (452-614)	661 (444-627)	437 (497-264)	0.034
Light chain restriction by IFE, N (%)	κ	117 (61)	112 (61.9)	5 (50)	0.412
	λ	45 (24)	42 (23.2)	3 (30)	
	Multiple bands	12 (6)	12 (6.6)	0 (0)	
	PD bands	17 (9)	15 (8.3)	2 (20)	
Hgb g/dL, mean (median, SD)		12.6 (13.0-2.2)	12.7 (13.1-2.1)	10.3 (10.8-2.2)	0.007
Lymphs % in aspirate, mean (median, SD)		12.4 (11.0-7.1)	12.5 (11.0-7.0)	11.5 (8.0-9.2)	0.75
PC % in aspirate, mean (median, SD)		1.7 (1.0-2.2)	1.7 (1-1.4)	1.9 (1-1.8)	0.747
Clonal PC by IHC N=171, N (%)		41 (24)	38/163 (23.3)	3/8 (37.5)	0.400
Clonal B cells by FC N=157, N (%)		43 (27)	39/148 (26.4)	4/9 (44.4)	0.259
Lymphoid aggregates, N (%)		61 (32)	55 (30.4)	6 (60)	0.077
Abnormal karyotype N=173, N (%)		22 (13)	21/163 (12.9)	1/10 (10)	1.000
MYD88 L265P N=56, N (%)		35 (63)	35/53 (66.0)	0/3 (0)	0.048
Anti-MAG antibodies N=31, N (%)		16 (52%)	16/31 (51.6)	0/0 (0)	1.000

https://doi.org/10.3324/haematol.2022.282389

Additional direct interactions between complement and **coagulation** are mediated by various complement proteins and other coagulation factors, which in turn activate complement. **Thrombin** also acts as a **C5a convertase**, while complement and **platelets** interact during the early atherogenetic process



CAD E RISCHIO TROMBOEMBOLICO



Survival Probability

Years after Diagnosis/ Cohort Entry	CAD Cohort	Matched comparisons
1	83.15%	96.71%
3	75.67%	89.83%
5	60.95%	82.11%
Mean survival	8.5 years	Not reached

Il rischio tromboembolico nei pazienti affetti da CAD è aumentato.
Rispetto alla popolazione di controllo, è osservato un RR:

- 1 anno (7.2% vs 1.9% del controllo),
- 3 anni (9.0% vs 5.3%),
- 5 anni (11.5% vs 7.8%).

aHR stimato a 1.65 (95% CI, 0.69-3.95; P 5 .257).

DOI 10.1182/bloodadvances.2019000476.

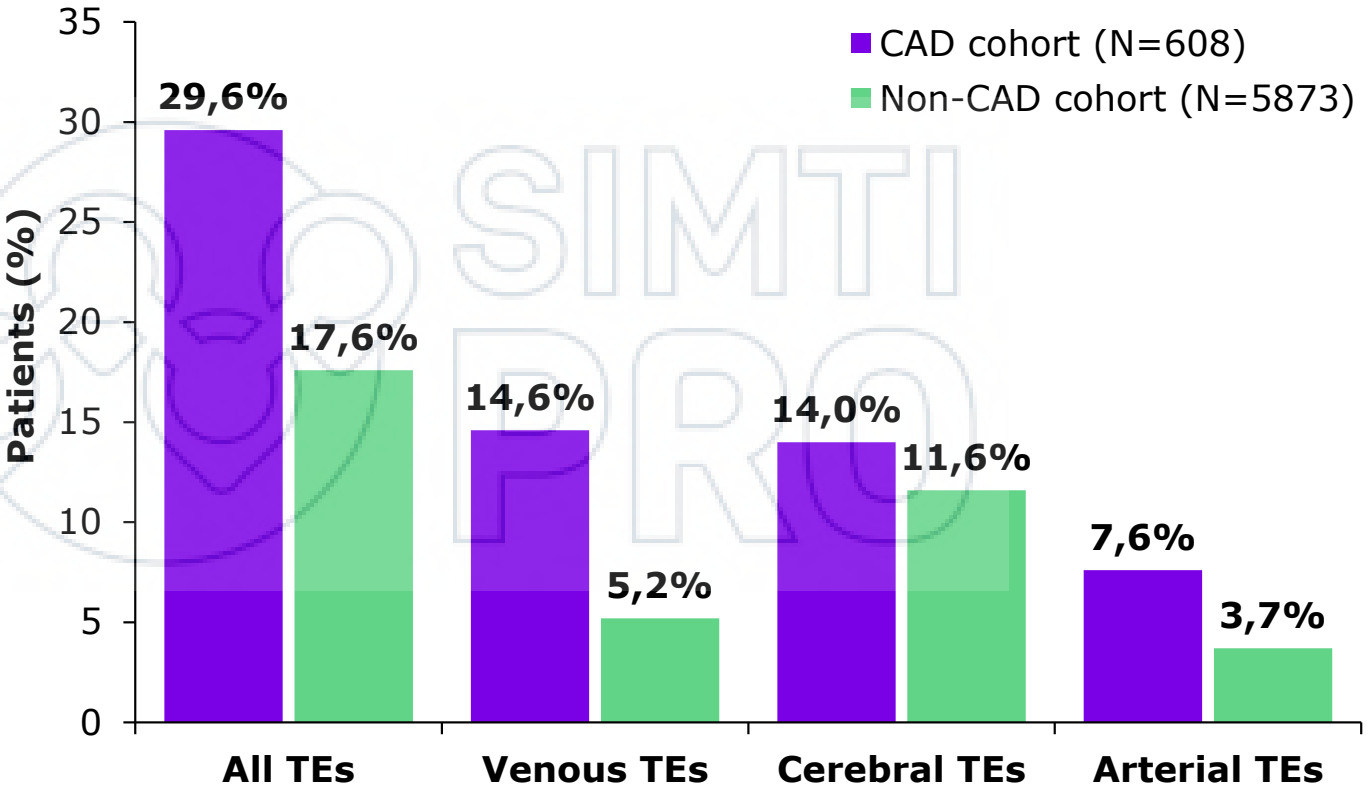
CAD E RISCHIO TROMBOEMBOLICO

ANALISI RETROSPETTIVA DI US Optum Database

608 pazienti con CAD, comparati con 5873 pazienti *matched-paired* (2006 – 2016)

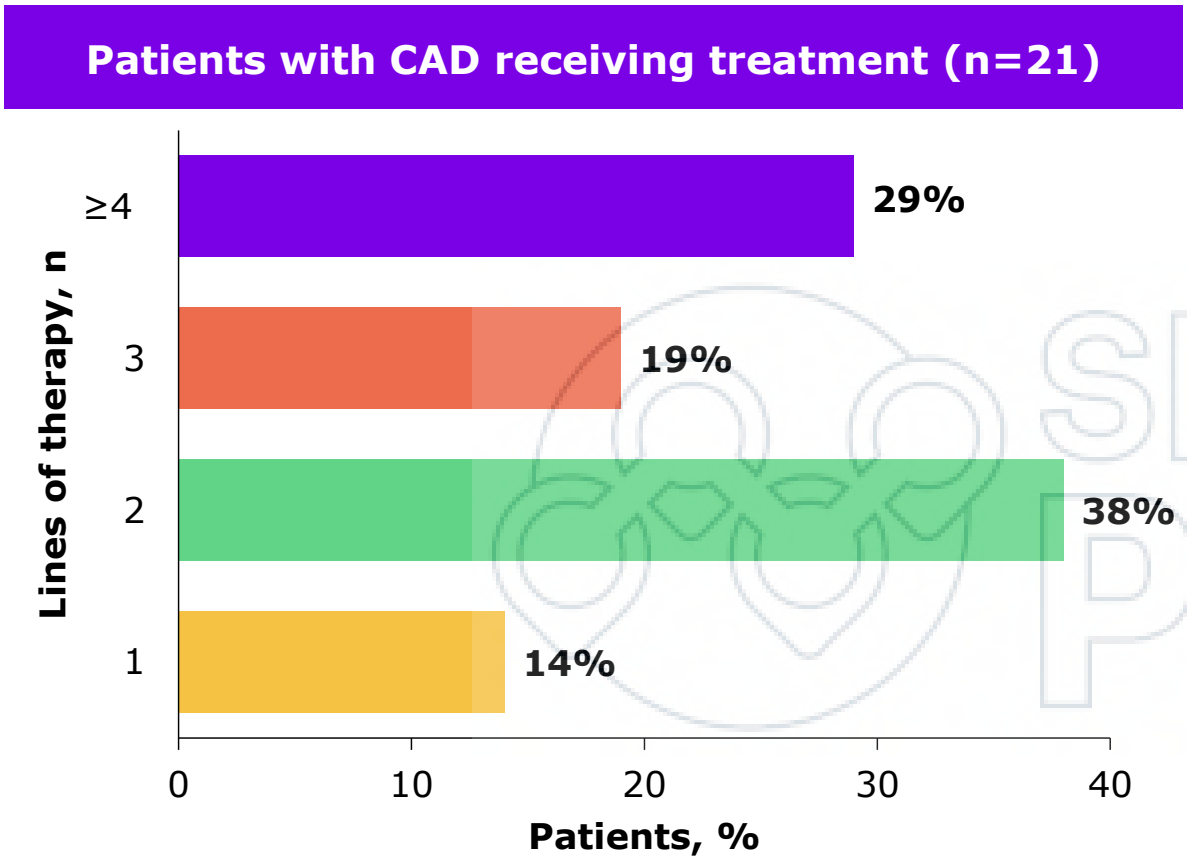
Conferma del maggiore rischio TE nei pazienti con CAD (adjusted hazard ratio: **1.94**; p<0.0001)

Overall rates of arterial, venous, and cerebral TEs[a]



STANDARD TERAPEUTICO

Stanford Healthcare Study



3.5

Linee di terapia che in media affronta un paziente con CAD

86%

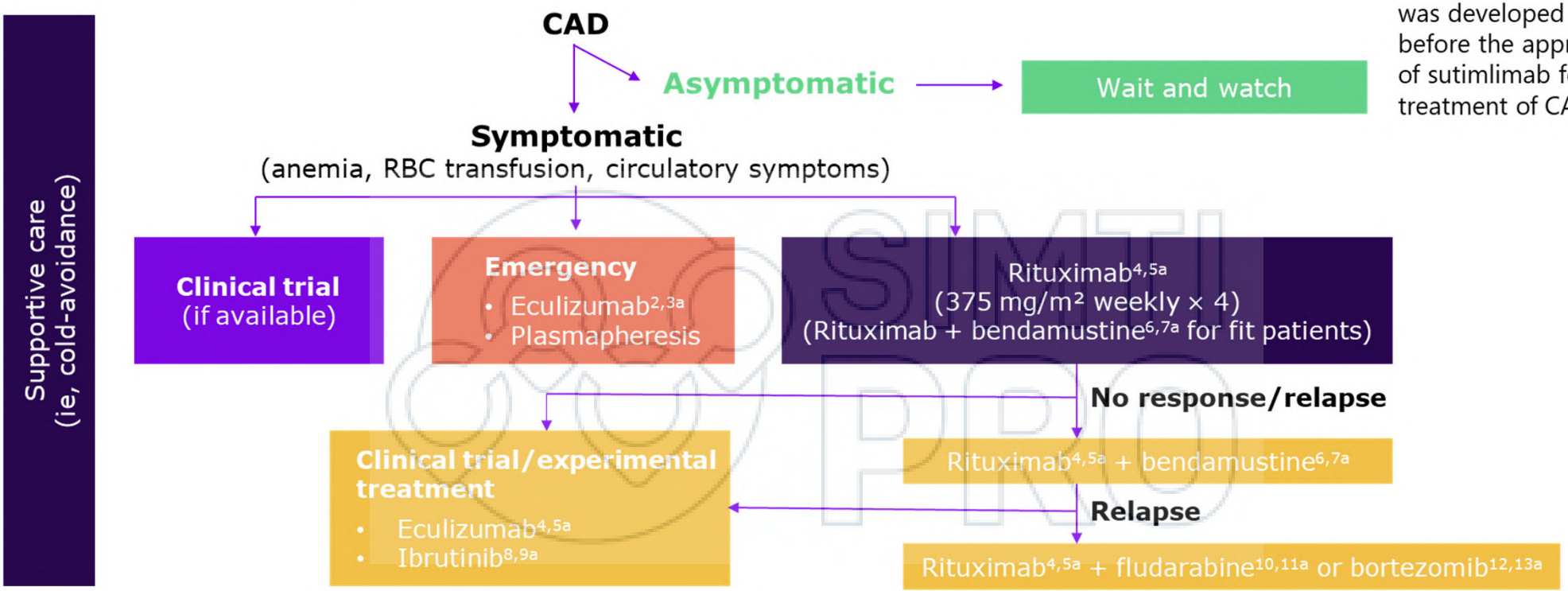
I pazienti che hanno ≥2 linee di terapia (29% sperimenta ≥4 line)

67%

I pazienti che sviluppano anemia grave all'esordio

STANDARD TERAPEUTICO

Recommendations From the First International Consensus Meeting (2020): Treatment Algorithm for CAD[1]



Note: This algorithm was developed before the approval of sutimlimab for the treatment of CAD

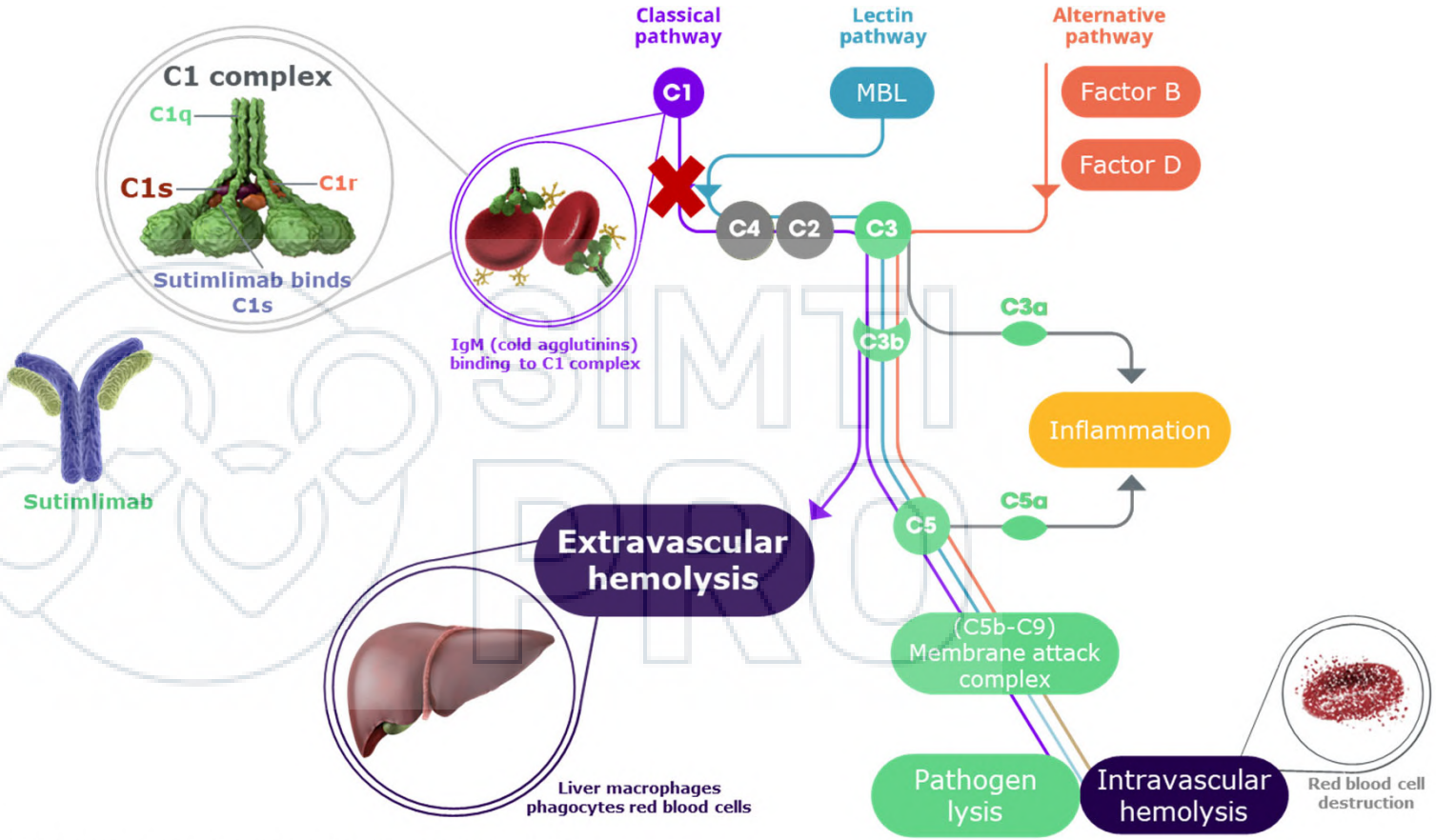
CAD, cold agglutinin disease; RBC, red blood cell. Figure adapted with permission of Elsevier. [a]off-label use[2–13].

1. Jäger U, *et al. Blood Rev*. 2020;41:100648; 2. Eculizumab, FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125166s431lbl.pdf [Last accessed March 2023]; 3. Eculizumab, EMA label. https://www.ema.europa.eu/en/documents/product-information/soliris-epar-product-information_en.pdf [Last accessed March 2023]; 4. Rituximab, FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf [Last accessed March 2023]; 5. Rituximab, EMA label. https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf [Last accessed March 2023]; 6. Bendamustine, FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208194s005lbl.pdf [Last accessed March 2023]; 7. Bendamustine, EMA label. https://www.ema.europa.eu/en/documents/referral/levact-article-29-referral-annex-i-ii-iii-iv_en.pdf [Last accessed March 2023]; 8. Ibrutinib, FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf [Last accessed March 2023]; 9. Ibrutinib, EMA label. https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf [Last accessed March 2023]; 10. Fludarabine, FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020038s032lbl.pdf [Last accessed March 2022]; 11. Fludarabine, EMA label. https://www.ema.europa.eu/en/documents/product-information/arzerra-epar-product-information_en.pdf [Last accessed March 2023]; 12. Bortezomib, FDA label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf [Last accessed March 2023]; 13. Bortezomib, EMA label. https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf [Last accessed March 2023].

NUOVI APPROCCI TERAPEUTICI FISIOPATOLOGICI

Sutimlimab selettivamente inibisce C1s, interattore centrale della via classica di attivazione del complemento

Sutimlimab (formerly BIVV009)[3]
Humanized monoclonal Ab
IgG_4 (S241P; L248E)
Designed to **inhibit the classical complement pathway**
Designed to leave the lectin and alternative pathways intact

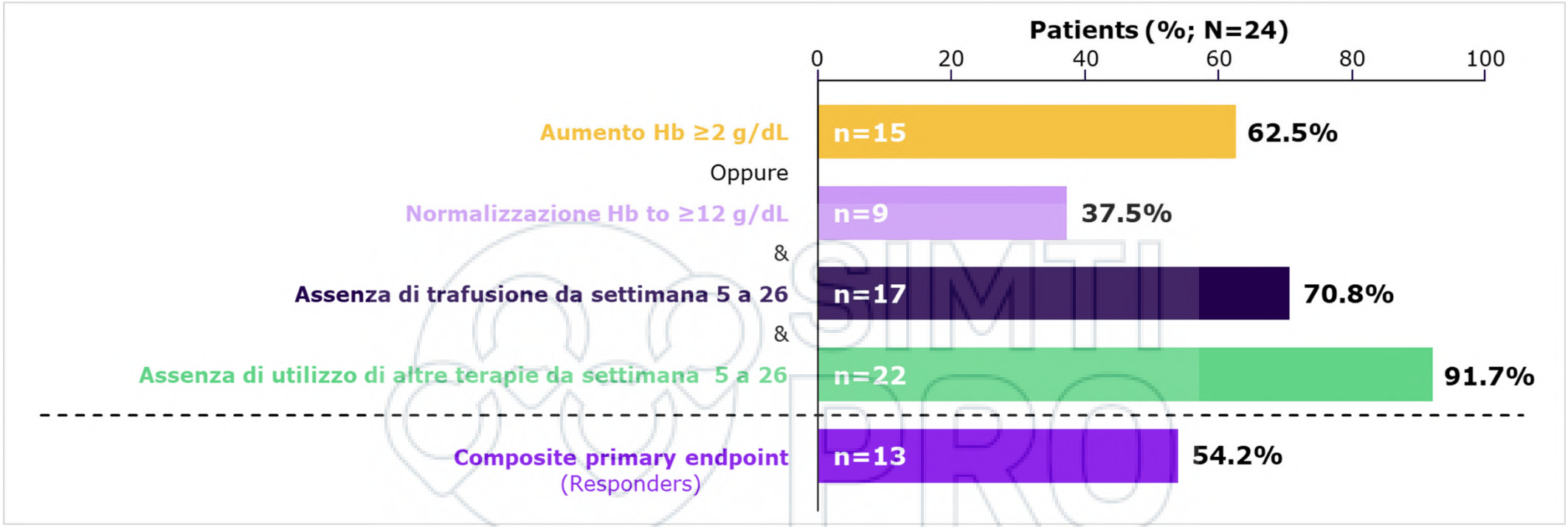


Ab, antibody; C, complement protein; Ig, immunoglobulin; MAC, membrane attack complex; MBL, mannose-binding lectin.
Jäger U, et al. Blood. 2019; 133(9):893–901. Figure adapted with permission of the American Society of Hematology.

1. Murphy K. *Janeway's Immunobiology*. 8th ed. New York, NY: Garland Science; 2012; 2. Jäger U, *et al. Blood.* 2019; 133(9):893–901;
3. Bartko J, *et al. Clin Pharmacol Ther*. 2018;104(4):655–63.

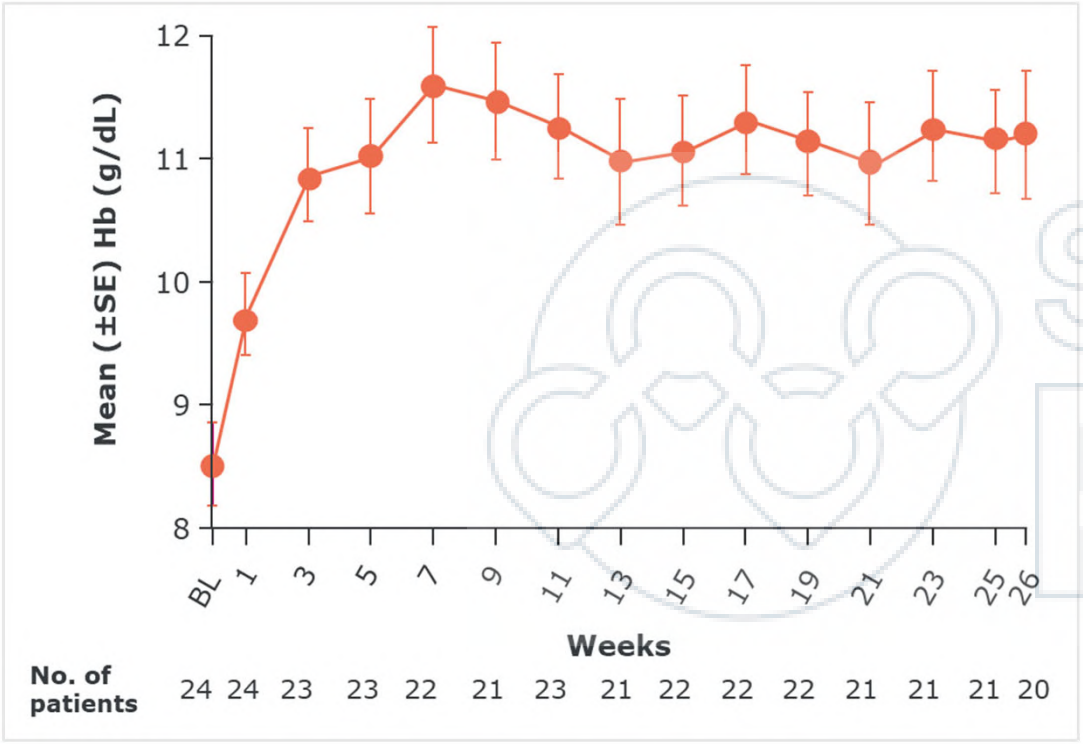
NUOVI APPROCCI TERAPEUTICI FISIOPATOLOGICI

VALUTAZIONE DI EFFICACIA DELLA INIBIZIONE DELLA VIA CLASSICA DEL COMPLEMENTO IN CAD



NUOVI APPROCCI TERAPEUTICI FISIOPATOLOGICI

Phase 3 CARDINAL Results: rapido aumento del valore di emoglobina



Rapido incremento dell'emoglobina

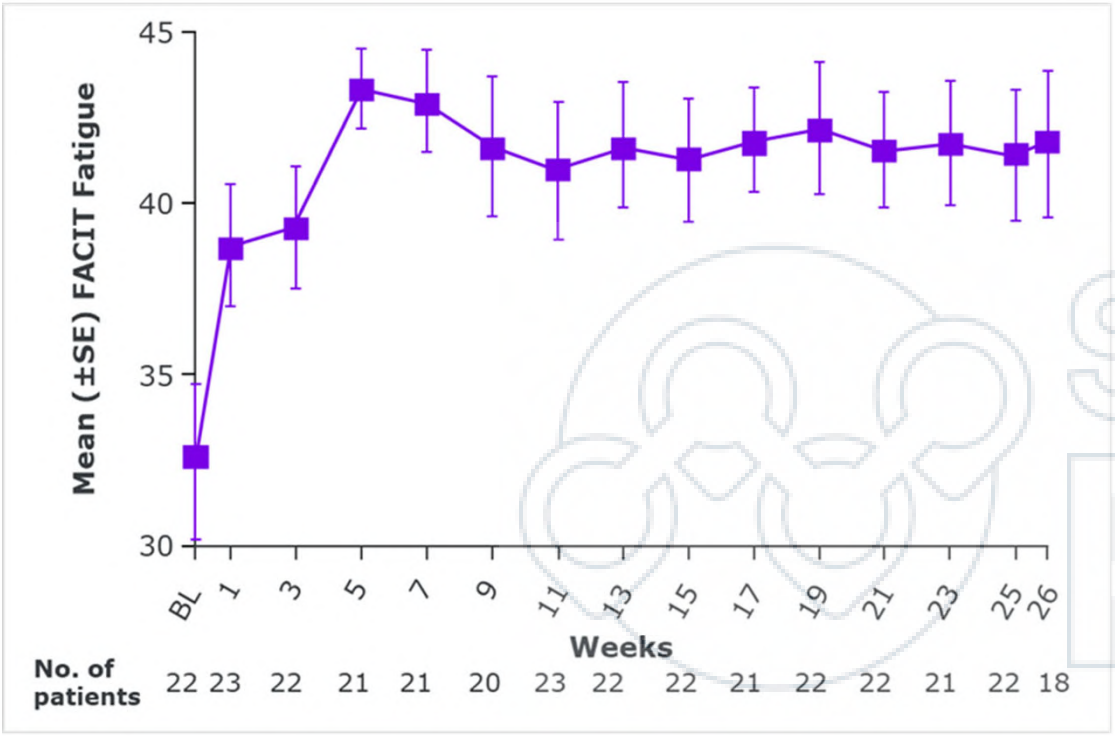
- Aumento medio di Hb >1 g/dL nella 1° settimana
- Aumento medio di Hb >2 g/dL nella 3° settimana
- Mantenimento del valore di Hb>11g/dL, durante il trattamento con sutimlimab

Sutimlimab aumenta in maniera significative il valore di Hb

Results presented from Part A of the Cardinal study. BL (Week 0) is defined as the last non-missing value prior to the first administration of sutimlimab.
[a]The treatment assessment timepoint is defined as the average of the values from the Week 23, 25, and 26 visits.
BL, baseline; Hb, hemoglobin, SE, standard error.
1. Röth A, *et al. N Engl J Med.* 2021;384:1323–34; 2. Röth A, *et al. Blood*. 2019;134(Suppl 2):LBA-2; 3. Data on file. CARDINAL Clinical Study Report, Sanofi Genzyme.

NUOVI APPROCCI TERAPEUTICI FISIOPATOLOGICI

Phase 3 CARDINAL: rapido miglioramento della QoL



Si assiste ad un significativo e stabile miglioramento del QoL (FACIT-Fatigue)

- Miglioramento medio dello score di 7 punti nella 1° settimana

Sutimlimab migliora lo score di valutazione del QoL

Results presented from Part A of the Cardinal study. BL (Week 0) is defined as the last non-missing value prior to the first administration of sutimlimab.
BL, baseline; EQ-5D-5L, EuroQol 5-dimensional questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; MID, minimally important difference; PGIC, Patient's Global Impression of Change; PGIS, Patient's Global Impression of (fatigue) Severity; PRO, patient-reported outcome; QOL, quality of life; SE, standard error; SF-12, 12-item Short Form Survey; TAT, treatment assessment time point. 1. Röth A, *et al. N Engl J Med.* 2021;384:1323–34; 2. Röth A, *et al. Blood.* 2019;134(Suppl 2):LBA-2; 3. Data on file. CARDINAL Clinical Study Report, Sanofi Genzyme; 4. Lai J, et al. *J Rheumatol.* 2011;38(4):672–79; 5. Reddy S, et al. *J Palliat Med.* 2007;10(5):1068–75.

NEW COMPLEMENT INHIBITORS & CAD

Pharmacologic treatment involves rituximab as the best first-line therapy, leading to remission (median duration, 1 year) in >50% of patients. In relapsed cases, alternative treatment options have been described: subsequent rituximab therapy; **fludarabine**/rituximab combination therapy, with a 75% response rate (median duration, >5 years) but significantly more toxicity; rituximab and **bendamustine** combination therapy; and **bortezomib**-based therapy.

Current updates of CAD management have focused on complement inhibition, after initial proof that classical pathway inhibition prevents generation of anaphylatoxins driven by cold agglutinin.
Sutimlimab is a first-in-class humanized monoclonal antibody that binds to **C1s** and inhibits **classical complement activation**.

All patients responded to sutimlimab within a few weeks, with a median rise in hemoglobin of almost 4 g/dL. It should be noted that sutimlimab does not affect the production of cold agglutinins or their binding to erythrocyte antigens; therefore, patients with CAD may still experience acrocyanosis.

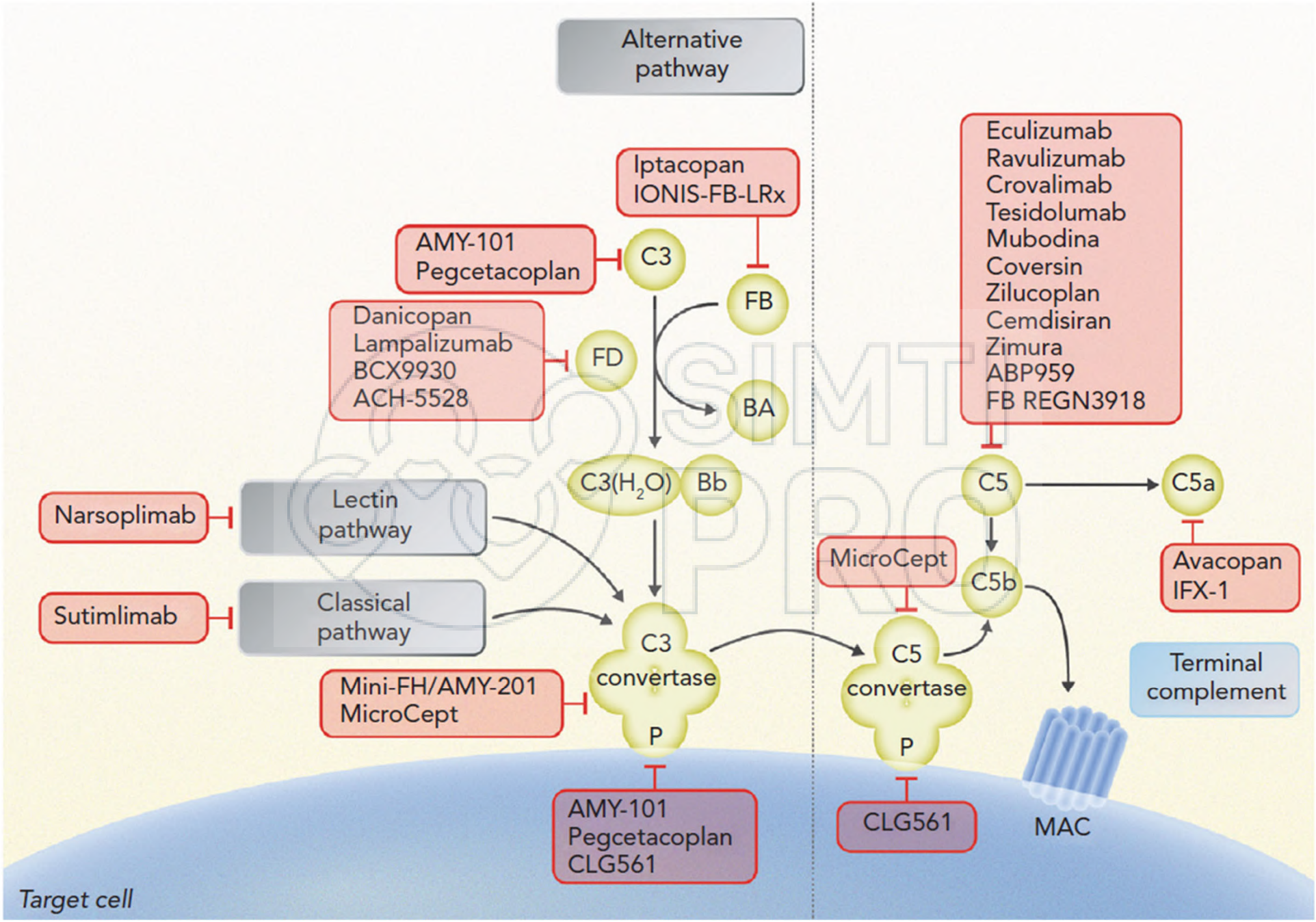
Serious (including bacterial) infections were reported, but no meningococcal infections were identified.

NEW COMPLEMENT INHIBITORS & CAD

Another complement inhibitor that targets C3, **pegcetacoplan**, was also studied in a phase 2 trial of autoimmune hemolytic anemia. The interim analysis of 10 patients with CAD showed improvements in hemoglobin, hemolytic markers, and fatigues scores. Therefore, targeted complement treatment is expected to become standard of care for CAD.

Pegcetacoplan acts upstream to the C5 convertase, binding to C3.
It appeared generally safe with no thrombotic events or severe infection complications, although high-grade hypersensitivity events occurred.
Notably, vaccines against S. pneumoniae and H. influenzae, in addition to those against N. meningitidis, are recommended before starting pegcetacoplan.
Pegcetacoplan has a shorter half-life. C3 is an acute phase protein, so that wide variations of its blood levels may occur, particularly in the presence of stressors/inflammation.

The C3 inhibitor pegcetacoplan, approved for PNH, inhibits both the classical and alternative complement pathways, and showed good activity in CAD and wAIHA with IgG + C DAT positivity.


Alternative pathway
Iptacopan
IONIS-FB-LRx
AMY-101
Pegcetacoplan
C3
FB
Danicopan
Lampalizumab
BCX9930
ACH-5528
FD
BA
Eculizumab
Ravulizumab
Crovalimab
Tesidolumab
Mubodina
Coversin
Zilucoplan
Cemdisiran
Zimura
ABP959
FB REGN3918
C3(H2O)
Bb
C5
C5a
Narsoplimab
Lectin pathway
MicroCept
C5b
Avacopan
IFX-1
Sutimlimab
Classical pathway
C3 convertase
P
C5 convertase
P
Terminal complement
Mini-FH/AMY-201
MicroCept
AMY-101
Pegcetacoplan
CLG561
CLG561
MAC
Target cell