An inflammatory surge seen during extracorporeal blood purification techniques due to host-membrane interactions

Turner Warwick Lecture
2nd July 2024

Duha Ilyas

Clinical Research Fellow, Renal Registrar[1]

PhD Student[2]

[1]Manchester Foundation Trust [2]University of Manchester

Disclosures

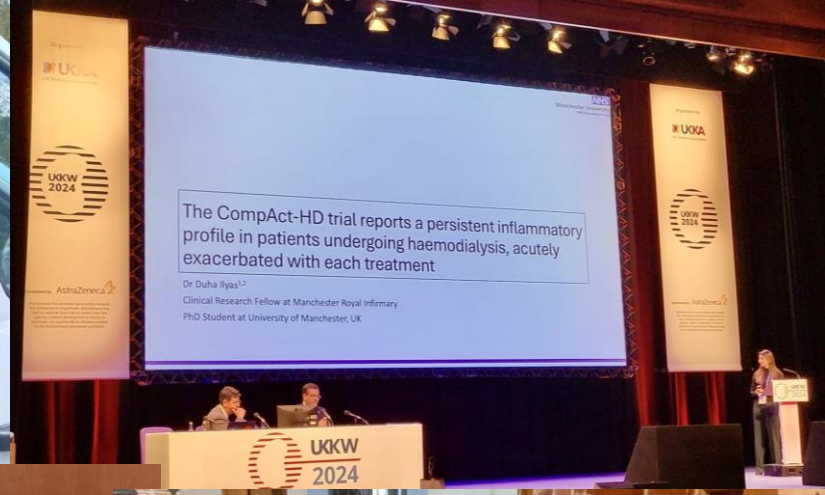
Declaration for Duha Ilyas

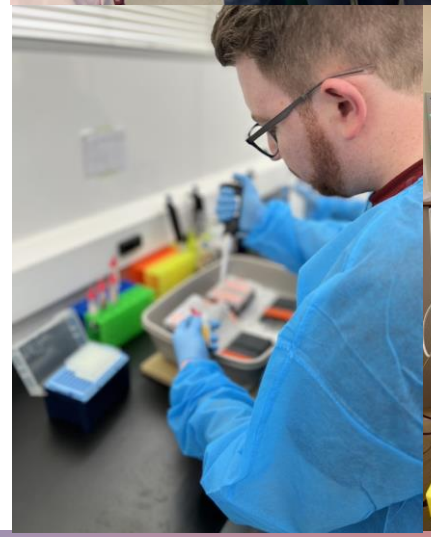
I have the following financial interest or relationship/s to disclose with regard to the subject matter of this presentation:

- Research funder: Invizius Ltd.

My Journey

- Nephrology Trainee in Yorkshire & Humber
- Clinical Research Fellow undertaking PhD at Manchester (2020-2024)
- Collaborative work between clinicians and industry
- Completed a large multi-centre observational study and Phase 1 Study
- 2024-2025 aims: PhD and CCT





Overview

Dialysis, saving lives for seven decades

Membrane-Host Bioincompatibility and Outcomes

CompAct-HD Trial

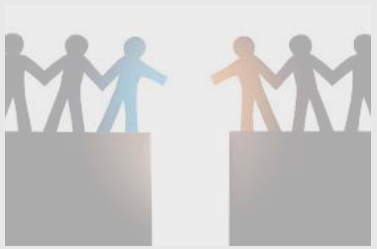
Closing the gap in dialysis

Overview

Dialysis, saving lives for seven decades

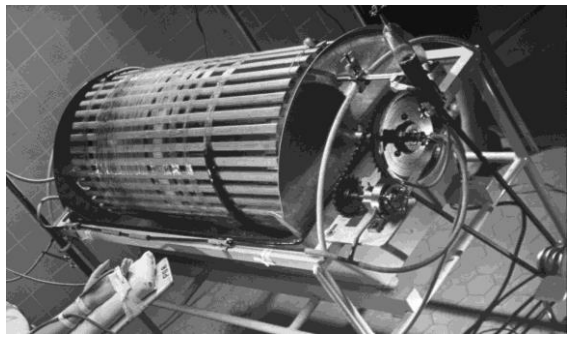
Membrane-Host Bioincompatibility and Outcomes

CompAct-HD Trial

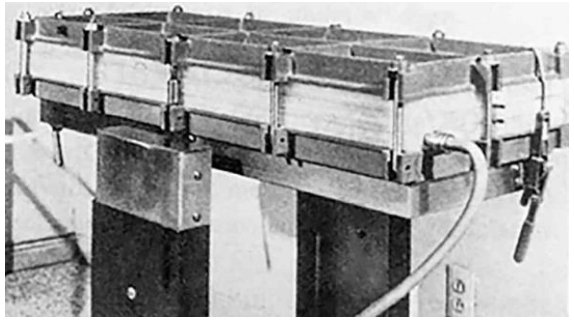


Closing the gap in dialysis

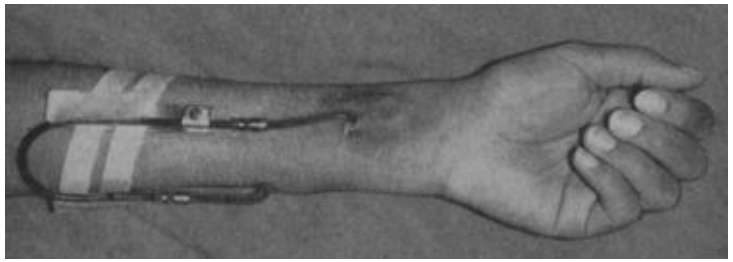
The Evolution of Haemodialysis



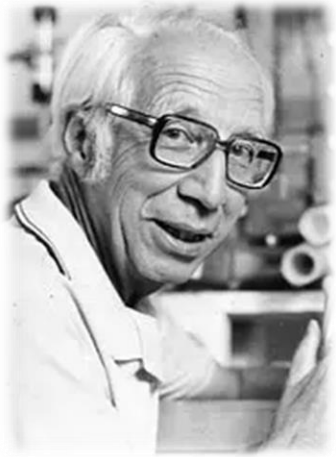
1943 – Rotating Drum



1960 - Kiil Dialyser

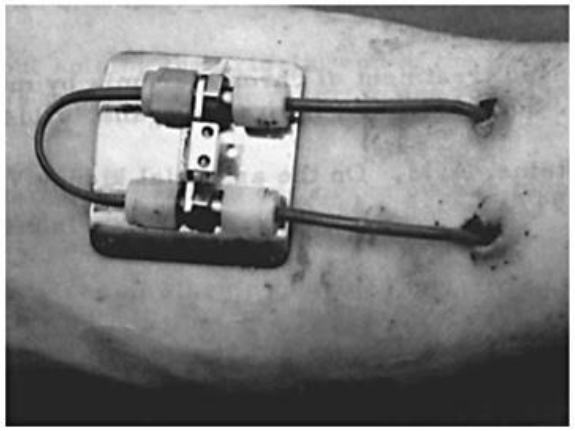


1966 – AVF Formation



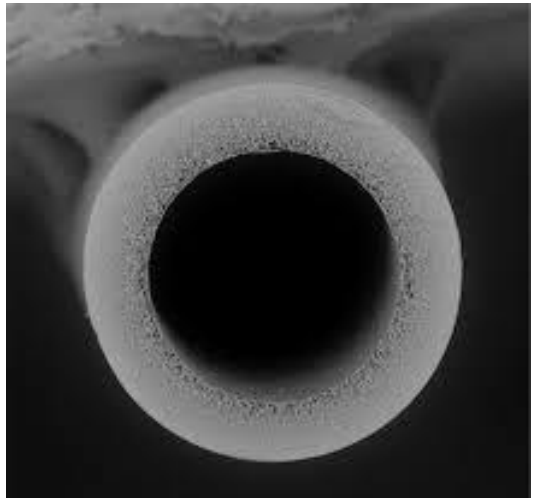
1955 – Twin Coil Dialyser

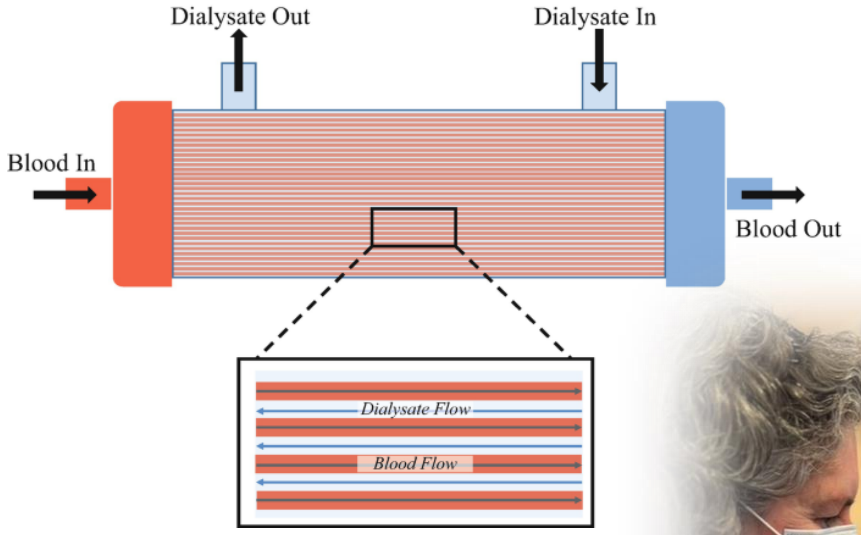
1960 – Schribner Shunt

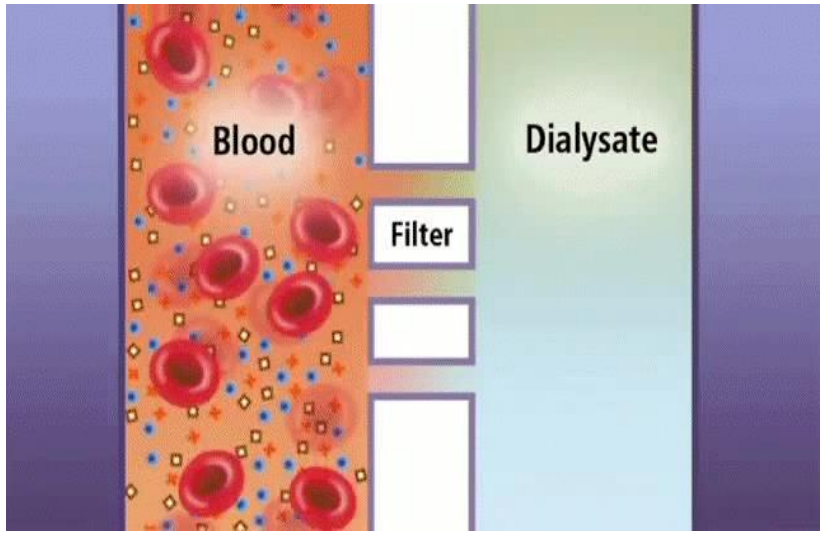


1964: Hollow Fibre Dialyser

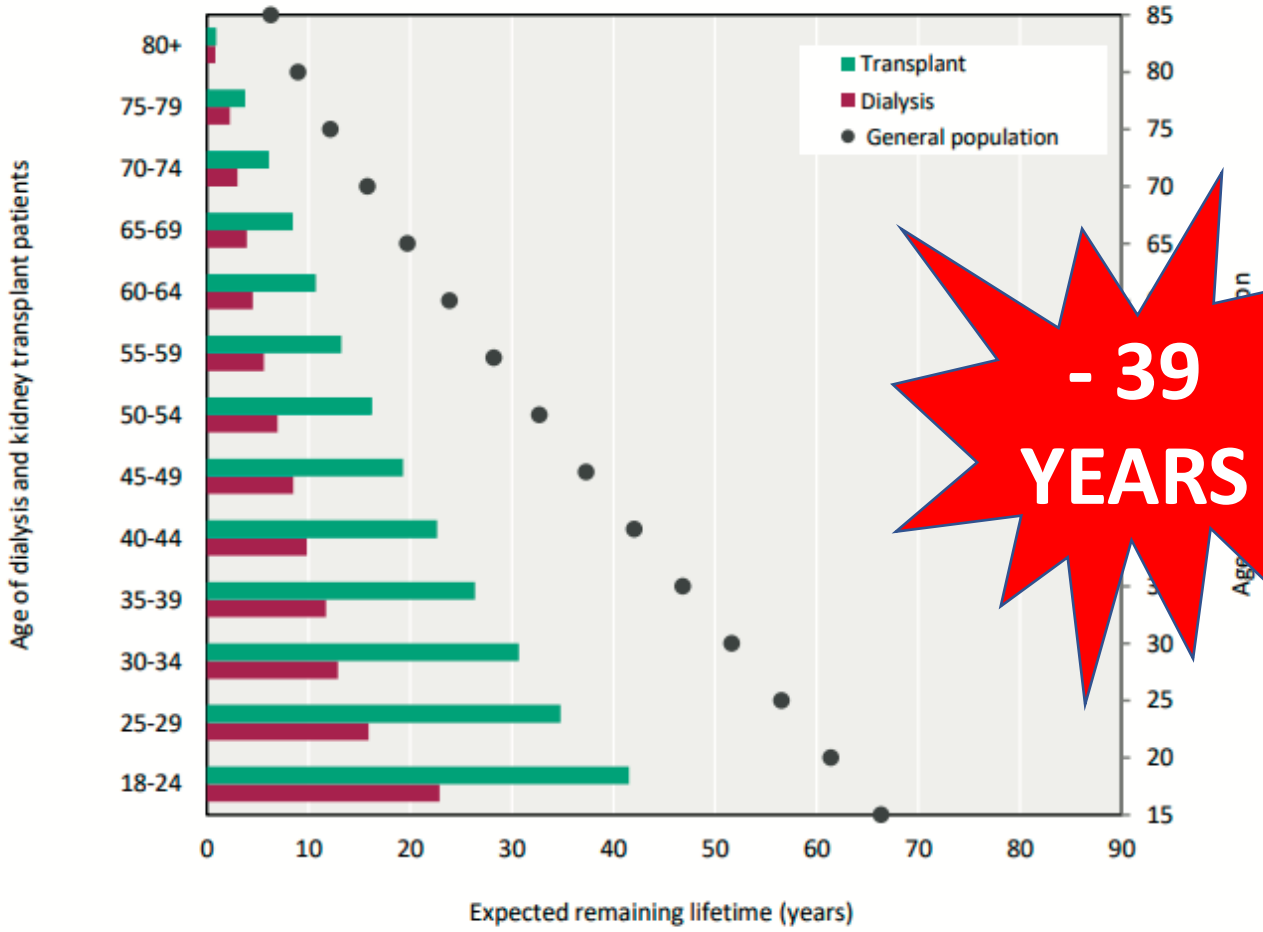
The “Artificial Kidney”







The reality of outcomes in dialysis patients



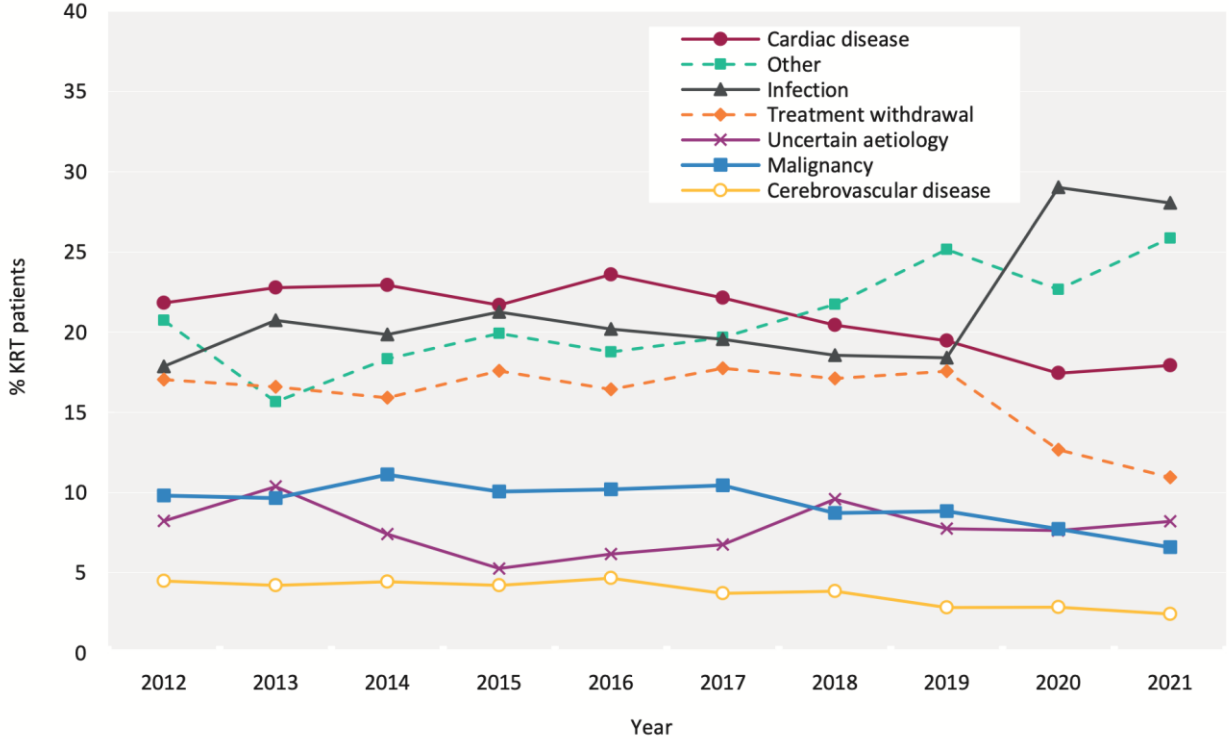
- 39 YEARS

My expected lifetime remaining in years = 52 years

Expected lifetime of someone my age with a transplant = 31 years

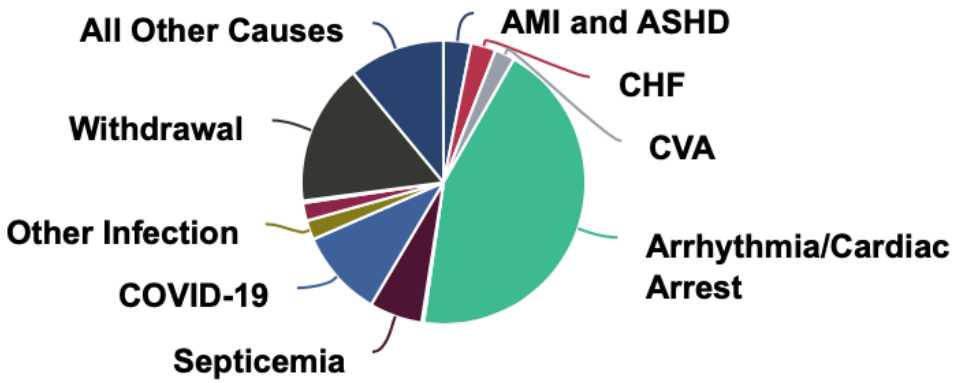
Expected lifetime of someone my age on dialysis = 13 years

Sudden, unpredictable cardiac events during dialysis risk early death



UK Renal Registry Data 2021

Cause of death (USRDS)	Percentage
Arrhythmia/Cardiac arrest	48.6%
Infection/Inflammation	21.7%



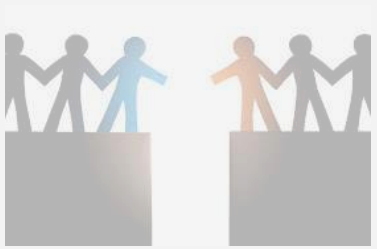
USRDS Renal Registry Data 2021

Overview

Dialysis saving lives for seven decades

Membrane-Host Bioincompatibility and Outcomes

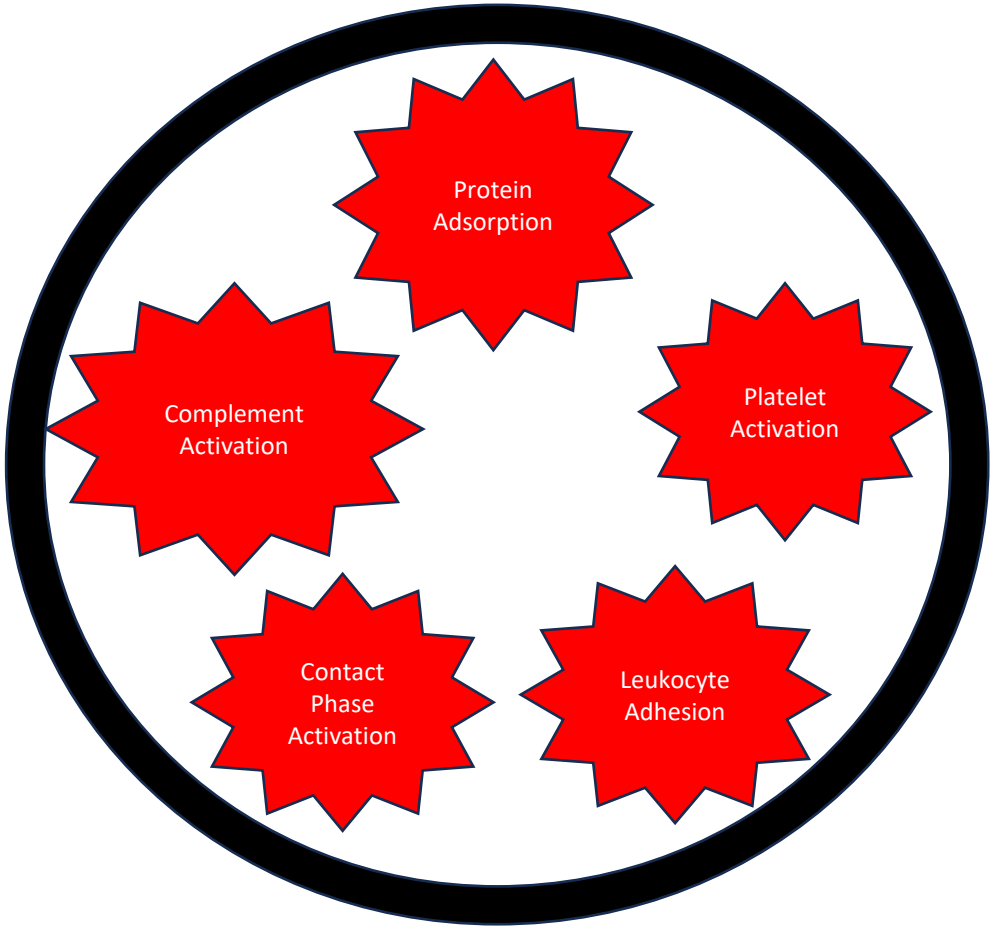
CompAct-HD Trial

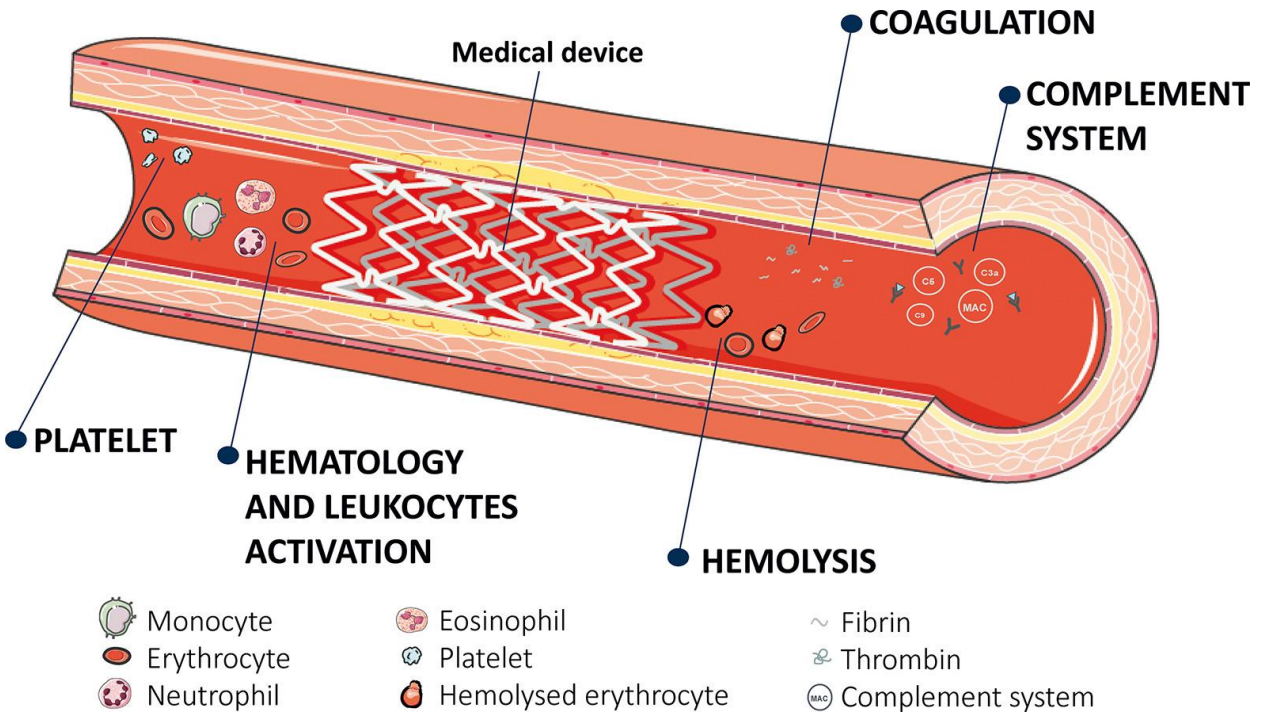


Closing the gap in dialysis

Biocompatibility of medical devices

A haemocompatible device is one that must be capable of coming into contact with blood without causing any clinically adverse reactions.

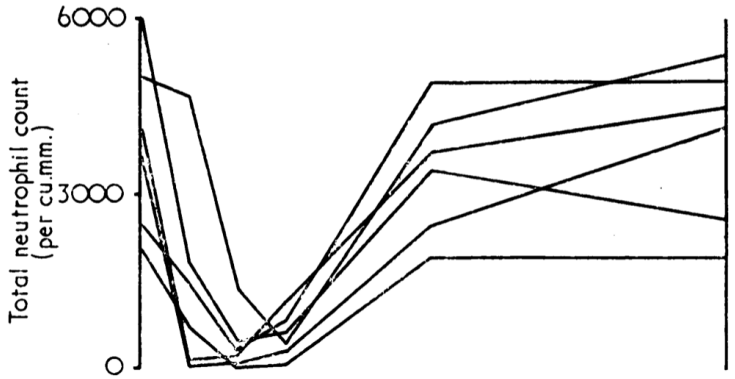




Bioincompatiblity in haemodialysis, an age-old problem

Observations on Neutropenia Associated with Haemodialysis

E. K. M. SMITH,* M.D., B.SC., M.R.C.P. ; K. JOBBINS,† F.I.M.L.T.



Hemodialysis Leukopenia

PULMONARY VASCULAR LEUKOSTASIS RESULTING FROM COMPLEMENT ACTIVATION BY DIALYZER CELLOPHANE MEMBRANES

PHILIP R. CRADDOCK, JORG FEHR, AGUSTIN P. DALMASSO, KENNETH L. BRIGHAM, and HARRY S. JACOB

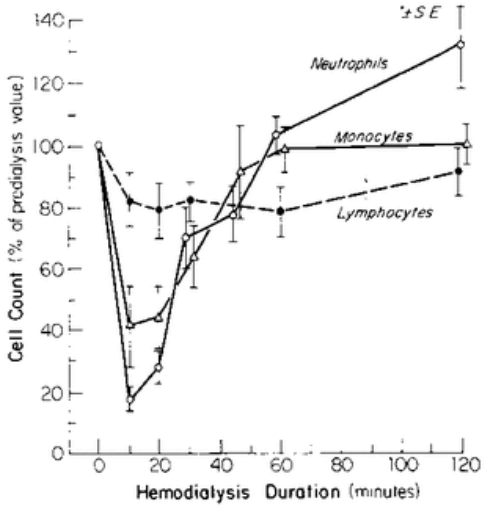


FIGURE 1 Neutrophil, monocyte, and lymphocyte counts expressed as a percentage of their predialysis values, during the first 2 h of hemodialysis in 34 patients.

Hemodialysis-Associated Platelet Activation and Thrombocytopenia

Raymond M Hakim, Andrew I Schafer

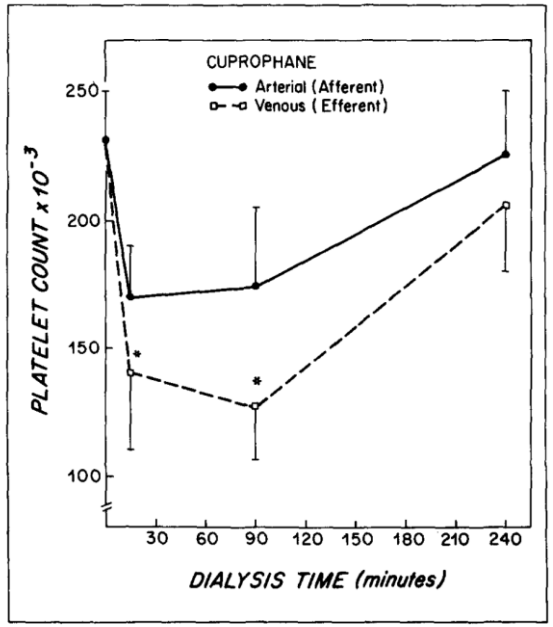


Figure 2. *Intradialytic afferent and efferent platelet counts with new cuprophane membrane. * = statistical significance.*

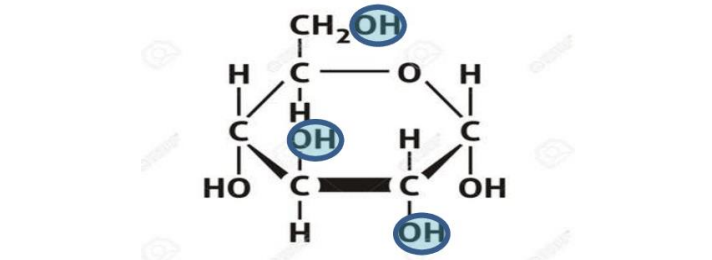
Development of ‘biocompatible’ membranes

Bio-incompatibility of cellulose membranes was attributed to the free hydroxyl group

Led to development of:

- Substituted cellulose membranes
- Synthetic non-cellulose membranes

Synthetic membranes shown to be the least immunoreactive when compared to modified cellulose and cuprophane.



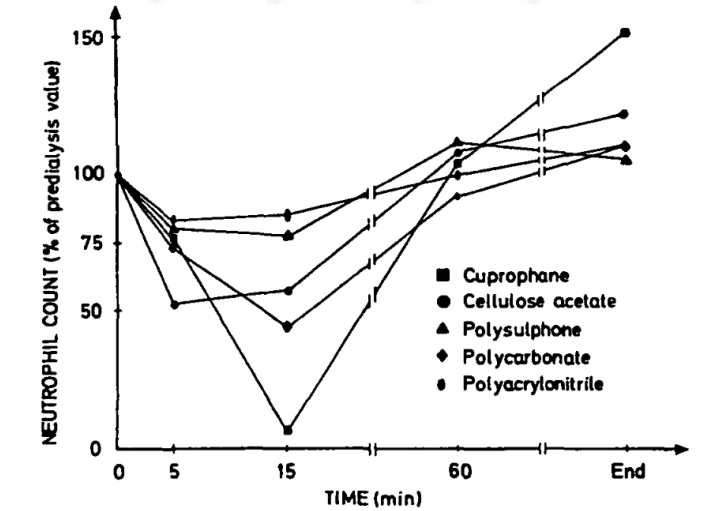


Fig. 1. Haemodialysis neutropenia during the first use of different dialyser membranes. For clarity, SEM are omitted but can be found in Table 2.

A problem solved?

On the Mechanisms of Haemodialysis-induced Neutropenia: A Study with Five New and Re-used Membranes

C. Heierli[1], M. Markert[2], P. H. Lambert[3], T. Kuwahara[1] and J. P. Wauters[1]

[1]Division of Nephrology, [2]Laboratory of Clinical Chemistry, University Hospital, Lausanne, Switzerland; [3]WHO Immunology Training Unit, Geneva, Switzerland

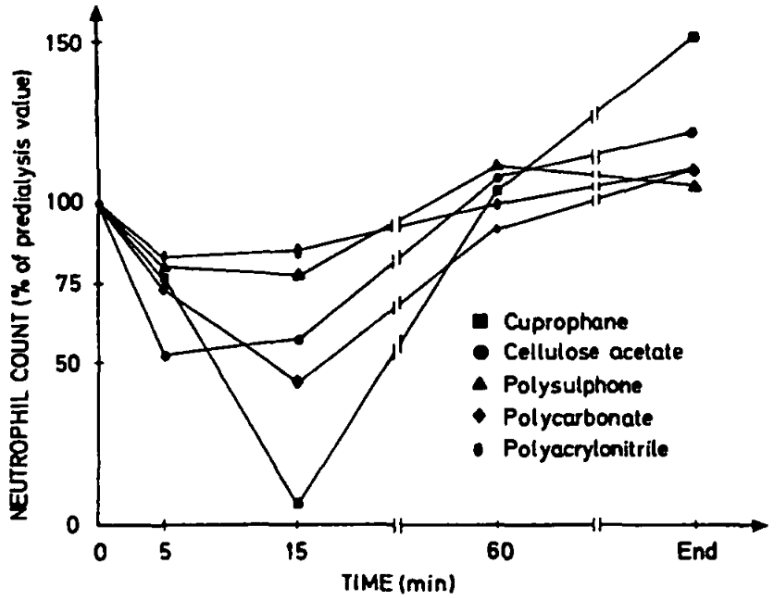
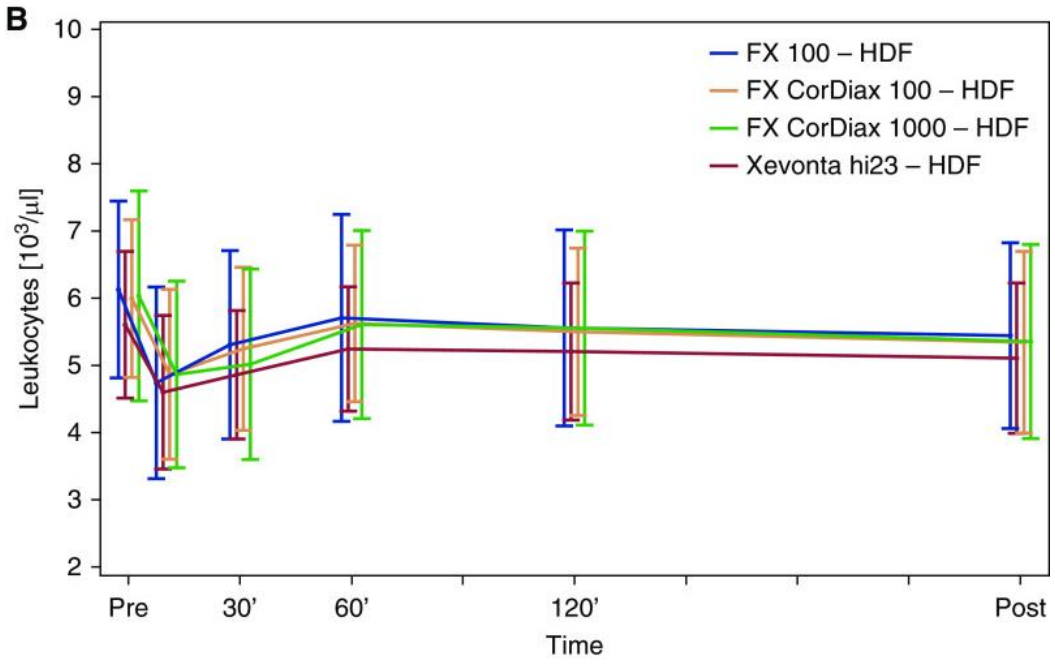


Fig. 1. Haemodialysis neutropenia during the first use of different dialyser membranes. For clarity, SEM are omitted but can be found in Table 2.

1988: A comparison of neutrophil changes amongst 5 haemodialysis membranes

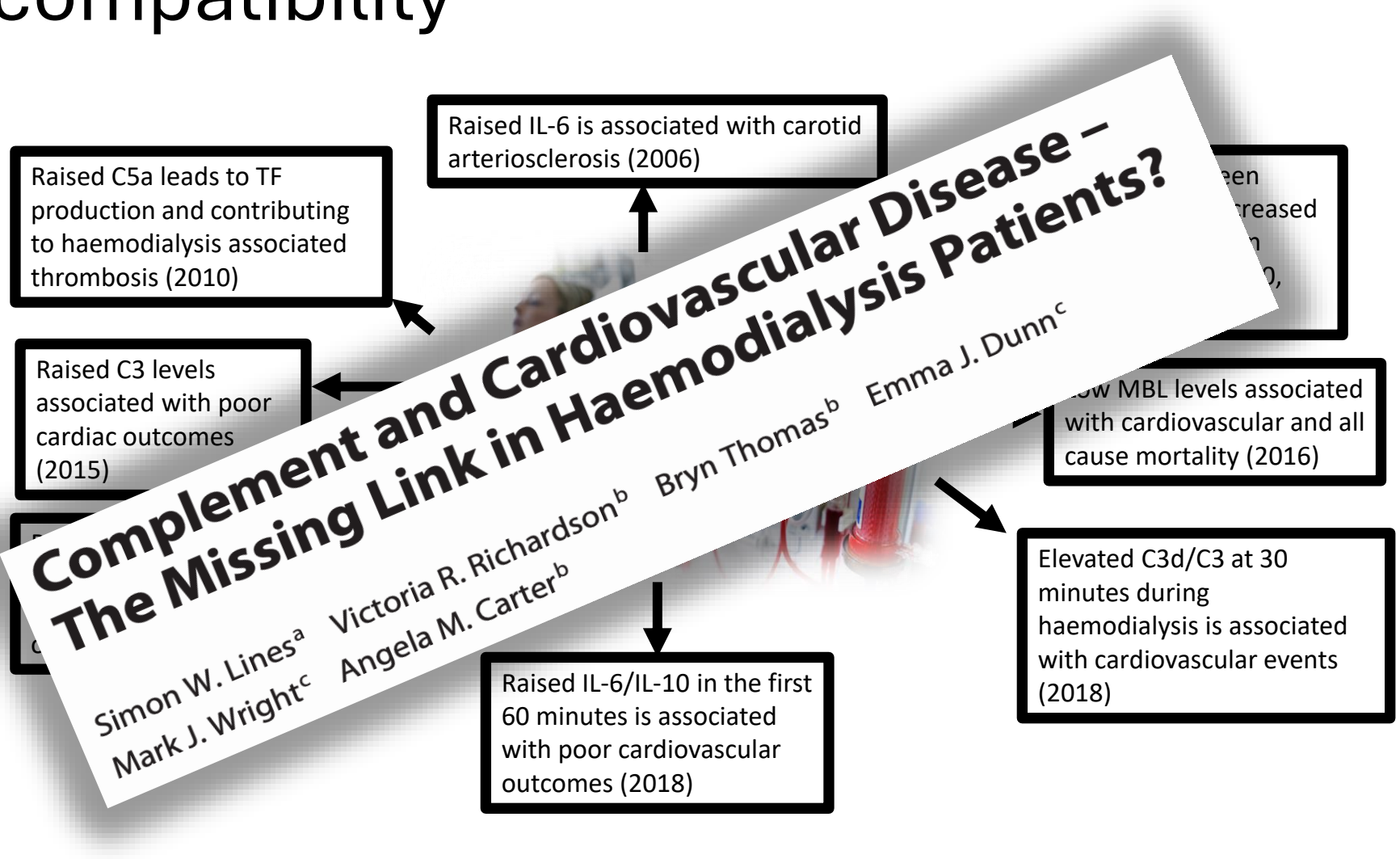
Hemocompatibility of Polysulfone Hemodialyzers – Exploratory Studies on Impact of Treatment Modality and Dialyzer Characteristics

Stephan Wagner,[1] Sebastian Zschätzsch,[1] Ansgar Erlenkoetter,[2] Lena Rauber,[2] Manuela Stauss-Grabo,[3] and Adelheid Gauly[3]



2020: Assessing the haemocompatibility of high flux polysulfone membranes today

Consequences of Haemodialysis Bioincompatibility



Bioincompatibility, a patient's perspective

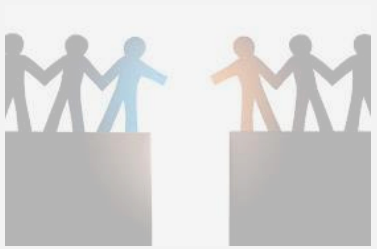
Type A - Anaphylactic	Type B – "Pseudo-anaphylactic"
Rare: <1%	Common: 2-3%
IgE Mediated	Non-IgE mediated
Within minutes of commencing dialysis	Early into dialysis, 15-30 minutes
Dyspnoea, wheeze urticaria	Related to complement activation
Manage as anaphylaxis	Self limited symptoms

Overview

Dialysis saving lives for seven decades

Membrane-Host Bioincompatibility and Outcomes

CompAct-HD Trial



Closing the gap in dialysis

CompAct-HD trial

Trial set up:

Large multicentre trial recruiting patients undergoing chronic haemodialysis

- 6 blood samples collected for each patient.
- Clinical data was simultaneously collected.
- Mobile lab unit used for prompt sample processing

Inclusion Criteria:

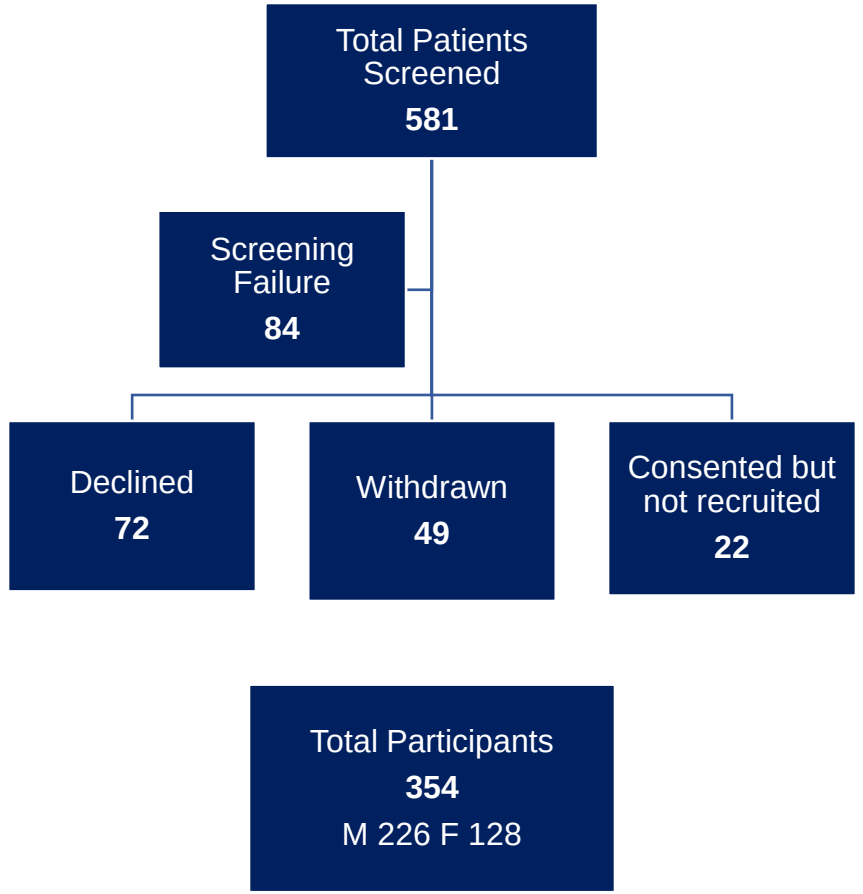
- Adult patients
- Undergoing chronic haemodialysis

Exclusion Criteria:

- Recent or active infection (within 28 days)
- Known blood borne virus
- Pregnancy

Sample handling and analysis:

- All samples were frozen within 50 minutes of collection until analysis
- Highly multiplexed assays were used for analysis of 27 biomarkers of inflammation.
- Single point samples from 14 healthy donors were analysed simultaneously for comparison



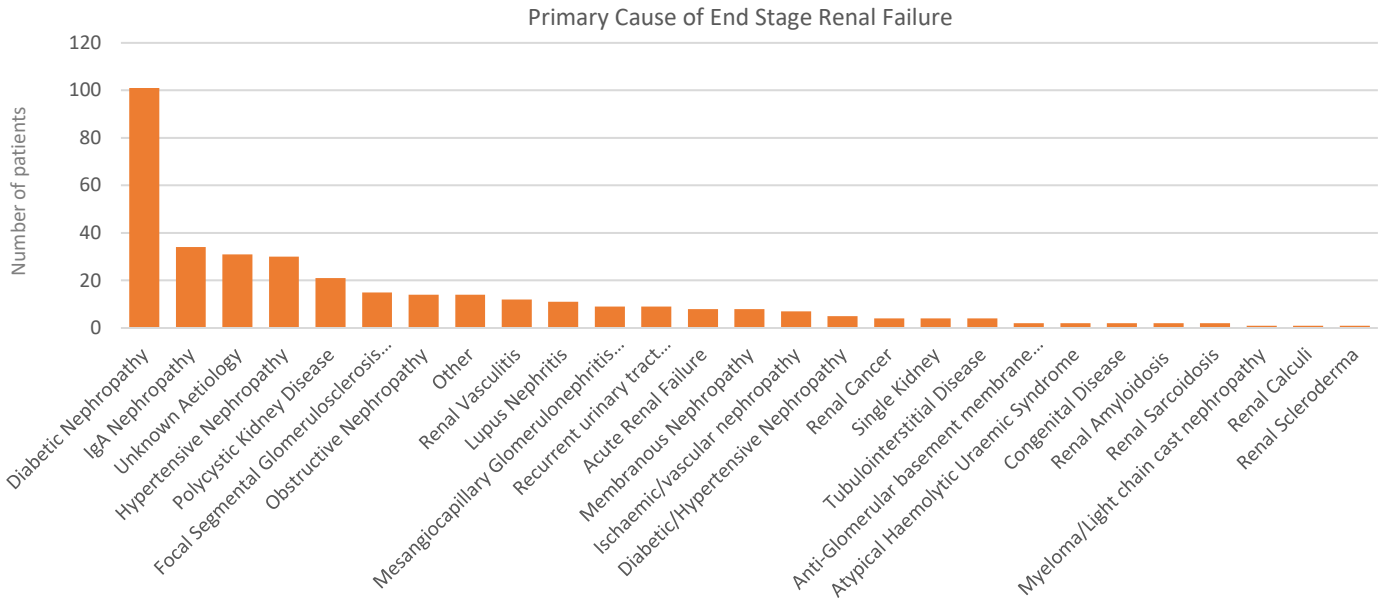
Complement Proteins

C1q C2 MBL C4 C4b C3 C3b/iC3b C5 C5a C9 FH Properdin FD FI FB

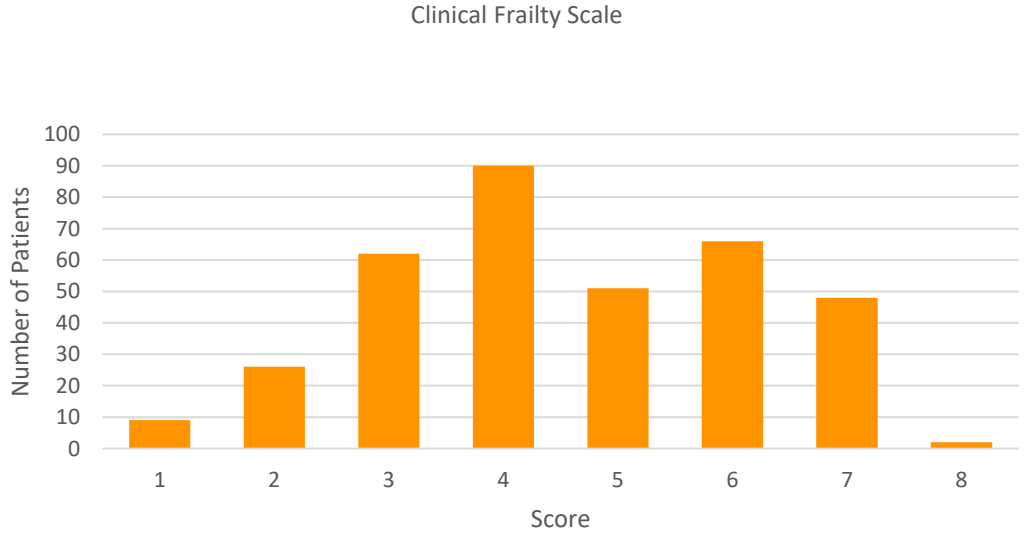
Cytokines + Growth Factors

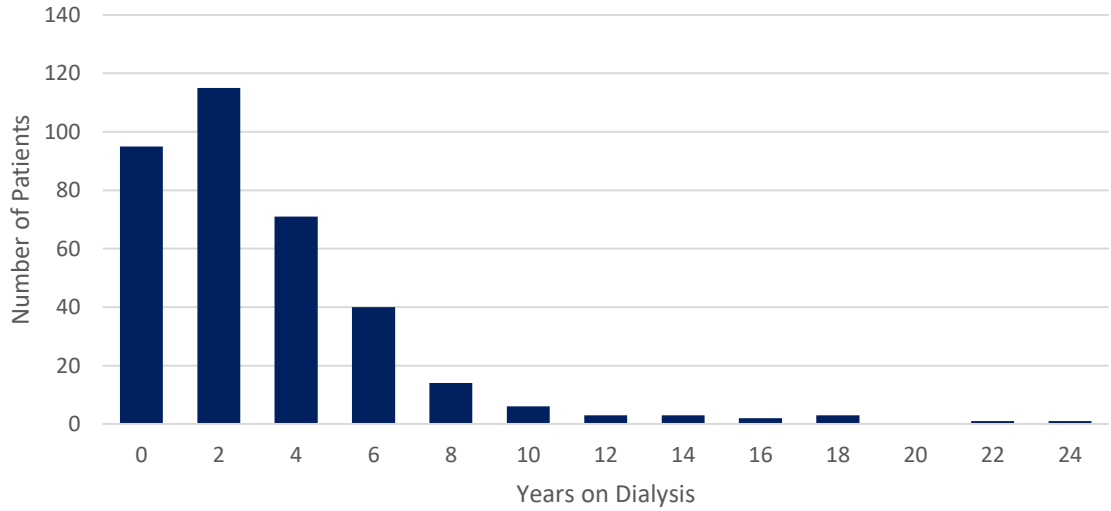
G-CSF, IFN-γ Il-1β Il-2 IL-4 IL-6 IL-8 IL-10 MCP-1 IL-12p40 Ilp-70 TNF-α IP-10

Clinical data from 8 dialysis units



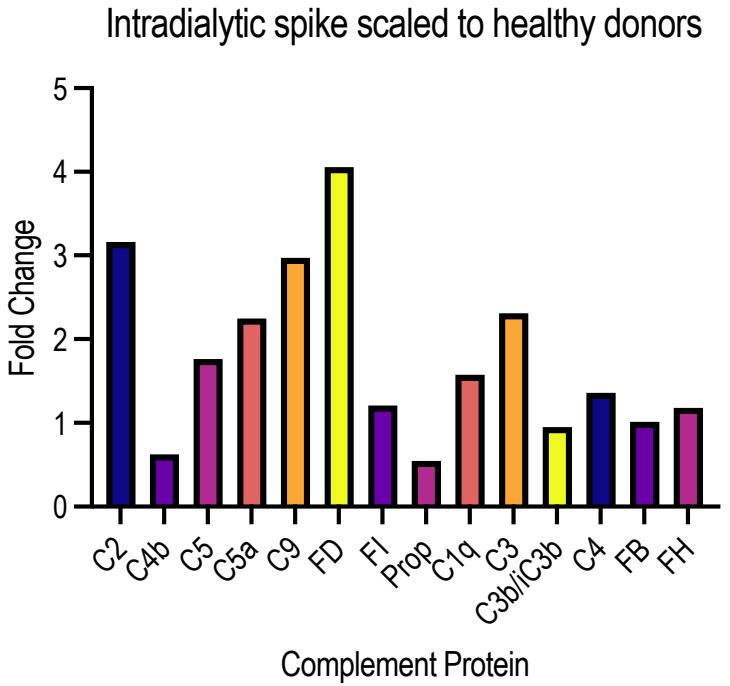
Baseline Characteristics	Total (N = 354)
Age	61.6(46.1-77.1)
Male	226(63.8%)
Ethnicity	
Arab	1(0.3%)
Asian/Asian British	70(19.8%)
Black/Black/British	39(11%)
Mixed	5(1.4%)
Other	5(1.4%)
White	234(66.1%)
Access	
Tunnelled Line	180(50.8%)
Graft	1(0.3%)
Fistula	173(48.8%)
Dialyser	
Fresenius Classix	144(40.7%)
Fresenius CorDiax	141(39.8%)
Nipro Sureflux	67(18.9%)
Baxter Theranova	2(0.6%)

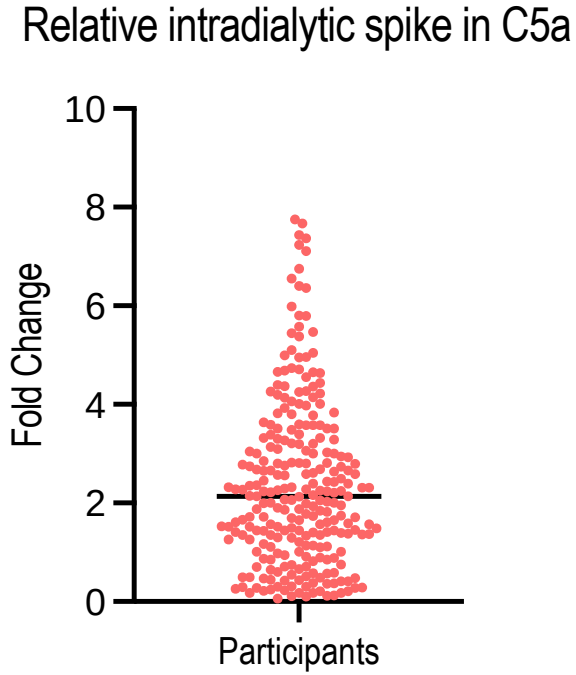




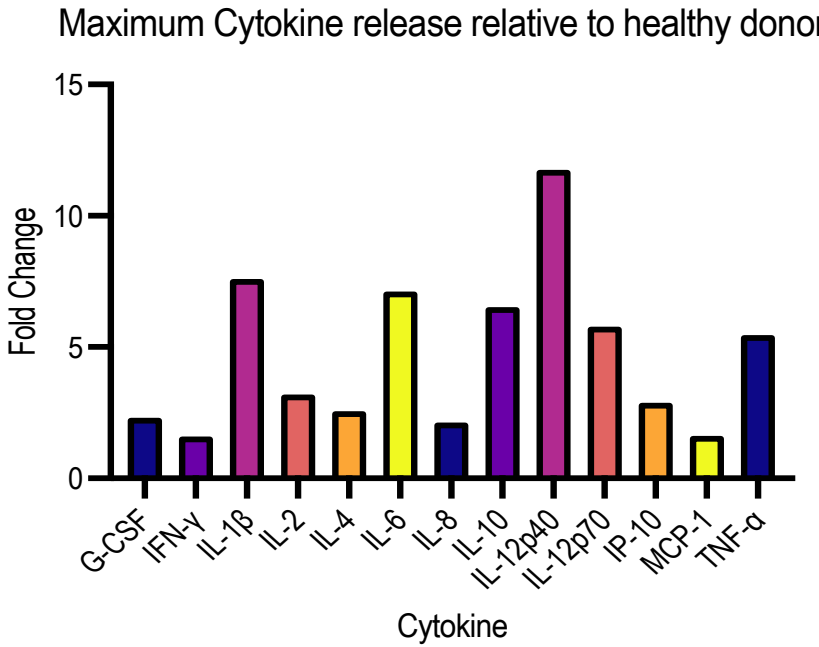
Results

An intradialytic spike could be seen for the majority of complement proteins relative to healthy donors.





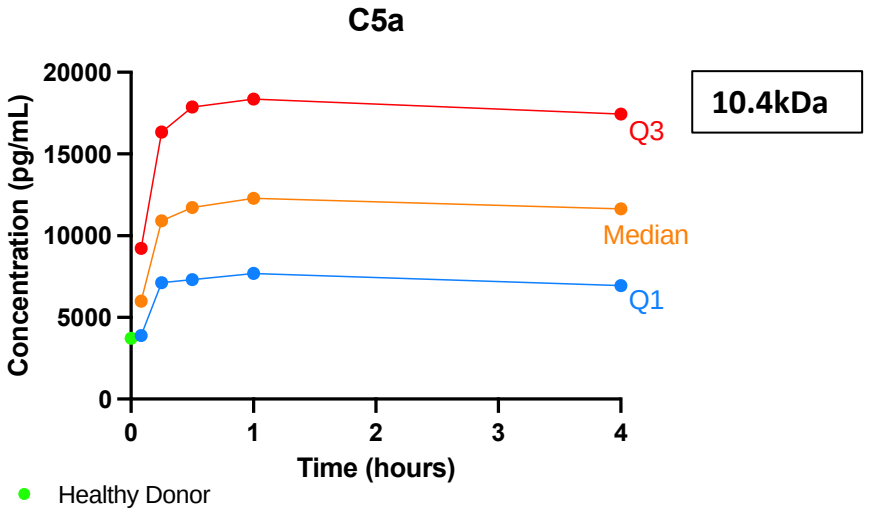
Similarly, a relative increase in cytokines could be seen amongst dialysis patients.

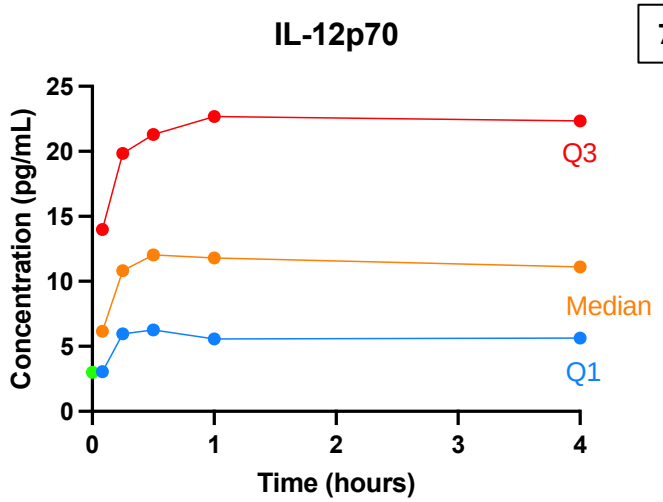


Cytokine	MW
IL-12p40	40kDa
IL-1β	17.5kDa
IL-6	21-28kDa
IL-12p70	70kDa
IL-10	18.5kDa
TNF-α	17.4kDa

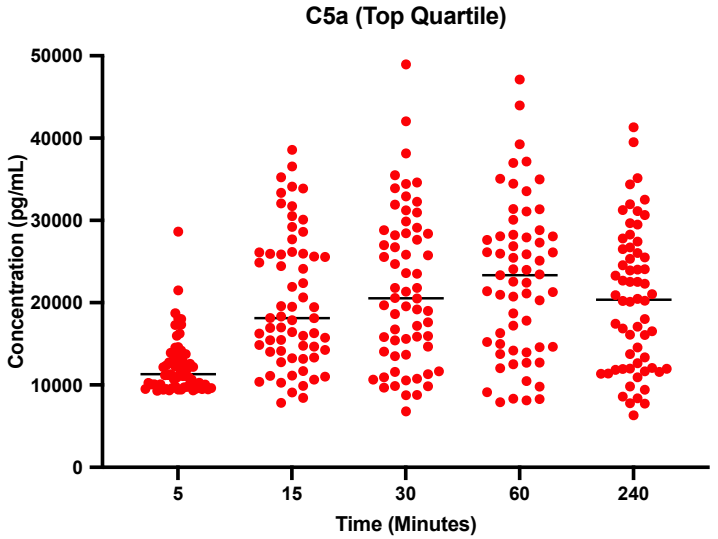
The temporal changes in complement and cytokine activity during a heamodialysis treatment

An acute rise in both complement proteins and cytokines can be seen in the first 30 minutes from the start of haemodialysis.

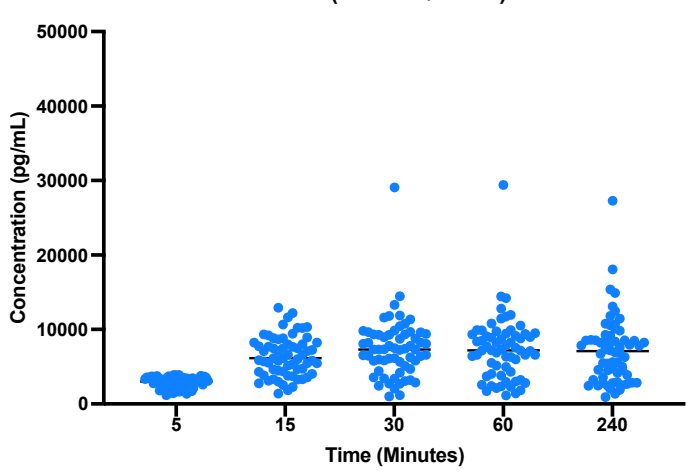




Patients follow their trajectory during the course of the session allowing them to be classified into low, medium and high responders.



Minutes	Top Quartile	All Participants
5	11319.27	5,989.22
15	18106.09	10,912.06
30	20544.33	11,722.44
60	23335.19	12,284.61
240	20355.97	11,635.97



Minutes	Lower Quartile	All Participants
5	3017.66	5,989.22
15	6156.51	10,912.06
30	7309.85	11,722.44
60	7198.48	12,284.61
240	7073.29	11,635.97

CompAct-HD: Summary of Findings

An **acute inflammatory temporal response** can be seen in patients undergoing haemodialysis with ultrapure water using high flux membranes.

Activation of the **complement system** during haemodialysis translates into an **acute inflammatory response** with release of cytokines, chemokines and growth factors.

Patients can be categorized **into low, medium or high** responders based on level of response during dialysis.

Patients exhibiting high levels of immune activation are likely to be at a **greater risk** of complications from chronic inflammation.

Using a risk stratified approach, we can identify patients most likely to benefit from **targeted, therapeutic interventions** to modulate complement activity

Overview

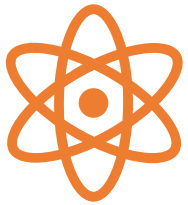
Dialysis saving lives for seven decades

Membrane-Host Bioincompatibility and Outcomes

CompAct-HD Trial

Closing the gap in dialysis

Mitigating bioincompatibility in medical devices



Modification of Biomaterial

Hydroxyl Group Substitution

Modification of surface charge

Coating of Biomaterial

Heparin Coating

Vitamin E Coating

Drug eluting

Supportive therapy

Anticoagulation

Antiplatelet therapy

What’s on the horizon for haemodialysis patients?

Complement Inhibitors

Compstatin (C3 inhibitor)

Soluble CR1 (C3 inhibitors)

5C6 (Factor H binder)

Coagulation pathway inhibitors

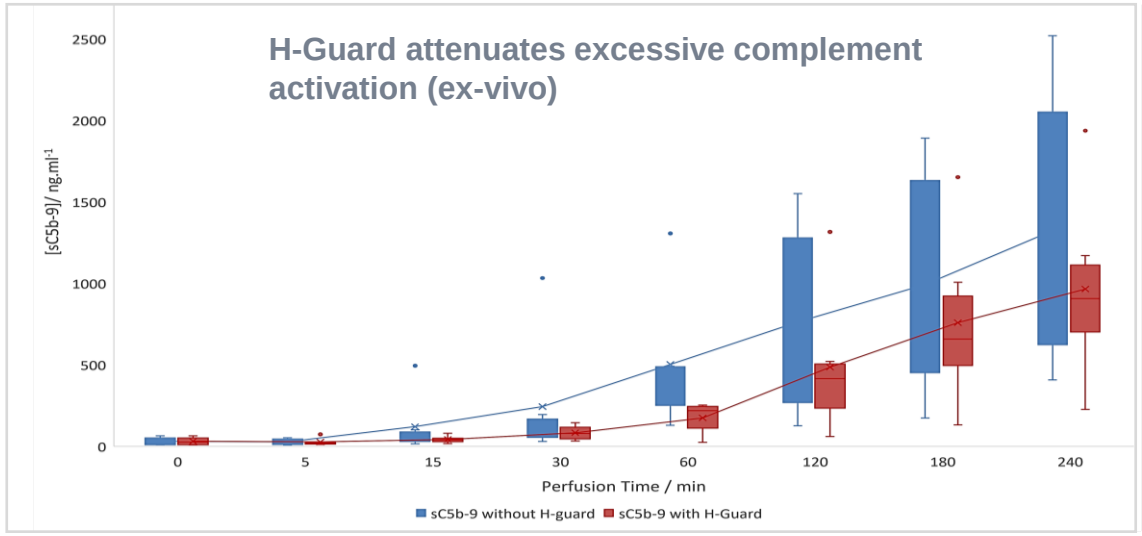
Oscocimab (Factor XI-a inhibitor)

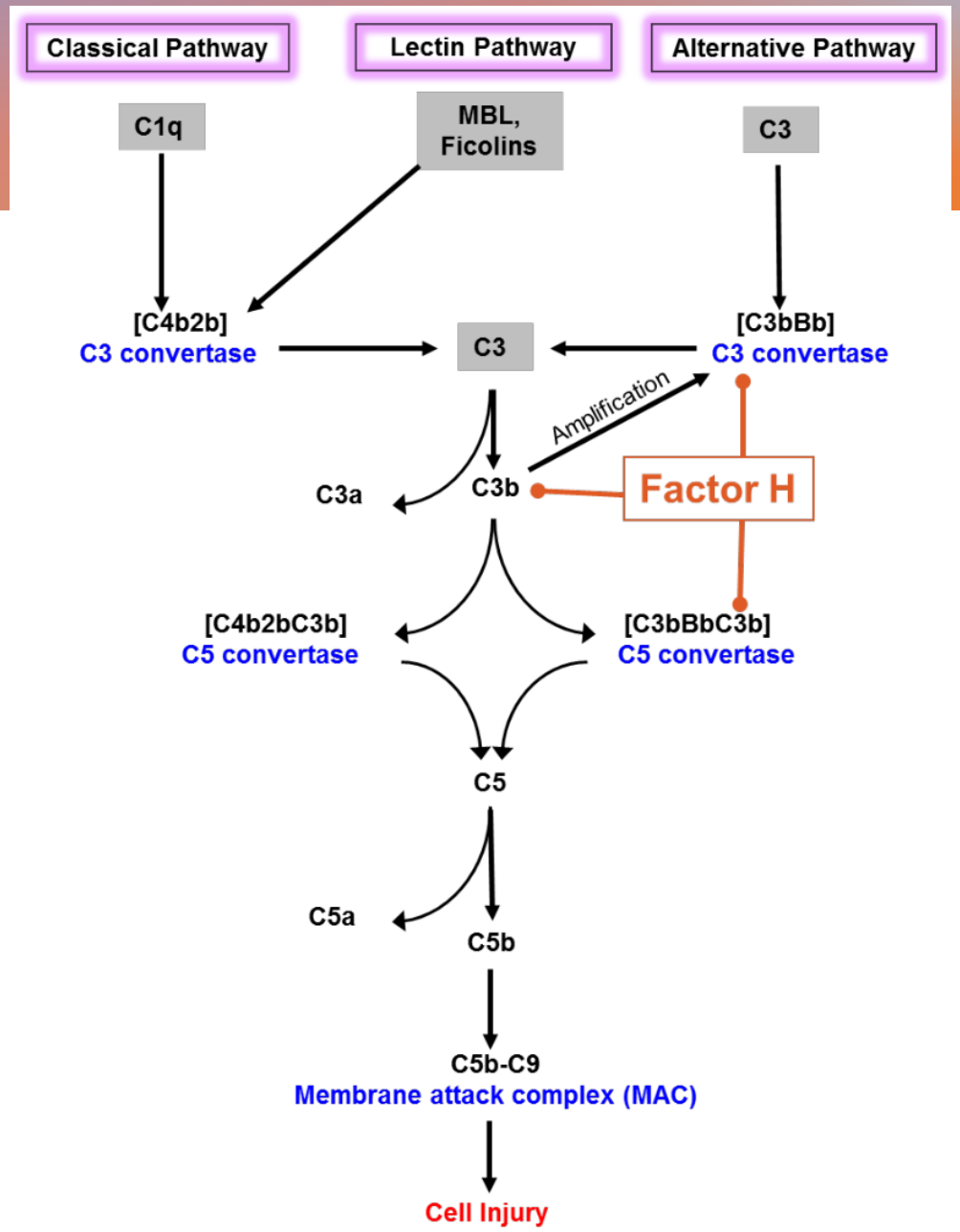
Membrane modification

CorAl membrane (hydrophilic, more biocompatible membrane)

H-Guard, a novel therapy

- Factor H is a potent down regulator of the complement system.
- PspC is a surface protein found on Strep. Pneumoniae, used to capture Factor H and evade the immune system.
- H-Guard uses PspCN biotechnology to coat the extracorporeal circuit, acting as an “invisibility cloak”, preventing activation of the immune system during treatment.





Completed Phase 1, First In Human safety and feasibility study (2024)

- Successfully completed treatment for 8 patients

- Safety/tolerability data was supportive in all patient studies

- Further analysis and clinical trials are underway

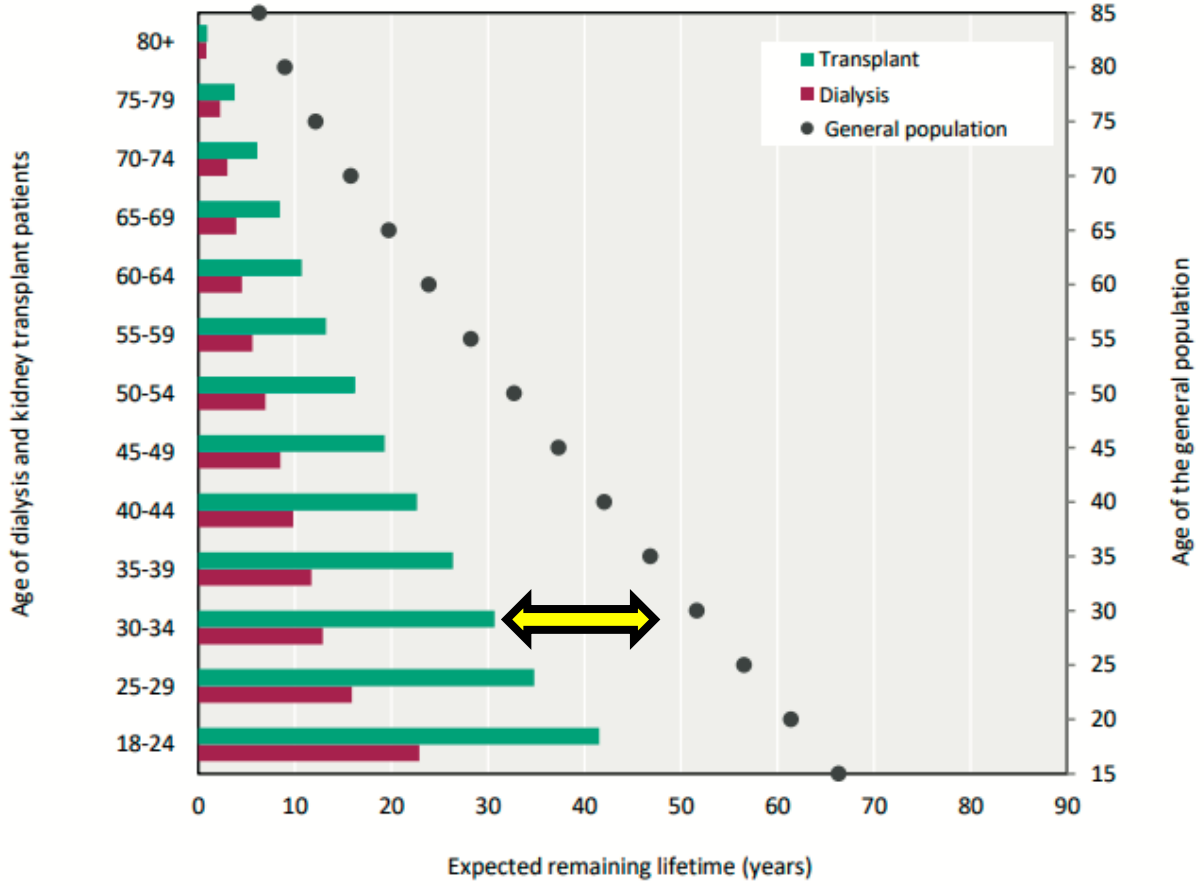
A better future in dialysis?

Bioincompatibility remains a problem in dialysis today

Evidence supports **complement activation** and **inflammatory changes** during haemodialysis

Potential for **targeted therapy** with novel agents

Addressing bioincompatibility could **close the wide gap** between outcomes in patients on dialysis and the general population.



Acknowledgements

Manchester Foundation Trust:

- Sandip Mitra
- Leonard Ebah
- Thomas Lindsay
- Jan Bendle
- Fatima Jelani
- Houda Chea
- Shelly Harris

Lancashire Teaching Hospitals:

- Andrew Nixon
- Sarah McLoughlin
- Alexandra McCarrick

Invizius:

- Andy Herbert
- Liz Blackburn
- Magnus Nicholson
- Joe Connor
- Jennifer Mackie

EMS:

- Vicky Sweeney
- Nicola Suggitt
- Sean Donohue
- Yasmiin Moallim