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Citation:

EMJ Cardiol. 2026;14[1]:85-91.
<https://doi.org/10.33590/emjcardiol/6TR782HP>

Q1 The European Society of Cardiology (ESC) Congress brings together experts from across the cardiovascular community. What have you seen so far at the meeting that has interested you most, and what are you most looking forward to during the remainder of this year's Congress?

It is always a great pleasure to be here with so many colleagues, friends, and experts gathered in one place. I also really enjoy seeing the opportunities that younger researchers are given. Moderated poster sessions are always a highlight for me. The environment is vibrant, and the young investigators are extremely well prepared and impressive in how they present their work.

Among this year's highlights, the Saturday Hotline sessions stood out. The STAREE trial¹ was particularly significant. This investigator-driven study addressed an important knowledge gap regarding statin therapy for primary prevention in healthy adults over 70 years of age. The findings demonstrated a clear benefit of statins in reducing major adverse cardiovascular events in this population. As our population continues to age, this evidence represents a major step forward in preventive cardiology.

Another important highlight was the REACT study,² which examined subclinical atherosclerosis using deep vascular imaging across multiple vascular territories in healthy participants from Spain and Denmark. The study created an unprecedented map of

subclinical atherosclerosis from early adulthood onwards. One of the key findings was that one in 13 individuals aged 18–29 years already showed signs of subclinical atherosclerosis.

For the first time, we have a very large evidence base that combines imaging, genetics, biomarkers, and extensive phenotyping. This opens enormous opportunities to investigate disease aetiology and, eventually, develop interventions aimed at preventing silent atherosclerosis from progressing to clinically evident disease.

For the remainder of the Congress, I am particularly looking forward to learning more about developments in inflammation research, both from the basic science and genomic perspectives and from emerging clinical trial data.

Q2 Much of your research focuses on identifying causal risk factors through genetics and genomics. How is this approach changing our understanding of cardiovascular disease?

Genomics has made a substantial contribution to how we understand cardiovascular biology.

One classical example is familial hypercholesterolaemia. Mutations in the low-density lipoprotein receptor cause elevated low-density lipoprotein cholesterol from birth and substantially increase the risk of premature atherosclerotic cardiovascular disease. This clear genetic model has demonstrated how understanding biology can directly inform treatment.

The challenge is applying the same principles to more complex pathways, such as inflammation. Inflammation is essential for defending against infection and responding to injury, but when it becomes dysregulated, it contributes to disease. To understand these mechanisms properly, we need truly translational approaches that combine genomics, molecular biology, clinical observational data, and clinical trials.

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I believe genomics can help us identify promising therapeutic targets while also highlighting potential adverse effects before therapies are widely deployed. If we implement sufficiently rigorous pipelines, genomics can better inform both drug discovery and drug repurposing.

Drug repurposing is a particularly important opportunity. Many anti-inflammatory therapies are already approved for autoimmune diseases and cancers and have well-established safety profiles. By systematically evaluating these therapies using comprehensive genomic data, we may identify treatments that could be beneficial in cardiovascular disease much more efficiently.

By applying these approaches, we have been able to validate pathways such as IL-1 β and identify additional pathways with existing therapies already available for other indications. We have also identified several novel signals that warrant further investigation.

Q3 There is increasing interest in the relationship between atherosclerosis and dementia. What are the most important findings that clinicians should be aware of today?

The short answer is that there is now sufficient evidence to say that, generally speaking, what is good for the heart is also good for the brain.

Although that statement may appear obvious today, it was not always supported by strong evidence. We now have access to large prospective biobanks and longitudinal cohorts that allow us to examine these relationships much more rigorously. These studies demonstrate that traditional cardiovascular risk factors, including high cholesterol, hypertension, diabetes, obesity, and smoking, are all associated with elevated dementia risk later in life.

These associations extend beyond vascular dementia and also contribute to the risk of Alzheimer's disease.

Our group places a genomic framework beneath these observations using Mendelian randomisation. Because genetic variants are randomly inherited, they allow us to study causal relationships in a manner analogous to a natural randomised clinical trial.

Using these approaches, together with large biobanks and multi-ancestry datasets, we are building stronger evidence for the causal role of cardiovascular risk factors in dementia development. This is particularly important because we currently lack highly effective therapies for preventing dementia. If we can establish causality more conclusively, we strengthen the case for repurposing existing cardiovascular therapies, such as lipid-lowering and antihypertensive medications, as preventive strategies.

Ultimately, the challenge is increasingly one of implementation and public health policy.

Q4 How important is it to include diverse populations in genetic research?

This is tremendously important. Historically, genomic studies have been dominated by populations of European ancestry, which limits global applicability.

One example from our own work involves a stratified genome-wide association study focusing on the APOE4 allele, a major genetic risk factor for dementia. We collaborated with Korean and Chinese researchers, who successfully validated our leading signals. We are now expanding these efforts through collaborations in China and Japan, as well as with colleagues in Central and South America.

Even when datasets differ in their available clinical information, we can still conduct meaningful subgroup analyses and begin understanding which findings are shared and which are population-specific. These global collaborations are essential for improving both the robustness and equity of genomic medicine.

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Q5 The title of your fireside chat is ‘From Hypothesis to Therapy: Inflammation Comes of Age’. What does the phrase ‘inflammation comes of age’ mean to you, and why is this such a pivotal moment for the field?

To me, it signifies that the field has matured. Inflammation research in cardiovascular disease has progressed beyond a theoretical concept and has now delivered important clinical evidence that demonstrates its therapeutic relevance.

From a clinical perspective, the defining moment was undoubtedly the CANTOS trial.³ It showed that targeting the IL-1 β pathway could reduce cardiovascular events, providing direct evidence that inflammation is not merely associated with atherosclerosis but is actively involved in driving disease progression. That finding fundamentally changed the way

we think about cardiovascular prevention and treatment.

Today, we also have colchicine as the only approved anti-inflammatory therapy for atherosclerotic cardiovascular disease, and we have several other pathways being explored through clinical development programmes. That is why I believe we are seeing inflammation truly come of age. The biological insights are now being translated into therapeutic strategies.

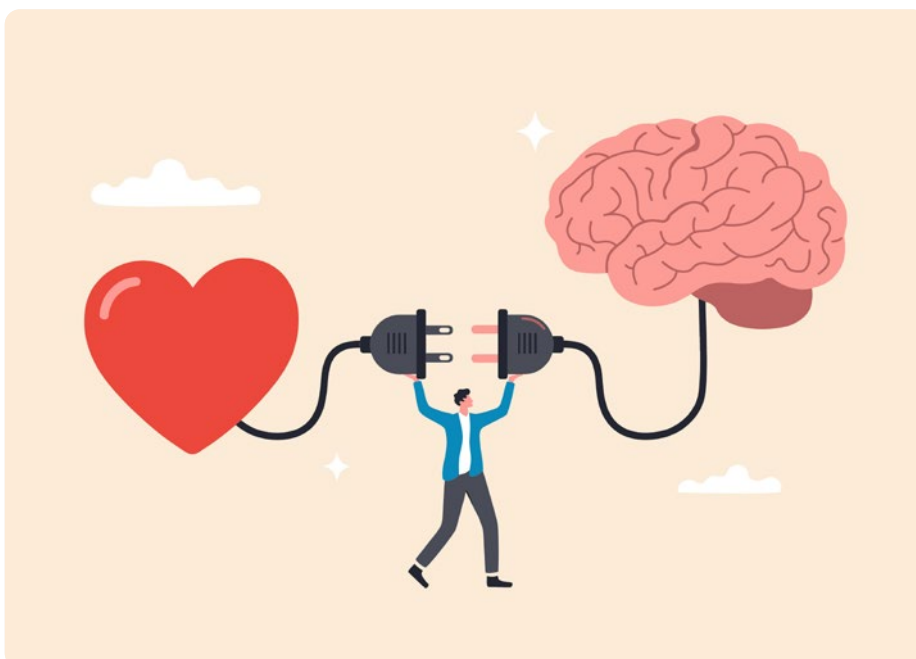
At the same time, we are continuing to learn from both successful and neutral trials. One of the major topics discussed during our fireside chat was the ZEUS trial,⁴ which targeted the IL-6 ligand pathway. The results were neutral, but that does not mean they were unimportant. ZEUS focused on a very high-risk population with chronic kidney disease, and it raises important

questions about patient selection, biological complexity, and the specific inflammatory pathways that should be targeted.

The ZEUS programme sits within a broader strategy that also includes the HERMES and ARTEMIS trials.^{5,6} HERMES was a trial evaluating anti-inflammatory therapy in heart failure, while ARTEMIS is investigating treatment in the acute phase of myocardial infarction, so these two studies involve very different patient populations. While HERMES was terminated on September 8th 2026 due to futility,⁵ ARTEMIS continues.⁶

From the genomic perspective, the story is equally interesting. Inflammation has long been supported by extensive basic science evidence. Researchers have clearly demonstrated the importance of inflammatory pathways in plaque formation, plaque progression, and plaque destabilisation. The challenge is to determine which specific molecular targets will provide the greatest clinical benefit when inhibited or activated.

The IL-6 pathway illustrates this complexity very well. Much of the genetic evidence centres on variants affecting the IL-6 receptor. These variants are associated with lower C reactive protein levels and lower coronary artery disease risk. However, the same variants can also result in higher circulating IL-6 ligand levels. Meanwhile, ZEUS targeted the ligand itself. This highlights an important point: receptor



biology and ligand biology do not always produce identical clinical consequences, and understanding those distinctions is critical.

That is why I continually advocate for integrating genomics into drug development. We need to combine the expertise of basic scientists, geneticists, trialists, clinical biochemists, and industry partners so that we fully understand the biology of a target before pursuing large-scale therapeutic programmes. This will help us identify the targets most likely to succeed and anticipate potential safety concerns early in development.

Most importantly, I believe we should continue revisiting the IL-1 β pathway. The evidence supporting it remains incredibly compelling. We already have safe and effective therapies targeting this pathway in other disease areas, and I think there is still substantial potential to explore their application in cardiovascular disease.

Q6 For many years, inflammation was viewed as an associated feature of atherosclerosis rather than a therapeutic target. What key discoveries helped change that perception?

For me, the answer is very clear: the CANTOS trial was the breakthrough.³ It demonstrated that inhibiting the IL-1 β pathway could significantly reduce cardiovascular events, confirming that inflammation is not simply a bystander in atherosclerotic disease.

Prior to CANTOS, there was already a substantial body of biological evidence linking inflammation to plaque development and instability. However, translating those

observations into therapeutic benefit was a major challenge. CANTOS provided the first definitive evidence that intervening directly in an inflammatory pathway could improve clinical outcomes in cardiovascular disease.

“The goal is to systematically integrate genomic information into drug development from the very beginning”

The findings also encouraged researchers to think more broadly about inflammatory signalling networks. If IL-1 β was important, then perhaps upstream pathways might be equally relevant. One obvious example is the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which sits upstream of IL-1 β activation. Genomic studies have provided additional support for this approach, particularly through evidence involving neutrophils and other immune-cell populations that participate in inflammasome signalling.

The central lesson is that inflammation is biologically complex, but we now have both clinical and genomic evidence showing that certain pathways genuinely influence cardiovascular outcomes.

Q7 How have genomic technologies and large-scale population studies contributed to identifying inflammatory pathways that are now being targeted therapeutically?

Genomics has played an important role by helping identify and prioritise pathways that may be causally involved in disease.

However, genomic findings need to be interpreted carefully because inflammation frequently involves multiple interacting components, including ligands, receptors, receptor antagonists, and downstream signalling molecules.

To address this complexity, my group has developed a comprehensive four-step framework for inflammatory target discovery. The goal is to systematically integrate genomic information into drug development from the very beginning rather than treating it as an afterthought.

The first step is genomic signal identification. We combine large genetic consortia datasets with major proteomic resources to identify genetic determinants of circulating inflammatory markers. This allows us to pinpoint markers that may have causal relevance.

The second step is replication. We take those candidate signals and test them in entirely independent cohorts representing multiple ancestries. Replication is essential because we need confidence that findings are robust and not specific to a single dataset or population.

The third step is observational validation. Once genetic evidence has been established, we examine large population biobanks to determine whether the biomarkers themselves are associated with future cardiovascular risk. Importantly, we only perform these analyses after establishing genetic support because



observational associations alone can be highly misleading.

The final step is drug-target profiling. We systematically review drug databases, assess whether therapies already exist for the relevant targets, examine their safety records, and evaluate whether repurposing opportunities may be feasible.

What is particularly encouraging about this approach is that it successfully identifies positive controls. We rediscovered pathways such as IL-1 β , IL-1 receptor antagonist signalling, and chemokine ligand 2 (CCL2), all of which have already been implicated in cardiovascular disease. In addition, we identified several novel inflammatory signals that are now being investigated further.

For me, this is exactly how genomics should contribute to therapeutic development: not by replacing basic science, but by strengthening the evidence base and helping focus resources on the most promising targets for subsequent randomised clinical trials.

Q8 Several landmark trials have demonstrated the potential of anti-inflammatory therapies in cardiovascular disease. Which findings do you believe have had the greatest impact on clinical practice and future drug development?

Again, I would highlight the CANTOS trial as the most important development.³

The trial demonstrated that IL-1 β is a highly relevant therapeutic target and provided a clear signal that inflammation can be modified to reduce cardiovascular events.

The FDA approval of low-dose colchicine for treating residual inflammatory risk in patients with stable atherosclerosis is also notable. The COLCOT trial established that daily treatment with 0.5 mg colchicine within 30 days of a myocardial infarction could improve long-term outcomes.⁷ The LoDoCo2 trial demonstrated that colchicine reduced risk of a composite endpoint of cardiovascular death, spontaneous myocardial infarction, ischaemic stroke, or ischaemia-driven coronary revascularisation.⁸ However, the use of colchicine

during acute active ischaemia remains uncertain for now.

I also believe there remains considerable untapped potential in revisiting approved anti-inflammatory therapies that target this pathway in other diseases and evaluating them systematically in cardiovascular populations.

Q9 Your research interests span both cardiovascular disease and dementia. Are there shared inflammatory mechanisms between these conditions that could open new therapeutic opportunities?

I believe there are, and this is one of the most exciting areas of ongoing research.

In a major genome-wide association study of Alzheimer's disease conducted through the European Alzheimer's and Dementia Biobank (EADB), one of the significant signals involved the TNF- α pathway.⁹ That immediately attracted attention because TNF- α is already targeted therapeutically in diseases such as rheumatoid arthritis and inflammatory bowel disease.

At present, we are applying our inflammatory discovery framework to atherosclerotic cardiovascular disease and stroke. Stroke is particularly relevant because it is a major risk factor for both vascular dementia and Alzheimer's disease. The next step will be to apply the same framework directly to dementia itself.

I expect that we will identify both shared and disease-specific inflammatory pathways. Some markers may prove relevant primarily to vascular disease, while others may be uniquely important in neurodegeneration. However, I would be surprised if there was no meaningful overlap between the two conditions.

One challenge is that many dementia studies rely on case-control designs, where inflammation is already present once disease has developed. In those cases, it can be difficult to determine whether inflammation contributed to disease onset or simply reflects ongoing neurodegeneration. Our genomic approaches allow us to look prospectively at healthy individuals and identify inflammatory pathways associated with future disease risk. That distinction is extremely important.

Ultimately, by comparing cardiovascular disease, stroke, Alzheimer's disease, and vascular dementia using the same framework, we should gain a much clearer understanding of which inflammatory pathways are shared and which are distinct. That knowledge could inform both cardiovascular and neurological drug development in the future.

Q10 Many clinicians are familiar with traditional cardiovascular risk factors. How do you see inflammatory biomarkers fitting into future risk assessment and patient management strategies?

I am very optimistic.

We already have strong biological evidence supporting several inflammatory pathways. If ongoing studies continue to be positive, anti-inflammatory therapies could become a routine component of cardiovascular management, particularly in carefully selected patient groups.

Looking further ahead, inflammatory biomarkers may become part of precision medicine strategies that help identify patients most likely to benefit from targeted interventions.

The key will be integrating biological knowledge, genomic evidence, biomarkers, clinical trials, and therapeutic development. If we can achieve that, we will move away from a 'one-size-fits-all' approach towards more personalised cardiovascular prevention and treatment.

Q11 What role do you think glucagon like peptide 1 (GLP-1) receptor agonists may play in inflammation?

GLP-1 receptor agonists are fascinating because they sit at the intersection of metabolism, obesity, diabetes, and inflammation.

We know that adipose tissue produces inflammatory cytokines, contributing to low-grade systemic inflammation. As people lose weight and reduce adipose tissue mass, inflammatory markers typically decrease.

The question remains whether GLP-1 therapies reduce inflammation primarily through weight loss or whether they also exert direct anti-inflammatory effects. That biological distinction is still being investigated.

As the population receiving these therapies continues to grow, we will gain much deeper insight into these mechanisms.

Q12 What emerging areas of inflammation research are generating the most excitement for you right now, whether in genomics, biotechnology, or drug discovery?

What excites me most is the convergence of genomics and biotechnology.

We have already seen remarkable successes in lipid-lowering therapy, beginning with statins and progressing to proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, as well as a range of other lipid metabolism targets. These advances were built upon decades of biological understanding and genetic evidence.

I hope to see inflammation follow a similar trajectory.

There are now multiple technological approaches available, including monoclonal antibodies, recombinant proteins, RNA-based therapies, and transcription-modifying technologies. These platforms offer many opportunities to target inflammatory pathways with increasing precision.

My hope is that future inflammatory drug development will make use of the same broad range of biotechnological innovations that have transformed

lipid medicine and will be guided by robust biological and genomic evidence from the earliest stages of development.

Q13 Looking at the theme for this year's ESC Congress, what role do you see AI playing in cardiovascular research and care?

AI represents an enormous opportunity, but we must remain in control of how it is implemented.

Coming from a background rooted in quality control and clinical validation, I believe that rigorous oversight is essential. We have access to extraordinarily rich datasets, including electronic health records, imaging data, genomics, and biomarkers. AI can help us extract clinically meaningful insights from these resources.

One example from our own work involves improving dementia risk prediction. We are exploring whether machine learning approaches can enhance existing risk models by incorporating

additional clinical information alongside established genomic and cardiovascular risk factors.

AI has already demonstrated promise in areas such as imaging interpretation and screening programmes. However, before these tools are fully integrated into clinical practice, they must undergo careful validation and quality control.

The potential is enormous, but maintaining scientific rigour must remain our priority.

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