CANTOS: One year on

When the findings of the CANTOS trial were unveiled at ESC Congress 2017 in Barcelona, there was a sense of hope that a new era in preventive cardiology was set to begin. One year on, CANTOS Principle Investigator and study author Paul M. Ridker discusses whether that optimism is being realized

In announcing the results of the CANTOS study at the ESC 2017 congress in Barcelona, study author Paul M. Ridker spoke of the findings ‘cracking the door open on’ a new era of preventive cardiology. Presented as a late-breaking trial, CANTOS (the Canakinumab Anti-inflammatory Thrombosis Outcomes Study) announced to the world that the IL-1ß inhibitor canakinumab lowers the risk of cardiovascular disease and lung cancer risk by reducing inflammation.

Professor Ridker, the Director of the Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital, Boston, Massachusetts, said at that time: ‘We found that in high-risk patients, a drug that targets inflammation but has no effect on cholesterol, significantly reduced the risk of major adverse cardiovascular events.

In my lifetime, I’ve seen three broad eras of preventative cardiology. First, we recognized the importance of diet, exercise, and smoking cessation. Then, we saw the tremendous value of lipid-lowering drugs such as statins. Now we’re cracking the door open on the third era, the treatment of patients with “residual inflammatory risk.”

So, one year on, how does the land lie?

• Has CANTOS made the differences that were forecast;
• is the drug going to change practice; and
• what is the way forward from here?

Speaking to CardioPulse, Prof. Ridker is confident that the advances CANTOS offered are more than beginning to be realized. ‘The most important issue stemming from CANTOS is the biology’, Ridker said, suggesting that CANTOS had opened the floodgates for research into novel anti-inflammatory approaches to atherosclerosis.

‘In the year that has passed since the formal presentation of CANTOS, we have seen a rapid change in our understanding of atherosclerosis not only as a disorder of cholesterol accumulation, but also as a disorder of innate immune function’, he said.

‘CANTOS has definitively proven that targeted anti-inflammatory therapy—at least with interleukin-1ß inhibition—can significantly lower rates of heart attack and cardiovascular death in the absence of any effects on lipids or blood pressure.’

Perhaps equally important, the magnitude of clinical benefit associated with canakinumab appears to be related in large part to the magnitude of inflammation reduction achieved; for example, those who achieved levels of hsCRP below 2 mg/L after a single dose of canakinumab enjoyed a 31% reduction in cardiovascular as well as all-cause mortality with continued therapy.

An inflammatory biologist and cardiologist, Prof. Ridker suggested to the Barcelona audience that the CANTOS findings ‘represent the end game of more than two decades of research’ and stemmed from a critical observation that half of heart attacks occur in people who do not have high cholesterol but have ‘residual inflammatory risk’. The trial definitively showed for the first time that lowering inflammation independent of cholesterol or blood pressure reduces cardiovascular risk.

CANTOS was heralded as having ‘far-reaching implications’; by leveraging an entirely new way to treat patients—targeting inflammation—cardiologists may be able to significantly improve outcomes for certain very high-risk populations.

Conducted across 39 countries, the trial aimed to test whether reducing inflammation in patients who had a prior heart attack can lower the risk of another cardiovascular event and included 10 061 patients who had previously had a heart attack and had persistent, elevated levels of high sensitivity C-reactive protein (hsCRP). These patients with ‘residual inflammatory risk’ are twice as common as those with ‘residual cholesterol risk’, yet prior to CANTOS had no effective therapy.

All patients received aggressive standard care, which included high doses of cholesterol-lowering statins. In addition, participants were randomized to receive 50, 150, or 300 mg of canakinumab, or a placebo, administered subcutaneously once every 3 months. Patients were followed for up to 4 years. The primary endpoint was the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The secondary endpoint was the first occurrence of any of the above, or of hospitalization for unstable angina requiring urgent revascularization.

Canakinumab at doses of 150 or 300 mg reduced the risk of a cardiovascular event (the primary endpoint) by 15%. The secondary endpoint was reduced by 17% in the groups taking 150 or 300 mg of canakinumab.

Further, exploratory analyses revealed that canakinumab dramatically cut rates of death due to lung cancer as well as the incidence of lung cancer. These latter findings are consistent with a long literature describing the role of inflammation in the growth, invasion, and metastasis of certain pro-inflammatory tumours.

Having continued the work over the past year, Prof. Ridker, who is also the Eugene Braunwald Professor of Medicine at Harvard Medical School, said a critical question coming out of CANTOS is what the appropriate target for treatment is. By selectively blocking IL-1ß, canakinumab also lowers IL-6. More recent analysis from Ridker’s study team was presented at ESC 2018 in Munich, where they reported that the benefits of therapy also directly related to the magnitude of IL-6 reduction after a single dose of canakinumab.

This effect was
minimally attenuated not only after multi-variable adjustment for all known determinants of IL-6 levels, but even after a sophisticated causal inference analysis. This provides considerable evidence that the benefits of IL-1ß and IL-6 lowering are due to drug effects and not to participant characteristics.

He said that the new data are important in showing that clearly targeting IL-1ß works.

The next steps in the process might include going one step upstream to target the NLRP3 inflammasome, though he suggested that is a technical challenge that is still several years away. ‘On the other hand, there are already multiple IL-6 inhibitors approved for clinical use to treat disorders such as rheumatoid arthritis and other immune conditions. Such agents might well have cardiovascular benefits, and thus treatment trials of these agents are needed’, added Prof. Ridker.

In the meantime, Prof. Ridker believes the time has come for clinicians to incorporate the idea of ‘residual inflammatory risk’ into practice. ‘We know that patients with elevated hsCRP are at high risk even if LDL levels are low, and we now know that targeting this residual inflammatory risk can reduce event rates’, he said. ‘Yet if we don’t measure hsCRP, we simply cannot know what the underlying biology driving risk is in individual patients. So, the time to move beyond simple lipid biomarkers has clearly come’.

The door of a new era in preventive cardiology, it appears, has been well and truly ‘cracked open’.

Conflict of interest: none declared.

References
References are available as supplementary material at European Heart Journal online.

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Adult congenital heart disease at the Royal Brompton

A historical perspective and future directions discussed by Michael Gatzoulis

The Royal Brompton started as a Hospital for tuberculosis (TB) in 1847 (Figure 1). Cardiology did see a major step forward and became of clinical relevance in the first half of the 20th century.

It was at a time that one of its true masters, Dr Paul Wood practiced at the Brompton as the Physician In Charge of Cardiology (Figure 2). The division between Paediatric and Adult Cardiology in the UK at the time was not clear-cut; Paul Wood had the benefit of seeing both children and adults with congenital heart disease (CHD), and thus understood its life-long nature.

His impact on Cardiology in general, and on CHD in particular was immeasurable. His textbook ‘Diseases of the Heart and Circulation’ remains a classic. He established the natural/unnatural history of CHD and elegantly described one of the common complications, namely pulmonary arterial hypertension (PAH). His clinical skills were unparalleled, his legacy of UK bedside medicine and inquisitive mind still lives on. He trained and inspired a myriad of distinguished cardiologists, including my predecessor Professor Jane Somerville, Drs Joe Perloff, and Alexander Nadas, of UCLA and Harvard Medical Schools respectively, and many others.

My personal journey brought me to London in 1987 for my postgraduate education after studying Medicine at the Aristotle University of Thessaloniki, Greece. I joined the Royal Brompton in 1992 to train initially in Paediatric Cardiology. It was a busy but very exciting time with steep learning curves. My London PhD was on right ventricular mechanics and their interplay with electrical instability in adults with repaired Tetralogy of Fallot. Many good things came out of this work, including a clear new focus for me on adult CHD (ACHD) or so called (Grown Up Congenital Heart (GUCH). I moved to Toronto, Canada,