

CMR-GUIDE: What Myocardial Scar Can Tell Us About Risk

Following the much-anticipated recent publication of CMR-GUIDE in JAMA, lead author Joseph Selvanayagam (JS) speaks with NewsBeat Editor-in-Chief Vass Vassiliou (VV) about the origins of the trial, the challenges of delivering a large international investigator-initiated study, its key findings, and their clinical implications. They also discuss what CMR-GUIDE may mean for the future of risk stratification in patients with myocardial scar and mildly reduced left ventricular ejection fraction, and how the trial could help shape future research in this field.



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VV: Joseph, thank you for joining us for this SCMR NewsBeat interview. Congratulations on your recent CMR-based paper in JAMA, the CMR-GUIDE trial. We will of course discuss CMR-GUIDE, but before we get to that, can you tell us a little about your background; where you grew up, how you came into medicine, and what first drew you to cardiology and CMR?

JS: I spent the first 14 years of my life in Sri Lanka and then moved to Adelaide, South Australia, because of the civil unrest in Sri Lanka. I finished high school in Adelaide and studied medicine at the University of Adelaide. After internship basic physician training, and fellowship examinations at the Royal Adelaide Hospital, I then completed cardiology training at Flinders Medical Centre.

Around 2001, I became interested in pursuing a higher degree and an overseas fellowship. Clinically I was interested in heart failure and cardiomyopathies. CMR was emerging as an exciting imaging subspecialty. Although I had no practical experience in it at that stage as none was being performed in Australia, my interest had really developed through reading papers. I had the opportunity to apply for a fellowship at the University of Oxford with Prof Stefan Neubauer and was fortunate to receive a Wellcome Trust fellowship as well as separate UK government funding for my DPhil (Editor's note: DPhil= Oxford University equivalent of a PhD). My wife and I moved to Oxford in January 2002, and that was really the beginning of my journey in CMR. Coincidentally it was also the time of OCMR commencing, and hence it was a great time to be involved in clinical and research CMR.

I completed my DPhil in about two and a half years and then held a British Heart Foundation intermediate fellowship for a further two and a half years. We returned to Australia in 2007, largely for family reasons, and since then I have been based at Flinders, where I established a CMR program alongside my interest in cardiomyopathy.

It was an extraordinary time to enter the field. Oxford was a great place to live and thrive academically. My DPhil focused on using CMR to define myocardial injury, particularly in the context of revascularization and hibernating myocardium. We were fortunate enough to get a number of high-profile papers out of that work. Beyond the science, one of the great strengths of both CMR and SCMR was the sense of community. Twenty-five years ago, the

global CMR community was relatively small, and SCMR meetings genuinely felt like family gatherings: science, friendship, and collaboration all came together.

VV: How did your research evolve from using CMR primarily to assess cardiac structure, function, and myocardial injury toward using tissue characterization, particularly scar, to understand risk and prognosis? Did that thinking begin during your time at Oxford?

JS: Initially, we recognized CMR as an excellent diagnostic tool for both ischemic and nonischemic heart disease. Its spatial resolution made it particularly valuable in ischemic heart disease for defining myocardial injury, and its ability to characterize tissue- including edema- allowed us to distinguish reversible from irreversible injury. That formed the basis of a number of my early studies.

What became increasingly apparent, however, was that late gadolinium enhancement (LGE) was not only diagnostically useful; it also carried prognostic information. Across ischemic and nonischemic conditions, studies from both sides of the Atlantic were showing that scar identified by CMR was a marker of risk. My own interests naturally moved in that direction.

After returning to Adelaide, we also pursued oxygenation imaging (which had initially commenced in Oxford) and, importantly, work in dilated cardiomyopathy. We studied patients presenting with DCM and examined whether LGE, alongside ECG findings, NT-proBNP, echocardiographic parameters, including strain, could identify those least likely to respond to medical therapy. That work was eventually published in the European Heart Journal in 2012, and CMR-GUIDE grew directly from the questions raised by that research.

VV: Leading on from that, what clinical observation or unmet clinical problem, made you feel that CMR-GUIDE was necessary?

JS: One of the strongest influences was a patient of my own who had been enrolled in our DCM study. Her ejection fraction was about 45%, and CMR showed mid-wall LGE in the mid-septum in a classical nonischemic scar pattern. She used to send me a Christmas card every year. One year the card did not arrive, and a few months later she also missed her clinic appointment. When I contacted her, I spoke with her husband and learned that she had collapsed and died suddenly while talking to a neighbor at a caravan park.

That experience stayed with me. At the same time, influential observational data, particularly from the Royal Brompton group, were showing that mid-wall scar in DCM was strongly associated with ventricular arrhythmias and sudden cardiac death. Several strands of evidence were converging.

At that stage, the idea that scar predicted prognosis was increasingly accepted within the CMR community, but it was not yet universally embraced across general cardiology, heart failure, and electrophysiology. And there was a second, much bigger step: even if scar

identifies arrhythmic risk, could we use a CMR finding to guide therapy: specifically, implanting an ICD to prevent a potentially fatal ventricular arrhythmia?

That was a radical concept in 2013–2015. Many colleagues and industry partners were not convinced, and funding was difficult because these were patients who would not ordinarily receive a device. But we persisted, formed a steering committee, secured funding, and ultimately launched the trial. The central question was where myocardial scar fits within the wider jigsaw of clinical, biochemical, and electrophysiological risk markers and whether it could identify patients whose risk was modifiable.

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VV: Why did CMR-GUIDE focus specifically on patients with an ejection fraction of 36% to 50%?

JS: We chose that range because it represented a clear treatment gap. Patients with an LVEF of 36% to 50% generally did not qualify for a primary-prevention ICD under existing guideline thresholds, yet a substantial number of sudden cardiac deaths occurred above an EF of 35%.

At the same time, improvements in acute infarct treatment, 24/7 PCI services, revascularization, statin therapy, and secondary prevention were reducing infarct size and the number of patients left with very low EF. The patients at highest relative risk, i.e. those with EF below 35%, remained important, but the overall population in that category was changing.

The problem was that you could not reasonably implant ICDs in everyone with an EF between 36% and 50%, because their average absolute risk was lower. The real challenge was to identify the higher-risk individuals within that much larger group. We selected this population because it was under-recognized, under-treated, and clinically difficult to risk-stratify.

VV: CMR-GUIDE was an ambitious investigator-initiated, international, multicenter trial. What were the biggest challenges in running it and what would you want younger investigators to learn from that experience?

JS: It was extremely challenging. The devices and much of the operational cost were supported by an industry partner, but this was not an industry-sponsored trial; it was academically sponsored and investigator initiated. That meant we had to work within a relatively lean budget while meeting the standards required for a major device trial.

The first challenge was clinical equipoise. These patients did not routinely receive ICDs, and the “scar hypothesis” was not yet a widely accepted concept outside the CMR community. We had to convince sites, investigators, coordinators, nurses, and patients that the question

was worth asking and that the proposed trial could answer it. During the pandemic, follow-up became difficult, and even implanting an ICD in patients already randomized to the device arm could be challenging because patients were being told not to come into hospital.

For younger investigators, the lesson is that work of this scale requires resilience, tenacity, courage, and faith in your own abilities and that of your team. Many people will tell you that something is too difficult or will never work. CMR-GUIDE took a little over a decade from its early development to completion, and no other trial entered exactly this space during that period. You have to believe in the question and be prepared to stay the course.

VV: When you first saw the final results, what was your immediate reaction?

JS: My first reaction was that there was clearly a signal for reduction in SCD with ICD, but I was surprised that the two components of the primary endpoint were moving in opposite directions. The composite primary outcome was therefore neutral.

Sudden cardiac death was significantly reduced in the ICD arm, with a hazard ratio of 0.26, approximately a 74% relative risk reduction, which was very much in keeping with what we had hoped to see. The unexpected finding was that hemodynamically significant ventricular arrhythmias (HSVA), the other component of the primary endpoint, moved in the opposite direction. That contrast was the major surprise.

VV: That creates an apparent paradox: fewer sudden cardiac deaths, but more hemodynamically significant ventricular arrhythmias in the ICD arm. How do you interpret that?

JS: In many ways, that is the crux of the trial. We did not expect the two components to diverge. Had HSVA moved in the same direction as sudden cardiac death, the overall primary endpoint would have been positive. That is, in fact, what we observed in the prespecified subgroup of patients younger than 70 years.

Our leading explanation relates to device programming. When we designed CMR-GUIDE, we were very conscious of data from MADIT-RIT showing the harms associated with inappropriate shock therapy. These trial patients were relatively well and would not ordinarily have received an ICD, so we deliberately programmed the devices conservatively with delayed therapy and treatment at relatively high ventricular tachycardia rates in order to reduce the risk of inappropriate shocks.

With hindsight, that programming probably meant that some patients, particularly older patients, experienced syncope before the device delivered therapy. Our definition of HSVA required ventricular arrhythmia associated with syncope or documented significant hypotension. In other words, an ICD patient could survive an arrhythmic event but still meet the primary endpoint because they had lost consciousness before therapy was delivered.

That, we believe, helps explain why the ICD arm appeared to have more HSVA even while sudden cardiac death was lower. A theoretical alternative is that ICDs themselves were pro-arrhythmic, but we consider that less likely. Our interpretation is that some patients in the ICD arm survived events that might otherwise have resulted in sudden death, while the

delayed programming allowed those events to become hemodynamically significant before treatment.

VV: The overall event rate was also lower than expected. How important is that when interpreting the trial?

JS: We had expected around 50 primary events and observed 30, roughly 60% of what we had anticipated. We had also assumed a sudden cardiac death rate of around 4%, whereas the observed rate in the loop-recorder arm was about 1.1% per year.

One explanation is simply that our original assumptions were too optimistic. But I think the more important explanation is that background medical therapy improved substantially during the long course of the trial. SGLT2 inhibitors did not exist as part of routine heart-failure therapy when we began; by the end of the study, around 10% of patients were receiving them. MRA use was around 40% to 50%, while use of renin–angiotensin system inhibitors and beta-blockers was understandably high.

Those advances in medical therapy may have reduced fibrosis, arrhythmic risk, and sudden death. The long duration of CMR-GUIDE meant that the therapeutic landscape evolved underneath the trial, and that almost certainly contributed to the lower-than-expected event rate.

VV: Age was a prespecified interaction and emerged as an important finding. What did you observe, and how should clinicians think about a patient with scar and mildly reduced EF, for example, someone aged 55 compared with someone aged 75?

JS: We prespecified six interaction variables, including age, baseline LVEF, sex, cardiomyopathy type, QRS duration and NYHA class. Age was the only statistically significant interaction, with a P value of 0.011. The cutoff was 70 years. In other words, in patients younger than 70, the ICD was associated with a significant reduction in the primary composite endpoint, not just sudden cardiac death, but the combined endpoint of sudden death and HSVA.

That age interaction is biologically plausible and is consistent with previous primary-prevention ICD trials in which age has also modified the treatment effect. In younger patients, there is less competing risk from non-arrhythmic causes of death, so preventing sudden cardiac death has greater potential to translate into meaningful long-term benefit.

The findings provide a basis for shared decision making in the clinic. For a 55-year-old with substantial scar and an EF around 40%, I would now have a very different discussion than I could have had before CMR-GUIDE. There is now randomized evidence in a space that was previously largely evidence-free. I would explain the patient's background risk, the potential reduction in sudden cardiac death, and the trade-offs of ICD implantation- including procedural morbidity, device-related complications, the small risk of inappropriate shocks,

and the finding that quality of life was marginally worse in the ICD group over long-term follow-up.

For an otherwise similar 75-year-old, scar still matters: it remains a marker of sudden-death risk despite good medical therapy. But competing risks of death from heart failure, stroke, cancer, and other causes, become much more important. The trial suggests that the overall value proposition of an ICD is therefore different in that age group.

More broadly, CMR-GUIDE adds randomized evidence to a substantial observational literature on scar. Existing guidelines already use observational risk markers to guide ICD decisions in conditions such as hypertrophic cardiomyopathy. Whether and how CMR-GUIDE changes future guidelines in patients with EF 36% to 50% will be a matter for the wider community and guideline committees.

VV: What research should come next? And how might the ongoing BRITISH trial complement or strengthen what CMR-GUIDE has shown?

JS The BRITISH trial is important and should complement CMR-GUIDE. It adopts some elements of the CMR-GUIDE methodology, including the use of a loop recorder in the control arm, but it also addresses a different population and a different primary endpoint.

A major distinction is that the BRITISH study is powered for all-cause mortality. We collected all-cause mortality as a secondary outcome, but an investigator-initiated trial in which every device had to be fully funded from the grant could not realistically be powered for that endpoint. We would have needed a trial of at least 3-4 times the size. All-cause mortality is an appropriately rigorous endpoint, but it is also a very high bar for an ICD trial because an ICD can prevent arrhythmic death but cannot prevent every competing cause of death.

The populations also differ. CMR-GUIDE enrolled patients with EF 36% to 50%, whereas the BRITISH trial starts with lower EF. That is likely to mean more pump-failure and heart-failure death, making the balance between arrhythmic and non-arrhythmic outcomes particularly interesting.

For future studies, CMR-GUIDE provides several things: proof that a trial like this can be done; further support for the scar hypothesis; real event rates for power calculations; and information about the population most likely to benefit. In my view, it particularly sharpens the rationale for studying younger patients with ischemic disease and myocardial scar.

VV: If there is one practical point you would like SCMR members to remember when they report myocardial scar in a patient with mildly reduced EF, what would it be?

JS: Report the scar in a way that is clinically translatable. In particular, report the number of involved myocardial segments and the transmural extent of LGE. That is how CMR-GUIDE was deliberately designed. We did not require fully quantitative scar burden because I wanted the findings to be usable not only in highly specialized tertiary CMR centers, but also

in smaller radiology and cardiology practices that may not have dedicated software for quantitative LGE analysis.

In the ischemic cohort, the trial required at least two myocardial segments using the 17-segment AHA model, with greater than 75% transmural LGE. If a referrer wants to look at a CMR report and understand how closely a patient resembles the population studied in CMR-GUIDE, the report needs to describe both the number of segments involved and the transmural grade. Quantitative scar assessment can certainly be added, particularly as AI-based and third-party tools continue to develop, but clear semiquantitative reporting remains highly valuable.

“Anything worth doing is usually hard. If it has the potential to be impactful, it will usually take time, effort, and perseverance. But ultimately it is for the benefit of **science and our patients.**”

VV: And finally, will we see you in Rome for the SCMR meeting in February?

JS: Yes, I should be there.

VV: I look forward to seeing you there and discussing many CMR-related topics and, of course, CMR-GUIDE!