Opinion Paper

The wisdom in ISCHEMIA

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A R T I C L E  I N F O

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The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) study was published recently demonstrating that over a period of 3.3 years a routine invasive approach along with optimised medical therapy (OMT) was not superior to OMT alone in patients with stable coronary artery disease and at least moderate to severe ischemia. Considerable interest and discussion have emerged over the applicability of the trial to real-world settings and the limitations of the trial. Given the fact that no clinical trial will ever be designed that will be perfect, it is important to prise out the pearls that the findings reveal and not interpret the findings as either positive or negative towards one approach or the other.

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Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?

TS Eliot, The Rock

A recent editorial and viewpoint discussing the role of cardiac imaging in the post-ISCHEMIA trial era tabulated the strengths and the limitations of the study.1 While every study has limitations and no trial will ever be perfectly designed, it is important that these limitations are put in perspective.

One limitation stated is that the predominant ethnicity or race was white (66%). However, its elder sibling COURAGE included a cohort that was 86% white.2 The increased number of patients who were identified as Asian is one of the strengths of the trial as it is representative of a population where the incidence and prevalence of ischemic heart disease (IHD) are high. Fittingly, India, which has approximately 18% of the world’s population contributed approximately 19% of the study population. The heterogeneity of the population ensures the applicability of the study findings globally.

Running a truly international trial implies an understanding of local social norms and customs and expectations should be calibrated accordingly. One of the reasons for lower enrolment of women is that, in some parts of the world where the trial was conducted, women lead sedentary lives indoors and rarely exercise to the point of having angina (Dr. BKS Sastry, personal communication). Unfortunately, in some parts of the world, men seek medical care more frequently than women. These factors preclude inclusion of equal numbers of women in clinical trials in some parts of the world. Among those enrolled but not randomized, 34% of women had no significant disease compared to 11% in men and 4% had left main (LM) compared to 1.4% in men, both being statistically significant.3 The absence of no significant disease or the presence of LM on CCTA were exclusion criteria for randomization, thereby decreasing further the number of women who were randomized.

There were multiple reasons for slow recruitment. Centres in some countries may not have participated also because it would result in a loss of hospital revenue linked to maintaining patients on OMT alone. Some centres were initial fence-sitters closely following the evaluation of the DSMB before deciding to participate. It is harder to maintain clinical equipoise in societies where there are high rates of malpractice litigation. Participation in a trial like ISCHEMIA with a long follow up requires a generous amount of trust as the foundation of the investigator/physician – trial participant relationship. Even while enrolling patients regularly several investigators confessed their internal misgivings about maintaining patients on OMT fearing that an event may occur in those patients as ISCHEMIA was an iconoclastic trial in many ways.

Free stents were provided after patients were enrolled and randomized and at no point was this availability mentioned to patients because this would constitute enticement which is illegal in many countries. The method of revascularisation chosen was not based on the availability of stents because individual centers often subsidised the costs of CABG as a gesture of equity. Stents were

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provided only for the original procedure for the invasive arm and not for any other procedures in either arm eliminating another potential incentive to revascularize. The patients in the invasive arm may have been treated heterogeneously in different centers and countries as some factors may mandate different technical approaches. Many Indian surgeons encounter small coronary arteries with diffuse disease requiring endarterectomy in up to 15% of cases, increasing the risk of perioperative myocardial infarction and early graft closure as noted by Western surgeons who have worked in India (Dr. I. Baqueero, personal communication).

Many social media users have pounced on the percentage of patients from the OMT arm who had an invasive procedure. It will be important to know the geographic distribution of the subsequent procedures in the OMT arm because a subjective symptom of angina can be interpreted by some physicians, based on their practice patterns, as an immediate indication for an invasive procedure. This threshold for an invasive procedure in the OMT arm can be determined by various factors including the fear of litigation. It is also possible that patients had increased anxiety after discovering that they had IHD and compounded by the knowledge that they would not be revascularized. In SCOT HEART, improvements in the symptoms of physical limitation, frequency of angina and quality of life were reduced when angina was definitively attributed to IHD. Notably moderate obstructive IHD fared worse than mild non-obstructive or obstructive IHD. Those whose diagnosis of IHD was refuted by CTCA showed remarkable improvement in symptoms especially if CTCA demonstrated normal or mild coronary artery disease. A similar phenomenon occurred in FAME 2 and DEFER. If physicians do not have clinical equipoise, we cannot expect our patients to have psychological equipoise in this frenzied world of sound bites.

While these discussions occur in the hallowed corridors of academic journals and meetings what are frontline clinicians like us supposed to take away from ISCHEMIA? In many countries with national healthcare systems, due to a lack of system capacity there are waiting lists for coronary angiography. For our anxious patients and many clinicians ISCHEMIA provides solace. An initial approach with OMT is as effective as the event curves do not cross for the entire length of follow up. Both COURAGE and ISCHEMIA have taught us that in the management of IHD we now have another precious resource – time – to think, ponder and make considered choices for our patients discussing options with colleagues and patients, before embarking on revascularization as the default choice. Waiting lists have become catastrophic after the start of the COVID pandemic and many centers across Europe are unable to perform any elective work. One wonders if this unfortunate situation is a blessing in disguise for those on a waiting list! Dovetailing many nationally funded healthcare systems are private healthcare facilities which provide for elective services when there is a lack of capacity in the former. Many people purchase additional health care insurance from providers or sustaint considerable out-of-pocket expenditure to access some services including coronary revascularisation even though its available free of cost within the national system, albeit after a waiting period. Therefore patients’ purchase of additional insurance coverage for such services at considerable additional cost may be unwarranted. For those with left main detected by CTCA, priority triage for angiography can be considered as we have done.

Even before the trial began the investigators had the odds stacked against them. The existent paradigms of clinical care, the complexity of the trial to ensure safety and efficacy, slow enrolment, and the inclusion of some centers with limited experience in clinical trials would have made many punters bet on the trial failing. The study chairs, their respective teams, site investigators and the patients need to be thanked and congratulated for having the COURAGE to participate in ISCHEMIA. Physicians will eventually use the data gathered by the investigators, transformed into information by the trial leadership, which after adequate scrutiny will become knowledge, that should be applied wisely to achieve the best outcomes for our patients.

As one watches the debate on social media, sometimes vitriolic, that has occurred with COURAGE, ORBITA and now ISCHEMIA one is reminded of Thomas Mann when he said — We are most likely to get angry and excited in our opposition to some idea when we ourselves are not quite certain of our own position and are inwardly tempted to take the other side.

Declaration of competing interest

No conflict of interest.

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