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REVIEWS

CONTROVERSY: CRITICAL REVIEW OF THE STICH TRIAL AND ASSESSMENT OF VIABILITY. "BACK TO THE FUTURE" OR MAYBE NOT

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Abstract. *The management of patients with coronary artery disease and heart failure has been debated for years. In the 1980's Braunwald coined the words "viability" and "stunning". Multiple trials have been done since then. Since the early eighties coronary bypass grafting was considered as gold standard for patients with impaired left ventricular fraction and coronary artery disease. Since then, nuclear imaging studies have been used to evaluate the "viability" of the impaired areas and to decide if revascularisation would be reasonable. Beginning with the CASS study and ending with the more recent STICH study we aim to provide a "bird's eye view" of the pros and cons for revascularisation. In addition, we aim to shed some light on the daily advancements in medical management, including devices and not just medication. We therefore chose the title "Back to the future" or maybe not.*

Key words: *viability, heart failure, coronary artery disease, systolic volume, nuclear medicine, revascularisation*

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INTRODUCTION

There is quite some controversy about the optimal management of cardiac patients with advanced left ventricular systolic dysfunction. Controversy also surrounds the management of elderly or medically compromised patients. Should they be treated via procedures such as angioplasty/stenting or coronary bypass surgery (CABG) or should they continue with drug therapy alone. There is a group of patients which are not suitable for diagnostic procedures due to multiple risk factors, advanced age, multimorbidity, kidney dysfunction etc. Should this group of patients take the risk of a coronary angiogram (or Computed Tomography of the coronaries [CT scan], in cases of advanced age and coronary calcifications), or should they undergo non-invasive diagnostic examination such as nuclear assessment for possible pathology/ischaemia.

THE STICH TRIAL WITH COMMENTARY

It is generally accepted that patients with left ventricular dysfunction and double or triple vessel obstructive disease should undergo CABG. Patients with single, or maybe double non complicated CAD and LV dysfunction should have PCI/stent. The cut-off for LV dysfunction of 35% ejection fraction is used in most of the studies that complement one or another management approach.

The cornerstone of the management of every patient is to reduce mortality.

In the recent two or three decades there has been significant improvement in the medical management of patients with coronary artery disease and left ventricular dysfunction on the medicinal front.

Multiple trials and research have been conducted in recent years to establish the best management strategy in patients with coronary artery disease and associated left ventricular dysfunction.

In 2009 the STICH trial was viewed as a potential "game changer" [1]. The trial reviewed patients who had coronary artery disease with some possible viability.

All patients had dilatative cardiomyopathy following infarction. The idea was that CABG surgery with ventricular reconstruction could potentially change the outcome in these patients. The original study assessed the role of the ventricular reconstruction [1].

The authors in the NEJM [2] concluded though that surgical reconstruction of the left ventricle attempting to reduce the left ventricular volume in CABG did not improve the symptoms of patients or their effort tolerance. The value of the decreased left ventricular size was shown by Dor [3]. The author documented an increased cardiac efficiency after excision of the scar in patients with previous myocardial infarction.

The study of SVR (reconstruction of the left ventricle) after Bypass based on a Registry of more than 5000 patients is however debatable [4, 5].

The STICH trial raised a number of controversies which we will review.

As reviewed by Gerard Buckberg [6] the goal of the STICH trial and its review should be to:

Exclude all patients with invalid echocardiographic volume measurements.

Include only patients in whom regional nonviability with akinesia greater than 35% is documented by nuclear medicine scans.

The Nuclear definition of "volume" and "scar" is of utmost importance in the management of these complex patients. The nuclear medicine collaborative approach has been used in quite a few studies [2].

In the JACC Cardiovascular Imaging, 2015, Robert Bonow concluded that among patients with severe cardiomyopathy, those with greater systolic volume and no substantial viability had a worse prognosis. The presence of bypass versus medical therapy did not influence the prognosis. This was not in line with the above mentioned comparisons between medical therapy, surgery and scar reduction surgery.

Systolic dysfunction is not always irreversible. This is due to a plethora of factors or interventions: beta blockers, cardiac resynchronisation, revascularization [8, 9].

Another point of importance lies in one of the conclusions of the STICH trial that found no interaction between myocardial viability and treatment strategy in respect to survival [10]. The interest of revealing the impact of LV remodelling on viability, revascularisation and therapy has been a topic of some studies [2, 4, 7].

In the studies the medical therapy was considered excellent with patients receiving statins, beta blockers, ACE or ARB at 1 year and most of them receiving aspirin or coumadin. One study related to the STICH trial performed by Bonow [7] enrolled 1212 patients and 601 had viability testing. The viability differed in its assessment though. One group of 471 patients were assessed via SPECT (single photon emission computed tomography) and the other group of 280 patients were assessed by dobutamine echocardiography.

An important conclusion of this article is that "patients with greater degrees of myocardial viability and lower values of end systolic index did not manifest a significant differential benefit of CABG over medical therapy compared with patients with less viability and/or larger volume of end systolic index" [10].

The debate about the revascularisation of patients with heart failure and low ejection fraction has been going on for the last 30 years [11]. The enigma that baffles the cardiologists is irrespective of the early trials in the 70s and early 80s analysing the registries of patients that had undergone a bypass and did "better" – is that the reality? Is this "do better" contrabalanced by early mortality. A comment on the results of the STICH trial: these were patients with some viability more than 10%, they were of all age groups, they were randomly selected for medical or surgical management, and those on medical management were on optimal medical therapy

The surgical approach – with or without bypass, was up to the particular surgeon to decide (it is to be noted that STICH greatly emphasises surgical management with or without left ventricular volume reduction). The death rate of above 25% for medical therapy alone, was considered significant. Important for the surgery group was the fact that it had to achieve 20% reduction in mortality and cardiac hospitalisation. Another key point to mention is that the use of PCI was not considered as a surgical, but rather as a medical procedure (the latter increases the interventional group without involving a real "procedure" in the group).

The STICH trial used a cut-off point for the ejection fraction of 35% but lower values were also accepted in the study. Physicians were encouraged to do any cardiac testing necessary to decide if a patient is a candidate for CABG, or reconstruction. The assignment

in the study was by permutated block randomization scheme after informed consent was obtained. Importantly the patients that were awaiting planned revascularisation were not included in the study. The follow up for STICH was at 4 months and 24 months data. The medications used in the medical therapy group included – statins, diuretics, ACE inhibitors, beta blockers, aldosterone inhibitors, antiplatelet agents. The use of defibrillators followed Guidelines.

One of the early trials for surgical therapy was CASS [12]. It enrolled patients with ejection fraction above 35% but less than 50%. At conclusion, 21% of the medical therapy group died after 10 years vs. 18% in the surgical group. Important is to mention that the medical therapy in the CASS study involved medication that does not decrease mortality namely diuretics and digitalis. Patients who had left ventricular resection surgery and no angina showed difference in survival rates. In the CASS study 5 years survival favoured medical therapy (this is important to know as more and more we deal with advanced age, debilitated patients that do not have great life expectancy in general) The patients in CASS that had angina did better however those with heart failure they did not. It is to be noted that CASS showed benefit for patients with ongoing angina and none for patients without angina (again the medication in CASS was not mortality decreasing) [12]. Here comes the point!

Why is it important to measure viability? Currently Technetium or Thallium nuclear scintigraphy is used, with good sensitivity and specificity. Dobutamine stress echocardiography is used in some institutions. There is significant heterogeneity and differences in clinicians' interpretation of the data from the viability studies. Viable myocardium predicts recovery. That is irrespective of surgical or medical therapy [13]. CASS showed significant survival difference only in the subgroup that had ejection fraction between 35 and 50% [14].

The criterion to decide on a strategy was the presence or absence of angina. Nevertheless, that can be a grey area in patients with heart failure

A study from E. Marc Jolicœur [15] shows that angina does not predict all-cause mortality in medically treated patients with LV systolic dysfunction and CAD, nor does it identify patients who have greater survival benefit from CABG. They do though conclude that CABG does improve angina to a greater extent than medical therapy alone.

In general, CABG is recommended to patients with angina, coronary artery disease and left ventricular dysfunction (19). Convincing evidence that the presence/absence of angina determines the therapy is lacking [1]. Importantly, the prognostic significance of presence of angina in heart failure has not been reported on [17, 18, 19]. Revascularisation is considered as a symptom relief for patients with advanced CAD, angina, and LV dysfunction. The presence or not of angina should not be the determining factor for revascularisation. This though contradicts several clinical studies that the presence of angina is a poor prognostic factor and requires revascularisation. The European guidelines recommend intervention/CABG in patients with persistent angina. Revascularisation is not recommended on patients without angina and viable myocardium [20]. Few studies confirm the presence of angina as a poor prognostic factor for survival and more likely the patient will undergo revascularisation. The latter is not recommended for patients without angina and viable myocardium [20, 21].

The big question is still – why can the presence/absence of angina not predict the benefit or the mortality risk for cardiac surgery compared to the population?

The STICH trial as well as the HEART trial suggest that neither myocardial ischaemia nor viability give prediction for patients' well-being after surgery [22].

Currently there are ongoing trials of CABG and medical therapy to determine which is better for the patient. "REVIVED-BRICS" addresses the revascularisation in heart failure by coronary intervention. These are patients with present angina [23].

Logically speaking the surgical or interventional therapy should be considered for patients that do not recover from medical therapy.

It is important to remind ourselves of the outcome of the BARI 2 and COURAGE trials. Both included few patients with LV dysfunction. The ischemic burden failed to provide positive data for the revascularisation on clinical endpoints. When the ischemic burden is significant and LV dysfunction is present then the data appears to back up revascularisation [24, 25]. This is important for the endpoint of these studies.

Consider as well the subjective and objective definition of angina. This can vary from physician to physician as well as from patients' complaints.

The current revision of the STICH trial results offer the view that angina does not make the prognosis better or worse with revascularisation than medical therapy alone.

In the past studies have suggested that CABG therapy in myocardial dysfunction is better than medical therapy in the management of the coronary artery disease. There is no demonstrated interaction between myocardial viability and treatment strategy in respect to survival [10].

Previous studies have suggested that there is direct relation between survival rates and the amount of left ventricular dysfunction. Irrespective of the CABG and the medical therapy approach. The high-

er the left ventricular systolic volume, the higher the mortality. The beneficial effect of CABG in left ventricular function is related to the presence of viable myocardium and smaller end ventricular systolic function [26].

If we again assess the STICH results, viability was defined by SPECT on 11 or more viability segments.

In the entire group of STICH there was no interaction observed between end ventricular systolic volume, viability status and therapy assignment to CABG versus medical therapy. Mortality for the patients with higher systolic volume was greater than those with lower systolic volume.

Medically treated patients in the trail adhered to guidelines [27]. A retrospective study performed by Tarakji et al. [28] showed that there is no significant improvement of viability in patients with revascularisation versus medical therapy regarding hibernation. An important point from the study is that the survival analysis started 92 days after the PET study. Thus, excluding early surgical mortality.

The current ACC/AHA recommendation regarding revascularisation of patients who do not have angina, is that CABG is recommended whenever viable myocardium is present or not as class IIb, level of evidence B. Contrasting to that – the Guidelines continue to give support for revascularisation where there is viability [29].

Generally speaking, lower end ventricular systolic index and the presence of viable myocardium does not preselect patients for better outcomes after CABG.

JACC 2002 published a meta-analysis on myocardium viability testing and revascularisation [30].

This study pooled data from published series examining late survival of patients from either revascularisation intervention versus medical therapy, after myocardial viability testing in patients with severe coronary artery disease and left ventricular dysfunction. It is long since then that myocardial viability has been identified as a phenomenon [31, 32].

Since then, the quest has been to establish myocardial viability and to predict the clinical benefit from it. The main idea is to prove the decrease in heart failure symptoms and increase in patient quality of life. The studies that have been published propose in general that improved viability improves survival.

In the area of nuclear cardiology there are many publications to say the least. Observationally attention has been paid to about 24 studies. Six of them used Thalium-201 perfusion imaging. Eleven used FDG with PET. Eight used Dobutamine Echocardiography. Analysis demonstrates strong associations between revascularisation and improved survival among patients with CAD and LV dysfunction. These patients had to have demonstrable myocardial viability. Interestingly (and in contrast with previous mentioned reports) meta-analysis found that the “likelihood for improved survival was greatest in patients with demonstrated viability and the most severe LV dysfunction” It is important to note the latter as the following studies disagree with that. Pre 1986 the view was (there were not many imaging techniques for viability) that the periprocedural risk is elevated for patients with extensive coronary artery disease and LV dysfunction. The risk increases as the LV dysfunction worsens; at that time the presence of angina was reported as a potential survival benefit from revascularisation. The studies viewed the benefit of revascularisation may extend beyond the angina benefit [33, 34].

Returning to the meta-analysis and studies around 2002 it was shown that there is “no apparent outcome benefit of revascularisation in the absence of demonstrated viability and there is a trend towards higher mortality with revascularisation” This is partially due to the higher periprocedural risk of the patients. The patients that were viewed in the meta-analysis were in mean NYHA 2,6 and mean EF of 32%. The meta-analysis well discussed that the presence of viability could mitigate the risk of the surgery in some way or other.

Regarding medical therapy, it was observed that the mean mortality rate of 16% per annum is comparable to the mortality rate of heart failure patients [35].

Some autopsy data from heart failure trials reveal that a considerable proportion of fatal events are associated with acute ischaemia or infarction even when the death is presumably from arrhythmia or advanced heart failure [36].

It is interesting to lift the veil a little on imaging techniques

Thallium-201 reflects cell membrane integrity. FDG reveals myocyte glucose consumption, Dobutamine echo shows the contractile reserve (something like a combination of the other two in the final effect).

There are measurement differences between the different techniques that are reported - but these generally involve small amounts of myocardium. One of the limitations during the meta-analysis was the comment of “present or absent” viability but being unable to quantify that between the different studies.

It appears that the longer 1-year survival is better in patients with viable but not dysfunctional myocardium [37]. There is a thought that sudden death occurs due to further reduction in blood supply and/or increased oxygen demand in hibernating regions. The latter could lead to re-infarction or to terminal arrhythmia [37]. Again, a key point is that the survival rate was better in patients that had minimal or no angina with revascularisation. Di Carli further stipulates that “patients with ischaemic cardiomyopathy who have minimal, or no angina can benefit from revascularisation.

If relatively large areas of viable myocardium can be identified before operation" The question of how much viable myocardium nevertheless remains open [37].

Surgical literature suggests that patients with poor left ventricular function do benefit from revascularisation irrespective of the amount of viable myocardium present; as the blood flow supplies the myocytes with blood and that improves the function [38].

In contrast, Di Carli's findings suggest that viability assessment is most important in patients with poor left ventricular function and minimal or no angina.

In the above consideration we come to the idea of "preconditioning". The first evidence emerged in the 1980s. It was shown that a brief episode of ischaemia slows the rate of ATP depletion during subsequent ischaemic episodes. Intermittent reperfusion may be beneficial to the myocardium by washing out catabolites that have accumulated during ischaemia [39]. The study showed after 40 minutes that preconditioning limited the infarct size to 25% from that seen in the control group. In 3hrs there was no difference between the infarct size of the preconditioned and the control group [40]. Short episodes of ischemia do not cause ATP depletion and cell death. Longer periods of ischaemia i.e., 40 min, do cause cell death [41].

Analysis of STICH confirms that the severity of CAD reveals the benefits of CABG [42] – but that nevertheless is not distributed throughout all groups. Problematic is the exclusion of early mortality. Problematic is the subjective manner of choice. Like CASS, in STICH (even though that was long before contemporary medical therapy) the benefit was visible in patients with LV dysfunction and triple vessel disease [14].

The questions according to J. Geske and B. Gersh [43] are:

1. Does angina have negative prognosis with left ventricular dysfunction?

2. Does the presence of angina predict a positive outcome after revascularisation?

3. Is CABG superior to medical therapy in patients with left ventricular dysfunction?

In review of the STICH trial when stratifying solely based on angina there was no difference in all-cause mortality between CABG and medical therapy. Patients with advanced class (Canadian class III and IV) had higher mortality.

A question that STICH raised is – should factors like ischemia, viability and hibernation be excluded from the account when we decide action? Certainly not. A point that Gersch et al. say could be quite viable that with the disease progress the viability scar and hibernation intermingle. They can progress further to more apoptosis and further remodelling which decreases the benefit of the revascularisation. In these patients the benefit from revascularisations could be minimal. Question – should viability testing be part of the work up of this type of patient? Doubtful but certainly helpful.

IN CONCLUSION

Patients with viable myocardium had better outcomes than patients without. Bypass did not result in significant benefit for patients with viability when compared to medical therapy. The reason for this can be debated- different way of assessing viability, relatively small amount of triple vessel disease patients, different level of LV dysfunction, significantly elevated end diastolic volumes. The latter questioned the utility of viability testing!

The question of treating the viability, the scar, the dysfunction, the triple vessel disease remains. The question of viability and the extent of the remodelling, ischemia, the length of the dysfunction remains a question of strategy. It is important to encompass the entire myocardial substrate. And following these thoughts the physiologic circumstances are especially important in the survival of the patients with ischaemic cardiomyopathy and the assessment must probably go beyond assessment of viability. Again and again the revascularisation in patients with left ventricular dysfunction remains a divisive topic.

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