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The World Post STICH: Is This a "Game Changer?" A Surgeon's Perspective — Revascularization Is Still the Treatment of Choice

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ABSTRACT

The Surgical Treatment for Ischemic Heart Failure (STICH) trial addressed the broader role of surgical revascularization in patients with heart failure due to reduced LV systolic function EF ≤35% and less severe CAD. The primary outcome (all-cause death) was not reduced by CABG. CABG did, however, reduce the secondary outcomes of cardiovascular death (RRR 19%) and death from any cause or cardiovascular hospitalization (RRR 26%).

However, 40% of patients enrolled were asymptomatic, and only 49% of patients underwent careful functional evaluation pre-randomization. Moreover, this assessment was for viability, and not ischemia. Careful scrutiny of these trial results illustrates important emerging trends in revascularization, namely the functional as well as anatomic assessment of patients prior to intervention with CABG, and the benefits of CABG in these patients.

These STICH findings illustrate the importance of these evaluations in all candidates for revascularization in ischemic heart disease; the results of the trial in terms of the efficacy of CABG need to be interpreted in this light.

A significant proportion of patients referred for coronary artery bypass grafting (CABG) have left ventricular dysfunction. These patients have an increased mortality due to their underlying left ventricular (LV) dysfunction compared to patients without LV dysfunction. The seminal studies evaluating CABG versus medical therapy, including the CASS, VA CABG and the European coronary surgery study group trials, all demonstrated greater benefit of CABG in patients with LV dysfunction.[1–4] However, all these trials excluded patients with severe LV dysfunction (ejection fraction (EF) <35%). Medical therapy has improved considerably since then and any benefits from surgical intervention may no longer be present. One arm of the Surgical Treatment for Ischemic Heart Failure (STICH) trial was designed to evaluate if CABG is better than contemporary medical therapy in patients with ischemic LV dysfunction.[5]

The STICH trial

The Surgical Treatment for Ischemic Heart Failure (STICH) trial addressed the broader role of surgical revascularization in patients with heart failure due to reduced LV systolic function EF ≤35% and less severe CAD. The primary outcome (all-cause death) was not reduced by CABG. CABG did, however, reduce the secondary outcomes of cardiovascular death

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Dr. Ferguson is co-copyright holder of the analytical software platform shown in Fig 1.

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CSA = chronic stable angina

EF = ejection fraction

FFR = fractional flow reserve

LV = left ventricle

MI = myocardial infarction

PCI = percutaneous cardiovascular intervention

SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery

STICH = Surgical Treatment for Ischemic Heart Failure

(RRR 19%) and death from any cause or cardiovascular hospitalization (RRR 26%). The trial randomized 1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to CABG assigned to medical therapy alone (602 patients) or medical therapy plus CABG (610 patients). In terms of the primary endpoint, the rate of death from any cause, even though lower in the CABG vs. medical therapy group, did not reach statistical significance (36% vs 41%, P= 0.12).[5] All-cause mortality from cardiovascular cause did reach statistical significance between the groups, but since the primary endpoint was negative this finding can only be interpreted as hypothesis generating. Overall in the general physician population, these findings from STICH have mostly been interpreted to suggest that surgical revascularization is not beneficial in patients with significant ischemic LV dysfunction.

Criticisms of the STICH trial

While the majority of patients in STICH would have what is now characterized as chronic stable angina (CSA), the STICH protocol excluded patients with class III angina or greater. These are presumably the patients who would have derived the most benefit from reversing the chronic stable angina process by supplying more sustained myocardial blood flow with CABG. In the medical treatment arm, 17% of the patients crossed over and underwent CABG, thus decreasing the potential outcome difference between the medical therapy and revascularization arms. Moreover when the analysis was performed including these patients in the CABG group the primary outcome was significant with a p-value of 0.039. While STICH was initially designed to enroll 2000 patients, due to slow enrollment the sample size was decreased, and 1212 patients were enrolled at 127 clinical sites in 26 countries over 5 years. This was an average of two patients per site per year, suggesting that these patients may not reflect general practice patterns. Perhaps most importantly, in the STICH trial 37% of the patients were asymptomatic, raising the following questions: Did these patients really need CABG, and by what objective indication(s)? Preoperative stress testing and documentation of the degree and magnitude of ischemia were not part of the STICH trial criteria, and these missing important data make it difficult to directly extrapolate the findings from STICH into more contemporary thinking about revascularization in chronic stable angina patients, including those with significant LV dysfunction.

Anatomy and functionality in revascularization

Recent randomized trials of early revascularization (PCI or CABG) and medical therapy versus medical therapy alone (COURAGE and BARI-2d) have shown that in selected patients who were randomly assigned after angiography, rates of death and myocardial infarction did not differ between revascularization and medical therapy.[6,7] These studies have sparked considerable debate among the cardiovascular community, again in part because the amount or degree of CSA ischemia was not able to be defined clearly. In contrast, Shaw and colleagues demonstrated in the nuclear sub-study of COURAGE that in patients with significant amounts of CSA ischemia (>10% by serial myocardial perfusion scintigraphy), there was a significant reduction in ischemic burden when revascularization was added to optimal medical therapy.[8]

Hachamovitch et al. retrospectively studied 10,627 patients who underwent stress SPECT myocardial perfusion scintigraphy. The patients were followed up for a mean of 1.9±0.6 years. Revascularization compared with medical therapy had greater survival benefit in patients with moderate (>10%) to large amount of ischemia, and the benefit was greater in patients with increasing levels of ischemia. In Patients with >20% ischemic myocardium, revascularization had a lower cardiac mortality than medical therapy (2.0% vs 6.7%, P<0.02), and furthermore CABG accounted for 60% of the revascularization procedures in these patients.[9] These results were duplicated in a larger study (n=13,555) by the same authors with longer follow up (mean of 8.7± 3.3 years).[9,10]

In all of these studies the value of revascularization over optimal medical therapy became significant only when more than 10%–12.5% of the myocardium was ischemic, establishing the importance of accounting for both anatomy (e.g., angiographic stenosis) and functionality (e.g., regional ischemia associated with the target epicardial vessel) in revascularization. Similarly, a fractional flow reserve (FFR)-based strategy for revascularization has been shown to be better than an angiography-based strategy for revascularization in single vessel disease (DEFER study) and multi vessel disease (FAME study).[11,12] In the Fractional Flow Reserve Versus Angiography in Multivessel Evaluation (FAME) trial, 1005 patients with multivessel CAD were randomized to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements of ischemia in addition to angiography. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was<=0.80, indicating a perfusion defect to the regional myocardium supplied by that arterial supply. The primary end point was the rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year. The 1-year event rate was 18.3%

(91 patients) in the angiography group and 13.2% (67 patients) in the FFR group (P=0.02). Seventy-eight percent of the patients in the angiography group were free from angina at 1 year, compared with 81% of patients in the FFR group (P=0.20).[12] The 2-year rates of mortality or myocardial infarction were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group (p=0.02).[13]

In an important follow-up, prospective study published in the surgical literature by Botman et al., 164 patients eligible for CABG using a traditional anatomic-based revascularization strategy underwent FFR measurement in all vessels identified (angiographic stenosis ≥70%) as target vessels for bypass grafting. At coronary angiography after 1 year, 8.9% of the bypass grafts on functionally significant lesions (FFR ≤0.75) were occluded, and 21.4% of the bypass grafts on functionally non-significant lesions (FFR >0.75) were occluded.[14] These are the first data to suggest that a target vessel coronary artery with anatomic but not functional criteria for bypass grafting results in increased graft failure at one year. Also the data from Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT IV) trial have shown that 22% of the grafts were occluded at angiographic follow up 12–18 months after CABG. The event rates at 4 year follow up were correlated with the number of graft failures suggesting that graft failure is not without consequence for repeat revascularization. However, graft failure on protocol-specified 12–18 month angiography was not associated with increased mortality or MI, perhaps suggesting that the graft failure occurred in part because there was a sufficient (and potentially protective) amount of perfusion to that target vessel myocardium to begin with; there was no physiologic 'functional drive' to maintain graft patency.[15]

Post-STICH revascularization of patient with CAD: ischemia vs. viability testing

In patients with left ventricular systolic dysfunction the first step is to determine if there is a reversible cause of the systolic dysfunction. Typically, this is achieved by a stress test (standardized exercise, stress echocardiography, nuclear SPECT) to assess severity of ischemia or coronary angiogram. In the absence of ischemia and if there is a myocardial scar or prior infarction, then one needs to assess the viability of the myocardium. Viable myocardium suggests hibernating myocardium due to chronic stable angina/ischemic heart disease, and is considered an important factor for choosing the option of revascularization. Viability testing of myocardium is commonly performed to estimate whether the myocardium will recover after revascularization be it CABG or PCI. The past studies have demonstrated that identification of viable myocardium increases survival after CABG.[16–18]

The original STICH design was that all recruited patients would undergo viability testing, but the patient enrollment difficulties led to making viability testing optional. In the substudy of the STICH trial 601 patients had viability testing performed, 487 patients had viable myocardium; after a median follow up of 5.1 years, the patients with viable myocardium had a lower death rate than those without viable myocardium(P=0.003), but after multi-variate analysis the difference was not statistically significant. Although there was no significant difference in outcome between medical therapy or CABG in patients with viability, the authors caution that this might be due to the small number of events.[19]

Viable myocardium does not equate to ischemic myocardium; even normal myocardium is viable but not ischemic. This sub-study of STICH trial does not report on whether the viable myocardium was ischemic or not.

At present, however, the summation of this information suggests that under most circumstances of chronic stable angina, revascularizing non-ischemic myocardium that is viable will not likely change the event rates. Patients with increasing degrees of LV dysfunction are more likely to have combinations of normal, ischemic and non-viable myocardium, however, and in the context of global multi-vessel revascularization and deliberate incomplete revascularization, the ability of surgical revascularization to provide an excess of blood flow and perfusion (compared to PCI) may be prognostically important.

Implications for surgical revascularization

Given these findings, what are the ways that the STICH trial results, and the subsequent studies and interpretations, might influence CABG going forward?

Traditional anatomic-based surgical revascularization strategy

For 50 years, CABG has been based on the anatomic 'roadmap' determined by the conventional coronary angiogram performed preoperatively, where it is typical to bypass all lesions with ≥50% or ≥70% stenosis. The application of this strategy in the absence of functional evaluation might account for the absence of an outcome effect in STICH. In FAME, of 1229 lesions with ≥50% anatomic stenoses, 513 lesions (41.7%) were not hemodynamically significant. In angiographic lesions between 50% and 70%, 65% were not significant.[20] Among the 115 patients classified by angiography in this trial as 3 vessel disease only 14% had hemodynamically significant 3 vessel disease and 9% had no hemodynamically significant lesions.[20] This underscores the inability of angiography to identify a hemodynamically significant lesion. Since angiography was the reason for referring these patients for CABG, perhaps CABG should not be expected to benefit the 37% of STICH patients without a significant amount of ischemia present.[21]

The importance of functional assessment in revascularization is becoming well-established in PCI revascularization, and this will continue to have important, and perhaps increasingly important, implications for surgeons and CABG. For example, in the 4-year results from the SYNTAX trial, mortality alone has emerged as a statistically significant discriminator between CABG and PCI in the high-tercile group, along with overall major adverse cardiac or cerebral events. SYNTAX was an anatomically-based revascularization trial for both CABG and PCI, and therefore, this difference in mortality cannot be attributed to anatomy; something else besides anatomy must be influencing this difference in

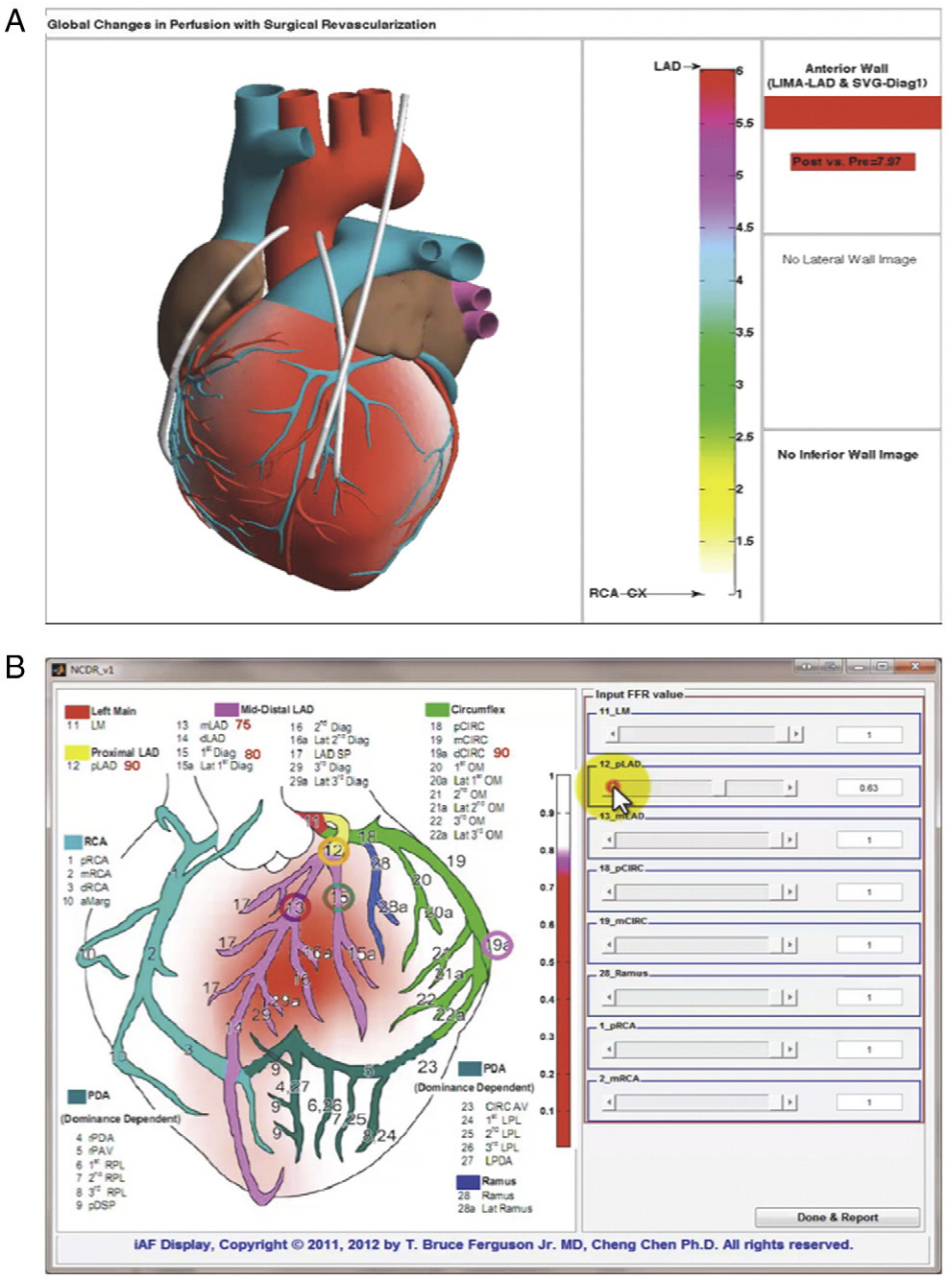

Fig 1 – Panel A. Functional Syntax display of SYNTAX anatomy score, plus functional FFR data integrated into a single software framework. The location and intensity of the red blush correspond with the degree of perfusion deficit documented by preop FFR of the LAD/Diag. Panel B. Real-time, 3-D illustration of the CABG result in the same patient in panel A. Here, the three grafts are depicted (Lima to LAD, Radial to DIAG1, SVG to RCAPD). The quantified change in myocardial perfusion as a result of bypass grafting is also shown, with a significant increase in the anterior wall supplied by the LAD and Diag target vessels, and no change in perfusion with grafting to the RCAPD. All grafts were imaged as widely patent angiographically. *Abbreviations:* LAD = left anterior descending coronary artery; Diag = diagonal branch of the LAD; SVG = saphenous vein graft; RCAPD = right coronary artery posterior descending.

outcomes. It may be that in these sicker patients with more severe anatomic disease, there is a greater degree of ischemia as well, and that CABG does a better, more sustainable job of relieving that ischemia over time than PCI. The emerging concept of a "functional syntax score" as a better indicator for revascularization is appropriate in this context.

The potential opportunity and importance of intraoperative evaluation in CABG surgery

The introduction of functionality into the CABG lexicon also suggests that strategies for intraoperative evaluation of the quality of revascularization should be re-evaluated. Surgeon

judgment that 'the graft is ok,' transit-time flometry, and intraoperative conventional angiography in the hybrid OR setting all lack one or more components of both anatomic-based (angiographic patency) and functional-based (relief of ischemia) evaluation of CABG.

We have utilized and built upon the technology of Indocyanine Green Near-Infrared Fluorescence Complex Angiography and Perfusion Analysis in over 500 patients at the East Carolina Heart Institute. In all grafts to all patients, the CAPA platform is used to assess intraoperatively both the bypass graft technical result (by angiography) and the functional result, by documenting and quantifying the relief of ischemia (preop stress/MRI) and/or degree of perfusion deficit (by FFR), as a result of the change induced in the target vessel regional myocardium by bypass grafting. We are now correlating this quantified intraoperative change in perfusion with the preoperative amount of regional ischemia/perfusion deficit, as shown in Fig 1. This technology holds the potential to provide intraoperative validation of the expected result of target vessel grafting, based on the expectation of an anatomic stenosis or a functional stenosis in the target vessel.

Other important predictors to improve survival in this ischemic heart disease population who are potential candidates for surgical revascularization include: 1) ICD (implantable cardioverter–defibrillator) placement in ischemic heart disease patients with reduced LV function.[22] In STICH, only 14.9% of the CABG arm compared to 18.6% patients in the medical therapy arm received ICD therapy. Despite this overall low implantation rate for ICD devices in this population, death from cardiovascular cause was lower in the CABG arm; and 2) patients with concomitant mitral disease undergoing valve repair and CABG had better survival, compared to CABG alone or medical therapy.[23] However this observation is being evaluated in the NHLBI Cardiac Surgery Network trials.

Conclusions

The STICH trial addressed the broader role of surgical revascularization in patients with heart failure due to reduced LV systolic function EF ≤35% and less severe CAD. This trial may therefore extend the indication for CABG to 'STICH-like' patients with a minimum of two-vessel CAD, including a left anterior descending stenosis, who are otherwise suitable for surgery and expected to survive >1 year with good functional status.

Included in this evaluation, however, should be assessment of the functional nature of these anatomic coronary stenoses, and if necessary assessment of viability, Patients with these characteristics, even with the depressed LV functional status of STICH patients, should do well with a revascularization strategy that will maximally and sustainably relieve ischemia and/or resolve perfusion deficits.

The benefit–risk balance for CABG in patients without angina/ischemia/documented perfusion deficit, or without viable myocardium, remains uncertain. The available data suggest that in STICH-like patients with >10% dysfunctional but viable LV myocardium, they may be more likely to benefit from myocardial revascularization although unfortunately the STICH design limited the ability to provide a definite answer at this time. Conversely, those with ≤10% would be less likely to benefit, although there may be other indications for surgical intervention (concomitant valve disease, certain anatomic sub-types of left main coronary artery disease). For patients with EF≥35%, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial will test this conditional hypothesis.

As has been clearly demonstrated in all recent major trials, the appropriate therapy assignment for the individual patient between percutaneous coronary intervention and CABG should be made by the Heart Team, including a heart failure specialist, and be based on the extent of CAD, expected completeness of revascularization, associated valve disease, and the presence of co-morbidities. Finally, all patients, regardless of intervention, should receive Optimal Medical Therapy for primary and secondary prevention of coronary artery disease.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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