Integrated coronary revascularization with drug-eluting stents: Immediate and seven-month outcome

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Objective: We sought to demonstrate the safety and feasibility of an integrated coronary revascularization strategy that combines minimally invasive left internal thoracic artery to left anterior descending coronary artery anastomosis with drug-eluting stent implantation to non-left anterior descending coronary artery lesions.

Methods: Over 18 months, 47 consecutive patients with multivessel coronary artery disease underwent thoracoscopic harvesting of the left internal thoracic artery to graft the left anterior descending coronary artery. Anastomoses were constructed by hand, off-pump, and under direct vision through a 4-cm non-rib-spreading, muscle-sparing chest incision. Non-left anterior descending coronary artery lesions were then treated percutaneously using sirolimus- or paclitaxel-eluting stents. Angiographic follow-up was performed in all patients.

Results: Within the first 90 days of hospitalizations, there were no deaths, myocardial infarctions, neurologic events, or wound complications. Forty patients underwent left internal thoracic artery to left anterior descending coronary artery grafting, and 7 patients underwent left internal thoracic artery to left anterior descending coronary artery/diagonal sequential grafting for a total of 54 anastomoses. Angiographic patency scores were FitzGibbon A 96.2% (52/54) and FitzGibbon A + B 100% (54/54). A total of 65 drug-eluting stents were implanted in 61 non-left anterior descending coronary artery lesions of which 49.1% (30/61) were type B2 or C lesions, including 5 left main lesions. Diabetes was present in 53.2% of patients (25/47). At a mean follow-up time of 7.0 ± 4.8 months, the target lesion or vessel repeat revascularization rate was 6.6% (4/61) for drug-eluting stents and 1.9% (1/54) for left internal thoracic artery to left anterior descending coronary artery grafting. One anastomosis required balloon dilation, but no patients have required repeat coronary artery bypass grafting.

Conclusions: Integrated coronary revascularization using drug-eluting stents is feasible and safe. There are sufficient data to justify a randomized comparison of integrated coronary revascularization with standard coronary artery bypass grafting.

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Integrated coronary artery revascularization denotes the intentional combination of coronary artery bypass grafting with percutaneous coronary artery intervention; more specifically, minimally invasive left internal thoracic artery (LITA) to left anterior descending artery (LAD) in conjunction with stenting of non-LAD stenoses. Historically, the primary rationale for integrated coronary revascularization (ICR) or

Abbreviations and Acronyms

DES	= drug-eluting stent
EF	= ejection fraction
endoACAB	= endoscopic atraumatic coronary artery bypass
ICR	= integrated coronary revascularization
LAD	= left anterior descending coronary artery
LITA	= left internal thoracic artery
LV	= left ventricular
PCI	= percutaneous coronary intervention
TLVR	= target lesion repeat revascularization

“hybrid” revascularization has been to decrease the periprocedural morbidity of traditional coronary artery bypass grafting (CABG) in high-risk patients. Since the first report of hybrid coronary therapy by Angelini and colleagues in 1996,¹ there have been 10 published series approaching a collective total of 400 patients.²⁻¹¹ The overall results of these series were recently summarized and discussed by Murphy and colleagues.¹² With the recent introduction of drug-eluting stents (DES) with a lower associated restenosis rate,¹³ integrated coronary revascularization may be a more durable option than previously reported for selected patients with multivessel coronary artery disease. We prospectively collected data on our patients managed by the hybrid approach since its application at our institution.

Materials and Methods**Patients**

During the 18-month period between October 2003 and April 2005, data from 47 consecutive patients undergoing ICR were prospectively entered into a customized database. The group was composed of 34 men (72.3%) and 13 women (27.7%) whose age ranged between 43 and 90 years (mean, 65.6 years). Thirty-nine of the patients had good left ventricular (LV) function (ejection fraction [EF] $\geq$ 50%), 5 had moderate LV function (35%-49%), and 3 had poor LV function ($<$ 35% EF). The preoperative demographic and clinical data are presented in Table 1. The study was approved by the institutional review board of Emory University on May 27, 2005.

Coronary angiograms were jointly reviewed by the operating surgeon and cardiologist before any procedure was performed. All patients underwent endoscopic atraumatic coronary artery bypass (endoACAB) grafting to graft the left anterior descending (LAD) coronary artery (with or without the diagonal coronary artery). Percutaneous coronary intervention (PCI) of the other stenotic lesions generally followed the surgery by 2 to 5 days, but on a few occasions preceded the surgery. Patients were considered suitable for ICR if the LAD was considered graftable and the non-LAD stenoses were approachable by stenting.

Contraindications to Integrated Coronary Revascularization

The following patient characteristics were considered contraindications for the endoACAB procedure: a nongraftable LAD, a

TABLE 1. Demographic and clinical baseline characteristics

Patient characteristics (n = 47)	Value	(%)
Age (y) $\pm$ SD	65.6 $\pm$ 11.15	—
Age (y) range	43-90	—
Male/female ratio	34/13	—
Smoking	17	36.2
Body mass index $\pm$ SD	31.3 $\pm$ 2.9	—
Severely obese: BMI $\geq$ 35	9	19.1
Diabetes	25	53.2
Hyperlipidemia	30	63.8
Hypertension	28	68.3
Chronic pulmonary disease	7	14.9
Chronic renal failure	5	10.6
Peripheral vascular disease	11	23.4
Cerebrovascular disease	6	12.8
LV ejection fraction $\pm$ SD	51.2 $\pm$ 7.9	—
Prior myocardial infarction	14	29.8
Prior intervention		
PCI	6	12.8
CABG	1	2.1
LAD lesion		
Type A	0	0.0
Type B1	3	5.6
Type B2	12	22.2
Type C	39	72.2
Coronary artery disease		
2-vessel	29	61.7
3-vessel	18	38.3
Left main	5	10.6
Angina class (CCS)		
I	7	14.8
II	12	25.5
III	24	51.1
IV	4	8.5

SD, Standard deviation; BMI, body mass index; LV, left ventricle; PCI, percutaneous coronary intervention; LAD, left anterior descending; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society.

previously used LITA, previous thoracic surgery involving the left pleural space, chronic lung disease with a forced vital capacity at 1 second of less than 1.0 liter, and a body mass index greater than 45. The following non-LAD lesion types were believed to be contraindications to PCI as part of the ICR approach because of the high predicted restenosis rate or technical complexity: chronic total occlusions, long lesions requiring multiple stents, a coronary vessel less than 1.5 mm in diameter, saphenous vein graft lesions, or the presence of fresh thrombus. A creatinine level greater than 2.0 was also considered a relative contraindication to ICR.

Procedures

The technical aspects of the endoACAB procedure have been discussed in detail but will be outlined briefly here.^{14,15} The overall objective of the endoACAB procedure is to graft the LAD, and on occasion, the diagonal artery, through a fairly atraumatic approach. The patient is induced under general anesthesia, and a

TABLE 2. Graft patency scores

Graft procedure	Patients	Anastomoses	FitzGibbon scores		
			A	B	0
LITA to LAD	40	40	38	2	0
LITA to LAD and diagonal	6	12	12	0	0
LITA to LAD ×2	1	2	2	0	0
Total	47	54	52	2	0

LITA, Left internal thoracic artery; LAD, left anterior descending.

double-lumen endotracheal tube is inserted for left lung isolation. With the left lung collapsed, the LITA is harvested thoracoscopically using three 5-mm incisions along the left anterior and mid-axillary lines. A 5-mm, 0-degree telescope with a 3-chip camera (Karl Storz Endoscopy-America, Culver City, Calif) is placed in the fifth intercostal space through a 5.5-mm port (Snowden Pencer, Tucker, Ga). Carbon dioxide insufflation is introduced through the port's side arm at an intrathoracic pressure of 8 to 10 mm Hg. For right-handed surgeons, the endoscopic grasper (Estech, Danville, Calif) is inserted in the seventh intercostal space without a port and a long, monopolar electrosurgery pencil with accompanying smoke evacuator (Valleylab, Boulder, Colo) is placed in the third intercostal space, also without a port. The LITA is harvested from its origin from the left subclavian artery to the bifurcation at the level of the sixth rib. The pericardium is opened vertically over the main pulmonary artery following the anticipated course of the LAD. A long spinal needle is then placed through the anterior chest wall to identify the exact skin location of the patient's LAD. Proper identification of the LAD and subsequent selection of the skin incision allows the surgeon to subsequently perform the anastomosis without rib spreading. In all patients, unfractionated heparin (400 IU/kg body weight) is administered intravenously. The LITA to LAD ± diagonal anastomosis is constructed using commonly adopted off-pump techniques. The preexisting LITA harvesting ports serve as the entry points for an epicardial stabilizer (Guidant, Santa Clara, Calif; Estech, Danville, Calif; Medtronic, Minneapolis, Minn) and carbon dioxide mister/blower (Medtronic). Intracoronary shunts are used selectively. Transit-time Doppler (Medi-stim AS, Medtronic) examination of the anastomosis is performed to verify graft patency.¹⁶ Patients are extubated in the operating room or immediately on arrival to the recovery unit whenever possible.

The order of the 2 procedures (endoACAB and PCI) is largely determined by the patient's coronary anatomy and is a joint decision between the surgeon and referring cardiologist. Most patients undergo the surgical procedure first because of the logistical issues relating to anticoagulation. The patient is administered 81 mg of enteric-coated aspirin daily before operation. Four hours after the endoACAB procedure, the patient is started on clopidogrel 75 mg daily. The PCI with stenting is usually performed in the same hospitalization within 48 hours of endoACAB. Depending on the patient, PCI may be delayed, with the patient returning several weeks later.

All patients underwent angiographic examination of the LITA to LAD ± diagonal grafts. Before stenting, patients received either unfractionated heparin (100 IU/kg body weight) or the appropriate

Figure 1. Comparison of lesion type between bypass grafts (LAD distribution) and stents (non-LAD distribution).

dose of bivalirudin intravenously. If patients were not already receiving a maintenance dose of clopidogrel, they were administered a loading dose of 300 to 600 mg. Platelet glycoprotein IIb/IIIa receptor inhibitors were given at the discretion of the operator. Patients received lifelong aspirin and clopidogrel for at least 3 to 6 months after DES implantation. All coronary bypass grafts and dilated coronary vessels, before and after stenting, were scored using computer processing of still images in multiple planes.

Clinical Definitions and Follow-up

A complete follow-up was performed in all 47 patients either by telephone or in-person with April 30, 2005, as the end point. Hospital and clinic records were reviewed from Emory University and outside treatment centers as appropriate. The mean follow-up period was 7.0 ± 4.8 months. Angiographic follow-up beyond the initial procedure was obtained only if clinically indicated and was not routinely performed in all patients. The events analyzed in the follow-up report included death (cardiac and noncardiac), myocardial infarction (Q-wave and non-Q-wave), neurologic event (cardiovascular accident or transit ischemic attack), restenosis, stent thrombosis, and target lesion or vessel repeat revascularization (TLVR). TLVR was defined as the need for repeat revascularization, either surgical or percutaneous) secondary to stenosis 50% or greater within the stent, anywhere within the graft or anastomosis, or within 5-mm borders proximal or distal to the stent or anastomosis at the follow-up angiogram. Major adverse cardiac events were defined as death, myocardial infarction, and TLVR.

Results

EndoACAB preceded stenting in 42 of 47 patients (89.4%) with a mean interval between procedures of 3.5 ± 1.3 days. In the 5 patients (10.6%) undergoing PCI first, the endoACAB procedure was performed while the patient remained on full-dose clopidogrel during a separate, later hospitalization. The mean time from PCI to endoACAB for these patients was 71.7 ± 41.1 days. Forty of the total 47 patients had a LITA to LAD graft. Six patients received a LITA to LAD and diagonal sequential graft, and 1 patient received a sequential LITA to 2 locations on the LAD. A total of 54

anastomoses were constructed in 47 patients. The angiographic patency scores for the coronary bypass grafts were FitzGibbon A of 96.2% (52/54) and FitzGibbon A + B of 100% (54/54), with the complete data provided in Table 2.

The types of coronary lesions treated are illustrated in Figure 1. Coronary lesions treated surgically tended to be complicated, whereas stented lesions were more uniformly distributed between the continuum of lesion types. A total of 65 stents (41 paclitaxel-eluting [63.1%], 23 sirolimus-eluting [48.9%], and 1 bare metal stent [1.5%]) were implanted in 61 non-LAD coronary lesions (mean of 1.1 stents per lesion and 1.4 stents per patient) of which 49.1% (30/61) were type B2 or C lesions, including 5 left main lesions. Review of the angiograms from all 47 patients revealed that all but 2 patients (95.7%) were completely revascularized. The 2 patients who remain incompletely revascularized are an 82-year-old woman with an untreated 80% obtuse marginal lesion and a 68-year-old man with an untreated 70% left ventricular branch, both of whom were elected by their cardiologists to treat medically.

The predicted mortality for standard CABG for the entire cohort of 47 patients was calculated at a mean risk of 5.8% + 6.1% (range 0.6%-33.7%) using the Society of Thoracic Surgeons risk model.¹⁶ The risk of permanent stroke was estimated to be 4.1% + 2.9%. Two patients had bleeding into the left pleural space requiring a second chest tube insertion and a blood transfusion. Neither of these patients required reexploration. Two patients had postoperative pericarditis that responded well to oral steroids. Thirty-nine patients (83.0%) were extubated within 90 minutes of the conclusion of the operation. The in-hospital transfusion rate was 19.1% (9/47). New-onset atrial fibrillation occurred in 7 of 45 patients (15.6%). The mean hospital length of stay starting from the day of the first procedure was 4.1 ± 1.8 days (range 3-17 days).

Clinical follow-up was available in all patients. The cumulative major adverse cardiac events rate was 10.6% (5/47). Four cases of TLVR occurred: edge restenoses (3 cases) and in-stent restenosis (1 case). Each case was treated by repeat stenting using DES. The 1 case of TLVR occurred in a patient 2 days after endoACAB during angiography for the planned PCI of the non-LAD lesions. The patient was found to have a 70% stenosis at the site of the LITA to LAD anastomosis, which was ballooned open using 2 atmospheres of pressure without the need for stenting.

Conclusions

The rationale for choosing integrated coronary revascularization over PCI or CABG alone stems from a number of observations: (1) the mean age and risk score of patients with multivessel coronary artery disease continues to increase every year;¹⁷ (2) the LAD is, arguably, the most important of the 3 coronary branches, supplying 50% to

60% of the ventricular mass and twice the mass of the circumflex or right coronary distributions; (3) the LITA has been clearly shown to be more effective than PCI with respect to event-free survival, relief of angina, and long-term patency;^{18,19} (4) conventional bypass surgery carries multiple potential complications attributed to both the sternotomy and the use of the cardiopulmonary bypass circuit, including neurocognitive impairment;²⁰ (5) the early restenosis rate of non-LAD vessels after PCI (using DES) may not be significantly different from the early occlusion rate of saphenous vein grafts. Perrault and colleagues²¹ found the 3-month occlusion rates of saphenous vein grafts to be between 14.8% and 15.6%. Similar results were found by Yun and colleagues²² with vein graft occlusion rates between 17.6% and 21.7% at 6 months.

The present report has some limitations: (1) It is a retrospective study, (2) not all patients have had midterm angiographic follow-up, and (3) clinical follow-up is limited to 7 months. Despite these limitations, this report represents a large cohort of patients with multivessel disease treated with ICR using DES. The main findings that can be drawn from this report are as follows:

- Combining DES with endoACAB seems to be safe and efficacious in early follow-up. Similar to off-pump coronary artery bypass surgery performed through a sternotomy, the avoidance of cardiopulmonary bypass seems to be an advantage in many subgroups of patients with certain comorbidities, namely, peripheral vascular disease, renal insufficiency, advanced age, diabetes, and poor ventricular function.²² In addition, endoACAB does not involve any manipulation of the aorta; the reported incidence of cerebrovascular complications is less than 1%.²⁻¹¹ Unlike off-pump coronary artery bypass surgery, however, endoACAB inflicts considerably less chest wall trauma. There is no division of bone or major thoracic musculature, which can cause considerable disability and pain after a sternotomy or traditional anterior thoracotomy. The fact that the incision is essentially a large thoracoscopy port provides an extremely low risk of wound complications particularly for the obese or diabetic patient. The procedure-specific morbidity associated with the traditional minimally invasive direct coronary artery bypass has not been seen with the endoACAB procedure.²³
- ICR can be safely performed in either sequence of procedures. In our experience, we prefer to graft the LAD first, to avoid operating on the patient on full-dose clopidogrel. However, in the 5 patients (10.6%) undergoing PCI first, intraoperative or postoperative bleeding was not increased. In each of these cases, the patients presented with a greater than 95% lesion of a large, dominant RCA. Revascularization of the RCA

before the LAD seemed to be the safer approach. It is conceivable that patients could undergo simultaneous LITA to LAD grafting and stenting of the non-LAD targets in a "hybrid" catheterization/operating room. At the completion of the anastomosis, the clopidogrel could be loaded, recognizing that surgical hemostasis could be achieved before the full anticoagulation effects were seen clinically.

- The hybrid approach may be the preferred approach in patients with coronary artery disease too complicated for multivessel PCI or patients with comorbidities too extensive for low-risk conventional bypass surgery. In our series, 23% of the patients (11/47) had a Society of Thoracic Surgeons predicted mortality of more than 20% and a predicted risk of stroke of 10% to 20%.
- The rate of TVR for DES of the non-LAD coronary arteries in this series compares well with the reported outcome data of the randomized clinical trials of DES versus bare metal stents, particularly when the high incidence (53.2%) of diabetes in our series is considered. In addition, a rough comparison of our cohort of 47 patients with the patients in the Sirius and Taxus I and II trials reveals a slightly more complex lesion set, signifying low DES TVR rates with even "real-world" lesions.²⁴⁻²⁶ Previously a significant limitation of the ICR approach, the DES TVR results present a more compelling argument for the hybrid concept.

At present, most centers are not performing hybrid coronary revascularization or are treating less than 5% of the population with coronary artery disease using this approach. If the ICR approach to coronary artery disease intervention is to grow, several key issues will need to be resolved. At present, the total cost of the hybrid procedure exceeds the cost of CABG in most centers, although presently, hospitals are able to collect reimbursement to cover the additional costs. Performing more procedures and further integrating the catheterization laboratory with the operating room, either as a combined procedure room or with coordinated protocols, is likely to drive efficiency. In addition, the hybrid procedure may be economically viable if it results in lower postprocedural adverse events and reintervention rates. Despite the lower restenosis rates of DES, the ICR approach is limited by the presence or absence of coronary anatomy amenable to stenting. Chronic total occlusions, long lesions requiring multiple stents, the presence of diabetes, vessels less than 1.5 mm in diameter, and bifurcation lesions continue to be problematic for the interventional cardiologist.

In summary, integrated revascularization requires close collaboration between the cardiologist and the surgeon because careful planning of the strategy and timing are necessary. The potential advantages of the hybrid approach are reduced short-term clinical events, such as death, stroke,

myocardial infarction, and infection, as well as a superior quality of life as a result of a quicker return to a "normal" lifestyle. The potential disadvantages of ICR are a higher propensity to incompletely revascularize the patient, a higher reintervention rate related primarily to stent restenosis, the cost of the procedure, requiring the use of both operating room and catheterization laboratory resources, and the possible negative effects on the long-term survival of these patients.²⁷ The procedure also requires special expertise in the endoACAB operation or in a similar minimally invasive bypass operation. However, without data from a large prospective, randomized trial comparing conventional bypass surgery with the hybrid approach, the potential advantages and disadvantages of ICR remain theoretic and largely unproven.²⁸

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Discussion

Dr. Cohen. Tom, that was a nice paper and I enjoyed reading your manuscript. I also really enjoyed seeing a video of your procedure recently on the surgical forum and would certainly recommend it to anybody who is interested in this operation.

The concept of the integrated coronary artery revascularization, the so-called hybrid operation, has been around for sometime. It offers the combination of a truly minimally invasive internal mammary artery to the LAD followed by drug-coated stents in any remaining lesions to achieve complete coronary revascularization. Dr. Vassiliades and his group are to be congratulated for their success with the endo-ACAB operation and for their excellent short-term clinical results. Having said that, one can't help but wonder where this procedure will take its place in the continuum of coronary revascularization procedures. After all, it requires learning specialized and new surgical skills, increased collaboration between cardiologists and cardiac surgeons, the potential for two or more hospitalizations, and as you've said followup is

extremely short. Now the rationale for this operation is based on some important assumptions that I'd like to discuss. The first is that a minimally invasive non-rib spreading left anterior approach with an off-pump anastomosis carries considerably less morbidity than an on-pump operation via sternotomy incision in selected patients. I agree with that. It's also suggested that this may be extremely suitable for high-risk patients. In fact, the predicted mortality for standard CABG in this study's cohort was a mean of 7.8% using the STS risk model. I thought that was pretty high and that brings me to my first question. When I looked at the demographics of your patient group, they actually seemed to be pretty typical or actually even low risk. The mean age was 65. The mean ejection fraction was 51%. Sixty percent of your patients had two-vessel disease, and you had what I thought to be the usual amount of diabetes, hypertension, pulmonary disease, cerebrovascular disease and renal failure. Given . . . (end of cassette) . . . and for heart surgery candidates, candidates for this operation, aren't they patients who actually have less coronary disease than most of the patients that we see for coronary bypass grafting?

Dr. Vassiliades. Well, to speak to the STS model, I was a bit surprised too. As you know, if you go to the STS website, you can interactively use their risk model and this is the data that was entered and this is the information we got, so I really don't what else to say about that other than it does seem pretty high to me as well. You wouldn't expect an 8% predicted mortality on that group of patients. So I don't necessarily make any claims that clearly there is improvement in mortality. We are just at this point demonstrating that it can be performed safely.

The second part of your question related to, don't these patients really have less coronary disease. I think that if you look, 60% of the patients only had two-vessel disease. I think because we are early in exploring the logistics of dealing with drug eluting stents, given the special anticoagulation needs of that particular stent, that we tended to be more conservative and I think that as we are moving along we are becoming much more aggressive and the cardiologists are becoming much more aggressive in feeling comfortable in proceeding with more complicated lesions. I think that as part of an early study, yes, we deliberately selected patients that had perhaps two-vessel or less complicated coronary artery disease with respect to stenting.

Dr. Cohen. Another assumption that you made in your manuscript, and it was an important one in justifying this procedure, it says the early patency rate of drug eluting stents in non-LAD lesions is no longer significantly different than that of saphenous vein grafts. This justified the use of PTCA for revascularization of non-LAD vessels in your series. The manuscript references the Barry(?) trial which was performed in the early 1990s, published in 2000, well before drug eluting stents became available. I really couldn't find a reference in that reference that really compared the patency rate of stents with vein grafts. Is there really current data which accurately compares the performance of drug eluting stents with that of current saphenous vein grafting techniques?

Dr. Vassiliades. No, there is not, and that is one of the tremendous pieces of information that could be gained by doing a randomized trial. There is a study ongoing that is being funded by Boston Scientific looking at drug eluting stenting in all three vessels compared to standard bypass surgery and we'll get some of that information, but the assumption there is a very broad one.

There has never been a head to head comparison. One generally is aware of the fact that the occlusion rate of vein grafts varies anywhere from 10 to 20% in the first year and then looking at the two-year data of the _____-4 results showing somewhere in the 10 to 12% range, but again these are apples and oranges. The lesion sets are different.

Dr. Cohen. Finally, yesterday in his president address our president described what he called the hope cycle for emerging technology and I thought that this procedure fit very nicely, where there is sort of a technology trigger and then you get this peak of inflated expectations followed by a trough of disillusionment. My concern is that this is an operation which, though innovative, is only applicable to a small number of patients with complex LAD disease and maybe a couple other coronary lesions. So having sort of put yourself in the middle, what's your strategy for convincing surgeons that we should stop short of completely revascularizing patients ourselves and at the same time for convincing interventional cardiologists that they can keep us in the loop at all?

Dr. Vassiliades. I think the data are there. The problem is that we are operating in a world where not everyone necessarily practices the way the data have directed us to practice and I think that there is little disagreement of the benefit of LIMA to the LAD and you could argue that is probably one of the last things that the surgeon has to offer in terms of revascularization surgery, so let's

not get rid of that. Let's just improve that operation and make it less traumatic. That's the reason patients are not necessarily being referred for surgery. It's not just the cardiologists. Patients are sort of demanding less invasive procedures. Now does that mean we should alter our procedure based on what the physical therapy wants? Well, it also has to do with whether or not we think it's right for the patient. I think it's just a difference of opinion. I think that this is a perfect opportunity to build a niche and create a much larger niche in terms of revascularization in an area in many places that is rapidly dying off and I think the LIMA to the LAD should be preserved and such ways to be able to make it better and I think given the fact that most patients are presenting with three-vessel disease, I think the hybrid approach is a very good way to explore it, but really the driving mechanism has to be good data. If we can some day get funding for a good randomized trial, I think that would help a lot.

Dr. Cohen. I think one thing that is for certain is your results are excellent. As long as you can continue to show excellent results with anything that you do as innovative you are going to have a good chance.

I really appreciate it and I appreciate the opportunity of the floor.

Dr. Vassiliades. Thank you for your comments.

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