

EVALUATING THE APPROPRIATENESS OF CORONARY REVASCULARIZATION PROCEDURES AT HADASSAH HOSPITAL: ADHERENCE TO CLINICAL PRACTICE GUIDELINES

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INTRODUCTION

Coronary revascularization procedures have proven to be life-saving for some patients and have revolutionized the treatment of cardiovascular disease¹. With the technology of these procedures improving rapidly, the choice of which method to use is becoming a harder one. Although some patients will clearly benefit from one procedure over another, several indications are less apparent and each procedure offers its own advantages and poses its own set of risks^{2,3}. In recent years, following trends in the United States, the number of coronary artery bypass graft (CABG)♦ operations performed at Hadassah University Hospital has declined in favor of percutaneous coronary intervention (PCI). In the United States in 2003, 664,000 PCI procedures and 467,000 CABG operations were performed. Rates of CABG surgery in the United States have steadily decreased since 1995, while rates of PCI procedures increased by 326% between 1987 and 2003.⁴

♦Table 1 - List of commonly used abbreviations

CABG – coronary artery bypass graft

LAD – left anterior descending

LM – left main

MI – myocardial infarction

PCI – percutaneous coronary intervention – refers to balloon angioplasty with and without the insertion of intracoronary stents

PTCA – percutaneous transluminal coronary angioplasty – refers to balloon angioplasty without the insertion of intracoronary stents

At Hadassah, before local guidelines for coronary revascularization were developed in 2004, according to senior doctors, the decision as to which procedure to use when both were technically feasible, was made according to ACC/AHA guidelines from 1999 for CABG and from 1993 for PTCA. Adherence to these guidelines has never been assessed and the subsequent technological advances in these procedures have necessitated the creation of new guidelines that incorporate the latest studies and levels of evidence. Hadassah Hospital's recently-developed clinical practice guidelines provide specific indications for each procedure and ensure that correct care is given to every patient.

This study evaluates the appropriateness of coronary revascularization procedures performed at Hadassah Hospital as judged by adherence to the 2004 clinical practice guidelines. Appropriateness studies are one method of detecting and eliminating underuse, overuse and misuse of medical procedures⁵. Underuse of proven effective treatments leads to missed opportunities to improve health and function and may even lead to preventable deaths⁶. A previous study demonstrating adverse effects as a result of the underuse of cardiac revascularization – both surgery and angioplasty – found that among patients who were considered candidates for coronary-artery revascularization but who received medical therapy instead, there was an increased incidence of death and of nonfatal myocardial infarction⁷. Among patients who were considered candidates for angioplasty but who received medical therapy instead, there was an increased incidence of angina at 30 days. The study showed that revascularization was not performed in about 30 percent of patients who were considered candidates for it.

Overuse occurs when the potential for harm exceeds the potential benefit of the procedure and misuse occurs when an appropriate treatment has been selected but

the patient undergoes a preventable complication. Reducing overuse spares patients the unnecessary risk involved in a procedure and reduces costs. Lowering the incidence of misuse improves quality of care by preventing complications and related costs.

There are several methods to assess the appropriateness of use of a procedure. The most accurate method evaluates the outcomes of applying that revascularization procedure for any given indication at a specific point in time.⁸ If the possible benefits (prolonged life, cure of disease, pain alleviation) sufficiently outweigh the risks (mortality, peri-procedural complications, pain) of a procedure, then performing that procedure is considered appropriate.⁹ Outcome studies strive to provide complete and consistent evidence for the risks and benefits of any treatment for any given indication, but they are frequently outdated by the time the results emerge and the data often lags behind technological advances. In addition, results of outcome studies often conflict, the conditions under which studies are carried out and the selection of patients vary, and findings in one population may not be generalizable to another. Additionally, outcome studies provide weaker evidence than randomized clinical trials, due to the difficulty in eliminating biases.

An alternative method is based on expert consensus. This method asks experts to decide which procedures are most appropriate for specific clinical scenarios after they have reviewed the available information. This method is limited by the available outcome data and its use of subjective opinions, but helps clarify which treatments are most appropriate for individual patients at a given point in time. It is efficient and comprehensive and the recommendations are applicable for the time they are rendered.

This study incorporates both of these methods by measuring appropriateness as determined by adherence to guidelines. The development of clinical practice guidelines is one method of improving appropriateness ratings by providing recommendations from specialists that are directly based on evidence. Guidelines are a product of expert consensus (among cardiologists and cardiac surgeons) and are based on randomized controlled trials, as well as available outcome data. With the enormous advances in outcomes research in the past few years, developing and assessing adherence to clinical practice guidelines explicitly linked to evidence have become valuable tools for improving quality in medicine.¹⁰

The first studies measuring appropriateness rates of CABG and PCI were intended to identify the possible overuse of CABG surgery¹¹. Since then, the improvements in PCI techniques and medical therapy have significantly changed the picture. With the decline in the number of CABG operations performed in recent years, cardiothoracic surgeons at Hadassah have raised the question as to whether there is an underuse of this procedure. Frequently, they claim, the decision as to which revascularization procedure to use is made when the patient is in the midst of undergoing diagnostic angiography and the choice is presented with an automatic bias in favor of PCI. In response, following suggestions by the director-general of Hadassah, a committee was appointed to draft coronary revascularization guidelines. This study, which evaluates adherence to these guidelines, provides valuable information regarding the prevalence of inappropriate use of these procedures as well as risk factors for inappropriateness and constructive feedback on how to improve the standard of care at Hadassah.

MATERIALS AND METHODS

I. STUDY DESIGN

This is a descriptive prospective observational study that evaluates a cohort of 318 patients who underwent left-sided cardiac catheterization at Hadassah Hospital in Ein Kerem from the period of January 17, 2005 until March 8, 2005. Excluded from this study were pediatric patients, patients undergoing right-sided heart catheterizations and patients who had previously undergone coronary artery bypass graft surgery who had catheterizations in this period. Treatment decisions for patients who are status-post CABG surgery are very individual and take into account the patient's specific anatomy, prior surgical complications and other variables not included in the guidelines and were therefore excluded from this study. Among patients who underwent both right and left-sided heart catheterizations, the left-sided heart catheterization was included in the study.

A total of 363 consecutive cardiac catheterizations were performed between January 17 and March 8, 2005. Of those, 45 catheterizations were excluded from this study for the following reasons: 26 patients had previously undergone CABG operations, 10 patients underwent right-sided heart catheterizations only, 6 were pediatric patients (six years-old and under) and 3 patients underwent repeat angiograms – as follow-up or for the treatment part of a previous angiogram in the same period. In cases of repeat angiograms for treatment, only one angiogram during this period was included in the study.

The primary outcome measure in this study is the percentage of patients undergoing diagnostic coronary angiography who were referred for coronary revascularization procedures deemed appropriate and inappropriate. The study also assesses the risk factors for inappropriate procedures.

Revascularization procedures include CABG surgery performed by cardiothoracic surgeons and PCI, i.e. balloon angioplasty, with or without bare-metal or drug-eluting intracoronary stents, performed by interventional cardiologists.

This study is intended to improve the quality of medical care in Hadassah and carries the approval of the Helsinki committee. In addition, it has been approved by the heads of the departments of cardiology, cardiothoracic surgery and the director-general of Hadassah Hospital.

II. DEVELOPMENT OF GUIDELINES

Experts in cardiology, cardiothoracic surgery and the chairman of the quality and safety committee in Hadassah Hospital jointly drafted guidelines for appropriate use of revascularization procedures based on review of the literature, evidence-based medicine and ACC/AHA Guidelines. These guidelines present a set of clinical scenarios or indications for use of CABG and PCI. Each indication takes into account clinical information, coronary anatomy according to angiography and other non-invasive cardiac imaging results as well as technical considerations. The definitions for terms in the indications accompany the text. The guidelines include levels of evidence for every indication for revascularization. They were reviewed, edited and approved by the staffs of both the cardiology and cardiothoracic surgery departments. The final version of the guidelines is included in the Appendix at the end of the paper.

III. APPROPRIATENESS RATINGS

Appropriateness is defined as choosing a procedure whose benefits (prolonged life, better quality of life) outweigh its risks (death, procedure-associated morbidity) according to latest evidence in the literature. Inappropriateness is defined as choosing

a procedure despite the fact that another procedure may have a better outcome according to evidence. A procedure was considered inappropriate if its risks outweigh its benefits. Because this study is based on adherence to guidelines, appropriateness was determined by the degree of adherence to guidelines and was scored on a scale of 1 to 5 as follows:

1- Complete adherence to guidelines.

2- Adherence to guidelines in cases where both revascularization procedures apply.

That is, in cases where the evidence does not support a specific recommendation and requires individual consideration for each patient, the guidelines leave room for either revascularization procedure. In these cases, either revascularization procedure performed would be considered appropriate.

3- Deviation from guidelines for medical reasons. This includes patients with comorbidities and/or advanced age who may benefit from less invasive procedures despite the recommendation of the guidelines. In these cases, clinical judgment was used to determine the correct treatment for every patient.

4- Deviation from guidelines due to patient preference. In cases of patient refusal of the procedure recommended by the guidelines, there is a deviation from the literal guidelines regarding the actual procedure used, though the choice is compatible with the Patient's Rights Law.

5- Complete deviation from guidelines, without notable reason.

Ratings of 1, 2, 3 and 4 were considered "appropriate" use of a procedure in a given case and a rating of 5 was interpreted as "inappropriate" use of a procedure in a given case. Although in cases where patients chose a procedure not recommended by the guidelines (ratings of 4), the medical risks may outweigh the benefits, these cases

were counted as appropriate to signify the importance of patient autonomy in treatment decisions.

IV. ASSESSING ADHERENCE TO GUIDELINES

Patients' catheterization reports and discharge letters were evaluated to determine adherence to guidelines. Each file was analyzed for the following variables: patient presentation and symptoms, number and type of coronary arteries involved, characteristics (location and complexity) of lesions, whether previous procedures were performed on the involved lesions and whether the patient suffered from diabetes mellitus or renal failure. Renal failure was determined by elevated levels of serum urea and creatinine (cases of only proteinuria were not counted). In relevant cases, evidence of ischemia in cardiac scans (reversible filling defects) and left ventricular function per echocardiogram or ventriculography were assessed. In cases where left ventricular function was unknown, it was assumed to be normal. In addition, demographic information was obtained such as gender and age. Based on the information obtained from the records each case was assigned an indication. The treatment decision was then interpreted as appropriate or inappropriate according to the indications in the guidelines.

The involvement of coronary arteries was determined as follows: significant stenosis of the left main artery was defined as narrowing of over 50%. Stenosis of all other coronary arteries was defined as narrowing of 70% or more. The number of vessels involved was defined by the four major coronary arteries: the left main (LM), left anterior descending (LAD), left circumflex and right coronary arteries. Stenoses (to the degree defined above) in any branches of the LAD, circumflex and right coronary arteries were considered to be diseases of the arteries themselves. If more

than one branch of only one of those arteries was involved to a significant degree, it was considered single-vessel disease.

In cases of missing information or ambiguity in the catheterization report, the angiogram film was reviewed by an expert in cardiothoracic surgery and the information was obtained based on that review.

Possible biases of this study include selection bias, information bias and Hawthorne bias. To minimize selection bias, all patients undergoing coronary catheterization procedures at Hadassah within a specific period of time were chosen. A provider selection bias may still exist if Hadassah doctors refer patients for revascularization procedures that differ significantly from those undergoing revascularization at other hospitals. As in any study, the Hawthorne bias, in which people perform differently when being scrutinized, must be taken into account.

In addition, the guidelines do not include all possible clinical scenarios. Several patients in the study underwent angiography for an indication that was unspecified in the guidelines. These patients (referred to as status-post myocardial infarction) had myocardial infarctions that underwent spontaneous reperfusion or were treated by thrombolytic therapy and within one month of the infarct, they were referred for angiography. The treatment decisions for these patients were assessed as though they presented as asymptomatic or with mild angina pectoris.

V. STATISTICAL METHODS

The sample population size was calculated using a confidence interval. Assuming an inappropriateness rate of 5%, $n=300$, the 95% CI would be $2.9\% \leq P \leq 8.3\%$, an interval which provides a sufficiently informative and precise estimation.

Studies testing appropriateness rates for CABG and PTCA in New York State have found low overall inappropriateness rates for both procedures.^{12, 13} (2.4% for inappropriate CABG operations and 4% for inappropriate PTCA.) This study postulated a similarly low rate of inappropriate revascularization procedures at Hadassah.

A computer-based algorithm was used to classify the patients into different groups based on presentation, angiogram results, treatment and score of appropriateness. The numbers and percentages of patients in every category, as well as the frequencies and percentages of appropriateness in every category were then calculated. All calculations and analyses were done with SPSS statistical software; charts are used to present some of the results.

RESULTS

318 patients – 251 males and 67 females - were included in the final analysis of the study. The mean age the study population was 61.8 years. 32 CABG operations were performed and 153 patients underwent PCI. (Two patients underwent PCI and then CABG). 51 patients were treated conservatively. 84 patients had normal or patent coronary arteries and no further intervention was required.

The overall inappropriateness rate of treatment for coronary disease in Hadassah for the period of January 17, 2005 - March 8, 2005 is 5.7% (n=18).

Overall ratings and scores of appropriateness are shown in Tables 2 and 3.

Frequencies and appropriateness rates of the various treatments are shown in Table 4.

Table 2 – Appropriateness rating

Rating	Frequency (Percentage)
Appropriate	300 (94.3%)
Inappropriate	18 (5.7%)

Table 3 – Scores of appropriateness of treatment

Score	Frequency (Percentage)
1	271 (85.2%)
2	19 (6.0%)
3	6 (1.9%)
4	4 (1.3%)
5	18 (5.7%)

1 – complete adherence to guidelines

2 – adherence to guidelines when both procedures are appropriate

3 – deviation from guidelines for medical reasons

4 – deviation from guidelines due to patient preference

5 – deviation from guidelines without notable reason

Amongst the 28 patients not treated in accordance with the guidelines (ratings of 3, 4, 5): Six patients (with a rating of 3) were managed according to clinical judgment and not in accordance with the guidelines for medical reasons. Of these, four had triple vessel disease (three were treated conservatively and one was rejected by the cardiac surgeons due to high surgical risk and was treated by PCI); two had

single or double-vessel disease and were treated conservatively due to considerable co-morbidities.

Table 4 – Ratings of appropriateness of treatment

Treatment	Frequency of treatment (Percentage of all patients)	Appropriate* (Percentage)	Inappropriate** (Percentage)
None	84 (26.4%)	84 (100.0%)	0 (0.0%)
Conservative	51 (16.0%)	46 (90.2%)	5 (9.8%)
PTCA	26 (8.2%)	23 (88.5%)	3 (11.5%)
PTCA + stent	125 (39.3%)	116 (92.8%)	9 (7.2%)
CABG	30 (9.4%)	30 (100.0%)	0 (0.0%)
PTCA + CABG	2 (0.6%)	1 (50.0%)	1 (50.0%)

* number (and percentage) of patients treated appropriately within a specific treatment group

** number (and percentage) of patients treated inappropriately within a specific treatment group

Four patients (with a rating of 4) chose PCI or medical therapy instead of the recommended treatment. Of these, one had triple-vessel disease and diabetes and chose PCI; one had stable angina, single-vessel disease, a scan positive for ischemia and reduced left ventricular function and chose medical therapy; one had single-vessel disease, an ostial lesion in the proximal LAD and chose PCI; one had triple-vessel disease involving the proximal LAD with a high risk for PCI and chose PCI.

Eighteen patients were treated inappropriately (rating of 5). Of these, eleven had triple-vessel disease and either diabetes mellitus, renal failure or both and were treated with PCI (four of these patients were status-post MI); three had coronary disease with proximal LAD involvement and a high risk for PCI (two were treated with PCI and one was treated conservatively); two had single-vessel disease, positive scans for ischemia, reduced left ventricular function and were treated conservatively; two had triple-vessel disease and were treated conservatively.

Among the groups of patients presenting with different symptoms the only group with a significantly high rate of inappropriateness is the group of patients undergoing angiography within one month of a myocardial infarction. This set of patients had a 26.7% rate of inappropriate treatment. Frequencies and appropriateness rates according to patient presentation are shown in Table 5.

Among the four patients treated inappropriately in this group (S/P MI): three underwent angiography more than a week after the infarct, were asymptomatic, suffered from diabetes mellitus and triple-vessel disease and were treated by PCI; one underwent catheterization five days after the MI, suffered from triple-vessel disease and diabetes mellitus and PTCA was attempted unsuccessfully. (The patient was subsequently referred to CABG surgery.)

Table 5 – Ratings of appropriateness according to clinical presentation

Presentation	Frequency of presentation (Percentage)	Appropriate* (Percentage)	Inappropriate** (Percentage)
Asymptomatic	53 (16.7%)	51 (96.2%)	2 (3.8%)
Stable angina pectoris	165 (51.9%)	154 (93.3%)	11 (6.7%)
Non ST-elevation acute coronary syndrome	54 (17.0%)	53 (98.1%)	1 (1.9%)
ST-elevation myocardial infarction	31 (9.7%)	31 (100.0%)	0 (0.0%)
Status-post myocardial infarction	15 (4.7%)	11 (73.3%)	4 (26.7%)

* number (and percentage) of patients treated appropriately within a specific presentation group

** number (and percentage) of patients treated inappropriately within a specific presentation group

Among patients with different angiogram results – patients with triple-vessel disease had the highest rate of inappropriate procedures – 21.0% (n=13). Frequencies and appropriateness rates according to angiogram results are shown in Table 6. Most of the inappropriate cases are accounted for by patients with diabetes mellitus or renal failure who were not treated by CABG.

Table 6 – Ratings of appropriateness according to angiogram results

Angiogram result	Frequency (Percentage)	Appropriate* (Percentage)	Inappropriate** (Percentage)
Normal coronaries or insignificant disease	86 (27.0%)	86 (100%)	0 (0%)
Single-vessel disease	99 (31.1%)	95 (96.0%)	4 (4.0%)
Double-vessel disease	71 (22.3%)	70 (98.6%)	1 (1.4%)
Triple-vessel disease^a	62 (19.5%)	49 (79.0%)	13 (21.0%)

* number (and percentage) of patients treated appropriately within a specific angiogram-result group

** number (and percentage) of patients treated inappropriately within a specific angiogram-result group

^a includes patients with triple-vessel disease and LM involvement (n=4)

Risk factors for inappropriate treatment were found in two groups of patients; patients with triple-vessel disease and diabetes or renal failure and patients with proximal LAD disease with a high risk for PCI procedures. A total of twenty patients in this study who presented as asymptomatic or with stable angina pectoris had triple vessel disease and either diabetes or renal failure. Only seven of them were treated with CABG, despite that being the recommended management (65% rate of inappropriateness). Mean ages for those treated with CABG (mean age 62.57) and those treated with PCI (mean age 62.46) were similar, and there was no significant gender difference among the patients treated with CABG and those treated with PCI (p-value 0.452 using the Chi-square test).

Additionally, only ten of seventeen patients who presented as asymptomatic or with stable angina pectoris who had coronary disease involving the proximal LAD

artery with a high risk for PCI (ostial, calcified, totally occluded or long lesions) were treated with CABG surgery (41.2% rate of inappropriateness). Amid the ones treated inappropriately, four were treated by PCI and three were treated conservatively. Again, ages were similar among those treated appropriately (mean age 61.7 years) and inappropriately (mean age 65.4 years) and no significant gender difference was found among those treated by CABG or other treatments (p-value 0.388 using the Chi-square test).

All patients with coronary disease involving the left main artery (n=10) received appropriate treatment.

DISCUSSION

The overall rate of complete deviation from guidelines at Hadassah is not high (5.7%) and is similar to rates found in the literature.^{14,15} Rates of inappropriateness are only high among certain subgroups of patients: patients suffering from triple-vessel disease (21.0%), especially those with co-morbidities, and those with coronary disease involving the proximal LAD (41.2%). A possible explanation for the high rates in these groups is the conflicting evidence and controversial recommendations for these sets of patients, as seen in the literature below.

Outcome studies comparing survival rates among patients with multi-vessel disease who underwent CABG or PCI exhibit contradictory results. One study comparing the incidence of major adverse cardiac and cerebrovascular events (MACCE) amongst patients with multi-vessel disease treated with CABG or stents showed no significant difference in death, stroke or myocardial infarction rates between the groups. However, the incidence of repeat revascularization was significantly higher in the stent group.¹⁶

But in a second study comparing CABG and stenting among patients with two or more diseased coronary arteries, CABG was associated with higher rates of long-term survival as well as less of a need for repeat revascularization.¹⁷ The lack of adherence to guidelines for patients with multi-vessel disease reflects the lack of conclusive evidence for these patients. Previous studies have shown that physicians are more likely to deviate from recommendations in situations where the treatment value is debatable and sometimes, later studies prove their judgment correct.¹⁸

An alternative explanation for the high rate of inappropriate use of PCI is lack of patient involvement in the decision process. Cardiologists are sometimes accused of “self-referral” – as a patient undergoes a diagnostic angiogram, the cardiologist will frequently determine the need for a revascularization procedure and perform the necessary intervention during the same session.¹⁹ The patient is often not in a position to rationally make a decision or consider alternative procedures and cardiothoracic surgeons are not always afforded the opportunity to present surgical options. To avoid this, patients have to be informed of all their choices prior to the diagnostic angiogram and input should be provided by both cardiologists and cardiac surgeons.

There are several limitations to this study. Because it is based on guidelines, problems inherent in the guidelines affect the validity of the conclusions. The guidelines are based on outcome data and randomized controlled trials available for the time they were written. Recommendations are rapidly changing, new outcome studies are constantly being concluded and new recommendations are continuously being published. This study is valuable in assessing appropriateness at a given point in time. As guidelines become outdated, the conclusions of this study become less relevant. Additionally, recommendations based on Level C evidence may lack

sufficient strength to determine appropriateness. Studies have demonstrated that adherence to guidelines improves when the guidelines are based on evidence from clinical trials.²⁰ It is difficult to render a treatment decision inappropriate when the evidence supporting the recommendation is weak.

A further limitation of this study is its reliance on catheterization reports. The results are based on data and angiogram reports written by the cardiologists performing the diagnostic angiography. During analysis of the data, the catheterization films were not reviewed by other cardiologists or by cardiac surgeons. If experts were to re-analyze the films, the angiograms may be interpreted differently, thereby affecting the reproducibility of the results. Studies have shown wide variations in angiographers' assessments of coronary disease that significantly affect treatment recommendations.²¹ Possible ways to avoid this include using computer programs to more objectively quantify arterial luminal narrowing or instituting second independent readings of angiograms before recommending revascularization.²²

To improve the validity of the results, a selection bias was minimized by including all patients undergoing angiography during the selected period of time, with minimal exclusion criteria. National registries indicate that patients at Hadassah are typical of patients undergoing revascularization procedures at other hospitals and the data is therefore comparable to rates at other hospitals. Each hospital has to be individually evaluated for correct appropriateness rates.

Several factors may contribute to the low rates of inappropriateness at Hadassah. First, the development of guidelines at Hadassah might indicate a greater interest in quality assurance and therefore higher appropriateness rates there. Involvement of the staffs of the cardiology and cardiac surgery departments in developing the guidelines also increases the likelihood of higher adherence rates. In

addition, at Hadassah, the decision to perform revascularization is usually undertaken by two cardiologists who review the angiogram prior to the procedure; when CABG is considered an option, a cardiac surgeon also examines the film. These second independent readings lower the chance of misinterpretation of the film and likely lower the rates of inappropriate treatment.

The guidelines primarily discuss invasive revascularization procedures, but just as interventional procedures are rapidly improving, medical therapy for coronary artery disease has drastically improved over the last few years. Breakthroughs in medical therapy have caused it to be the subject of a few studies comparing it as an alternative procedure to PCI. Recent studies have demonstrated that medical therapy alone, in cases of low-risk stable coronary artery disease (1 or 2 major coronary arteries narrowed by >50%, an ejection fraction >40%, and mild to moderate symptoms of angina pectoris) is at least as effective as PTCA in preventing acute myocardial infarction and other major cardiovascular events as discussed below.

In 2003, the second Randomized Intervention Treatment of Angina (RITA-2) studied the long-term effects of PTCA vs. anti-anginal medical therapy. Although symptoms of angina improved after either PTCA or medical therapy, there was no significant mortality benefit for patients undergoing PTCA after seven years of follow-up.²³ Likewise, the Trial of Invasive vs. Medical Therapy in Elderly Patients (TIME) analyzed elderly patients (mean age of 80) with chronic angina who were randomly assigned to coronary angiography with revascularization or medical therapy. After one year, the number of patients with anginal symptoms, death or nonfatal myocardial infarction in both groups was similar.²⁴

These studies demonstrate the fast pace of change in the management of coronary artery disease. Guidelines need to be updated regularly to incorporate the

latest outcome data for all treatment options. Adherence rates may improve with stronger evidence and presentation of all possible treatments.

CONCLUSION

This study found a low overall rate of inappropriate coronary revascularization procedures performed at Hadassah. Risk factors for inappropriate use of procedures were found among specific groups of patients, particularly those with multi-vessel disease. Raising adherence rates includes more thoroughly informing the patients of their treatment options as well as updating guidelines regularly to incorporate the latest outcome data and available evidence.

SUMMARY

Background - Coronary revascularization procedures have proven to be life-saving for some patients and have revolutionized the treatment of cardiovascular disease. Though these procedures are widely employed in Hadassah Hospital, no formal assessment of the appropriateness of their use has been done. With the recent development of clinical practice guidelines, the appropriateness of the performance of these procedures can now be evaluated. Determining appropriateness rates is at the heart of improving quality of medical care and reducing the overuse, underuse and misuse of interventional procedures.

Objective – This study sought to determine appropriateness rates of coronary revascularization procedures performed at Hadassah as measured by adherence to 2004 clinical practice guidelines.

Methods – This is a prospective observational cohort study that includes 318 patients who underwent coronary angiography at Hadassah between January 17 and March 8, 2005. Patient files and angiogram reports were analyzed for the following variables: patient presentation, number and type of coronary arteries involved, characteristics of lesions, previous procedures on the involved lesion, co-morbidities – such as diabetes mellitus or renal failure and in relevant cases, results of cardiac scans and left-ventricular function were assessed. Each case was assigned an indication according to the guidelines and the level of adherence to guidelines was determined on a scale of 1-5. Ratings of 1-4 were deemed appropriate and a rating of 5 was considered inappropriate. The number and percentage of patients with scores of appropriateness and inappropriateness were calculated.

Results - The rate of inappropriateness for revascularization procedures during this period was 5.7%. The overall rate of inappropriateness was found to be

low, but significant risk factors for inappropriateness were found among two groups of patients: patients with triple-vessel disease (21.0% rate of inappropriateness), especially those with diabetes mellitus or renal failure and patients with coronary lesions in the proximal left-anterior descending artery at high-risk for percutaneous coronary intervention (41.2% rate of inappropriateness).

Conclusions - Possible explanations for the high rates of inappropriateness among these groups of patients include contradictory outcome data for patients with multi-vessel disease, as well as the problematic set-up of the catheterization and lack of sufficient presentation of all treatment options prior to angiography. Improving guideline adherence and appropriateness rates includes updating guidelines regularly to ensure correct care.

REFERENCES

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- ¹ Alderman E, Bourassa M, Cohen L, et al. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. *Circulation* 1990; 82: 1-18
 - ² Charlson ME, Isom OW. Care after coronary-artery bypass surgery. *N Engl J Med* 2003; 348: 1456-1463
 - ³ Levine GN, Kern MJ, Berger PB, et al. Management of patients undergoing percutaneous coronary revascularization. *Ann Intern Med.* 2003; 139: 123-136
 - ⁴ Heart Disease and Stroke Statistics – 2006 Update, A report from the American Heart Association statistics committee and stroke statistics subcommittee. Available on the world wide web at <http://circ.ahajournals.org>
 - ⁵ Kravitz RL, Laouri M, Kahan J, et al. Validity of criteria used for detecting underuse of coronary revascularization. *JAMA* 1995; 274: 632-638
 - ⁶ Chassin MR, Galvin RW. The urgent need to improve health care quality: Institute of Medicine National Roundtable on Health Care Quality. *JAMA* 1998; 280: 1000-1005
 - ⁷ Hemingway H, Crook AM, Feder G, et al. Underuse of coronary revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med* 2001; 344: 645-654
 - ⁸ Leape LL, Hilborne LH, Park RE, et al. The appropriateness of use of coronary artery bypass graft surgery in New York State. *JAMA* 1993; 269: 753-760
 - ⁹ Kahan JP, Bernstein SJ, Leape LL, et al. Measuring the necessity of medical procedures. *Medical Care* 1994; 32: 357-365
 - ¹⁰ Anderson GM, Adalsteinn DB. Appropriateness ratings: overuse, underuse or misuse? *Lancet* 2001; 358: 1475-1476
 - ¹¹ Winslow CM, Kosecoff JB, Chassin M, Kanouse DE, Brook RH. The appropriateness of performing coronary artery bypass surgery. *JAMA* 1988; 260: 505-509
 - ¹² Leape LL, et al. The appropriateness of use of coronary artery bypass graft surgery in New York State, 753
 - ¹³ Leape LL, Hilborne LH, Bernstein SJ, et al. The appropriateness of use of percutaneous transluminal coronary angioplasty in New York State. *JAMA* 1993; 269: 761-765
 - ¹⁴ Ibid.
 - ¹⁵ Gandjour A, Neumann I, Lauterbach KW. Appropriateness of invasive cardiovascular interventions in German hospitals (2000–2001): an evaluation using the RAND appropriateness criteria. *European Journal of Cardio-thoracic Surgery* 2003; 24: 571–577
 - ¹⁶ Serruys PW, Ong AT, Van Herwerden, LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease. *JACC* 2005; 46: 575–581
 - ¹⁷ Hannan EL, Racz MJ, Walford G, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 2005; 352: 2174-2183
 - ¹⁸ Leape LL, Weissman JS, Schneider EC, et al. Adherence to practice guidelines: the role of specialty society guidelines. *Am Heart J* 2003; 145: 19-26

¹⁹ Popp LS, Smith SC, Peterson LS, et al. Task Force 4: Appropriate clinical care and issues of “self-referral.” *Circulation* 2004; 110: 2528-2534

²⁰ Leape LL, et al. Adherence to practice guidelines: the role of specialty society guidelines, 24

²¹ Leape LL, Parke RE, Bashore TM, et al. Effect of variability in the interpretation of coronary angiograms on the appropriateness of use of coronary revascularization procedures. *Am Heart J* 2000; 139: 106-113

²² Popp LS, et al. Task Force 4: Appropriate clinical care and issues of “self-referral,” 2530.

²³ Henderson RA, Pocock SJ, Clayton TC, et al; Second Randomized Intervention Treatment of Angina (RITA-2) Trial Participants. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol.* 2003; 42:1161-1170

²⁴ Pfisterer M, Buser P, Osswald S, et al. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial. *JAMA* 2003; 289: 1117-1123

הנחיות לרה-ווסקולריזציה לבבית – בי"ח הדסה, 2004

הקדמה – עקרונות כלליים

רה-ווסקולריזציה של הלב, מטרתה לטפל בתסמינים או למנוע סיבוכים של מחלת העורקים הכליליים ובמידת האפשר להאריך את תוחלת החיים של הלוקים במחלה זו. רה-ווסקולריזציה באה כתוספת לטיפול הכולל במניעת תחלואה ותמותה מטרשת על-ידי שיפור גורמי סיכון בעזרת שינוי הרגלים (הפסקת עישון, פעילות גופנית, תזונה) וטיפול תרופתי (חוסמי בטא, מעכבי ACE, אספירין וסטטינים).

שתי הדרכים המקובלות לרה-ווסקולריזציה הן באמצעות בלונים ותומכונים במעבדת הצינתור (PCI¹) או על-ידי ניתוח מעקפים (CABG²). דרך נוספת, השמורה למקרים בהם אף אחת משתי הדרכים הראשיות לא נראית מתאימה, היא לנסות לעודד התפתחות עורקים קולטרליים על ידי הפעלת לחץ חיצוני מתוזמן לדיאסטולה על עורקי הגפיים (EECP³).

עצם קיומה של מחלה כלילית והיכולת הטכנית לטפל בממצא אנטומי, אינם צריכים לשמש הוראה לביצוע רה-ווסקולריזציה. השיקול צריך להיות שיפור באיכות או בתוחלת החיים. לחולה עם תסמונת אנגינטיית יציבה, CABG למרות היותו פולשני יותר מ-PCI מחד, יעיל יותר למניעת כאבים והתערבויות חוזרות מאידך (ראה טבלאות בסוף) ושניהם יעילים יותר מטיפול תרופתי. לגבי שיעורי התקף לב חוזר או תמותה, אין הבדל בין שתי השיטות ומוגבלים הנתונים בהשוואה לטיפול תרופתי. במחקרים שנעשו בעבר CABG נמצא יעיל בעיקר בהיצרות העורק השמאלי הראשי ומחלה תלת-כלית עם ירידה בתפקוד הלב ו-PCI נמצא יעיל בעיקר בשלב החריף של אוטם ותעוקה בלתי יציבה.

על פי חוק זכויות החולה (התשנ"ו), יש להסביר לחולה את הסיכויים והסיכונים של כל אחת מן החלופות, כולל היתרונות והמגרעות או היות הטיפול חדשני. כמו כן, יש לציין אם קיימת התלבטות באשר לגישה העדיפה בקרב חברים לצוות הרפואי.

העקרונות המנחים בבחירת הגישה הטיפולית לרה-ווסקולריזציה הם:

1. השגת רה-ווסקולריזציה מלאה ככל שניתן.
2. מתן פתרון ארוך טווח ככל שניתן.
3. ביצוע הטיפול בסיכון המיזערי ביותר – הן למוות והן לסיבוכים קשים.

עקרון נוסף אשר נלקח גם הוא בחשבון הוא עלות הטיפול.

¹ PCI, percutaneous coronary intervention
² CABG, Coronary artery bypass grafting
³ EECP, Enhanced external counterpulsation

גם כאשר מאפייני המטופלים מוגדרים היטב ומוכרים במלואם לצוות המטפל, הרי שההחלטה על הטיפול המועדף עלולה להיות קשה מטעמים שונים. ביניהם ניתן למנות את מצב החולה מבחינה לבבית מול קיומן והשפעתן של בעיות רפואיות אחרות ואיכות המידע הקיים לגבי הסיכונים והסיכויים באותו צירוף מיוחד של נתונים. בנוסף, ההתפתחות המהירה והמתמדת בשיטות הטיפול השונות גורמת לכך שכאשר מצטבר מעקב מספיק ארוך אחרי תוצאות שיטה כלשהי, לעיתים קרובות זאת הוחלפה בינתיים על-ידי שיטה הנחשבת למתקדמת ויעילה יותר. ההנחיות המובאות להלן מבוססות על הספרות הרלוונטית והעדכנית היום, ומתייחסות לקבוצות חולים בעלי מאפיינים משותפים. המאפיינים המשותפים נוגעים להסתמנות הלבבית, לממצאים האנטומיים בעורקי הלב ולתפקוד הלב.

יש לציין כי בשנים האחרונות יש התקדמות מהירה בטכניקות של הטיפול המלעורי וכניסה של תומכונים חדישים מפרישי תרופות. דבר זה הקטין מאוד את שיעור הסיבוכים המוקדמים והמאחרים של PCI והביא פתרון חלקי לבעיות העיקריות של טיפול מלעורי שהן - בטיחות הטיפול בלזיות בסיכון גבוה וההצרויות החוזרות. במקביל יש שיפור גם בטכניקות הניתוחיות המאפשר ביצוע מעקפים בפולשנות מינימלית וללא שימוש במכונת לב-ריאה. כל זאת מביא לכך שיתכנו שינויים מהירים במדיניות הטיפולית ולעתים ההנחיות יכולות להשתנות בטווח של חדשים. לאור זאת מוסכם כי ההנחיות להלן יבחנו מחדש כל שישה חדשים ויוכנסו בהם שינויים בהתאם לספרות העדכנית.

מחלות רקע נלוות

בהנחיות ניתן ביטוי להשפעתה של סכרת או אי-ספיקת כליות על ההחלטה הטיפולית ואין ביטוי למחלות נלוות או מצבים רבים אחרים. מצבים אלו כוללים בעיקר:

(א) תוחלת חיים צפויה נמוכה – כתוצאה מגיל ביולוגי מתקדם או מחלת רקע קשה כגון: סרטן, שחמת או אי-ספיקת-לב דרגה IV.

(ב) איכות חיים ומצב תפקודי ירודים מאוד למשל כתוצאה מקיפוח נוירולוגי כגון: דמנציה, מצב סיעודי, ניוון שרירים וכד'.

(ג) סיכון ניתוחי מוגבר כתוצאה ממחלת רקע – מחלת ריאות קשה, הפרעה בקרישה, ניתוח לבבי קודם, מחלה דלקתית או זיהומית פעילה, הסתיידות הוותרין, מצב לאחר ארוע מוחי וכד'.

במצבים אלו תהיה עדיפות לטיפול פחות פולשני כלומר לטיפול שמרני תרופתי או ב- PCI לצורך שיפור סימפטומים ולא תהיה המלצה לניתוח מעקפים לעתים בניגוד למצויין ב- guidelines. אלו הן המלצות ולא הוראות מחייבות, אך הן משקפות את אופן הטיפול הצפוי

להביא לתועלת הרפואית המירבית תוך שמירה על רמת סיכון הנמוכה ביותר. בבואנו לדון בחולה הבודד, יתכן שיישום העקרונות המתאימים לקבוצת חולים בעלי מאפייני מחלה זהים מבחינה לבבית אינו מתאים לחולה המסויים הזה עקב גורמי סיכון ייחודיים שאינם מפורטים בטבלת ההנחיות. הנימוקים לסטייה מן ההנחיות במקרה כזה מושתתים על שיקול דעת קליני, ומן הראוי שיתועדו בכתב ברשומת החולה.

המראה האנגיוגרפי והשיקול הטכני

נושא נוסף שאינו בא לידי ביטוי בטבלת ההנחיות הוא השיקול הטכני. קיימים מספר משתנים המשפיעים על היכולת הטכנית לבצע רווסקולריזציה טובה יותר בשיטה מסוימת (CABG או PCI). הגורמים העיקריים הם:

(א) סוג ההיצרות – מורכבת, התפצלות עורקים, נוכחות קריש, הסתיידות

(ב) מספר חסימות שיש בכל עורק

(ג) מידת הזרימה הדיסטלית לחסימה (run off).

(ד) טיב העורק וגודלו – קוטר וכמות ענפים.

(ה) חיוניות האיזור אותו מספק העורק.

ה- guidelines תקפים למקרים בהם הן CABG והן PCI אפשריים ונחשבים ליעילים מבחינה טכנית, לאחר שנלקחו בחשבון כל השיקולים הנ"ל.

הסכמת החולה

ההחלטה הטיפולית תלויה כמובן גם בהסכמתו או אי-הסכמתו של החולה לפעולה ניתוחית או מילעורית. כאמור יש להסביר לחולה את היתרונות והסיכונים של כל אחת מן החלופות או היות הטיפול חדשני ולציין אם קיימת התלבטות באשר לגישה העדיפה בקרב חברים לצוות הרפואי.

הגדרת רמת ה-evidence

המלצות מבוססות על נתונים הקיימים בספרות הרפואית לפי רמות שונות של ביסוס מדעי:

רמת ביסוס A: מסקנות מחקרים קליניים רנדומלים פרוספקטיביים.

רמת ביסוס B: מסקנות ממחקרים לא מבוקרים ולרוב רטרוספקטיביים (בעיקר registries).

רמת ביסוס C: חוות דעת מוסכמת של מומחים (קונצנזוס של בעלי סמכות) על פי נסיון מצטבר ופרסומי מקרים ללא ביסוס ברור יותר במחקר.

הגדרות נוספות

1. PCI בסיכון גבוה – חסימות מלאות או לזיות מסוידות, ארוכות בפיצול או במוצא של עורקים.
2. חוסר הצלחת טיפול ע"י PCI יוגדר כהיצריות חוזרות באותו מקטע לאחר שני טיפולים ב- PCI או לאחר טיפול בברכיטרפיה או לאחר השתלת תומכונים מפרישי תרופות.
3. היצרות חוזרת מוגדרת כהיצרות מעל 50% באותה לזיה בה בוצע PCI בטווח זמן של עד 9 חודשים.

א. המלצות לכלל החולים - כולל חולים אסימפטומטיים או עם אנגינה קלה (דרגה I).

מצבים בהם ההמלצה היא לביצוע CABG:

1. היצרות משמעותית (מעל ל- 50%) של העורק השמאלי הראשי (ראה הערה) או הצרות (שווה או מעל ל- 70%) המערבת את מוצא העורק השמאלי היורד ואת מוצא העורק העוקף ("Left main equivalent") (רמת ביסוס A*)
 2. מחלה תלת-כלית בחולים סכרתיים. (רמת ביסוס A)
 3. מחלה המערבת את העורק הקידמי היורד הפרוקסימלי עם סיכון גבוה ל-PCI. (רמת ביסוס B)
 4. מחלה תלת-כלית או מחלה המערבת את העורק הקידמי היורד הפרוקסימלי וחוסר הצלחת טיפול על-ידי PCI. (רמת ביסוס C)
- *מבוסס על מחקרים המשווים CABG לטיפול שמרני.
- הערה** - בהצרות של העורק השמאלי הראשי (LM) היתה בעבר אינדיקציה ברורה לניתוח מעקפים אך היום יש מחלוקת האם עדיין זה הטיפול היחיד והמועדף. מדיניות הטיפול בהצרות בחלק הפרוקסימלי של LM הוא כיום נושא הנתון לבחינה מחדש – כאשר מרכזים רבים מבצעים PCI לעורק זה עם תוצאות ראשוניות טובות והתוצאות לגבי יעילות טיפול זה לטווח הרחוק יהיו בעתיד. לאור זאת במקרים של הצרות בעורק השמאלי הראשי בחלקו האמצעי או הפרוקסימלי תשקל אפשרות של PCI תוך תיאום עם כירורג לב בכיר.

מצבים בהם CABG ו-PCI בעלי יעילות דומה והנתונים המיוחדים של החולה יהוו השיקול

עיקרי:

1. מחלה תלת-כלית ללא סכרת או אי ספיקת כליות (רמת ביסוס A)
 2. מחלה תלת כלית בסכרתיים כאשר ניתן לבצע רווסקולריזציה מילעורית טובה ע"י תומכונים מפרישי תרופות (רמת ביסוס B)
 3. מחלה המערבת את העורק הקידמי היורד הפרוקסימלי (רמת ביסוס A*).
 4. מחלה חד/דו כלית (שאינה מערבת את העורק הקידמי היורד הפרוקסימלי) עם עדות לאיסכמיה הפיכה במיפוי וירידה בתפקוד חדר שמאל. (רמת ביסוס C)
- *מבוסס על מחקרים מבוקרים בחולים ללא לזיות בסיכון ל PCI – (כגון ostial lesions). מתצפיות רטרוספקטיביות. במקרים של לזיות מורכבות עם צפי גבוה להיצרות חוזרת, עדיף CABG.

מצבים בהם ההמלצה היא לביצוע PCI או לטיפול שמרני:

- מחלה חד/דו כלית שאינה מערבת את העורק הקידמי היורד הפרוקסימלי. (רמת ביסוס A)

ב. המלצות נוספות לחולים עם תעוקה יציבה משמעותית (רמת ביסוס C)

מצבים בהם ההמלצה היא לביצוע CABG:

תעוקה משמעותית עם הגבלת איכות חיים שלא הגיבה לטיפול שמרני מקסימלי וחוסר הצלחת טיפול באמצעות PCI.

מצבים בהם ההמלצה היא לביצוע PCI:

תעוקה משמעותית עם הגבלת איכות חיים שלא הגיבה לטיפול שמרני מקסימלי ולאחר טיפול קודם באמצעות CABG (חסימה של מעקפים).

ג. המלצות נוספות לחולה עם Non ST Elevation Acute Coronary Syndrome

(רמת ביסוס C)

מצבים בהם ההמלצה היא לביצוע CABG:

עדות ל- ongoing ischemia למרות טיפול תרופתי מקסימלי וללא יכולת לפתרון מלא באמצעות PCI.

מצבים בהם ההמלצה היא לביצוע PCI:

עדות ל- ongoing ischemia למרות טיפול תרופתי מקסימלי והערכה שהסיכון הניתוחי גבוה מדי או שלא ניתן טכנית לבצע רווסקולריזציה על-ידי CABG.

ד. המלצות לגבי חולה בשלב החריף של ST Elevation Myocardial Infarction

מצבים בהם ההמלצה היא לביצוע CABG דחוף

1. כשלון רפרפוזיה באמצעות PCI בפרק זמן של עד 12 שעות מהתחלת האוטם ועדות לאיסכמיה שארית משמעותית או מצב המודינאמי לא יציב. (רמת ביסוס C).
2. מחלה רב כלית בחולה סכרתי וזרימה תקינה (3 TIMI) בעורק שגרם לאוטם.

מצבים בהם CABG ו- PCI בעלי יעילות כנראה דומה ונתונים מיוחדים לחולה יהוו

השיקול עיקרי:

1. חסימה חריפה בעורק השמאלי הראשי. (רמת ביסוס C).
2. מחלה רב כלית וזרימה תקינה (3 TIMI) בעורק שגרם לאוטם (רמת ביסוס C).

מצבים בהם ההמלצה היא לביצוע PCI:

1. כל חסימה חריפה בת פחות מ-12 שעות בעורק כלילי כטיפול ראשוני (Primary PCI) או לאחר כשלון של טיפול טרומבוליטי (Rescue PCI). (רמת ביסוס A).
2. עדות לאיסכמיה פעילה או לאי ספיקת לב למרות רפרפוזיה מוצלחת בעורק שגרם לאוטם, כתוצאה ממחלה משמעותית בעורקים שאינם באיזור האוטם. (רמת ביסוס B)

סיכונים בביצוע CABG (נתוני הדסה) * או PCI (נתונים מן הספרות) *

שכיחות בצינתוח	שכיחות בניתוח	סיכון
0.5-1%	1-2%	מוות
עד 0.4%	1%	אירוע מוחי
0.4-1%	2-3%	אוטם טרנס מורלי בשריר הלב
0.2%	פחות מ-1% (מדיאסטיניטיס)	זיהום משמעותי
0.02-0.6%	0%	קרע עורק כליל
		ירידה קוגניטיבית
		פריקרדיטיס
3%		סיבוכי פצע הניתוח/צנתור

* שכיחות הסיכונים היא לכלל אוכלוסיית המנותחים עם תמהיל חולים ברמות סיכון שונות. לגבי צינתור, רמת הסיכון והתוצאות לכלל אוכלוסייה זו לא נבדקו עד כה בהדסה.

שכיחות של צורך ברוסקולריזציה חוזרת:

<u>זמן ממוצע</u>	<u>שכיחות</u>	<u>סוג התערבות</u>
1-4 חדשים	25-35%	בלון
3-6 חדשים	15-25%	סטנט רגיל
4-12 חדשים	5-10%	סטנט מצופה תרופה
שנה	3-7%	מעקפים

מעבר לשנה הראשונה לאחר הפרוצדורה:

שיעור הצרויות חוזרות לאחר PCI הוא זניח.

שעור חסימת שתלים ורידיים הוא 5% לשנה בערך

REFERENCES

1. Eagle and Guyton et al. ACC/AHA guidelines for coronary artery bypass graft surgery. JACC 1999; 34(4): 1262-1347.
2. Smith et al ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines). JACC 2001; 37(8): 2239.
3. Davis KB, Chaitman B, Ryan T, Bittner V, Kennedy JW Comparison of 15-year survival for men and women after initial medical or surgical treatment for coronary artery disease: a CASS registry study. Coronary Artery Surgery Study. J Am Coll Cardiol. 1995 Apr; 25(5): 1000-9.
4. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. Circulation. 1995 May 1; 91(9): 2335-44.
5. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASS experience. Circulation. 1995 May 1; 91(9): 2325-34.
6. Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. Lancet 1995;346:1184-1189
7. Henderson RA, Pocock SJ, Sharp SJ, Nanchahal K, Sculpher MJ, Buxton MJ, Hampton JR. Long-term results of RITA-1 trial: clinical and cost comparisons of coronary angioplasty and coronary-artery bypass grafting. Randomised Intervention Treatment of Angina Lancet. 1998 Oct 31; 352(9138): 1419-25.
8. King SB 3rd, Kosinski AS, Guyton RA, Lembo NJ, Weintraub WS. Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST) J Am Coll Cardiol. 2000 Apr; 35(5): 1116-21.
9. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. N Engl J Med. 1996 Jul 25; 335(4): 217-25.
10. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randomized trial. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. JAMA. 1997 Mar 5; 277(9): 715-21.

11. Rodriguez A, Mele E, Peyregne E, Bullon F, Perez-Balino N, Liprandi MI, Palacios IF. Three-year follow-up of the Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (ERACI). *J Am Coll Cardiol.* 1996 Apr; 27(5): 1178-84.
12. Patrick W. Serruys, M.D., Felix Unger, M.D., J. Eduardo Sousa, M.D., Adib Jatene, M.D., Hans J.R.M. Bonnier, M.D., Jacques P.A.M. Schonberger, M.D., Nigel Buller, M.D., Robert Bonser, M.D., Marcel J.B. van den Brand, M.D., Lex A. van Herwerden, M.D., Marie-Angele M. Morel, B.Sc., Ben A. van Hout, Ph.D., for The Arterial Revascularization Therapies Study Group. Comparison of Coronary-Artery Bypass Surgery and Stenting for the Treatment of Multivessel Disease. *NEJM* 2001; 344(15):1117-1124
13. Versaci F, Gaspardone A, Tomai F, Crea F, Chiariello L, Gioffrè PA. A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997;336:817-822.
14. *Clinical Evidence*, Issue 10. BMJ Publishing Group 2003.
15. Legrand, Victor M.G. MD, PhD; Serruys, Patrick W. MD, PhD; Unger, Felix MD, PhD; van Hout, Ben A. PhD; Vrolix, Mathias C.M. MD; Fransen, Geert M.P. MD; Nielsen, Torsten Toftegaard MD, DMSc; Paulsen, Peter Kildeberg MD, DMSc; Gomes, Ricardo Seabra MD; de Queiroz e Melo, Joao M.G. MD; Marques dos Santos Neves, Jose P. MD; Lindeboom, Wietze MSc; Backx, Bianca PhD; on behalf of the Arterial Revascularization Therapy Study (ARTS) Investigators Three-Year Outcome After Coronary Stenting Versus Bypass Surgery for the Treatment of Multivessel Disease. *Circulation.* 109(9):1114-1120, March 9, 2004.