REVIEW ARTICLE

Modern Therapeutic Strategies for Coronary Artery Bypass Grafting (CABG)

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SUMMARY

Introduction: The conventional approach to coronary artery bypass grafting using extracorporeal circulation has been the standard for many decades. This review aims to evaluate novel approaches to bypass grafting in cardiac surgery. Methods: Selective literature review. Results/Discussion: The use of extracorporeal circulation remains the goldstandard in the surgical treatment of coronary heart disease. The use of arterial bypass grafts could replace the use of venous grafts especially in young patients, because of their good long-term patency rate. Aortocoronary bypass grafting without the use of extracorporeal circulation („off-pump") has fallen short of expectations. However, this type of operation might help to reduce perioperative morbidity in selected patients with extensive comorbidity. Dtsch Arztebl 2007; 104(48): A 3334–9

Key words: coronary artery bypass grafting, myocardial revascularization, mortality, outcome, study

Approximately 54 000 surgical myocardial revascularizations were performed in Germany in 2005. This number represents a downward trend since the year 2000 *(diagram 1)*, largely owing to the increased use of interventional procedures, i.e., percutaneous balloon angioplasty (PTCA) and/or stent implantation, to treat coronary heart disease (CHD).

The aim of this review is to summarize the modern surgical treatments of CHD on the basis of a selective reading of the literature. We will deliberately not address the somewhat controversial topic of the interventional treatment of CHD with medication-coated stents (also known as drug-eluting stents, DES).

The standard technique

The first operative treatments of CHD consisted of direct implantation of the internal thoracic artery into the hypoxic myocardium, as described by Vineberg in 1949 (e1), and resection of the stenotic coronary segment with venous interposition grafting, as described by Murray in 1952 (e2). After Gibbon introduced the heart-lung machine in 1953 (e3), Favaloro was the first to bypass stenotic coronary vessels with vein grafts in 1967 (e4). From 1971 onward, Green used the internal thoracic artery as the standard bypass graft (e5). This operative treatment of CHD, i.e., the use of the left internal thoracic artery combined with vein grafts under assisted circulation with a heart-lung machine, remains the standard in cardiac surgical clinics around the world today. The safety and efficacy of all newer techniques must be measured against it.

Historical survival studies

The Coronary Artery Surgical Study (CASS), performed in the early 1970's, was one of the first randomized studies of bypass grafting (1). The mortality in this study was 1.1% per year. Most patients in that era did not receive any beta-blockers, aspirin, or statins. In a later study, the Coronary Artery Bypass Graft Surgery Trialists Collaboration of 1984, the mortality was 23% in 7 years (e6). As early as 1989, Loop et al. were able to demonstrate that the most important factor promoting survival was the anastomosis of the internal thoracic artery to the left anterior descending artery (LAD), rather than the use of a venous bypass alone (2). In the meta-analysis of Yusuf et al., published 10 years later, the 7-year mortality was only 16% (e7). The BARI study of 1996 (Bypass Angioplasty

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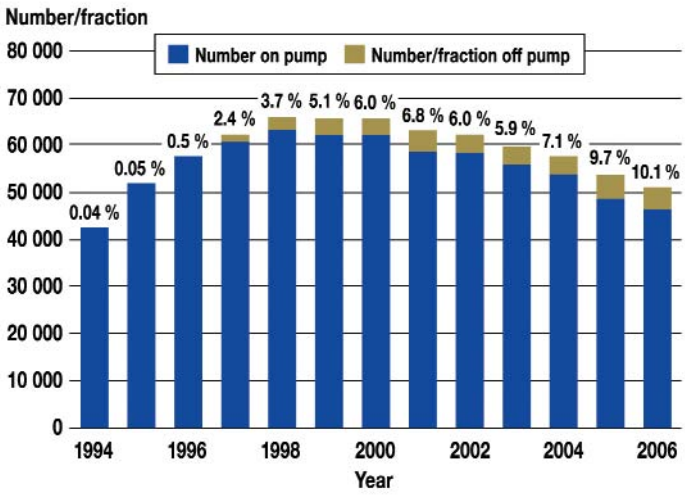
Revascularization Investigation), performed in the era of percutaneous transluminal angioplasty (PTCA), revealed a 5-year mortality of 10.7% (3). This study was the first to show a significant survival advantage for bypass surgery in comparison to PTCA for patients with diabetes mellitus. The internal thoracic artery was used in 82% of the operations in this study. In the Arterial Revascularization Therapies Study (ARTS), the 5-year mortality was still lower, at 7.6%. The *table* provides an overview of the various studies.

Interventional techniques versus surgery

Supplementing these survival studies of coronary artery bypass surgery, some of which were performed in an earlier era, most the major studies today compare interventional treatments with operative myocardial revascularization. The 8-year results of the Emory Angioplasty Versus Surgery Trial (EAST) were presented in 2000 (5). From 1983 onward, 392 patients were followed in a single center after randomization to transluminal angioplasty (PTCA) or surgery. The mortality of the patients who had undergone surgery was 17.3% at 8 years and did not differ significantly from that of the angioplasty patients (20.7%). The CABRI trial (Coronary Angioplasty versus Bypass Revascularization Investigation) was a European multicenter study of more than 1000 patients who were followed for 4 years (6). The overall mortality after surgery was 6.8% and did not differ significantly from the mortality after PTCA (12.5%). The special finding of this study, however, concerned patients with and without diabetes mellitus. In diabetic patients, the operative mortality after surgery was somewhat higher than in non-diabetics at 8.1%, but it was nevertheless significantly lower than the mortality of diabetic patients after PTCA, which was 17.8%. The Medicine, Angioplasty or Surgery Study (MASS-II) involved 611 patients randomized to receive pharmacotherapy, PTCA, or surgery (e8). No significant differences in survival were found among these 3 treatment groups in 5 years (12.6%, 16.2%, and 15.5%, respectively) (7). Nevertheless, bypass surgery was significantly better than interventional and conservative treatment with respect to the secondary endpoints (myocardial infarction, revascularization, and angina pectoris; $p = 0.0026$). In a North American multicenter study with 8-year follow-up of more than 10 000 patients undergoing bypass surgery and more than 4000 undergoing PTCA, surgery was found to provide a significant survival advantage only to patients with three-vessel coronary disease (80.6% versus 76.6%) (8). The study with the longest follow-up was the German Angioplasty Bypass Surgery Investigation (GABI) (9), in which more than 300 patients were followed for 13 years after either bypass surgery or PTCA. The mortality was 35% after surgery and 41% after PTCA; the difference was not statistically significant. In this

DIAGRAM 1



The development of isolated coronary artery surgery in Germany from 1994 and 2006, divided into on-pump and off-pump procedures. With permission of the German Society for Thoracic and Cardiovascular Surgery.

TABLE

Randomized studies comparing operative myocardial revascularization with percutaneous interventional procedures

Study	Ref. No.	Year	Study design		Patients	Study interval	Mortality CABG	Mortality PCI	Significance
BARI	(3)	1996	Multi-center	PTCA vs ACB	1 829 357*1	5 years	10.7 % 19.4 %	13.7 % 34.5 %	No $p < 0.01$
EAST	(5)	2000	Single-center	PTCA vs ACB	392	8 years	17.3 %	20.7 %	No
CABRI	(6)	2001	Multi-center	PTCA vs ACB	1 045 125*1	4 years	6.8 % 8.1 %	12.5 % 17.8 %	No $p < 0.001$
AWESOME	(23)	2002	Multi-center	PTCA vs ACB	1 343	5 years	20.0 %	19.0 %	No
New England Study	(8)	2005	Multi-center	PTCA vs ACB	14 493	8 years	19.4 %	23.4 %	$p < 0.01$*2
GABI	(9)	2005	Multi-center	PTCA vs ACB	359	13 years	35 %	41 %	No
New York State Registry	(25)	2005	Multi-center	PTCA vs ACB	37 212	3 years	10.7 %	15.6 %	$p < 0.001$
MASS-II	(7)	2007	Single-center	PTCA vs ACB	611	5 years	12.8 %	16.2 %	No
SOS	(24)	2002	Multi-center	BMS vs ACB	988	3 years	1.0 %	3.0 %	No
ERACI-II	(10)	2005	Multi-center	BMS vs ACB	450	5 years	7.2 %	11.6 %	No
ARTS	(4)	2005	Multi-center	BMS vs ACB	1 200	5 years	7.6 %	8.0 %	No

BARI = Bypass Angioplasty Revascularization Investigation; EAST = Emory Angioplasty Versus Surgery Trial; CABRI = Coronary Angioplasty Versus Bypass Revascularization Investigation; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; GABI = German Angioplasty Bypass Surgery Investigation; MASS = Medicine, Angioplasty, or Surgery Study; SOS = Stent or Surgery; ERACI = Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease; ARTS = Arterial Revascularization Therapies Study; ACB = Aortocoronary Bypass Operation; PTCA = percutaneous transluminal angioplasty; BMS = bare metal stent.
*1 Subgroup with diabetes mellitus.
*2 Only in 3-vessel CHD.

study, however, the internal thoracic artery was used for grafting in only 37% of all operations.

After the first bare metal stents (BMS) were implanted, the Argentine multicenter study ERACI-II randomized 450 patients into a BMS group and an operative group (10). No significant difference in survival was found after 5 years of follow-up (88.4% versus 92.8%). Alongside these single- and multicenter studies, meta-analyses yielded further important information: In a meta-analysis of 8 randomized studies with 1100 patients and a median follow-up interval of 5 years, bypass surgery was found to be superior to interventional therapy with respect to mortality, the rate of myocardial infarction, and the new development of angina pectoris (11). The weak point of this analysis, however, was the mixing together of minimally invasive and conventional surgery on the one hand, and of PTCA, BMS, and DES (drug-eluting stents) on the other. In a Cochrane analysis, bypass surgery was found to be significantly better than stent implantation after 3 years with respect to the need for new revascularization procedures, though no difference in mortality or the rate of myocardial infarction was detected (12).

Since the introduction of the newer drug-eluting stents, there has been as yet no major multicenter study comparing DES with surgical myocardial revascularization. 2 studies that are currently in progress, ARTS-II and ERACI-III, have shown no difference to date in the survival rates of surgery and DES (e9, e10). Questions have been raised about the validity of the comparison, because the ARTS-II study compares the DES group with the historical operative group from the ARTS-I study.

Only the results of single-center studies are currently available. Studies with a follow-up interval of 1 year revealed no significant differences between operative and interventional treatment (e11, e12). Nevertheless, in single-center studies with 2 or 3 years of follow-up, the rate of re-revascularization procedures after interventional treatment was significantly higher than that after surgery (2.8% versus 10.4% at 2 years, 2.6% versus 35.5% at 3 years), while the mortality and rate of myocardial infarction was no different (e13, e14). Studies involving only diabetic patients showed even more marked differences (e15, e16).

Multicenter studies that are now in progress are expected to shed more light on these issues. The multicenter, prospective SYNTAX study (Synergy Between Percutaneous

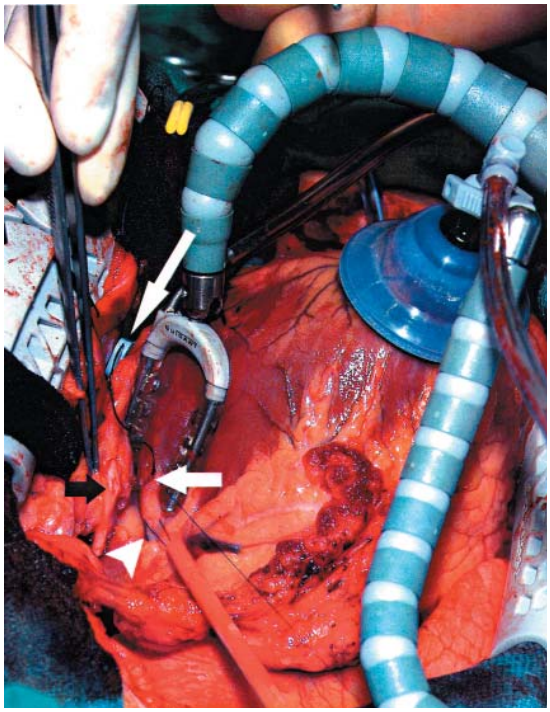


Figure: Off-pump operation without heart-lung machine. The suction cap holds the heart ventrally while the octopus stabilizer stabilizes the posterior interventricular branch (short white arrow).
The anastomosis is performed with the radial artery (black arrow).
The arrowhead points to a temporary ligature on the coronary vessel until the coronary shunt is introduced (long white arrow).

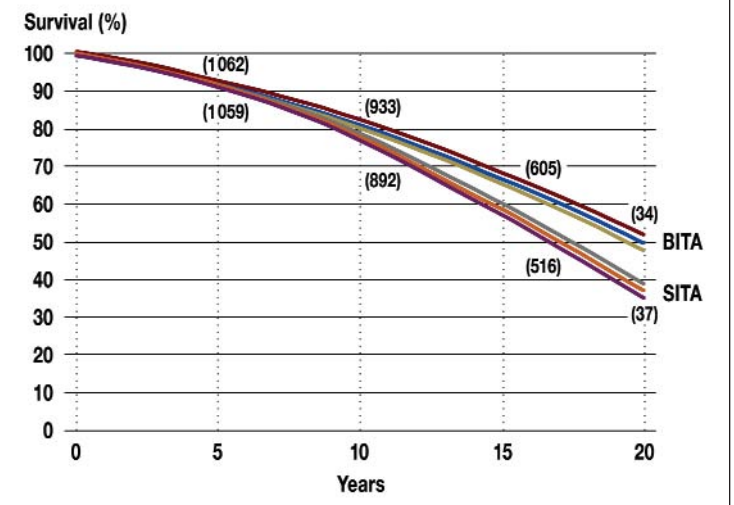
Coronary Intervention with Taxus [trade name of a paclitaxel-coated stent] and Cardiac Surgery) will involve 1500 patients with three-vessel coronary disease and accompanying main stem stenosis (e17); its results are expected to appear in 2012. The FREEDOM study (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) is intended to compare multiple DES implantation with bypass surgery in diabetic patients with multivessel disease; initial results are expected in 2010. Only a small amount of clinical data has been published to date regarding the latest generation of bio-absorbable drug-eluting stents. These have been successfully implanted in patients with acute myocardial infarction but were found to have a restenosis rate equal to that of BMS (13, e18).

Off-pump versus on-pump

Off-pump coronary artery bypass grafting (OPCAB) is operative myocardial revascularization on the beating heart without the use of a heart-lung machine. Already in 2003, about 17% of all bypass operations in the United Kingdom and 21% in the U.S.A. were performed off pump. As shown in *diagram 1*, this operation is performed far less often in Germany. This surgical technique is made possible by mechanical aids that enable displacement (rotation) and local stabilization of the beating heart without hemodynamic compromise. So-called octopus stabilizers are used to hold the site of the anastomosis in place with mild suction *(figure)*. Displacement of the heart, which is necessary for surgical access to the vessels of the posterior wall, is performed with a suction cap applied to the cardiac apex.

The theoretical advantages of this technique are its potentially lower morbidity and mortality because of its lesser invasiveness compared to on-pump surgery. To date, however, only a few large randomized studies on this topic have been published. The current prospective data show that the two techniques (bypass surgery with and without the use of a heart-lung machine) yield the same rate of postoperative survival in patients with multivessel disease (14, 15). Large prospective and retrospective studies have revealed, however, that patients undergoing "off pump" surgery have a slightly lower rate of

DIAGRAM 2



20-year survival after the use of both internal thoracic arteries (BITA, bilateral internal thoracic arteries) versus the left internal thoracic artery alone (SITA, single internal thoracic artery) (18).

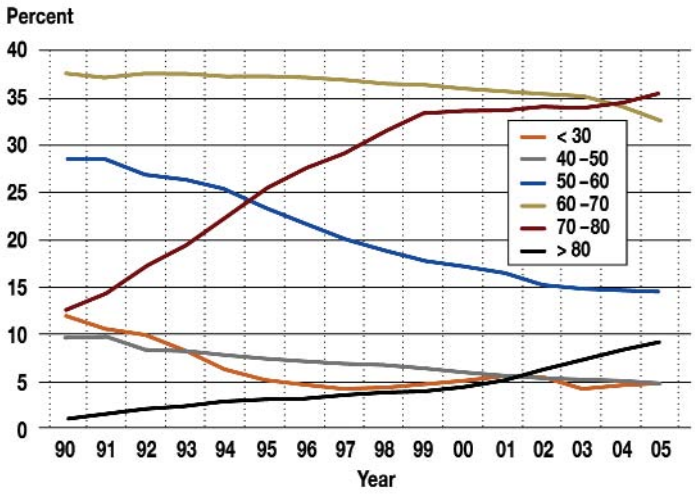
postoperative stroke (16, e19). The rate of postoperative myocardial infarction or new angina pectoris was not different in the two groups (15, e20), yet 2 meta-analyses revealed a lower bypass patency rate for the off-pump technique (e21, e22). There is some evidence that older patients with additional cardiovascular risk factors stand to benefit the most from off-pump as compared to on-pump surgery (e20, e23, e24), but this must be interpreted in the light of the fact that patients whose intended off-pump procedure needs to be converted to an on-pump procedure intraoperatively are subject to a considerably higher mortality (e25). In selected patients, revascularization of the left anterior descending artery with the left internal thoracic artery can be performed with minimally invasive technique (MIDCAB, "minimally invasive direct coronary artery bypass") through a lateral approach (e26). This therapeutic option has proven its worth particularly in cases of isolated involvement of the LAD. In older patients with major comorbidity and diffuse multivessel disease, MIDCAB provides an opportunity to treat patients with a hybrid approach, in which the LAD is revascularized with this minimally invasive technique and the remaining affected vessels are revascularized with interventional procedures (e27).

This special topic will be dealt with in another review article in this journal in the near future and will therefore not be discussed any further here.

Total arterial revascularization

Although the standard method of operative revascularization to date has involved the use of the left internal thoracic artery in combination with venous grafts from the leg, complete arterial bypass grafting is now being performed more and more commonly. The occlusion rate of venous grafts after 10 years is circa 50%, largely because of accelerated atherosclerotic degeneration and intimal proliferation. The more common surgical technique involves anastomosis of the left internal thoracic artery in situ to the LAD. It was shown as early as 1986 that bypass grafts remain patent for a much longer time if the left internal thoracic artery is used rather than a venous graft (97% versus 50% at 10 years) (2). Over the last 20 years, therefore, arteries have been used more commonly, either for total arterial revascularization or in combination with venous bypasses. Although alternative arterial bypass grafts from the abdominal area (inferior epigastric artery, gastroepiploic artery) have not been adopted in widespread use because of the need for a separate surgical opening, the use of both of the internal thoracic arteries simultaneously has been found to provide a significant survival advantage *(diagram 2)* (17, 18, e28). As only 2 coronary vessels can be revascularized with the two internal thoracic arteries, the radial artery is often used at present as an additional graft source (19, e29). The patency rate of bypasses with this

DIAGRAM 3



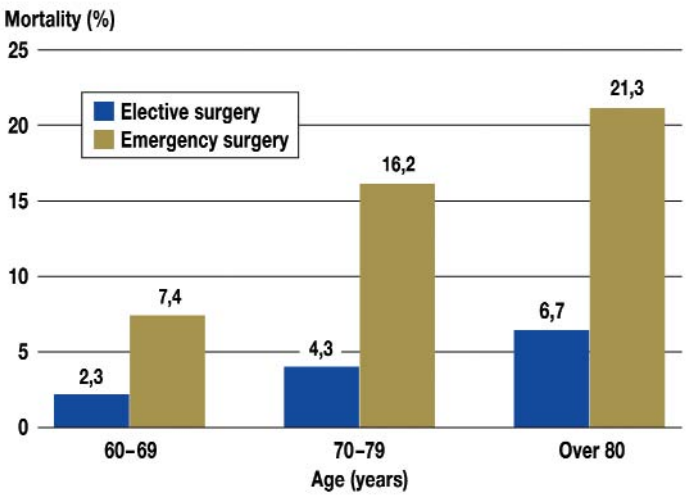
The diagram reveals the marked increase in patients over 80 years of age undergoing cardiac surgery in recent years. Reproduced with permission from the "Bruckenberger Herzbericht 2005."

vessel, however, is not any better than that of bypasses with the internal thoracic artery; this is primarily because the radial artery usually is not used to revascularize the LAD (e30, e31). However the patency rate is significantly better compared to venous bypasses (19, e32). The major factor conferring a long-term advantage with respect to patency appears to be a skeletonizing technique, rather than a pedicle graft technique, for the preparation of the vessel (e33). In the former technique, only the vessel itself is dissected free; in the latter, the vessel is removed together with the accompanying veins and adipose tissue.

Surgery in older patients

The number of older patients undergoing cardiac surgery has risen steadily over the past decade *(diagram 3)*; the number of patients over 80 years of age, for example, has risen from 2.3% in 1994 to 8.5% in 2000 (e34). This raises the question whether there is any associated change in morbidity and mortality after surgical myocardial revascularization. In a comparative study published in 1999, Carver et al. showed that mortality rises significantly with age *(diagram 4)* (20). In 2000, an American multicenter study revealed that the in-hospital mortality of patients over 80 years of age was with 8.3% significantly higher than that of younger patients with 3.0% (e35). Above all, the rate of perioperative stroke was markedly higher in elderly patients. In view of the higher mortality of conventional on-pump bypass surgery in this patient group, the question of whether off-pump surgery confers any advantage in this regard was addressed. A meta-analysis published in 1996, involving 4,921 patients, showed that the mortality and the rate of postoperative development of atrial fibrillation were significantly lower in patients over 70 years of age undergoing off-pump rather than on-pump coronary bypass surgery (21). In this study, however, the incidence of stroke was no different in the on-pump and off-pump groups. A similar study by Jensen et al. revealed no difference in cognitive function 3 month after surgery in patients over 76 years of age who had undergone either on-pump or off-pump procedures (e36). On the other hand, another meta-analysis involving 4,475 patients over age 70 revealed a considerably lower stroke rate in patients who had undergone off-pump as compared with conventional bypass surgery (1% versus 3%) (22). In a large study with data collected by the New York State Department of Health on more than 88,000 patients, patients over age 80 had significantly longer hospital stays (14.1 versus 11.5 days) and increased mortality (5.1% versus 2.7%) mainly because of postoperative respiratory insufficiency (e37). In another, similar study, patients over age 80 had significantly higher mortality (8% versus 2%) and a significantly higher length of hospital stay (8.7 versus 6.7 days), as well as

DIAGRAM 4



The diagram reveals the increased mortality associated with advanced age and emergency surgery (20).

significantly more frequent neurological, pulmonary, and renal complications (e38). Nevertheless, despite all of these risks, patients who have been successfully treated with surgery in this age group have a considerably better quality of life than comparably aged patients who do not undergo surgery, with no difference in life expectancy (e39, e40).

Summary

The use of the heart-lung machine remains the gold standard for aortocoronary bypass surgery. Surgical methods not involving extracorporeal circulation have failed to fulfill some of the expectations placed on them. Most studies have revealed no advantage with respect to survival or complications compared to conventionally performed (on-pump) surgery. The data on bypass graft patency after off-pump surgery should be interpreted critically and with caution. Nonetheless, because conventional surgery is now being performed with markedly higher risks than before because of the increasing number of elderly patients, it is perhaps precisely in this patient group that off-pump surgery will find its most useful application. There are not yet enough data to permit a reliable comparison with interventional stent implantation and the use of the new, medication-coated stents. The results of larger studies comparing stent implantation with total arterial revascularization will not be available until a few years from now.

The use of complete arterial bypass revascularization (the two internal thoracic arteries and the radial artery) can be expected to yield a further improvement in long-term bypass patency.

Conflict of Interest Statement
The authors state that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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