Comparison of Bypass Surgery and Stenting for the Treatment of Multivessel Disease: Results from the ARTS Trial in Israel

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Abstract

Background: The Arterial Revascularization Therapies Study was a multicenter, randomized trial designed to compare percutaneous coronary intervention with stenting versus coronary artery bypass graft surgery in 1,205 patients with multivessel coronary artery disease. The most appropriate type of treatment for these patients is still a matter of considerable debate.

Objectives: To evaluate the clinical characteristics of patients enrolled in the ARTS trial in Israel in comparison to those worldwide, and to assess the 1 year outcome in these patients.

Methods: Between April 1997 and June 1998, a total of 1,205 patients with multivessel coronary artery disease, who were considered to be equally treatable with both modalities, were randomized to either stenting (n = 600) or CABG (n = 605) at 67 centers around the world. In Israel, 53 patients at four participating medical centers were randomized to either PCI with stents (n = 27) or CABG (n = 26).

Results: Clinical and angiographic characteristics were similar in the two groups, except for a significantly higher incidence of diabetic patients in Israel who were randomized to CABG, compared to those worldwide (35% vs. 16%, $P = 0.01$). Also, there were more patients with unstable angina in Israel (63 vs. 37%, $P = 0.006$). At 1 year follow-up, overall mortality and cerebrovascular accident rates were similar between the two groups and equivalent to results obtained around the world. There was a significantly higher incidence of myocardial infarction rates in patients randomized to stenting in Israel compared to patients worldwide (7.4 vs. 5.3%, $P = 0.01$) or to patients randomized to CABG in Israel (7.4 vs. 0%, $P = 0.006$). Similar to the overall ARTS results, there was a higher incidence of repeat revascularization procedures in patients assigned to the PCI with stenting arm (22.2 vs. 3.8%, $P = 0.004$) compared to those randomized to CABG, respectively.

Conclusions: The results of this analysis of the Israeli ARTS population indicate that coronary stenting and bypass surgery yield similar findings with regard to mortality and stroke and are comparable to those obtained in the whole study group. Likewise, coronary stenting was associated with an increased incidence of repeat revascularization procedures as compared to CABG. However, patients in Israel randomized to stenting had a higher rate of myocardial infarction as compared to the overall results and to patients who underwent CABG in Israel. The present analysis provides important data for the safety and efficacy of either stenting or bypass surgery in treating patients with multivessel disease in Israel.

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ARTS = Arterial Revascularization Therapies Study
CABG = coronary artery bypass graft surgery
PCI = percutaneous coronary intervention

Since Gruntzig performed the first percutaneous transluminal coronary angioplasty in a patient in 1977 as an alternative to coronary artery bypass graft surgery, the results have steadily improved. The number of patients with complex disease who undergo this procedure has substantially increased, due to the widespread use of stents and the introduction of potent adjuvant pharmacologic agents. Currently, more than 60% of all patients who undergo coronary artery revascularization by either CABG or percutaneous coronary intervention have multivessel disease that is amenable to treatment by either one of these procedures. The most appropriate type of treatment for these patients is still a matter of considerable debate. In experienced hands, both techniques are relatively safe, highly effective in reducing angina and have similar mortality and myocardial infarction rates, albeit fewer additional revascularization procedures in patients who undergo CABG [1–3].

The Arterial Revascularization Therapies Study [4] was a multicenter, randomized trial that was designed to compare PCI with stenting versus CABG in 1,205 patients with multivessel coronary artery disease. The purpose of the present study was to evaluate the clinical characteristics of patients enrolled in the ARTS trial in Israel, and to assess the 1 year outcome in these patients.

Patients and Methods

Study design

The details of the ARTS trial have been described previously [4,5]. In brief, a total of 1,205 patients with multivessel coronary artery disease, who were considered to be equally treatable with both modalities, were randomized to either stenting (n=600) or CABG (n=605) between April 1997 and June 1998 at 67 participating centers worldwide as part of the ARTS trial. Fifty-three patients at four participating medical centers in Israel were included in the study. Patients included in the study had stable or unstable angina, silent ischemia, with at least two lesions that were located in different vessels and territories that were potentially amenable to stent implantation. Patients excluded from the trial were those with left main artery disease, reduced left ventricular function (<30%), overt heart failure, prior cerebrovascular accident, recent myocardial infarction (less than a week), severe hepatic and renal dysfunction, or the need for major concomitant surgery. Conven-

tional balloon angioplasty was permitted in vessels with a diameter of 1.50–2.75 mm, as complementary to stenting, if at least two substantial lesions were targeted for stenting (each patient was required to have more than one stent). Bypass surgery was performed according to standard techniques, preferably using the left internal mammary to graft the left anterior descending coronary artery.

Clinical definitions

Clinical and angiographic data from all patients were analyzed and adjudicated by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands). Myocardial infarction was defined in the presence of documented new Q waves and either a ratio of serum creatinine kinase MB isoenzyme to total cardiac enzyme that was greater than 0.1 or a CK-MB value greater that 5 times normal values. Post-procedural non-Q wave MI was defined as a CK-MB enzyme elevation >5 times the upper normal value in the absence of new Q waves. A major adverse cardiac or cerebrovascular event – defined as death, stroke, transient ischemic attacks and reversible ischemic neurologic deficits, documented non-fatal myocardial infarction, or repeated revascularization (either percutaneous or surgical) – was the primary endpoint of this study.

Statistical analysis

Continuous variables are expressed as mean $\pm$ 1 standard deviation and categorical variables as percentages. Comparisons among the groups were performed by analysis of variance for independent samples and the chi-square test for comparison of categorical values. Cox proportional hazards methodology was used to develop models for 1 year mortality. Statistical analysis was performed with SAS software (SAS Institute, Cary, NC, USA). A P value <0.05 was considered significant.

Table 1. Baseline clinical characteristics

	Israel (n=53)		Whole study population (n=1,205)	
	Stenting (n=27)	CABG (n=26)	Stenting (n=600)	CABG (n=605)
Age (yrs)	60	63	61	61
Women (%)	30	27	23	24
Diabetes (%)	30	35*	19	16*
Hypertension (%)	41	46	45	45
Hyperlipidemia (%)	59	42	58	58
Family history (%)	26	35	39	42
Current smoker (%)	22	19	28	26
S/P myocardial infarction (%)	63	50	44	42
Stable angina (%)	37	50	57	60
Unstable angina (%)	63**	46	37**	35
Silent ischemia (%)	0	4	6	5

* P = 0.01, ** P = 0.006; all other values P = NS

Table 2. Angiographic characteristics

	Israel (n=53)		Whole study population (n=1,205)	
	Stenting (n=27)	CABG (n=26)	Stenting (n=600)	CABG (n=605)
Vessel territory				
LAD (%)	100	100	90	90
LCx (%)	93	88	71	72
RCA (%)	81	85	71	72
Bifurcation (%)	42	26	34	31
Total occlusion (%)	1	9	3	5
Ejection fraction (%)	59	60	61	60

LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery

Results

Clinical and angiographic characteristics

Data of the 53 consecutive Israeli patients who underwent either PCI with stents (n=27) or CABG (n=26) were available for analysis. For ease of interpretation of the data, they will be compared to the 1,205 patients who were recruited worldwide (PCI with stents, n=600; and CABG, n=605) [4]. The baseline clinical characteristics of all patients are shown in Table 1. There was a higher incidence of diabetic patients in Israel who were randomized to CABG, compared to worldwide (35% vs. 16%, P = 0.01). Although there was also a higher number of diabetic patients who underwent stenting in Israel, it did not reach statistical significance. Also, there were more patients in Israel who underwent stenting with unstable angina (63 vs. 37%, P = 0.006). In the CABG arm it did not reach statistical significance (46 vs. 35%, P = 0.2). Angiographic characteristics are shown in Table 2.

Clinical outcomes

One year clinical outcomes for all groups are shown in Figures 1 and 2 (only statistically significant values are shown). Overall, 12 month MACCE-free survival (including repeat revascularization procedures) was similar for patients who underwent stenting either in Israel or worldwide, whereas there was a non-significant lower incidence of MACCE in patients who underwent CABG in Israel compared to the whole study group (7.7 vs. 12.2%, P = 0.3). MACCE rates were significantly lower in patients who underwent CABG compared to those who had been randomized to stenting (33.3 vs. 7.7%, P = 0.0008), driven by a significantly higher incidence of repeat revascularization procedures in patients randomized to PCI and stenting (22.2 vs. 3.8%, P = 0.004) [Figure 2A]. Half of all patients who required repeat revascularization procedures in Israel (11.1%) underwent such procedures by PCI, whereas the other half underwent CABG (11.1%), and in the whole study group 12.7% had PCI and 4.7% CABG (P = NS). Also, there was a significantly higher incidence of myocardial infarction rates in patients assigned to stenting in Israel compared to those who underwent CABG in Israel (7.4 vs. 0%, P = 0.006) or the whole study group (7.4 vs. 5.3%, P = 0.01) [Figure 1B]. The rate of cerebrovascular accidents in

CK-MB = creatinine kinase MB
MI = myocardial infarction

MACCE = major adverse cardiac or cerebrovascular events

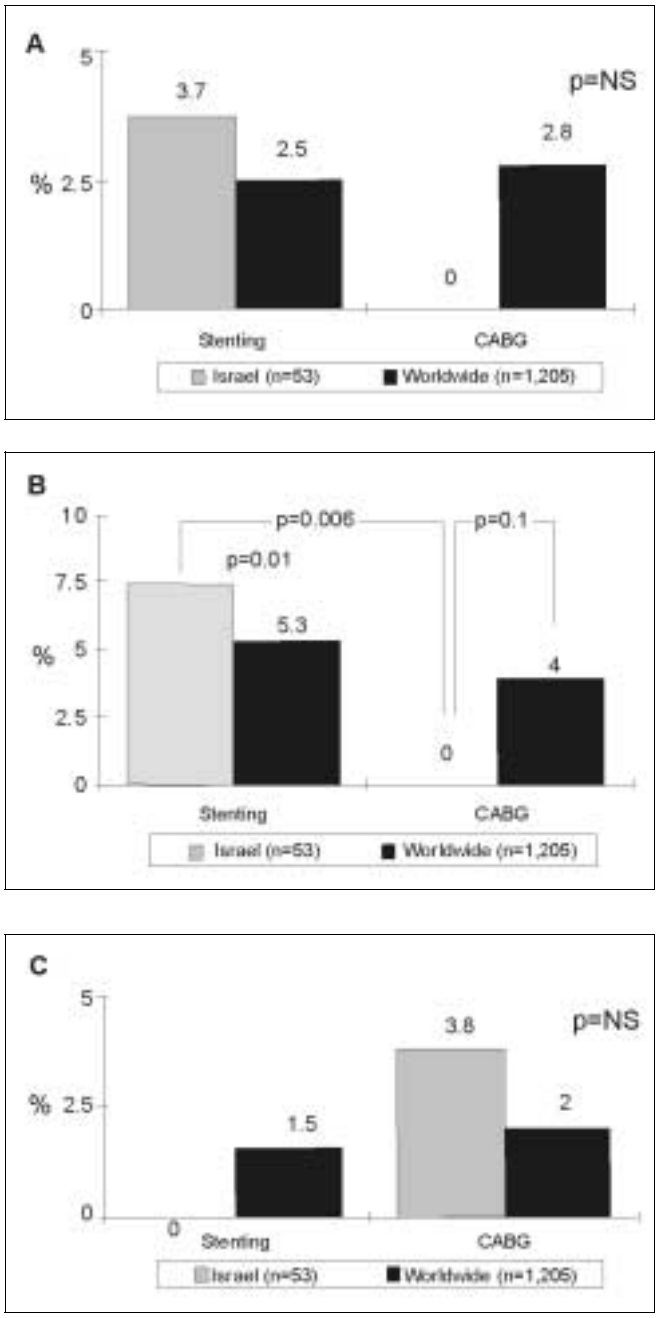

Figure 1. [A] One year mortality rates for patients randomized to PCI with stents or CABG in Israel (gray bars) or in the whole study population (black bars). **[B]** One year MI rates. **[C]** One year cerebrovascular accident rates.

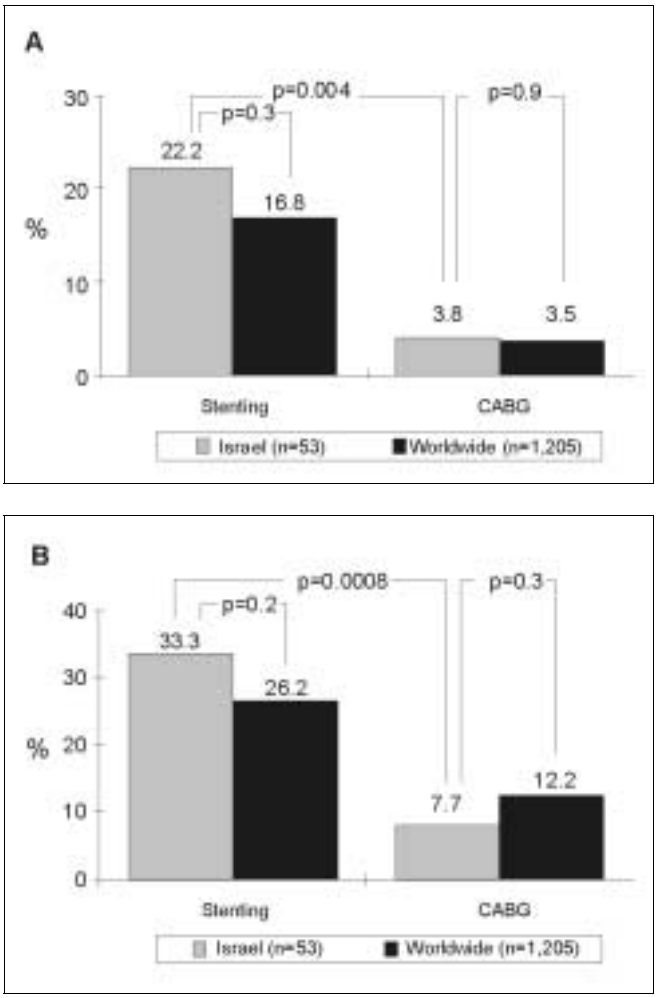

Figure 2. [A] One year repeat revascularization rates for patients randomized to PCI with stents or CABG in Israel (gray bars) or in the whole study population (black bars). **[B]** One year overall MACCE rates.

patients who underwent CABG was 3.8% compared to 0% in patients randomized to stenting (P = 0.15); this rate was higher than the 2.0% seen in the whole study group but did not achieve statistical significance (P = 0.37).

Discussion

In this study, we analyzed the clinical characteristics and clinical outcomes of patients who underwent coronary artery revascularization for multivessel disease in four medical centers in Israel as part of the ARTS trial. We observed that the Israeli patients had a higher incidence of diabetes and unstable angina compared to patients in the 67 participating centers worldwide. MACCE-free survival (including death, cerebrovascular events, myocardial infarction or repeat revascularization) was similar in patients who underwent stenting in Israel and worldwide. Similarly, patients who underwent CABG in Israel had equivalent outcomes as compared to patients who underwent the same procedure in other countries. On the other hand, patients randomized to CABG in Israel had a significantly better outcome when compared to patients who underwent stenting. It is important to note that the higher MACCE rates seen in patients randomized to PCI with stents was driven by a significantly higher rate of revascularization procedures and myocardial infarction in these patients. This may be explained by the significantly higher number of patients with unstable angina and diabetes enrolled in Israel. In the surgical group in Israel, the 1 year follow-up MACCE rates are remarkably low, especially regarding myocardial infarction and/or mortality. The increased

rate of MI in patients randomized to the stent arm in Israel compared to worldwide results and to CABG patients is disturbing. A possible explanation could be the small number of patients, but this should be addressed in future trials in Israel.

Previous studies

These results are consistent with previous reports that analyzed the outcomes of patients who underwent coronary artery revascularization with either balloon angioplasty or CABG. It is important to note that few trials have directly compared the outcomes of patients who undergo stenting in comparison to CABG, as previous trials were performed in the era before the stent was introduced. Two other recently published studies have compared the use of stents to CABG. The ERACI II Study was a multicenter randomized trial that compared PCI using stents versus coronary artery bypass graft surgery [3]. A total of 405 patients with multivessel disease were randomized to either stenting or CABG. The composite primary endpoint was the occurrence of a major adverse cardiac event, defined as death, Q wave myocardial infarction, or stroke at 30 days. Follow-up was obtained at 1, 3 and 5 years. Survival at long-term follow-up (18.5 $\pm$ 6.4 months) was 96.9% for patients randomized to the stents vs. 92.5% for patients randomized to the surgical arm ($P < 0.017$). Moreover, in this trial there was a significantly higher rate of revascularization procedures in patients randomized to PCI with stents. The AWESOME Trial was a multicenter study in 454 patients with medically refractory ischemia and a high risk of adverse outcomes [6]. Patients were randomized to either PCI strategy, which could include stents (n=222), or to CABG (n=232). Survival was identical at 36 months follow-up (79 vs. 80%, $P = 0.46$) for both groups, respectively. A survival free of unstable angina and survival free of unstable angina or repeat revascularization were significantly better among patients randomized to CABG [6]. A smaller trial of 200 patients from Korea that compared multivessel stenting vs. CABG showed that there was no significant difference in cardiac events in both groups at 2 year follow-up, albeit a higher rate of recurrent angina (19 vs. 8%, $P = 0.03$) and target lesion revascularization (19 vs. 2%, $P < 0.01$) in each arm, respectively [7].

The present study was a subgroup analysis in a limited number of patients, and therefore the results and conclusions are subject to the limitations inherent in all such reports. Only 53 patients were enrolled in Israel (4.4% of the whole patient population), which markedly reduces the comparative power of the study. Nevertheless, we were able to demonstrate significant differences between the groups.

Conclusions

This study suggests the following:

- In a large population of patients with multivessel disease, multiple stenting as an alternative to CABG is technically feasible and can be performed safely, with a high rate of procedural success and an acceptable rate of peri-procedural and long-term complications.
- There was no significant difference between the groups in the combined rate of death, stroke, and myocardial infarction in Israel, which was similar to the results achieved worldwide.
- Patients randomized to stenting had a significantly higher incidence of myocardial infarction and repeat revascularization procedures compared to patients assigned to bypass surgery
- The preferred means of repeat revascularization procedure was PCI for all patients worldwide, whereas in Israel half of all patients were referred to CABG and the other half underwent repeat PCI.
- There was a trend towards lower MACCE rates in patients who underwent CABG in Israel compared to those in the whole study group. At present, both techniques are complementary, and the results achieved in Israel represent the high level of cardiovascular care in our country. With current revascularization patterns, we can be assured that stenting in patients with multivessel stenting is as safe and effective as bypass surgery.

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References

1. The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 2000;35:1122–9.
2. King SB III, Kosinnski AS, Guyton RA, Lembo NJ, Weintraub WS, for the Emory Angioplasty versus Surgery Trial (EAST) Investigators. Eight year mortality in the Emory Angioplasty versus Surgery Trial (EAST). *J Am Coll Cardiol* 2000;35:1116–21.
3. Rodriguez A, Bernardi V, Navia J, et al., for the ERACI II Investigators. Argentine Randomized Study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II): 30-day and one-year follow-up results. *J Am Coll Cardiol* 2001;37:51–8.
4. Serruys PW, Unger F, Sousa E, et al., for the Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med* 2001;344:1117–24.
5. Costa MA, Carere RG, Lichtenstein SV, et al. Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). *Circulation* 2001;104:2689–93.
6. Morrison DA., Sethi G, Sacks J, et al., for the Investigators of the Department of Veterans Affairs Cooperative Study 385: the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. *J Am Coll Cardiol* 2001;38:143–9.
7. Kim SW, Hong MK, Lee CW, Park SW. Multivessel stenting versus bypass surgery in patients with multivessel coronary artery disease and normal left ventricular function: immediate and 2-year long-term follow-up. *Am Heart J* 2000;139:638–42.

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