

In-Depth Late-Breaking Clinical Trials II: BEST, PRAGUE-4, Euro-SPAH, OPTIMAAL, ACE

Luis Gruberg, MD [Disclosures](#)

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Chairpersons: *J.F. Martin (London, GB) and L. Erhardt (Malmo, SE)*

Balloon Equivalent to Stent (BEST)

Presenter: F. Schiele (Besancon, FR)

Background

Intravascular ultrasound (IVUS) provides very important and useful data about the lumen and the wall of the coronary arteries. Furthermore, it provides vital information during the angioplasty and/or stenting of the lesion(s), and thus it is believed to improve the outcomes post-percutaneous coronary intervention (PCI).

Methods

The purpose of the BEST trial was to compare the angiographic, IVUS, and clinical outcomes of systematic stent use to those of IVUS-guided balloon angioplasty. A total of 254 patients were randomized to IVUS-guided balloon angioplasty (n = 132) or stenting (n = 122). At 6 months, quantitative coronary angiography (QCA) analysis was performed to measure the rate of restenosis and the minimal lumen diameter of treated vessels. In addition, clinical event-free rate was assessed at 1 year.

Patients with angiographic lesions < 20 mm in length and > 3.0 mm in diameter by visual estimation were included in the study. Heavily calcified, angulated, ostial, or bifurcation lesions were excluded. Stents were implanted only under angiographic guidance. Patients in the balloon group had balloon sizing according to IVUS before balloon angioplasty was performed, and patients were crossed over to the stent arm if they had a residual stenosis > 30% by online QCA analysis or a > 30% area stenosis by IVUS.

Results

The patients in the 2 arms were similar with regard to baseline clinical characteristics, as shown in Table 1.

Table 1. BEST Baseline Clinical Characteristics

	Balloon (n = 132)	Stent (n=122)	P
Age (yrs)	62	61	0.7

Female (%)	16	16	0.9
Diabetes (%)	20	11	0.1
Hyperlipidemia (%)	60	62	0.8
Hypertension (%)	45	40	0.5
Active smoking (%)	52	52	0.9
Unstable angina (%)	27	17	0.06
LAD lesion (%)	39	34	0.35
RCA lesion (%)	45	49	0.35
LCx lesion (%)	15	16	0.35

LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

For patients randomized to the IVUS-guided angioplasty, failure to cross the lesion *prior* to the procedure occurred in 4% of cases, 3% *after* balloon angioplasty, and 3% following stenting. Among the IVUS-guided procedures, stents were implanted in a total of 37 cases (29%), 28 cases (22%) because of an unsatisfactory angiographic result, and 9 cases (7%) due to occlusive dissection. Additional procedural results are shown in Table 2, and 6-month outcomes are reported in Table 3.

Table 2. BEST Procedural Results

	Balloon (n = 132)	Stent (n = 122)	P
Balloon nominal size	3.6 +/- 0.52	3.37 +/- 0.47	.003
Stenting rate (%)	44	100	.001
Glycoprotein IIb/IIIa (%)	11	6.5	.2
Minimal lumen diameter (post) (mm)	2.55 +/- 0.49	2.75 +/- 0.49	.013
Diameter stenosis (post) (%)	16 +/- 7	13 +/- 6	.001
Lesion cross sectional area (post) (mm ²)	6.60 +/- 2.05	7.28 +/- 2.22	.02

Table 3. BEST 6-Month Results

	Balloon (n = 132)	Stent (n = 122)	P
Minimal lumen diameter (post) (mm)	1.97 +/- 0.72	2.03 +/- 0.62	.38
Diameter stenosis (post) (%)	31 +/- 20	28 +/- 17	.14
Lesion cross-sectional area (post) (mm ²)	5.12 +/- 2.80	5.24 +/- 2.51	.57
Late loss (mm)	0.56 +/- 0.60	0.71 +/- 0.54	.06
In-stent restenosis	5.0	15.6	.045

The primary end point, 6-month restenosis (defined as > 50% diameter stenosis at follow-up), was 18.1% in the stent group vs 16.8% in the balloon group, and according to the study design, non-inferiority was achieved (< 8% difference).

Conclusions

IVUS-guided balloon angioplasty with provisional stenting:

1. Is a safe, yet complex and operator dependent procedure
2. Leads to similar long-term results as systematic stenting
3. Yields a lower incidence of restenosis at 6 months
4. May or may not have an impact in the era of drug eluting stents

In his commentary on the BEST study, B. Meier (Berne, CH) stated that the idea behind the trial was interesting in the sense that it challenged the established benchmark of therapy -- systemic stenting. However, he believes that while the results were convincing, the procedure may be unaffordable, especially with respect to the emergence of drug-eluting stents, adding that investigators would not be able to show non-inferiority to the new therapy. Therefore, he concluded, the study is already obsolete. However, Meier was apt to point out that the emergence of drug-eluting stents does not mean in any way that every single lesion should be stented. Approximately 70% of all lesions that undergo balloon angioplasty have a perfect result, and therefore do not require stenting.

The PRimary angioplasty in AMI patients from General community hospitals transported to PCI Units versus Emergency thrombolysis (PRAGUE-4)

Presenter: P. Widimsky (Prague, CZ)

Background

Surgical coronary artery revascularization has had to undergo a series of changes to be able to challenge the increasing use of percutaneous techniques for coronary artery revascularization. One such technique has been the implementation of coronary artery bypass graft (CABG) surgery without the use of heart lung machine (off-pump). PRAGUE-4 was designed to determine whether off-pump CABG is as effective and safe as performing the surgery using the cardiopulmonary bypass pump.

Methods

PRAGUE-4 was a randomized, single-center study in which patients were randomized by the cardiac surgeon to either on-pump CABG (n = 203) or off-pump (n = 185), and the surgeon had the capacity to change the technique at any time if considered necessary (Figure 1).

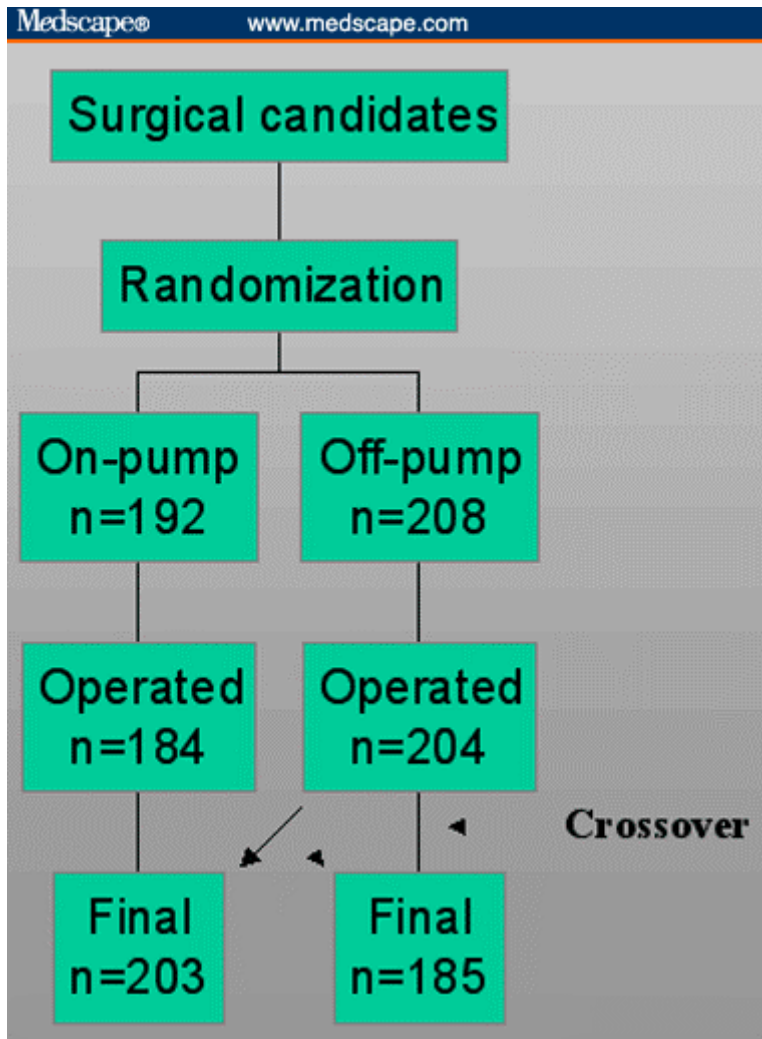


Figure 1. PRAGUE-4: Study Design.

Results

The clinical characteristics of the patients and their respective procedures were similar in both arms, including those with distal anastomoses (Table 4).

Table 4. Clinical and Procedural Characteristics

	On-Pump (n = 203)	Off-Pump (n = 185)
Age (yrs)	62	62
Female (%)	16	22
Diabetes (%)	30	28
LIMA used (%)	91	97
Distal anastomosis	2.8	2.1
Length of stay (days)	6.8	5.8
Cost (Euro)	5757	3777

LIMA = left internal mammary artery.

There was no significant difference between on-pump and off-pump on either an intention-to-treat or actual treatment basis, with respect to the primary composite end point of incidence of death, myocardial infarction (MI), stroke, and hemodialysis at 30 days (Figure 2). However, a clear trend for lower rates of adverse events were noted in patients randomized to off-pump CABG ($P = .12$). The individual end points of mortality, stroke, MI, and hemodialysis (Figures 3 and 4) at 30 days were also similar in both groups.

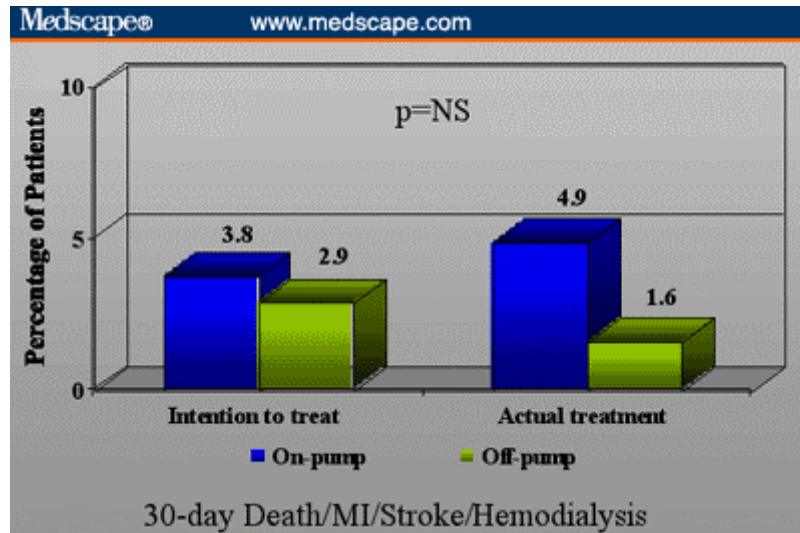


Figure 2. PRAGUE-4: Intention to Treat vs. Actual Treatment.

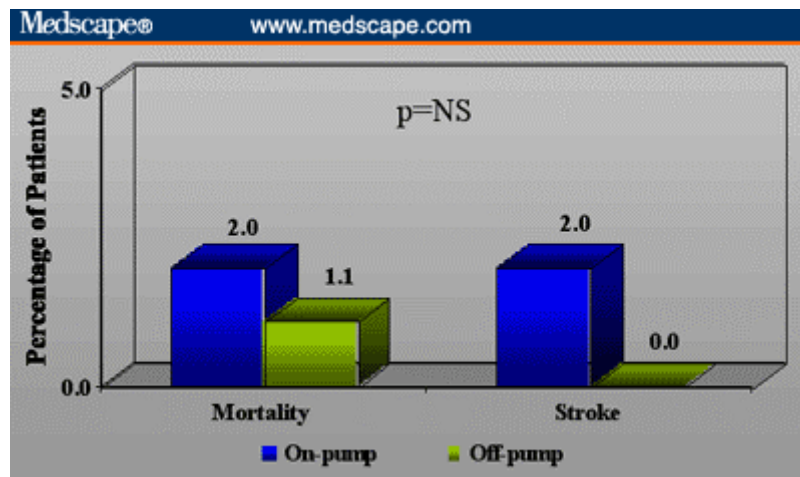


Figure 3. PRAGUE-4: 30-day Outcomes (Mortality & Stroke).

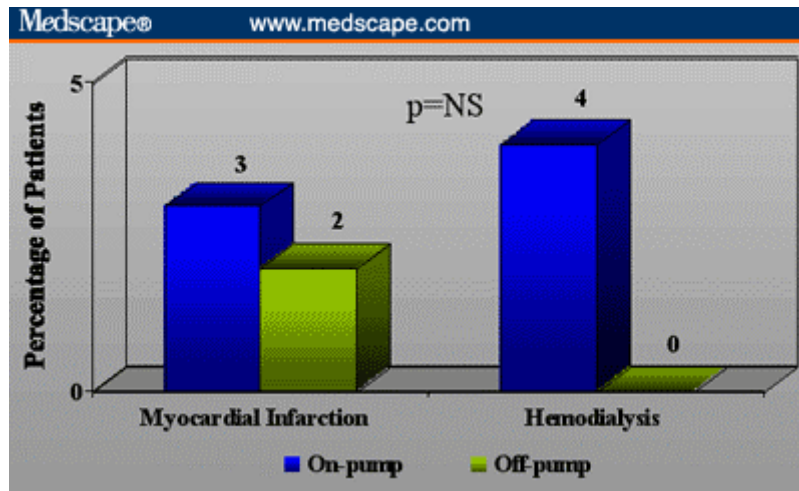


Figure 4. PRAGUE-4: 30-day Outcomes (MI & Hemodialysis).

Conclusions

PRAGUE-4 demonstrated that off-pump CABG is:

1. Applicable in 84% of surgical candidates for coronary artery revascularization;
2. Significantly more cost-effective;
3. As effective and safe as traditional on-pump surgery; and
4. Associated with a positive trend toward decreased rates of adverse events at 30 days compared with on-pump.

In commenting on the PRAGUE-4 results, Dr. P.P.T. De Jaegere (Utrecht, NL) noted that approximately 800,000 CABG surgeries are performed each year, with perioperative complications known to occur in as many as 35% of procedures. In addition, the costs associated with hospitalization following the surgery are incredibly high, considering the fact that about 10% of patients remain in the hospital longer than 14 days following surgery. Given these statistics, and the results from PRAGUE-4, De Jaegere believes that an off-pump approach offers some significant advantages, including the fact that it is safer, more effective, cheaper and better tolerated by the patient. Questions remain, however, regarding degree of revascularization and quality of anastomosis.

Euro-SPAH: A European Trial on the Anti-Restenotic Effect of Intravascular Sonotherapy (IST) After Multivessel Stenting of de Novo

P.W. Serruys (Rotterdam, NL)

Background

Sonotherapy has a series of unique effects that may prevent restenosis after revascularization injury. It has a mechanical effect by inhibiting adhesion and migration of smooth muscle cells (SMC) in vitro and possesses an antiproliferative effect by producing microtubule and microfilament disassembly in SMCs and a healing effect, without inducing cell toxicity. Preclinical trials have shown a 50% reduction in mean intimal thickness in stented pig arteries treated with 1 Mhz intravascular sonotherapy (IST), compared with those who did not receive the treatment. The sonotherapy catheter is a simple device, consisting of a 5F monorail type, which is 132 mm in length and has 6 piezo-electric crystals.

Methods

Euro-SPAH was a prospective, randomized, multicenter, double-blind trial in 23 centers in 9 European countries that randomized a total of 403 patients with multiple de novo lesions or nonstented restenotic lesions to either IST (n = 202) or sham (n = 201) treatment. Angiographic and IVUS follow-up was conducted at 6 months, and clinical follow-up was performed at 1, 6, and 12 months. Efficacy of the trial was based on a 25% reduction in late loss at 6-month angiographic follow-up.

Results

The baseline clinical characteristics of the patients, by stratum, were similar, as shown in Table 5.

Table 5. Euro-SPAH: Baseline Clinical Characteristics

	IST (n = 202)	Sham (n = 201)
Age (yrs)	61	62
Female (%)	22	21
Diabetes (%)	17	15
Hyperlipidemia (%)	79	80
Hypertension (%)	58	56
Smoking (%)	65	68
Previous CABG (%)	4	2
Previous PTCA (%)	17	15
Unstable angina (%)	29	26
Lesion Location:		
LAD:	42	46
RCA	37	34
LCx	21	20
Lesion Type:		
Type A	5	6
Type B1	26	29
Type B2	61	59
Type C	8	5

CABG = coronary artery bypass graft; LAD = left anterior descending artery; LCx = left circumflex artery; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.

Angiographic follow-up was available for 181 of the 202 patients enrolled in the IST group and for 181 in the sham procedure group. Consistent throughout all analyses conducted by QCA, while not significant, there was a positive trend indicating reduced restenosis rates for in-stent (Table 6), IST-treated (Table 7), and vessel segment analyses (Table 8).

Table 6. Euro-SPAH In-stent Restenosis Rates by QCA

	IST (n = 202 lesions)	Sham (n = 219 lesions)	P
Late loss (mm)	0.86	0.94	.09
Late loss index	0.56	0.60	.23
Restenosis rate (%)	23	25	.73

Table 7. Euro-SPAH: IST-treated Segment by QCA

	IST	Sham	P
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	(n = 202 lesions)	(n = 219 lesions)	
Late loss (mm)	0.61	0.65	.39
Late loss index	0.54	0.58	.68
Restenosis rate (%)	23	28	.31

Table 8. Euro-SPAH: Vessel Segment by QCA

	IST (n = 202 lesions)	Sham (n = 219 lesions)	P
Late loss (mm)	0.42	0.47	.26
Late loss index	0.43	0.50	.54
Restenosis rate (%)	25	28	.44

In assessing clinical outcomes, a significant reduction (39%, $P = .02$) in the need for revascularization was noted in the IST group and resulted in a 27% reduction in major adverse cardiac events (MACE), based on intention-to-treat analysis (Table 9 and Figure 5).

Table 9. Euro-SPAH: MACE at 210 Days

	IST (n = 202 lesions)	Sham (n = 219 lesions)	RR (95% CI)
Death (%)	1.0	1.0	1.0 (0.1-7.0)
Q-wave MI (%)	1.5	1.5	1.6 (0.5-4.8)
Revascularization (any) (%)	14.4	23.4	0.61 (0.4-0.9)
MACE (%)	18.8	25.9	0.73 (0.5-1.1)

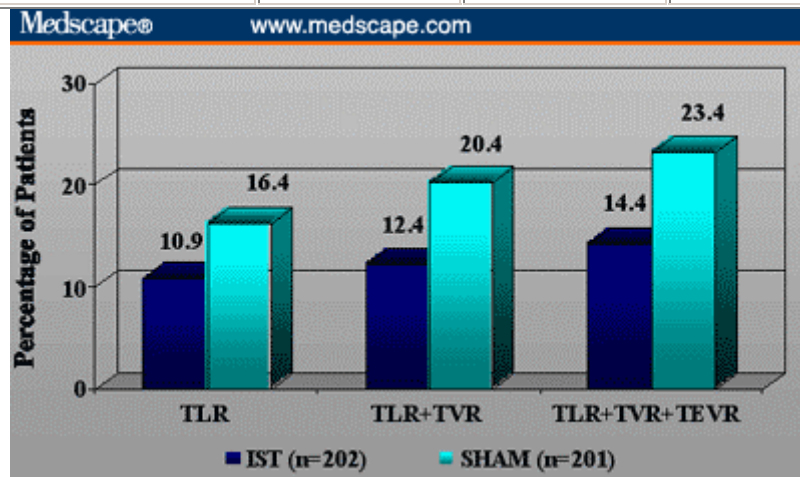


Figure 5. Euro-SPAH: Revascularization at 210 days.

Conclusions

Euro-SPAH demonstrated that:

1. IST is feasible and safe, based on the lack of side effects;
2. The expected difference in in-stent late loss (0.21 mm) was not achieved (primary end point of the study), and only an actual difference of 0.08 mm was observed in favor of the IST group;
3. Qualitative angiographic parameters measured showed a trend in favor of IST; and

4. IST significantly reduced the need for revascularization, and subsequently lowered the incidence of MACE.

Dr. K.A. Karsch (Bristol, GB), in commenting on the results of Euro-SPAH, noted that because there is limited background data published on the effect of IST on restenosis and neointimal hyperplasia, a series of future trials will be necessary to address outstanding concerns regarding the efficacy of the IST. Prior to greater acceptance, issues such as identifying the exact mechanisms involved, determining the optimal level of ultrasound power to use, and the optimal duration of administration require future investigation.

Comparison of the Effects of Losartan and Captopril on Mortality and Morbidity in Patients Following Acute Myocardial Infarction: the OPTIMAAL Trial

K. Dickstein (Stavanger, NO)

Background

In large randomized clinical trials, angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce mortality in high-risk post-MI patients. Selective angiotensin II receptor antagonists are also an available alternative because they are known for more complete blockade of the tissue renin-angiotensin-aldosterone system, and also because they are better tolerated by patients.

Methods

OPTIMAAL, a double-blind, randomized, parallel, multicenter study, was conducted to compare the effects of losartan (50 mg, n = 2744) to those of captopril (150 mg, n = 2733) on all-cause mortality in high-risk acute MI (AMI) patients, who also had either heart failure or new anterior wall Q-wave MI.

A non-inferiority margin of 10% was chosen based on placebo-controlled trials, and analysis was performed by intention-to-treat. Prespecified end points of the study included:

- All-cause mortality;
- Sudden cardiac death/resuscitated cardiac arrest;
- Reinfarction;
- Reinfarction/all-cause mortality;
- Cardiovascular mortality;
- Stroke;
- Revascularization;
- First all-cause hospitalization; and
- Safety and tolerability

Results

The clinical characteristics of the patients in both arms were similar (Table 10).

Table 10. OPTIMAAL: Clinical Characteristics

	Losartan (n = 2744)	Captopril (n = 2733)
Age (yrs)	68	67
Female (%)	28	29
Diabetes (%)	18	17
Hypertension (%)	36	36
Dyslipidemia (%)	42	41
Previous infarction (%)	18	18

Thrombolytic use (%)	54	55
Time to randomization (hrs)	85	85

After a mean follow-up period of 2.7 years, there were 946 deaths, 763 reinfarctions, 272 strokes, 9183 hospitalizations, and only 1 patient was lost to follow-up.

The Kaplan-Meier curves at 7 months started to divide in favor of captopril, although it did not reach statistical significance (relative risk [RR]= 1.13, CI = 0.99-1.26, $P = .069$). After this time, the curves remained identical. All-cause mortality was 18.2% in the losartan group and 16.4% in the captopril group at 36-month follow-up. When analysis was performed by early events (< 210 days) and late events (> 210 days) for all-cause mortality, 9.4% of all deaths in the losartan group occurred within 210 days vs 7.5% in the captopril group. After 210 days, mortality rate in the losartan group was 8.9% vs 8.8% in the captopril group. For sudden cardiac death/resuscitated cardiac arrest, the pattern was also very similar, 8.7% vs 7.4%, respectively (RR = 1.19, CI = 0.99-1.43, $P = .07$). Likewise, for reinfarction, the ratio was similar, 14.0% vs 13.5%, respectively (RR = 1.03, CI = 0.99-1.18, $P = .72$). The only outcome that was statistically significant, however, was cardiovascular death, with fewer deaths in the losartan group (15.3%) compared with captopril (13.3%) (RR = 1.17, CI = 1.01-1.34, $P = .032$). Of note, drug discontinuation was significantly higher in the captopril group.

Conclusions

The results from OPTIMAAL indicate that:

1. There was a nonsignificant trend toward decreased all-cause mortality in favor of captopril;
2. There was a significantly higher incidence of cardiovascular mortality in patients randomized to losartan;
3. Both drugs were essentially the same when reinfarction, stroke, revascularization and all-cause hospitalization were analyzed;
4. There was a significantly better tolerability to losartan, with less discontinuation of the treatment due to adverse events; and
5. ACE inhibitors should remain the first line of therapy in patients after complicated AMI, and losartan should not be generally recommended in this population.

Dr. H. Drexler (Hannover, DE), in his commentary on the study, stated that although OPTIMAAL was a well-designed study, one should not be surprised by the results. He attributed the findings to the low dose of losartan (50 mg) prescribed in the study. For instance, in the LIFE and RENAAL studies, losartan was used at a dose of 100 mg, and showed a significant benefit. Drexler also believes that the role of bradykinins is a factor that needs consideration. Overall, Drexler does not believe that angiotensin blockers have a role in post-MI patients, with the exception of those with intolerance to ACE inhibitors. He stressed that ACE inhibitors continue to be the drug of choice in post-MI patients.

Anticoagulation for Cardioversion Using Enoxaparin (ACE Trial)

C. Stellbrink (Aachen, DE)

Background

Embolic events are a major concern in patients with atrial fibrillation (AF). Currently, patients who will undergo cardioversion are treated with at least 3 weeks of combination therapy consisting of heparin and coumadin. Present problems encountered in patients with AF include a long delay because of the need for anticoagulation, the need for frequent monitoring, the risk of bleeding and embolization, and a high recurrence rate due to the long delay. New alternatives include transesophageal echocardiography (TEE)-guided cardioversion and new antithrombotic agents.

Methods

Anticoagulation for Cardioversion using Enoxaparin (ACE) was a prospective, randomized, open-label, multicenter trial that examined whether subcutaneous low-molecular-weight heparin (enoxaparin) could be used instead of the combination of unfractionated heparin and phenprocoumon in cardioversion of nonvalvular AF.

The study was designed such that heparin was administered as an IV bolus 80 U/kg and continued as an infusion 18 U/kg/h for > 72 hours overlapping with phenprocoumon (INR = 2-3) for the rest of the study's duration (Figures 6 and 7). Enoxaparin was administered subcutaneously at a dosage of 1 mg/Kg twice daily for 3-8 days and then 40 mg (for patients weighing < 65 kg) or 60 mg/kg (for patients heavier than 65 kg) for the rest of the study. The primary end point of the study consisted of a composite of cerebrovascular ischemic events, systemic thromboembolism, major bleeding complications, and death (any cause). Secondary end points included:

- Successful cardioversion;
- Sinus rhythm at the end of the study;
- Other bleeding complications; and
- Large injection hematoma

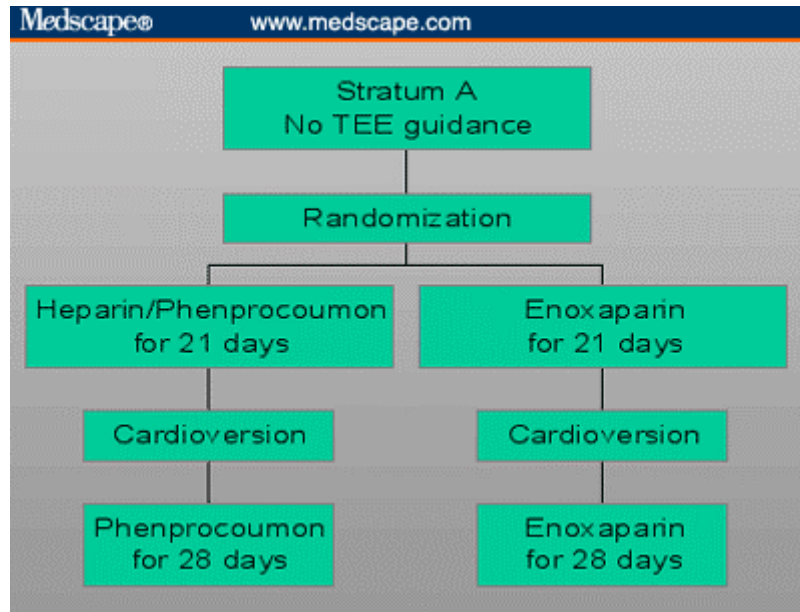


Figure 6. ACE Trial: Study Design.

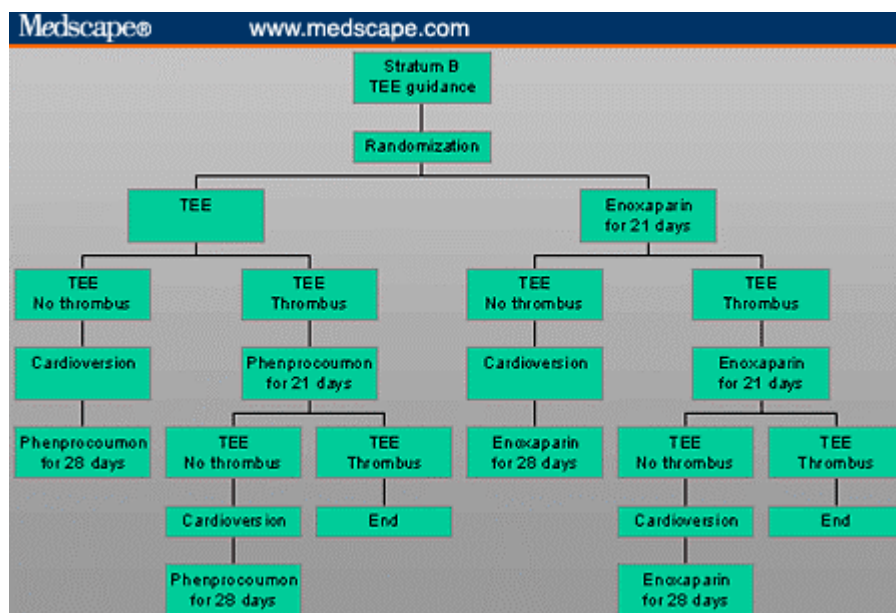


Figure 7. ACE Trial: Study Design II.

Results

The baseline clinical characteristics of the patients in both arms were similar, except for a higher incidence of heart failure in the enoxaparin group (Table 11).

Table 11. ACE: Baseline Clinical Characteristics

	Heparin/phenprocoumon (n = 248)	Enoxaparin (n = 248)
Age (yrs)	65	66
Female (%)	19	19
Heart failure (%)	24	33
Hypertension (%)	73	73
LA diameter (mm)	44	44
LV hypertrophy (%)	43	37
AF duration (days)	11	15

AF = atrial fibrillation; LA = left atrial; LV = left ventricular.

Although the incidence of the combined end point was higher in the heparin/phenprocoumon group, it did not achieve the 2% requirement for the non-inferiority test (Figure 8). The individual primary end points are shown in Figure 9.

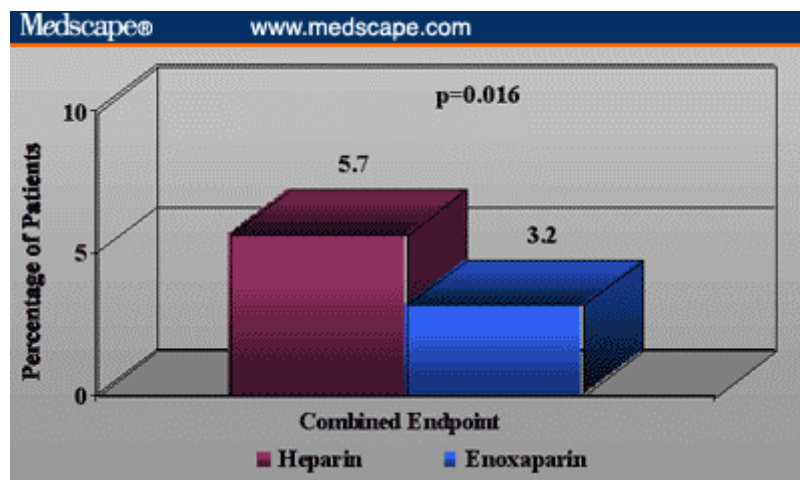


Figure 8. ACE Trial: Combined Endpoint.

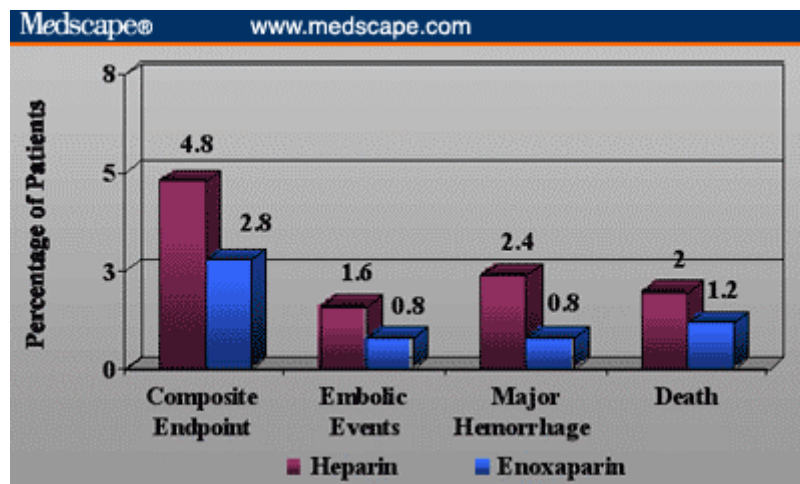


Figure 9. ACE Trial: Individual Endpoints.

Conclusions

Based on the results of the ACE trial:

1. Enoxaparin is non-inferior to the combination of heparin/phenprocoumon for the prevention of bleeding embolic and complications during cardioversion for nonvalvular AF; and
2. Enoxaparin offers ease of administration and reduces the need for anticoagulation monitoring.

According to L.C. Wallentin (Uppsala, SE) in his commentary, low-molecular-weight heparin seems to be replacing unfractionated heparin for most indications of cardiovascular diseases, such as for the prevention of venous thrombosis and pulmonary thromboembolism, in acute coronary syndromes, ST-segment elevation MI (with and without thrombolytic therapy), PCI, and cardioversion in patients with AF. The problem associated with conducting AF conversion trials, Wallentin believes, is the low rate of thromboembolic and bleeding complications, combined with a low mortality rate and a high recurrence rate. In the ACE trial, 86% of patients were treated in Stratum B (TEE-guided), therefore there is little information regarding patients without TEE-guided cardioversion. Based on the results of this trial, compared with heparin/phenprocoumon, one can say that enoxaparin has at least a similar safety profile, probably the same efficacy, may shorten the length of hospitalization, and may influence the economic component of the treatment of these patients. Therefore, Wallentin concluded that confirmatory studies are needed.