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## The Comparison of Restenosis Rates of Endarterectomy and Stent Following Carotid Artery Stenosis

The article *"Carotid Revascularization Endarterectomy vs. Stenting Trial"* (CREST) comparing endarterectomy and stenting in the carotid artery showed no difference between the two methods in the primary termination points of myocardial infarction, stroke or mortality rate (1). In the secondary analyses, it was shown that stroke is more likely after stroke and myocardial infarction is more likely after endarterectomy.

Previous studies reported the stenosis frequency at 5-10% for either one of these methods. In the CREST study, the results showing that the two revascularization methods did not differ at the primary termination point raised the importance of the question of a possible difference in the long-term restenosis frequency between the methods. Lal et al. published an article in Lancet in 2012 on the restenosis risk in the two year follow-up of the CREST study (2).

In the CREST study, 2287 patients coming from 117 centers across the USA and Canada between 2000 and 2008 were randomized into carotid artery stent and endarterectomy groups. The study included both symptomatic and asymptomatic patients. For the symptomatic patients, the patient had to have at least 50% carotid artery blockage in the conventional angiography, or 70% in the ultrasonography, computerized tomography (CT) or magnetic resonance (MR) angiography in order to be included in the study. In the asymptomatic patients, the inclusion criteria were 60% carotid artery blockage in angiography, 70 in ultrasonography and 80% in CT or MR angiography. The procedure was conducted in the 2 weeks following the randomization.

Carotid endarterectomy was conducted as standard or aversion endarterectomy. Stenting was done using a self-expanding nitinol stent and an emboli prevention device (RX Acculink ve RX Accunet, Abbott Vascular, Santa Clara, USA). Doppler ultrasonography was conducted before the procedure and repeated on the 1st, 6th, 12th, 24th and 48th months. The primary termination point of the study was the 70% or higher restenosis frequency following either one of the procedures.

At the end of the study, despite the lack of a significant difference between the groups in terms of basal demographic properties, it is interesting that endarterectomy group patients had their procedures later than the stent group patients. In addition, stent patients received more antiaggregant drugs compared to endarterectomy patients.

After 17.2 months on average, 58 of the stent and 62 of the endarterectomy patients showed restenosis or occlusions. According to Kaplan-Meier prediction, the restenosis or occlusion frequency at the end of two years would be 6% for the stent group and %6.3 for the endarterectomy group (hazard rate 0.90, 95% confidence interval 0.63-1.29, p=0.58). The number of restenosis was 56 in the stent group and 57 in the endarterectomy group. There were no significant differences between the groups in terms of occlusion.

According to Kaplan-Meier prediction, the restenosis or occlusion frequency at the end of four years would be 6.7% for the stent group and %6.2 for the endarterectomy group (hazard rate 0.94, 95% confidence interval 0.66-1.33, p=0.71). In a multivariate analysis, it was found that women, diabetics and dyslipidemic patients had higher risk for reaching the shared outcome.

Furthermore, there was no difference between symptomatic and asymptomatic patients in terms of restenosis rates (p=0.11). However, smoking remained risky for the stent group while it is not risky for the endarterectomy group. There were no difference between groups in terms of patients who needed a repetition of the procedures. Twenty of the patients required restenting and 23 required re-endarterectomy (p=0.69).

CREST study defined restenosis as the as least 3.0 m/s peak systolic velocity. However, in the "Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis" (EVA-3S) study, peak systolic velocity threshold for the carotid artery stent group was 3.0 m/s while it was 2.1 m/s in the endarterectomy group. The reason for this was the increased blood flow speed in the stented vessels.

The restenosis rates according to hemodynamic criteria at the end of two years was 10.7% for the stent group in the study "Stent-protected Angioplasty versus Carotid Endarterectomy"(SPACE), and 4.6% in the endarterectomy group (p<0.001). When they used the 2.1 m/s peak systolic velocity, CREST researchers saw that the restenosis rates for the stent group becomes 14.8% and 10.5% for the endarterectomy group (p=0.02). This finding is compatible with the results of the SPACE study. In the CAVATAS study, this threshold was also used. In short, restenosis rates are closely related to the peak velocity rates assumed in the Doppler ultrasonography and the threshold values used in the CREST study were actually much higher than the preceding studies. This is possibly another justification for the lack of significant differences between the groups.

In summary, Lal et al.'s study highlights two important findings: 1) carotid artery stenting or endarterectomy did not cause differences between the groups, 2) women, diabetics and dyslipidemics are under increased risk in both of these groups while smokers are under increased risk only in the endarterectomy group.

## References

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## The Effect of Interferon Beta 1-b on the Survival of Patients with Multiple Sclerosis

Numerous studies showed how immunomodulating drugs decrease disease activity and slow down the rate of debilitation in multiple sclerosis (MS). However, the effects of these treatments on the long-term debilitation are not fully known. The role of early treatment on the survival is also completely unknown. In their study published last year in Neurology, Goodin et al compared the life spans of patients using interferon beta-1b in their pivotal study with those who used placebo (1).

372 relapsing remitting MS (RRMS) patients with attacks coming from 11 centers across North America participated in the study. These patients received 50 or 250 µg interferon beta-1b until the year 1993. The choice of treatment following the study was left to the treating centers. It was seen that interferon beta-1b was used exclusively at the beginning and immunomodulatory drugs became commercially available after 1996.

In this study that was completed 20 years ago, all of the 372 patients except for 6 were contacted again. At the end of the study it was seen that 81 out of 366 were found to be dead (22.1%). There were no differences between the placebo group and the interferon beta-1b groups in terms of basal properties. Mortality was higher in the placebo group, than the 250 µg interferon beta-1b group (hazar rate 0.532, 95% confidence interval 0.314-0.902, p=0.02). This condition corresponds to a 46.8% drop in the hazard rate between the two groups. The same result was also observed on the patients taking 50 µg interferon beta-1b (46% drop in hazard rate).

It is interesting that the survival rates in the Cox models were higher for the patients who took 250 µg compared to those who took 50 µg. In addition, it was found that patients with lower EDSS, smaller T2 lesion load and ventricle volume in the MRI had higher survival rates. Even the presence of interferon neutralizing antibodies was seen to be ineffective in changing the survival rates.

Numerous random controlled studies showed the positive effect of interferon beta-1b on clinical and MRI outcome parameters. Since this effect is more pronounced in the 250 µg dosage, this usage was able to become more prolific.

In conclusion, interferon beta-1b treatment produces 46.8% drop in the hazard rates for the 250 µg dose and 46% drop for the 50 µg dose. The 29 year survival rate of 70% observed in the study is in line with the 70.4% survival rate observed in the natural course studies. After the end of pivotal studies, there were no differences found between the placebo and the treatment groups. This is another evidence supporting the benefits of an early start to the interferon treatment. Furthermore, since the onset parameters like T2 lesion load and MRI ventricle volumes do not affect the risk, it is possible to argue the causes of mortality for the patients were related to processes involving the progress of MS.

It is interesting that even the smaller dose of interferon has a positive effect on survival. Over 21 years, the placebo group received 6.9 years, 50 µg group 13.6 years, and 250 µg group 12 years of interferon treatment on average. Because of this, it is not possible to say whether the extended life span of the active treatment patients seen in pivotal studies is due to the extended treatment duration or the early onset of the treatment.

## References

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