Title: ESC 23: Day 2 Wrap-Up with Dr Alasnag and Dr Al-Shaibi
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Dr Mirvat Alasnag

" Hello everybody. I'm Mirvat Alasnag from Amsterdam at ESC Congress with day two wrap-up from the meeting. And with me is Dr. Khalid Al-Shaibi to bring you the latest hotlines. So today we're going to cover the BUDAPEST-CRT trial, the FIRE trial, ECLS shock trial, and the STOPDAPT 3 trial.

So I'll go ahead and start with the BUDAPEST-CRT trial, just give you a quick summary of it. We know the background for this trial is really that approximately 1 million devices, ICDs, and Pacemakers are implanted across the globe on a yearly basis. Approximately 30% of those ultimately end up having LV dysfunction induced by RV pacing and the Dysynchrony that ensues. And this is actually coupled with a rise in the hospitalizations due to heart failure.

And the guidelines have consistently recommended upgrading. However, they've also acknowledged the gap in the evidence and the unmet need. And really, the BUDAPEST CRT trial does address that. This trial was conducted in Budapest and it enrolled patients who had heart failure with reduced ejection fraction, defined as an ejection fraction of less than 35%, and had an ICD or a Pacemaker implanted in the last six months.

Now, these patients were symptomatic. They also required to have heart failure symptoms, NYHA class two to four. And these patients were also on guideline-directed medical therapy. And the QRS complex needed to be at least 150 milliseconds with a high burden of RV pacing of more than 20% in. Those who were enrolled, those who had CRT indication or those who had advanced valvular heart disease or a recent acute myocardial infarction within the last three months were actually excluded from this trial.

And then they were randomly assigned to ICD only or CRTD. Now, the randomization was three to two and those who already had an ICD at enrollment, this was left to the

discretion of the operators there and it was. They are either no device or they get a CRT, but the CRT function is suspended during the trial period.

The primary outcome was heart failure, hospitalizations, all-cause mortality, and less than 15% reduction in LV and systolic volumes. Secondary outcomes included compositive, heart failure, hospitalizations, all-cause mortality, and echocardiographic response in addition to safety parameters. A total of 360 patients were enrolled from 17 sites in seven countries and it was randomly assigned to receive, as I mentioned, this CRTD in about 215 of those and 145 in the ICD.

The mean age, they were actually older patients, they were 72.8 years and 11% only were women. The follow-up was about a median follow-up of twelve months. And the primary outcome occurred in 32.4% of those who received a CRTD and 78.9% of those who got an ICD only. So very significant.

The beneficial effects of CRTD upgrading was consistent across all the subgroups that were prespecified and the secondary endpoints as well. There was favored the CRTD, including the LV morphology and echocardiographic parameters. In fact, the LV and systolic diastolic volume of 39 mils was noted at twelve months, and the ejection fraction of 9.7% was noted in the subgroup analyses.

The rate of adverse events was half in the CRTD arm, although device-related complications per se were equivalent in both arms. But there were more major ventricular arrhythmias that were noted, and it was significant in the ICD alone group. And so the conclusion from this trial really is that CRTD upgrading of patients who have heart failure with a reduced ejection fraction is beneficial, and perhaps they shouldn't wait until it's time for a programmer change or a battery change, but really an immediate upgrade for these patients.

Dr. Al-Shaibi, I know you attended the FIRE trial as well, so do you think you can tell us a little more about that?

Dr Khaled Al-Shaibi

Sure, I'd like to. Well, we all know that older patients, especially those over at the age of 75, are frequently excluded from many trials, including many of the IACS trials. For example, complete coronary revascularization is well established in the guidelines for most patients, but the data to include older patients in that recommendation is somewhat lacking due to the lack of enrollment of these old patients in those trials.

To address this gap in knowledge, the FIRE trial was designed to examine whether or not complete revascularization based on coronary physiology is superior to a culprit only strategy in these older patients, that intervention obviously carries greater risk. Patients were eligible if they were over the age of 75, had a qualifying stem or NSTEMI hospitalisation, had undergone successful culprit vessel PCI. They were then randomised to either a physiology guided complete revascularization, or just had the culprit PCI done, and non-culprit lesions were left alone, were not even evaluated physiologically.

Patients were eligible if they were 75 years or old, had a qualifying STEMI or NSTEMI, and had, had a successful revascularization of the Culprit lesion in the presence of multivessel disease. After successful treatment of the culprit lesions, patients were randomised to either a culprit-only strategy or a physiology guided complete revascularization strategy. If they were randomised to the physiology-guided complete revascularization strategy, they underwent this either with a wire-based technology or an angiography-based technology, and there subsequently underwent non-culprit PCI for all physiologically significant lesions. While if they were randomised culprit only lesion, they did not undergo a physiological assessment and only the culprit was treated.

The primary outcome was a composite of death, MI, stroke, or ischemia-driven reavascularization within the one year following randomization. The secondary outcome was the one-year composite of cardiovascular death or MI. Other secondary outcomes included the individual components of the primary composite outcome. The study enrolled just under 1500 patients, 36% of them being women. The primary outcome occurred in 15.7% of the patients randomised to physiology guided complete

revascularization strategy and in 21% of those that were randomised to a culprit only strategy. That is, a 27% relative risk reduction with a hazard ratio of zero point 73 and a p value of zero one. So significant, in fact, the number needed to treat to prevent the occurrence of one primary outcome was 19 patients.

The key secondary outcome, which was the composite of cardiovascular death or Mi, was again lower in the physiology guided complete revascularization strategy compared to the culprit only strategy with a hazard ratio of 0.64. The number needed to treat again to prevent a secondary outcome was 22 patients. With the exception of stroke, each component of the primary endpoint that is death, MI and ischemia-driven revascularization in the ensuing one year was lower in the physiology-guided revascularization group with a 30% relative risk reduction, which was significant with the number needed to treat again to prevent one adverse outcome being of 27 patients. So a highly significant trial that again establishes that a complete revascularization that is physiology-guided should probably be pursued in older patients.

Dr Mirvat Alasnag

Yeah. And then remarkable that the investigators were able to do a trial in elderly patients and that's pretty exciting and novel. I'll move on to the next trial, which is the ECLS shock, and many of us have been waiting for that. Now, the background for this trial is that cardiogenic shock is the leading cause of death in hospitalised patients with acute myocardial infarction reaching 40% to 50% within 30 days. Many efforts are ongoing really to improve these outcomes and they include use of mechanical circulatory support.

Now, veno atrial extracorporeal membrane oxygenation or VA-ECMO has gained a lot of traction and the use of ECMO or ECLS, which is extracorporeal life support, has increased tenfold in the last few years. And yet we don't have a lot of robust data looking at outcomes in this group of patients. And this is considered the first randomised trial where they investigate the impact of ECLS on mortality in patients presenting with an acute myocardial infarction complicated with shock.

So in this trial, 420 patients with an acute myocardial infarction and cardiogenic shock were scheduled for early revascularization, were enrolled in 44 centres in Germany and Slovenia. The median age of the participants was 63 years and 19% only were women. Patients were randomly assigned to get ECLS plus standard of care or just standard of care, and the primary endpoint was all-cause death at 30 days. Secondary endpoints included the duration of mechanical ventilation, hemodynamic stabilisation and the need for renal replacement therapy. Now, safety endpoints are the standard, which is moderate to severe bleeding or any peripheral vascular complication requiring intervention.

Ultimately, 417 patients were enrolled in the trial and were analysed and the primary endpoint of all-cause death at 30 days occurred in 100 of the 209 patients in the ECLS group, which is 47.8%. In the control group it was 49%. So it didn't really meet statistical significance in terms of the secondary endpoints. The median duration of mechanical ventilation was longer in the ECLS seven days compared with five days in the control group, and the time of hemodynamic stabilisation and rates of renal replacement therapy were actually equivalent between the groups.

Safety endpoints, the moderate to severe bleeding was more frequent in the ECLS group, occurring at 23.4% compared with 9.6% in the control. And then likewise peripheral vascular complications occurred in 11% in the ECLS group compared with 3.8% in the control. So really, the results of the ECLS shock demonstrate that no reduction in 30-day mortality when we have an early ECLS strategy and the complications may be increased. So the findings may lead to the discontinuation of routine use of these devices. However, individualized decisions may very well remain in practice.

So it's a good time now to move onto another trial that you looked into, which is the STOPDAPT 3 trial again perhaps impacting practice.

Dr Khaled Al-Shaibi

Well, yes, in fact this I think is a very important trial. All guidelines mandate the use of DAPT in the first month following PCI irrespective of bleeding, because it is thought of as being an essential component. Nevertheless, we also know that the incidence of major bleeding within that one month of mandatory DAPT therapy continues to be a real problem for a significant number of patients, especially more older patients with high bleeding risk. So removing aspirin from a DAPT regimen in high bleeding risk patients early after PCI has the potential to reduce major bleeding events without compromising cardiovascular events. And this was sort of the premise for the design of the STOP DAPT 3 trial.

The trials investigated the efficacy and safety of an aspirin-free prasugrel monotherapy compared with a one month of DAPT with aspirin and prasugrel in patients with ACS or high bleeding risk undergoing PCI with a cobalt-chromium everlast eluting stent randomization was one-to-one, either to prasugrel monotherapy or to DAPT with prasugrel. And aspirin of both groups received a loading dose of prasugrel of 20 milligrammes. Just over 6000 patients were randomised from 72 centres in Japan. There were two primary endpoints major bleeding events at one month and this was analysed for superiority and cardiovascular events at one month, which included the composite of death, cardiovascular death, myocardial infarction, definite or probable stent thrombosis or stroke, and this was analysed for non-inferiority.

A secondary endpoint was a composite of the two primary endpoints, that is, the bleeding and the cardiovascular event rates. Just under 6000 patients were randomised 2984 to prasugrel monotherapy and 2982 to DAPT. The average age was just under 72 years and 23% were women at one month for the primary endpoint. At one month, the no aspirin strategy was not superior to DAPT for the co-primary endpoint of bleeding with a p-value for superiority of 0.66, so it clearly did not meet the superiority clause.

At one month. The no-aspirin strategy was non-inferior to DAPT for the cardiovascular composite event rate with a non-inferiority p-value of zero one. The secondary endpoint, which was the composite of the two co-primary endpoints, occurred in 7.14% of patients in the no aspirin group and 7.38% of the patients in the DAPT group. So no difference between the two groups. And this analysis really suggested there was no net clinical

benefit for one therapy really over the other. Nevertheless, an important caveat here there was an excess of coronary revascularization and definite or probable stent thrombosis in the no aspirin group compared with the DAPT group. And in a subgroup analysis stratified by ACS patients versus non-ACS patients, this excess risk of coronary repeat coronary revascularization or definite or probable stent thrombosis seemed to be in those patients who had presented with an ACS presentation.

So really the aspirin-free strategy compared with the DAPT strategy failed to attest to superiority of the aspirin-free strategy, especially concerning bleeding risk. And the conclusion was really DAPT therapy during the first month should remain the standard for now. But there is clearly a signal to potential harm in an aspirin-free strategy here.

Dr Mirvat Alasnag

Yeah, absolutely agree with you. And perhaps a future trial would need to look selectively or exclusively at those who had no acute coronary events but required some form of revascularization to see if that strategy works in that subgroup patients. And analysing looking at intravascular ultrasound, looking at the complexity of the PCI may also shed a little more light into these findings.

So thank you for tuning in and those were four trials from today from ESC and we'll see you again tomorrow with another wrap-up."