Prof Jan Belohlavek:

My name is Jan Belohlavek. I'm a cardiologist, intensivist, and invasive cardiologist. I'm a Professor of Medicine and in my clinical practice, I focus mainly on acute cardiology, cardiac arrest, post CPR care and refractory cardiac arrest, and extracorporeal CPR. Research wise I'm also involved in animal research and lab research again on extracorporeal CPR microcirculation and animal models of cardiogenic shock and cardiac arrest.

Prof Jan Belohlavek:

It's been a long time ago, it was actually in 2006, and I remember exactly well, what happened. It was one of the cases I had: We resuscitated a young woman who was 25 years old, and I resuscitated her for two hours and she died under my hands. And in that case, that the time I decided we have to do something more for those patients, whatever so-called refractory cardiac arrest means that patients with cardiac arrest don't react or are not able to get the ROSC, a return of spontaneous circulation.

Prof Jan Belohlavek:

And it was a impulse to start an ECMO and using ECMO in cardiac arrest cases. So we started using ECMO in 2007, we started putting patients on ECMO during cardiac arrest in 2010. Then we thought about the protocol of the study because we were not sure whether this works so it was necessary to undergo a randomised trial. So we designed randomised trial during 2010 and 2011, it took us quite a long time to get an approval from the ethics committee because the trial is very difficult, actually. And then in 2012, we published our protocol. And in 2013, we started to run the randomised trial.

Prof Jan Belohlavek:

The Prague OHCA, we call OHCA Out of Hospital Cardiac Arrest study means that this study is focused on patients with cardiac arrest. And this is not the routine cardiac arrest as you know, from other studies like TTM or TTM2 or from many registries. We are focusing on patients with refractory cardiac arrest. As I said before, those are those patients who don't get ROSC within the reasonable time. And the average time for patients in majority of studies and registries is below 25 minutes of CPR. And we are focusing on patients who have a much longer time, they need to be resuscitated. And in those cases where refractory, their outcomes are very poor and majority of them are basically, all of them die if you use routine measures. And therefore we started to use the ECMO and immediate transport into hospital and putting patients on ECMO and then to investigate them invasively, meaning we did a coronary angiography and eventually a PCIs. As a lot of those patients have a acute coronary disease as a cause of their refractory cardiac arrest because coronary ischemia or myocardial ischemia is a frequent cause of refractoriness in this setting.

Prof Jan Belohlavek:

The study design was actually comparing a bundle of interventions, intra-arrest transport on the mechanical CPR, which means that we put a patient on a mechanical device, which performs cardiac massage. And we, after transporting to hospital where the patient has ongoing cardiac arrest on admission to the hospital, we put the patient emergently on ECMO, which is called ECPR, extracorporeal cardiopulmonary resuscitation. And immediately after that, we perform invasive investigation, which is mainly coronary angiography. And eventually, we treat acute coronary disease like coronary occlusion, or we perform other invasive investigations like pulmonary angiography or whatever needed at this point.

Prof Jan Belohlavek:

And we compare this bundle of interventions to standard advanced cardiac life support, meaning that the patient has been resuscitated on scene and then we get a return of spontaneous circulation. The patients transported to hospital and treated regularly as everybody following a cardiac arrest with regular post CPR care. Concerning endpoints, we actually have chosen a very hard endpoint for our study, which was 180 days survival with a normal or a favourable neurological outcome, which is cerebral performance category 1 and 2. And it's important to point out that majority of studies in cardiac arrest and comparing ECPR in the non-randomised fashion, was only 30 days of outcome or hospitalisation outcome.

Prof Jan Belohlavek:

And we have also seen in our study that there is a evolution of a neurological outcome during the weeks after cardiac arrest. And we had several patients who actually awaken after those 30 days. So it's important to have such a hard point to prove or not prove the benefit. So our primary endpoint was survival with favourable neurological outcomes, 180 days. And our secondary important outcomes was no recovery within 30 days, meaning that those patients will recover within 30 days and cardiac recovery within 30 days which means that the patients don't have any pharmacological or mechanical support during those 30 days.

Prof Jan Belohlavek:

Our findings are, we actually did not prove a statistically significant improvement in primary outcome. Despite the fact that we have seen numerically obvious difference in the appearance of primary outcome. It was 32% of favourable survival of those 180 days in the hyperinvasive arm. And it was 22% in the standard arms. So there was almost 10% absolute difference, but it did not reach statistical significance. However, we have seen a statistically highly significant difference in the neurological outcome after 30 days, so our secondary outcome. And we have also seen a statistically significant benefit in two subgroups. First was the subgroup of patients who have been resuscitated for more than 45 minutes. And there's been a very strong... It was very strong in favour of those patients who had undergone the hyperinvasive approach, meaning those transport and the CPR versus those who were transported after crossovers to hospital.

Prof Jan Belohlavek:

And to be exactly the size, we had both patients who were resuscitated more than 45 minutes. We had 20 patients who survived in the hyperinvasive arm, such a long CPR versus only six patients in the standard arm survived such a long CPR. And it's important to point out that in those six patients who survived in the standard arm, four of them are actually patients who are crossed over from the standard to hyperinvasive arm, which brings me to an issue of crossover as we know, in such a difficult studies, crossover occurs, and we allowed crossover. And in those patients who crossed over from standard to hyperinvasive, and there were only 11 patients or below 8%, five of them. So five of 11 patients survive favourably. So it's important that we pick up to the right patients to crossover, and this actually brings even more significant difference to our results, and it brings more strengths to support the results.

Prof Jan Belohlavek:

Within that based on this trial, and this is important to realise because there is no other larger trial as we have randomised 256 patients and during almost 80 years of study. And this is difficult to find the proper patients and other studies have shown similar to ours that between 5-7% of patients with cardiac arrest are suitable for such kind of study. So it took us a long time to enrol enough patients. And it's so important to say that those patients may benefit from what we are doing. So they may benefit from the early transport to cardiac centre and early ECPR. The extremely important point to discuss is when to start this transport and when to think that a patient might be suitable for this is a time issue. It must not be too early, it must not be too late.

Prof Jan Belohlavek:

There's been other studies showing that probably within 15, 16 minutes of advanced cardiac life support, if we don't get to ROSC, which is together with a phase before the emergency service comes to scene. So it's around 10 minutes plus 15 minutes. So around 25 minutes, if the patient doesn't get ROSC the chance for favourable survival goes very steeply down. So this is the right point to think about the ECPR trial. So to keep CPR and bring patients to hospitals. So what we think is based on our trial, we cannot recommend so-called one fits all recommendation because our study was not as significant in its primary endpoint. However, we have shown that appropriate patients in subgroups may benefit. So there's stronger benefit, and there's stronger evidence right now for doing this in very selected subgroup of patients first and in a selected scenarios and the demographic area, which is well covered by the well functioning pre-hospital care and cardiac centre, which is available 24/7 for performing CPR.

Prof Jan Belohlavek:

The next steps are definitely we need an answer in a multicenter study, randomised to prove the benefit, to prove the concept that we came out with and our immediate steps now will be that we'll try to perform the analysis from the results of randomised study (...), which are available at the moment. And then we'll set up a multicenter randomised trial.

Prof Jan Belohlavek:

That our study is the first one that has shown in a randomised fashion that intra-arrest transport would make mechanical CPR plus immediate ECPR plus innovators if investigation was feasible and may function well. And it's also safe. We have also shown that subgroup patients may survive much better when we use this approach. And now we have to definitely define the demographic carriers and the type of patients that should be, or shouldn't be enrolled in such a trial.