Title: KABUKI: Edoxaban in Patients with Chronic Thromboembolic Pulmonary Hypertension
Participants: Dr Kotaro Abe and Dr Kazuya Hosokawa
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Dr Koraro Abe

My name is Kotaro Abe, who is a lecturer. Department of the Cardiovascular Medicine, Kyushu University, Japan. And I'm PI of this KABUKI trial.

Dr Kazuya Hosokawa

And I am Kazuya Hosokawa, Cardiologist, Assistant Professor from Kyushu University. And I am a trial manager of this KABUKI trial.

Dr Koraro Abe

Annual incidence of chronic thromboembolic pulmonary hypertension CTEPH is reported to be five per 100,000 population and estimated prevalence of the CTF in the general population is 50 per million. The KABUKI trial is the first randomised control trial designed to evaluate the efficacy and safety of edoxaban in CTEPH. Our major clinical guideline recommend only warfarin as standard anticoagulation in CTEPH. But as you know, the warfarin has some limitations dietary restriction, drug interaction and mandatory blood monitoring. So we believe this study provides the better choice of the lifelong anticoagulation in CTEPH patients.

There are two papers comparing DOACs and vitamin K antagonists included warfarin. The first, we reported the prospective observational results from the Japan CTEPH registry in approximately 900 CTEPH patients. The mortality rate, the incident of the symptomatic venous thromboembolism and the clinical worsening of CTEPH were comparable between the DOACs and warfarin. But interestingly, the incident of the major breathing was lower in DOACs. And second, as an international prospective survey of the CTEPH patients using [indistinct] reported the risks of DOACs and vitamin K antagonists, including warfarin. And this study shows a similar clinical mortality and adverse bleeding events between the DOACs and vitamin K antagonist. But the rate of

the venous thromboembolism was higher in DOACs group. So this existing evidence suggested that the risks of the bleeding was not higher in DOACs, but the risks of the thromboembolic events was similar or higher in DOACs.

Dr Kazuya Hosokawa

The KABUKI trial was multicenter randomised, single blind, warfarin controlled, non-inferiority trial. It was designed to prove the efficacy and safety of edoxaban compared to the warfarin in CTEPH patients. And inclusion criteria were CTEPH patients with who functional graph one two three on stable warfarin treatment and primary endpoint was the ratio of pulmonary vascular resistance at 48 weeks to baseline. And the safety endpoint was the critically relevant breeding including major breeding. And the calculated sample size was 74 patients.

In terms of baseline characteristics, 60% were female with an average age of 62 years old and 44% met criteria of low-dose use of edoxaban. And because the trial prohibited pulmonary end atherectomy or balloon pulmonary angioplasty, so all participating patients have previously undergone pulmonary end, atherectomy or balloon pulmonary angioplasty. So at baseline who functional graph one or two was predominant and baseline six-minute walk distance was greater than 450 meters and average pulmonary artery pressure was less than 20 millimetre mercury and average pulmonary vascular resistance was less than three units. So in this trial, a study population was mild CTEPH patient after reperfusion treatment.

The key finding is as I mentioned, the primary endpoint was the ratio of pulmonary vascular resistance at 48 weeks to baseline. So the ratio was zero point 93 in the edoxaban group and 1.1 in the warfarin group. So the treatment effect of edoxaban was 0.92 and the upper 95 confidence interval was 1.3. The non-inferiority margin was 1.19. So the non-inferiority of edoxaban was demonstrated in terms of safety endpoint. The clinically relevant breeding was observed in 2.7% in edoxaban group and 5.4% in the warfarin group. There was no statistical difference between the group and no symptomatic venous thromboembolism and worsening CTEPH event and deaths were observed in any of the groups. So this trial demonstrated the non-inferiority of edoxaban

to warfarin in terms of preventing worsening pulmonary hemodynamics with similar breeding risk compared to warfarin.

The inclusion criteria was CTEPH patient on stable warfarin treatment. So this trial have a bias in edoxaban group disadvantageous. But the trial demonstrated the clinically relevant bleeding and serious adverse event rate were lower in edoxaban group than in the warfarin group. So we believe edoxaban is safer anticoagulant compared to warfarin in general CTEPH population. We hope that edoxaban benefits many CTEPH patients taking warfarin. Thank you."