Hi everyone, my name is Davide Cao. I'm a research fellow at the Icahn School of Medicine at Mount Sinai in New York, and I'm also an interventional cardiology fellow at Institut Mutualiste Montsouris in Paris.

Today I'm going to present the results of the HBR sub-study or the TWILIGHT trial.

The importance of TWILIGHT-HBR

So TWILIGHT-HBR is important for a number of reasons, the most important one, in my opinion, is that HBR patients are extremely prevalent in clinical practice, and this is because we have seen advances in device technologies and operator expertise, which have allowed extending the indication to PCI to increasingly complex patient population.

And as a result, about 40% of patients undergoing PCI presents with high bleeding risk conditions, which increase their risk of adverse events and bleeding particularly while on a term of dual antiplatelet therapy, especially with potent P2Y12 inhibitors.

And against this background, current guidelines lack specific recommendation on the management of HBR patients, especially because of the low level of evidence that is available.

Another important reason why TWILIGHT-HBR is very important is that TWILIGHT was developed using, to enrol patients at high risk of ischemic and bleed events. According to a broad range of ischemic and bleeding risk criteria, clinical and angiographic, that were developed nearly six years ago.

Over the last years, the definition of HBR has been revised to include risk score, prediction models, and consensus based definition.

So we thought it was important to see whether the treatment effects of the main TWILIGHT trial were preserved in a contemporary HBR population as defined by the recent academic research consortion criteria.

Study design and patient population

So in brief, TWILIGHT was a large randomised, double-blind placebo-controlled trial who was conducted at 187 sites across 11 countries. Patients were eligible for inclusion in the trial if they had undergone successful PCI with drug eluting stents and they fulfilled the pre-specified conditions.

Patients were discharged on three months dual antiplatelet therapy with ticagrelor and after three months they were randomised, one-to-one to aspirin or matching placebo on a background therapy with ticagrelor for an additional 12 months.

In this pre-specified analysis of the pilot trial, we evaluated the treatment effects of ticagrelor monotherapy versus ticagrelor plus aspirin, according to HBR status.

So patients were considered to be at HBR, according to the ARC-HBR definition, that is if they fulfilled one major or two minor criteria, at least. A number of criteria, of ARC-HBR criteria were available for the study, but of course not all of them. And it's important to note that TWILIGHT, the TWILIGHT trial excluded patients on oral anticoagulation and with a prior stroke who are too established ARC-HBR criteria.

On the other hand, we were able to use all, most of others, ARC-HBR criteria, most importantly, the most prevalent ones, such as anaemia, chronic kidney disease, of course, age, use of non-steroidal anti-inflammatory drugs and so on.

For the purpose of these analysis, we use the same study endpoints as the main trial, which is BARC 2 to 5, as primary bleeding endpoint, and death, MI or stroke as key secondary ischemic endpoints.

But in addition, we also evaluated, we considered outcome of interest for these analysis, those that were recommended recently by the academic research consortium for HBR trial design principles, that is major BARC 3 to 5 bleeding and cardiovascular death, MI or ischemic stroke.

Key results

The key findings were that HBR patients experienced significantly higher rates, of not only bleeding, but also ischemic events. And it was also interesting to see that there was a gradient in the risk of ischemic and bleeding events, according to the number of ARC-HBR criteria that were fulfilled.

In other words, patients with multiple criteria were at much higher risk of other HBR patients with only one major or two minor criteria, and of course at a greater risk compared to non HBR patients. ticagrelor monotherapy, reduced the risk of the primary endpoint of BARC 2 to 5 bleeding without increasing ischemic events, including death, MI or stroke consistently among HBR and non-HBR patients.

And also the same treatment effects were observed among very HBR patients who fulfilled multiple HBR criteria. The most relevant finding of this study, however, was the fact that the absolute reduction in major bleeding events, namely BARC 3 or 5 bleeding, was significantly larger among HBR patients compare with non HBR patients, which is particularly important when we evaluate the effectiveness of a treatment strategy, for example, in terms of number needed to treat. So the impact of TWILIGHT-HBR on clinical practice is critical, and that is, I mean, we just need to consider and take a look at the guidelines.

The current European guidelines on non-ST-elevation ACS say, reserve a strategy of ticagrelor monotherapy to patients at low-risk, and this recommendation is justified by the lower than expected event rates that were observed in TWILIGHT, at one year. Against this background, we demonstrated that the treatment effects of ticagrelor monotherapy in reducing bleeding without increasing ischemic events are preserved, that were observed in the main trial are preserved in the higher risk cohort of HBR patients.

And not only these, we also showed that these HBR patients are likely to derive a greater benefit in terms of absolute reduction of major bleeding complications compared to non-HBR patients.

Impact on practice and influence on further research

Regarding next steps and future research, it is important to remember that TWILIGHT randomised patients to ticagrelor monotherapy versus ticagrelor plus aspirin.

So it is very important to evaluate whether the facts of an early aspirin discontinuation strategy on ischemic and bleeding events are true, also when using other P2Y12 inhibitors like clopidogrel and especially prasugrel. And it is also important, in light of recent evidence, such as the HOST EXAM trial, to evaluate and to compare the effects of a P2Y12 inhibitor monotherapy versus aspirin for long-term cardiovascular prevention.

We also need more data on patients with STEMI that were excluded in TWILIGHT and in whom physicians are usually more conservative and reluctant to implement bleeding-violent strategy based on a short DAPT regimen.

Finally, it must be remembered that TWILIGHT-HBR was a substudy of a trial and therefore by definition, it was underpowered to detect significant differences, especially with respect to ischemic events and therefore prospective studies using the ARC-HBR criteria are warranted, especially based on the observed results of the TWILIGHT-HBR substudy.