Title: PICSO-AMI-I: Pressure Controlled Intermittent Coronary Sinus Occlusion in Acute Myocardial Infarction
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"I am Dr Di Maria. I am an interventional cardiologist. I work at the John Radcliffe Hospital, Oxford University NHS Foundation Trust in Oxford, UK. Thanks for the invitation and for sharing with you an update and results of the PICSO-AMI-I clinical trial assessing the application of PICSO therapy in patients with anterior ST-elevation myocardial infarction.

Unmet Needs of Acute Myocardial Infarction Patients

We need to say that our way, our treatment in patients with ST-elevation myocardial infarction is dramatically improved over the last few decades. As a matter of fact, in 2023 we can celebrate the 30th birthday of the first clinical trial of the clinical trial that demonstrated the benefit of primary PCI over thrombolysis in patients with STEMI. But the reality is that 30 years down the line we are now in a position where we'll improve the way we can treat these patients. But our performance is kind of plateaued and we are now at a point where actually we are not managing to improve even farther the clinical outcome despite reducing, for example pre-procedural ischemic time.

And we know that still today a variable proportion that can go between 20-25% roughly according to national or international registries, we know that 20-25% of patients might still develop heart failure sooner or later after presentation with ST-elevation myocardial infection. Which is the reason why there is a potential still unmet clinical need.

In this regard the PICSO therapy is an evolution, is a percutaneous evolution of an old concept about reperfusing the heart, let's say from the back door, from the coronary sinus, which as we know is the main venous drain system of the heart. Already back in the 40s it was demonstrated that it was possible to reperfuse the heart in a retrograde manner. Indeed, that was even before the coronary artery bypass grafting era. And then

of course with the PICSO therapy now this concept now has become potentially suitable in a percutaneous manner.

The PiCSO Impulse System and Its Unique Features

So, the PICSO therapy consists of a PICSO impulse catheter which is a balloon-tip catheter that is inserted in the coronary sinus via the femoral venous axis. And the second component of the system is a dedicated console. So, the PICSO impulse console, which in other words by looking at the ECG and variation of pressure within the coronary sinus, applies a proprietary algorithm that regulates the inflation and deflation cycles of the balloon once it is in place in the coronary sinus.

In other words, what the PiCSO therapy does, we have a balloon that is placing the coronary sinus and the balloon inflates in the coronary sinus, it stays inflated for a few cardiac cycles and then it does deflate. So, during the inflation phase, what happens there is an increase in venous pressure that even [indistinct] to redistribute myocardial blood flow from the non-ischemic myocardium to the ischemic myocardium and it is exactly the mechanism advocated by which the therapy could reduce, for example, infarct size or improved myocardial reperfusion.

And on the other end, when the balloon does deplete, of course, the normal venous drainage of the heart is guaranteed. So, there is little risk in terms of myocardial engorgement of risk of intramyocardial haemorrhage because again, this is not a permanent device. It's a device that during the deflation, the balloon allows for the normal drainage to take place.

Study Design and Patient Population

So, the study was the result of previous of course investigations. So, starting from data available from the animal model and from preliminary non-randomised proof of concept study that showed a possible effect in terms of infrastructure reduction associated with therapy, the PICSO-AMI-I clinical trial was designed as an international multicenter parallel group one to one randomised clinical trial.

Patients were randomised one-to-one to PICSO assisted primary PCI or conventional primary PCI. The main inclusion criteria looked at patients presenting with an anterior ST elevation myocardial infarction according to electrocardiographic criteria and done with documentation of an occluded left anterior descending artery, specifically at TIMI zero one flow at the time of the invasive angiogram. And another point to remember, patients with an ischemic time less than 12 hours were eligible for the study.

The primary endpoint of the study was to look at a reduction in emphasise at five days cardiac MRI scan and the study was powered to show a 25% reduction infarct size as [indistinct] at 26% emphasise in the control group. And in this regard, an overall sample size of 144 patients was calculated to account for a power of 80%, an alpha error of 0.5 and assuming a 20% drop off rate at follow-up.

Key Results

The study was conducted over roughly two years, three years period. Of course, there was a halt during the COVID-19 pandemic and the study involved 16 centres, tertiary centres across Europe.

The first point to make to highlight is that it was proven that PICSO therapy was feasible in patients presented with a primary PCI with an anterior STEMI going for primary PCI. And it was also proven that the additional PICSO therapy did not associate with increase in adverse events at six month follow up, nor there was an increased rate of device-specific adverse events like vascular access, complication, or coronary sinus injury, for example.

However, the PICSO therapy of course represented an increase in terms of procedural time. By protocol, the operator was asked to provide at least 45 minutes, if possible, of PICSO therapy. So consequently, what we did observe is that in the active group, procedural time, contrast, dye volume and radiation exposure expectedly were of course significantly higher than in the controlled group.

So, when it comes to the primary endpoint of the study, so difference in infarct size at five days cardiac MRI scan, unfortunately we could not observe, as initially pointed in the preliminary non-randomised clinical trial, a reduction in infarct size in the active group. So, the infarct size at five days was comparable between the PICSO assisted primary PCI group and the control group and this was true in the intention to treat analysis as well as in the per-protocol analysis.

On top of that, also we looked at possible subgroup analysis and the absence of reduction in infarct size was pretty much consistent across the various subgroups that were eventually included and analysed. It was not the primary endpoint of the study, but we looked also at variation in infarct size. six months. This was not available in the whole court of patients enrolled, but also at six months. We could not detect a significant variation in infarct size between the active group and the control group. And equally, there was no difference between the PICSO assisted primary PCI group and the control group in terms of microvascular obstruction and intramyocardial haemorrhage at five days, Cardiac MRI Scan.

Next Steps

So, now, of course, the main result of the study is that we have a one-ended therapy. That, of course, is felt to be feasible, is felt to be safe. But, of course, it could not show the anticipated benefit that was initially, let's say at least advocated by the non-randomised study that represented the preliminary work leading eventually to the PICSO-AMI-I clinical trial.

Of course, the next step now will be to have a clear understanding about whether the therapy could potentially be viable in specific, let's say, settings and I'll explain myself. One of the possible explanations is that the inclusion criteria that we consider in the study, so just looking for example at TIMI zero one fluid presentation could have been not enough to select that subgroup of patients with truly high chance of experiencing a large infarct and that could eventually potentially benefit from an additional procedure.

From preliminary work we know indeed already that primary PCI works well in most patients. And then there is the idea that we should probably have a tool on top of TIMI zero one that can help us to identify truly high-risk patients that are anticipated to not respond well to the conventional treatment with primary PCI and then targeted them specifically with an additional therapy like PICSO for example.

In this regard. One of the preliminary studies that were conducted on this therapy the PICSO that was performed here in Oxford we did look at the index of microvascular resistance, so IMR measured before the procedure, so measured before the implant of the stent as a possible criterion to establish whether there was a scope to provide additional treatment with PICSO or not.

So, this approach was not, let's say, adopted in the study. And of course, a possible open question would be whether a new study using more, let's say, specific or ad-hoc inclusion criteria beyond just TIMI Zero flow could eventually help to have a clearer understanding whether this therapy still has a scope in patients with anterior ST elevation myocardial infection."