of those lesions in the stent deployment strategy and did not score ither at baseline or as residual risk score after PCI. In other words, our PCI strategy in those angiographic scenarios left them with OMT alone [7]. The SYNTAX II study also demonstrated that functional lesion ssessment allowing fewer stents per patient with similar risk score achieved better results compared with previous SYNTAX I data [8].

Almost 30% of normal instantaneous wave-free ratio (iFR) found in ORBITA patients are in agreement with our comments mentioned above [1].

Now if from the 200 study group patients, we discard these 82 patients, now we are saying that only around 0.5% of the population aving severe CAD in the centers involved in the study should be included and randomized in ORBITA trial. However, this does not end here, and we recently noticed, from unpublished data, that 85% of atients not initially treated with PCI were ultimately treated with PCI for unknown reasons [9].

After >25 years of having seen first randomized studies published between coronary artery bypass surgery, OMT or PCI [10–13]in patients with severe CAD and stable angina, it is very difficult for those who participate in these experiences to understand the behavior of those who try to minimize the benefits of PCI in certain groups of patients, including relief of angina and improved functional class as was demonstrated by other randomized studies [10–13] with appropriate long-term follow-up data.

In summary, I don't want to dismiss how the investigators conducted and performed the ORBITA trial, although I would like to emphasize that 40 years after the first coronary angioplasty performed by Gruentzig, a right lecture of coronary angiogram including lesion severity together with the amount of myocardium at risk and jeopardized score remains the "gold standard" to selected the right treatment option for our patients with severe CAD [14,15].

I would like to see ORBITA authors performing a new sham-controlled randomized clinical trial, ORBIT 2, including a "true" all severe (≥70%) stenosis in the proximal/mid portion of large epicardial vessels to replicate findings recently reported in Lancet paper [1].

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https://doi.org/0.1016/j.carrev.2018.07.018

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The "new" syndrome of delayed coronary obstruction after transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is now the treatment of choice for patients with severe aortic stenosis with increased surgical risk [1,2]. Outcomes have continually improved, but due to the nature of the procedure, by displacing an old valve with a new valve, complications such as coronary obstruction persist, especially in patients with high risk features. It is generally recognised to occur acutely; however, recently data were reported from a large international registry regarding the new phenomenon of delayed coronary obstruction (DCO), in which the coronary obstruction occurs after the index procedure [3,4]. We collected data from 18 centres on 17,092 TAVI procedures over an 11-year period (2005–2016) and the reported incidence was lower than acute coronary obstruction (n = 38, 0.22% versus approximately 1% with acute obstruction) [3]. However, more cases may occur than we realise. For example, DCO could present with sudden cardiac death and therefore go undiagnosed if out of hospital and no autopsy is performed. Additionally, patients could be relatively asymptomatic if DCO develops in the context of a patient with prior CABG and therefore not seek medical attention [5]. Whilst we found that in 2 out of every 3 patients, one well known risk factor associated with acute coronary obstruction was present, we also found that in contrast to acute obstruction that DCO occurred more commonly with self-expandable valves (0.36% vs. 0.11% balloon expanding; $p < 0.01$). DCO broadly fell into two categories: early (≤7 days; n = 24, 63.2%) and late (≥60 days; n = 14, 36.8%). Early DCO presented more with acute presentations including cardiac arrest and STEMI, in contrast to late that presented with stable angina. This is probably related to two different mechanisms, for example, early DCO may be related to the displacement of native/surgical valve leaflet due to continuing expansion of the new valve, in contrast to late whereby valve stent endothelization, fibrosis or thrombus embolization may be responsible (Fig. 1). Whilst PCI was the management of choice and successful in 68.8%, the mortality associated with the condition was high at 50% [5]. Therefore, although thankfully the incidence is rare, clinicians should be aware since it is often a deadly condition, and since one third of patients did not have a classical risk factor for acute coronary obstruction; thus future studies are needed to define new risk factors. For example, calcium distribution, leaflet length and morphology are possible risk factors that

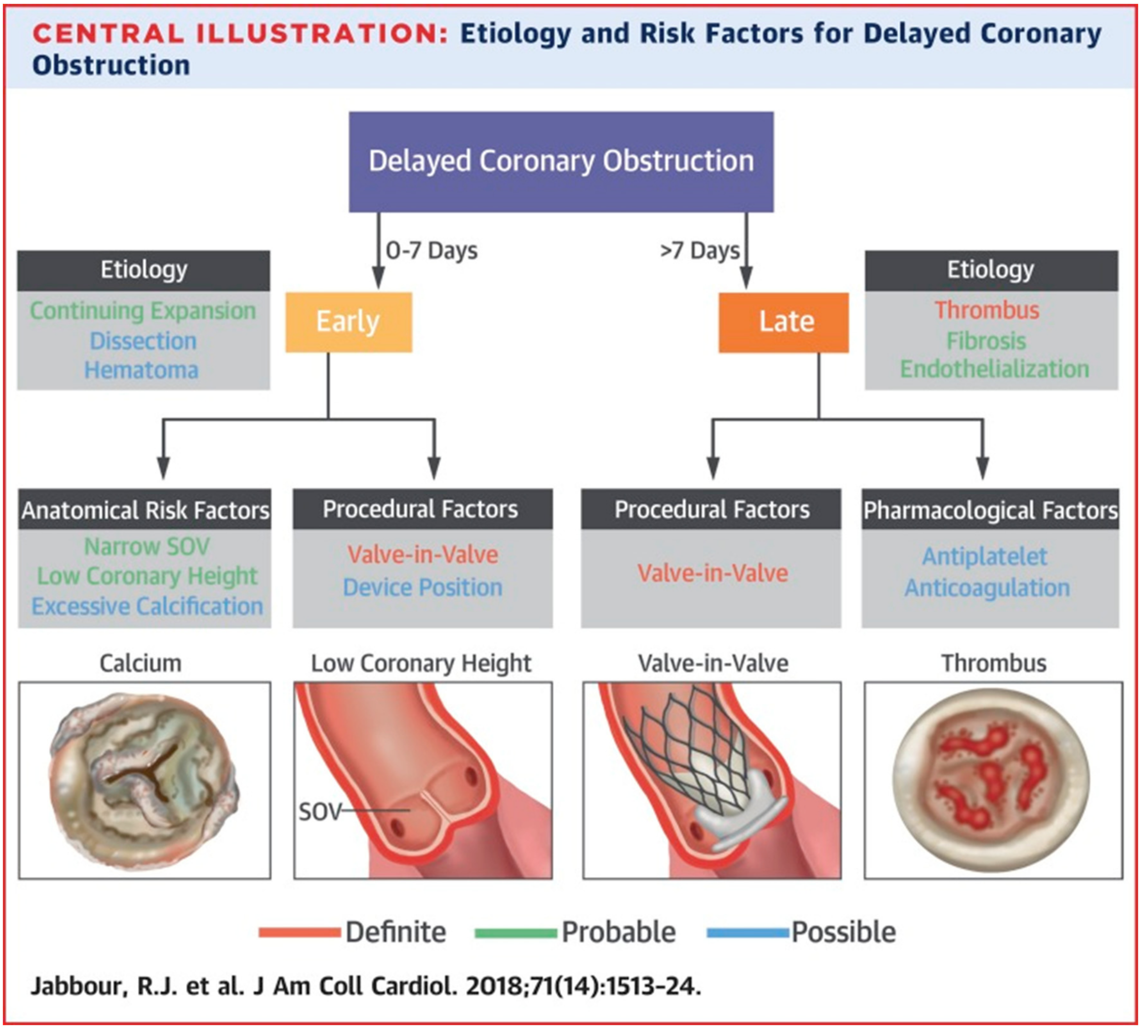

Fig. 1. Delayed coronary obstruction can be divided into 2 groups: early (up to 7 days) and late (>7 days). Early delayed coronary obstruction may be due to continuing expansion of the implanted valve, or a dissection or hematoma that expands, causing obstruction. In contrast, thrombus or valve stent endothelization (fibrosis) may cause late delayed coronary obstruction. Late expansion may be a possible additional cause. Definite causes/risk factors are in red, probable in green, and possible in blue.
Reproduced with permission from Elsevier [4].

require detailed evaluation in a large cohort of cases. In addition, newer generation valves should be designed in ways to mitigate risk of DCO occurring. For example, valves with larger cells would minimize the effect of persistent inflammation or valve stent endothelization. Larger cells would also facilitate future access to the coronary arteries post TAVR which will become of increasing importance as inevitably devices will be inserted into patients with longer life expectancies. Notably, since most TAVR devices in use today use radial force to fix the valve in place, this will not prevent native valve leaflet prolapse which could then potentially result in obstruction. Certain newer generation valves can prevent native leaflet prolapse whilst fixed in place thereby minimizing the risk of prolapse and DCO (Accurate Neo [Boston Scientific] and JenaValve [JenaValve]). Data from an Accurate Neo registry of 1000 patients, reported no cases of coronary obstruction up to 30-days follow-up and in another smaller registry of 89 patients there were no DCO events at 1-year follow-up [6,7]. In contrast, data regarding the JenaValve is limited so far. Minimizing valve skirts may also help, whilst valve skirts are important for minimizing paravalvular leak, DCO has occurred with self-expanding valves because of prosthesis skirt obstruction [8]. Theoretically, the chance of obstruction would be greater in high implantation cases. For example, a recently reported case of delayed DCO described the development of adhesions of the transcatheter heart valve skirt to the aortic wall causing delayed coronary obstruction [9]. This was an unusual case since the obstruction was successfully managed by conventional open heart surgery and therefore the adhesions most likely due to persistent inflammation were clearly visualised. Another interesting area of current research is the clinical importance of antithrombotic therapy post TAVR. Since the pathogenesis of DCO is likely to be related to or contain a thrombotic element, anticoagulation may be useful for both treating and preventing DCO. For example, since the publication of this report, a case involving thrombus of the ostial RCA was reported. This was unable to be treated by PCI but resolved with anticoagulation just 2 weeks later [10]. Ongoing studies will evaluate the efficacy of anticoagulation with or without antiplatelet therapy (ATLANTIS - NCT02664649, GALILEO-4D - NCT02833948, NCT03557242). Finally, we need to understand what to do during high risk cases for risk factors for obstruction. Whilst coronary protection with a guidewire and/or stent is currently used by many operators, might we also gain benefit from prophylactic stenting to prevent DCO from occurring? This is a difficult question to answer, since we found that in 7 out if 38 DCO cases, a left main stent was deployed during the index procedure. In 6 cases, a stent was deployed prophylactically and in 1 patient, an acute partial obstruction developed which was treated with PCI. In 5 cases the "chimney" stenting technique was used. Therefore, the use of stents with greater radial strength or chimney stenting needs investigating for evidence of benefit. At present, there is no recommendation to change practice from conventional guidewire and/or stent protection. Interestingly though, the BASILICA procedure has been recently shown to be feasible in lacerating both surgical or native valve leaflets prior to TAVR and seems a promising strategy to prevent both acute and DCO that is currently under investigation in a prospective clinical trial (NCT03381989) [11]. In summary, the newly recognised syndrome of DCO is thankfully rare, but clinicians should be aware of this complication that is similar to acute coronary obstruction and is associated with a high mortality rate. As there is a natural movement towards TAVR in lower risk patients with longer life expectancies, DCO will be less tolerable in this group. Ongoing research studies should specifically recognise DCO as a complication so data can be gathered to characterise this phenomenon further. Also, in cases of sudden cardiac death out of hospital, post mortem studies where possible could help shed light further on the real incidence and pathogenesis of this condition.

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29 August 2018

https://doi.org/10.1016/j.carrev.2018.10.004

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Changing the paradigm in renal denervation: Is trans-urethral access the key to effective blood pressure reduction?

To the Editor:

We read with interest the article by Petrov et al. [1], in *Cardiovascular Revascularization Medicine* entitled, "Comparison of standard renal denervation procedure versus novel distal and branch vessel ablation with brachial arterial access." The authors should be congratulated on their publication demonstrating greater blood pressure (BP) improvement with 'Y-pattern' compared to standard renal denervation (RDN) in patients with resistant hypertension, and the feasibility of brachial access for such procedures.

The key to success with percutaneous RDN is ablation of the renal nerves, with resultant reduction in sympathetic outflow and improvement in BP. The SYMPLICITY HTN 3 [2] trial failed to demonstrate a benefit of RDN for blood pressure control over placebo. One hypothesis for the study's failure was that there was inadequate ablation of renal nerves [3–5]. The SPYRAL HTN-OFF MED [6] trial where RDN was performed in both the main and branch arteries resulted in significant reduction in BP compared to placebo supporting this hypothesis. This study by Petrov et al. [1] elegantly compares 'Y-pattern' with standard RDN, and further validates that the putative factor for RDN success in achieving blood pressure control is effective renal nerve ablation.

We propose that RDN via trans-urethral approach may be more efficacious than the peri-arterial approach. To understand why requires a brief review of renal physiology. The kidneys are innervated by both afferent (kidney ➔ brain) and efferent (brain ➔ kidney) nerve fibers. Both types of fibers can in theory mediate blood pressure control. Ablation of afferent renal nerves can decrease arterial pressure by decreasing sympathetic drive to the kidney and other organs. On the other hand, ablation of efferent renal nerves can reduce blood pressure by reducing renal vascular resistance, renin release, and sodium and water reabsorption [7]. However, recent studies in the rat model suggest it is ablation of the afferent nerves that mediate the antihypertensive effects of RDN [8,9].

Histopathologic studies suggest that the majority of afferent nerves controlling sympathetic tone are in the renal collecting system [10–14]. This intuitively makes sense since the presence of afferent renal sensory nerves in the renal pelvic wall is ideal for sensing stretch of the renal pelvic wall. Within the renal pelvis, there is also an abundance of efferent nerves, and afferent and efferent nerves are in close proximity and often intertwined [10]. This is in stark contrast to the peri-arterial area where the renal nerves are predominantly composed of efferent with few afferent fibers [15]. This begs the question whether

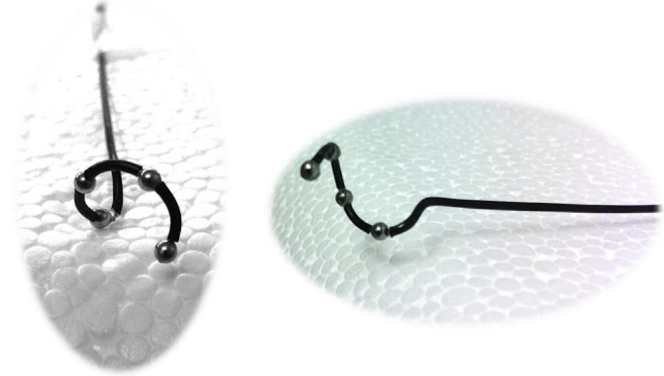

Fig. 1. The NephroBlate™ device with its helical probe.