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A UNIVERSAL call for the optimisation of vascular closure devices

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Clinical practice guidelines give a class I recommendation to the radial approach in preference to the femoral approach in patients undergoing coronary angiography (CA) and percutaneous coronary intervention (PCI)[1]. However, femoral access is still frequently utilised for large-bore access (i.e., complex PCI, percutaneous mechanical circulatory support, structural heart interventions) or in scenarios where a transradial approach is technically challenging or unfeasible. In the contemporary era of widespread radial adoption, a paradoxical increase in vascular complications with femoral artery catheterisation has been described, potentially attributable to declining operator experience with non-radial approaches[2]. Therefore, best practices need to be defined for safe femoral access to achieve the best possible patient outcomes.

In this issue of EuroIntervention, d'Entremont et al[3] report a prespecified subgroup analysis of patients utilising vascular closure devices (VCD) within the UNIVERSAL (Routine Ultrasound Guidance for Vascular Access for Cardiac Procedures) trial. UNIVERSAL was an open-label, investigator-initiated, randomised clinical trial of 621 patients referred for CA or PCI at two sites in Canada, randomised in a 1:1 ratio to ultrasound (US)-guided (on the background of fluoroscopic landmarking) versus fluoroscopic-guided femoral access. Importantly, both centres were default radial sites; the enrolled patients were non-consecutive and femoral access was selected because of either anatomical factors or operator preference. The primary endpoint was a 30-day composite of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding and major vascular complications. The UNIVERSAL trial was negative for the primary endpoint: US guidance did not reduce the incidence of bleeding or vascular complications: 12.9% vs 16.1%; odds ratio (OR) 0.77, 95% confidence interval (CI): 0.49-1.20[4].

Article, see page 73

UNIVERSAL is one of 3 well executed, multicentre trials comparing US-guided versus fluoroscopic-guided access; there is a remarkable consistency to all 3 trial primary endpoint analyses: all 3 are unequivocally negative **(Table 1)**. Despite this primary negativity, two prior trials have suggested possible benefit for routine US guidance via secondary endpoint analysis. For example, in the Femoral Arterial Access With Ultrasound Trial (FAUST) trial, secondary endpoints of first-pass success rate, number of access

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Table 1. Randomised trials of ultrasound-guided versus fluoroscopic approach to femoral artery access.

Study/country/year	Population	Sheath sizes (Fr)	Primary outcome	Key secondary outcomes	Overall VCD use (%)	VCD subgroup results
Seto et al[5]. FAUST Trial, United States, 2010	Diagnostic or interventional coronary/ peripheral (N=1,004)	5-7	Primary outcome: negative No benefit for US Successful CFA cannulation; 86.4% vs 83.3%; p=0.17	↑ First-pass access; ↓ vascular complications; ↓ number of attempts, venipunctures, and time to access.	61.6	Not reported
Nguyen et al[7]. SURF trial, Australia, 2019	Diagnostic or interventional coronary procedures (2X2 factorial trial of radial vs femoral and ultrasound vs standard access; N=688)	5-7	Primary outcome for radial vs femoral: positive, radial superior. Primary outcome for US vs standard femoral access: negative, no benefit for US Composite of ACUITY major bleeding, MACE (death, stroke, MI, or urgent TLR), and vascular complications at 30 days; 2.3% vs 2.5%; p=0.76	↑ First-pass access; ↓ venipunctures, access time, and difficult accesses.	37.9	Not reported
Jolly et al[4]. UNIVERSAL trial, Canada, 2022	Diagnostic or interventional coronary procedures (N=621)	5-8	Primary outcome: negative No benefit for US BARC 2,3, or 5 bleeding or major vascular complications at 30 days; 12.9% vs 16.1%; p=0.25	↑ First-pass access; ↓ arterial puncture attempts and venipuncture; no Δ in time to access	52.2	Non-randomised analysis for primary endpoint: positive for US 11.8% vs 23.4%; $p_{interaction}$=0.004

ACUITY: Acute Catheterization and Urgent Intervention Triage strategy; BARC: Bleeding Academic Research Consortium; CFA: common femoral artery; MACE: major adverse cardiovascular events; MI: myocardial infarction; TLR: target lesion revascularisation; US: ultrasound; VCD: vascular closure device

attempts, inadvertent venipunctures, median time to access, and vascular complications (driven by a reduction in large haematomas), showed benefit for an US-guided strategy[5]. In this context, UNIVERSAL is also consistent with prior trials: a prespecified secondary endpoint or subgroup analysis suggests potential benefits from US-guided femoral access not reflected in the main trial results, namely the routine use of US-guided access specifically benefits the subgroup of patients receiving VCDs.

In the main trial, the utilisation of VCDs was 54.7% vs 51.0% in the US versus non-US groups, respectively. ANGIO-SEAL (Terumo) was the most frequently utilised VCD (85.5%) with ProGlide (Abbott; 14.5%) being used in the remainder of the cases. In the VCD cohort, there was a significant reduction in the composite endpoint with US guidance (11.8% vs 23.4%; OR 0.44, 95% CI: 0.23-0.82). In contrast, in the manual compression group, there was no difference in the primary endpoint in the US versus no US groups (14.2% vs 8.6%; OR 1.76, 95% CI: 0.80-4.03; $p_{interaction}$=0.004). The results of the current *post hoc*, prespecified subgroup study suggest that the safety of femoral artery access may hinge on US guidance, particularly in patients chosen for VCD closure. These findings are plausible. However, this conclusion contradicts the result of the main trial outcome and therefore, further perspective is required to contextualise these subgroup findings into clinical practice.

First, the current VCD substudy is a subgroup analysis of an overall negative trial; therefore, the findings are hypothesis-generating. Second, VCD use was a post-randomisation variable and US guidance might have biased the decision to use a VCD or the type of VCD used. Therefore, the study results, especially the comparisons of event rates in the ANGIO-SEAL versus ProGlide groups must be interpreted with caution. Next, the superior results in the US arm in the VCD subgroup were driven by a 3-fold reduction in large haematomas ≥5cm (4.1% vs 12.0%; OR 0.32, 95% CI: 0.11-0.81); there was no difference in other vascular complications (pseudoaneurysm, arteriovenous fistula, retroperitoneal haematoma, limb complications) or the co-primary bleeding endpoint between the US versus no US groups. While major bleeding has been shown to be an independent predictor of both early and one-year mortality, large haematomas may have less effect on 30-day ischaemic events or 1-year all-cause mortality[6]. Lastly, micropuncture access was not utilised in the UNIVERSAL trial and thus the angiographic detection of arterial disease that may have precluded VCD utilisation is not well described. There were no differences in VCD failure rates in the US versus no US groups in the current study. Therefore, the greater number of haematomas in the no VCD arm were most likely due to bleeding arising from multiple arterial punctures or inadvertent venipunctures (both higher in the no US group). Whether or not a femoral angiography-guided micropuncture approach to VCD utilisation would have improved the results of the non-US-guided arm cannot be determined from this study design.

The authors are to be congratulated for reinvigorating a crucial topic in the "radial first" era where there is diminishing experience in femoral access and closure. Therefore, the importance of defining the optimal technique in femoral access in conjunction with VCD use cannot be overemphasised. UNIVERSAL is the first randomised trial to focus on the particular subgroup of patients receiving VCD and thus this subgroup analysis is of key importance for clinical conclusions and future trial design **(Table 1)**. US guidance is mandatory in venous access procedures (for which palpable pulse, fluoroscopic landmarks and micropuncture are of limited utility) without any further trial evaluation. But can we conclude that

US guidance is mandatory for femoral arterial access in conjunction with VCD utilisation? Or could the careful use of the micropuncture technique for femoral access, with femoral angiography as a screening prior to sheath placement and ultimate VCD utilisation, provide an equivalent strategy? Furthermore, how effective and operator-dependent is US guidance in detecting the full extent of femoral artery disease as compared to a mandatory femoral angiogram? And finally, does best practice change for large-bore access with predominant ProGlide utilisation as compared to smaller sheath procedures that are predominantly closed with the ANGIO-SEAL device?

This important UNIVERSAL trial subgroup analysis suggests that fluoroscopic-guided femoral arterial access in the context of VCD utilisation may no longer be best practice. But, to prove this, randomisation not stratification is required: among patients with micropuncture access with adequate angiographically defined femoral access to permit the safe use of a VCD (femoral artery diameter of greater than 5.0 mm diameter, not severely calcified), can we perform a multicentre randomised clinical trial to determine if the initial puncture, guided by US versus fluoroscopy, leads to the elusive positive primary endpoint? Given the changing landscape, utilisation, and applications of femoral versus radial access, finding a conclusive answer to this question may be more important than ever. While the findings reported by d'Entremont et al[3] do not yet mandate the use of US guidance for femoral access prior to VCD use, they do point to a universal need for more knowledge regarding best practice in VCD use.

Conflict of interest statement

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