Eur J Vasc Endovasc Surg (2019) 57, 755–756

EDITORIAL

The ATTRACT Trial Becomes More Attractive

Results from the large scale and long awaited ATTRACT trial were published at the beginning of 2017.[1] The analysis of the femoropopliteal and iliofemoral cohorts as a single group has been one of the major reasons that the trial was heavily criticised. It has been known for many years that post-thrombotic syndrome (PTS) is more frequent and serious with iliac and common femoral vein involvement than with more distally thrombosed vein segments.[2] Equally, it has been "old wisdom" that there is a 4–5 fold higher rate of recanalisation of the femoral vein than the iliac vein in patients managed with medical measures alone, particularly on the left side.[3,4] Furthermore, post-thrombotic changes at three months, assessed with ultrasound, are directly correlated with an increased risk of recurrent deep vein thrombosis (DVT) and PTS.[5]

The ATTRACT principal investigator, in a previous *EJVES* editorial, highlighted that "Once the detailed subgroup analyses of PTS severity and QOL [quality of life] are completed, physicians will have a stronger foundation of high quality evidence from which to judge which patients should or should not receive thrombolytic therapy, a major step forward in the treatment of DVT".[6] This is provided with the new publication from the ATTRACT trial investigators, which has now shed more light on the trial with an analysis of a subgroup with iliofemoral disease alone, including 196 patients treated with pharmacomechanical catheter-directed thrombolysis (PCDT) and 195 patients in the control group.[7] The outcome still indicates that there is no difference in PTS assessed by Villalta score $>$ 4 or ulcer between the thrombus removal group with PCDT and the control group: 49% vs. 51%, respectively (risk ratio [RR] 0.95; 95% confidence interval [CI] 0.78–1.15; $p = .59$). However, a difference was found in patients with moderate to severe PTS (Villalta score $>$ 9 or ulcer) in favour of PCDT 18% vs. 28% (RR 0.65; 95% CI 0.45–0.94; $p = .021$) and likewise concerning severe PTS (Villalta score $>$ 14 or ulcer) 8.7% vs. 15% (RR 0.57; 95% CI 0.32–1.01; $p = .048$) as in the main study. Moreover, there is a strongly significant difference between the groups if Venous Clinical Severity Score (VCSS) is used as the primary outcome measure (VCSS $>$ 7 was 6.6% vs. 14% in favour of PCDT ([RR 0.46; 95% CI 0.24–0.87; $p = .013$]). This highlights the current difficulty in reaching a clear answer from the ATTRACT data. From baseline and through to 24 months, PCDT led to greater improvement in venous disease specific quality of life (QOL; $p = .029$) but not in generic QOL ($p = .21$). Finally, and importantly, no difference was found concerning major bleeding and recurrent DVT between the two groups.

The study has raised a major question concerning treatment modalities in the thrombus removal group based on a heterogeneity of interventions: infusion, rheolytic thrombectomy, isolated thrombolysis, large bore catheter aspiration, balloon maceration supplemented with balloon dilatation alone, and iliac stenting, making it impossible to ascertain from the trial data whether one method or another of clot removal is superior. It is imperative that in the publication of updated guidelines attempts are made to provide better standardisation of treatment, which will ultimately require some form of direct comparison as has been seen with the multitude of treatments for ablation of the saphenous vein. Indeed, the heterogeneity of data in many publications regarding endovenous thrombolysis makes even meta-analysis of these outcomes difficult.[8]

A further observation is that the rate of PTS in the ATTRACT trial in the PCDT arm is higher than previous publications and, in particular, when compared with that of large volume centres with long experience. The Copenhagen group demonstrated a rate of any PTS of 17% in 109 patients with iliofemoral DVT treated with catheter-directed thrombolysis (CDT) after a median follow up of 71 months.[9] In addition, other groups have recently published similarly low rates of PTS, albeit after 1–2 years, and this appears to be the experience of most mature centres.[10,11]

This problem of randomizing patients to low volume centres, still on the learning curve, has plagued many trials of intervention vs. medical therapy. This is similar to the experience of the introduction of clot removal techniques for both coronary disease and stroke where a cycle of improvement in technique and repeat of trials made early clot removal the standard of care. Medical management has advanced considerably but, as yet, has never been shown to be an effective prevention of PTS. The ATTRACT study, and similarly with CaVenT study, show it only prevents PTS 50% of the time in the acute setting.[12] There are few, if any, additional advances to be made in medical management and therefore it appears that improvement in clot removal techniques provides the only viable option to seek a long-term solution to prevent PTS following acute DVT. Furthermore, the CaVenT study, with many of the same methodological flaws as ATTRACT, has shown the difference in PTS at the longer term follow up (5 years) to be much more pronounced with an increased rate of PTS in the control group, but still without a difference in QOL.[13] This trend toward difference fits with our knowledge that PTS might take time to evolve, which may call for a longer follow up in the ATTRACT trial.

https://doi.org/10.1016/j.ejvs.2019.03.017

The widespread use of the Villalta scale has been criticised in many publications and the discrepancy in results between this and VCSS makes the point that we are distinctly lacking a broad, common consensus to classify both the initial disease (e.g., proximal DVT vs. iliofemoral) and outcomes. Had Villalta been used as continuous data (the second outcome table presented in the ATTRACT study) as opposed to the chosen binary outcome or VCSS chosen as the primary outcome then the ATTRACT trial would have been strongly positive in favour of PCDT. This gap requires urgent attention to enable us to move treatment forward and allow comparison of published data to better inform decision making.

CDT for iliofemoral DVT was questioned in 2014, in a previous editorial in this journal, as "myth or reality?",[14] which was published after presenting the two year results from the Norwegian CaVenT study, which, though in favour of CDT over medical management alone, were not overwhelming.[12] The publication of the iliofemoral alone data from ATTRACT trial continues to highlight that the focus should remain on this segment. The ATTRACT trial has undoubtedly become more "ATTRACTIVE" and continues to support the notion that endovenous therapy for acute iliofemoral DVT confers benefit to our patients and averts the plight of PTS: the benefit is both real and helpful.

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