Where do We Go to in the Treatment of Acute Limb Ischaemia?

Acute limb ischaemia (ALI) threatens life and limb, and especially quality of life. Optimal treatment of ALI entails shared decision making between the clinician and the patient and family based on best available evidence. The current European Society for Vascular Surgery (ESVS) 2020 ALI management guidelines, published in this issue of the Journal, offer up to date guidance on therapeutic decision making. However, they also highlight that both the mix of the underlying causes of ALI and the limited amount of high quality evidence remain major limitations in defining universal treatment algorithms. The natural question that arises from this background is: Where will we go to in the treatment of ALI in the future? Therefore, the ESVS guidelines not only provide systematic appraisal of the available evidence, but also clearly map out the areas for future research in a dedicated chapter.

Although various therapeutic approaches are being used nowadays to achieve revascularisation of ALI (ranging from pharmacological (e.g. thrombolysis) to interventional or surgical revascularisation techniques) none has been shown superior. Treatment comparisons are primarily challenged by the various aetiologies of ALI, ranging from acute cardioembolic causes to thrombotic occlusion of pre-existing atherosclerotic lesions, popliteal aneurysms, or bypass grafts. It is intuitive that primary embolic disease requires local clot removal/resolution, whereas thrombotic ALI aetiologies also need correction of the underlying lesions for successful and sustained revascularisation. Hence available outcome data should be evaluated within distinct patient subgroups; and consensus regarding patient classification and risk stratification should be reached first. As the guidelines rightly point out, no biomarkers yet exist to assist with classification and outcome prediction. Use of artificial intelligence with deep learning could be an alternative approach if available data were amalgamated.

For instance, surgical revascularisation vs. local catheter directed thrombolysis has been a longstanding topic of interest; and several (small and large) trials during 1990s have shown that thrombolysis was equivalent in the treatment for ALI regarding amputation free survival up to one year. However, increased risk of bleeding and, possibly of stroke were observed. Overall the results from these studies suggest that the benefit of thrombolysis depends on the severity of ischaemia at presentation, the time since occlusion, and whether the occlusion was related to a previous bypass graft. Nonetheless thrombolytic therapy remains limited by bleeding complications and the duration of treatment. Thrombolysis may take several hours or days for revascularisation, needing high doses of thrombolytic agents, several angiograms and blood samples, all adding to the patient’s burden. In addition, different thrombolysis strategies with various thrombolytic agents and doses are used around the world. Therefore, stratified analyses of combined outcome data would be important to define optimal thrombolytic regimens and to improve current therapeutic options for ALI.

In this context, the pertinent research questions are: How can we further lower the complication rate, and still offer rapid and safe thrombolysis? Is aggressive endovascular treatment or more precise delivery of the thrombolitics the solution? In an era of constantly improving imaging and endovascular techniques, newer materials, advancing interventional skills and local medical agents, the future of ALI management probably does not only lie in early detection but mainly in rapid, precisely targeted and safe revascularisation to save more limbs and lives and to preserve quality of life. Thereby, the availability of hybrid operating rooms offering the full range of both endovascular and open surgical techniques in the same setting, simplifies comprehensive ALI management without delay.

Novel developments to accelerate revascularisation include endovascular mechanical thrombectomy with rheolytic or microfragmentation catheters that can be used solely or in combination with thrombolysis. This approach has not yet become daily practice in many hospitals as early experience showed a risk of vessel perforation or re-thrombosis, and because mechanical thrombectomy catheters do not fit into every artery. In addition, embolisation resulting in occlusion of smaller vessels downstream has been reported. However, newly designed endovascular thrombo-aspiration devices (e.g. Penumbra/Indigo catheter, Penumbra Inc, CA, USA) are becoming available and are increasingly applied by vascular specialists. More data will be needed to identify the optimal circumstances in which each of these devices provides a distinct clinical advantage.

Other promising concepts include ultrasound accelerated thrombolysis with the EKOS Endowave system (EKOS Corporation, Bothell, WA, USA). High frequency, low intensity ultrasound is used as a cavitation mechanism to speed up enzymatic clot lysis by increasing thrombus permeability for thrombolytic agents. Randomised comparisons show that the EKOS Endowave system indeed accelerates thrombolysis but that it also increases the risk of bleeding, because...
of the handling of the introducer sheath.\(^6\) As with any new device, this approach will also face the challenge of defining its cost effectiveness.

An interesting further development is the combined use of sonothrombolysis and microbubbles (MBs) to accelerate thrombolysis even more. MBs are small gas filled bubbles of 1–10 μm with a lipid shell and may act as cavitation nuclei lowering the threshold for US effectiveness. Exposed to low intensity US, MBs increase dissemination of thrombolytics throughout the thrombus. Exposed to high intensity US, MBs may collapse and damage the thrombus surface leading to increased drug transport and lysis. The ‘Micro-bubbles and Ultrasound-accelerated Thrombolysis (MUST)’\(^7\) for peripheral arterial occlusions is a phase-II clinical trial that has been performed at Amsterdam UMC and will assess feasibility and patient safety.

An additional potential benefit of MBs is that they can be loaded with medication and be targeted directly to the site of treatment. The concept can even be extended to include magnetic nanocapsules for magnetically controlled thrombolysis. Thrombolytic drugs are buried within the magnetic nanocages with the added benefit of a prolonged period of local action and prolonged half life in human plasma. This has not been performed for ALI yet but has been tested in \textit{in vitro} and \textit{in vivo} models.\(^8\) MB technology may also be interesting for targeted pharmacotherapy delivery in the context of other controlled reperfusion approaches (including for example hypertonic saline with dextran 70 or iloprost\(^9\)) that have been proposed to reduce mortality and adverse event rates after ALI. Such novel approaches need to be evaluated on a larger scale but could be promising in the future.

The chances are that with advanced imaging guided treatments and precise delivery of thrombolytic agents, ground breaking techniques for fast and safe revascularisation may be developed in the (near) future. Meanwhile vascular specialists should be familiar with all the currently available techniques, including both open and endovascular interventions, to ensure the best available treatment for their patients. The present guidelines provide both, a critical synthesis of current knowledge and a convincing layout of future research needs.

\textbf{REFERENCES}

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