EuroIntervention
2024;20:e1122-e1123
published online e-edition xxx 2024
DOI: 10.4244/EIJ-E-24-00050

EDITORIAL

Acute limb ischaemia from stent thrombosis: bad luck or bad protoplasm?

Sahil A. Parikh*, MD; Robert S. Zilinyi, MD, MS

**Corresponding author: Columbia University Irving Medical Center, Center for Interventional Cardiovascular Care, Division of Cardiology, Department of Medicine, 161 Fort Washington Avenue, 6th Floor, New York, NY, 10032, USA. E-mail: sap2196@cumc.columbia.edu*

Acute limb ischaemia (ALI) is a vascular emergency resulting from the acute occlusion of a major artery of the extremities. The range of aetiologies includes *in situ* thrombosis – often due to restenosis after prior intervention with a balloon/stent/stent graft (SG) – an athero- or cardioembolic event, arterial dissection, or trauma. During the height of the COVID-19 pandemic, inflammatory thrombophilia in the setting of coronavirus infection was also common and increased the incidence of ALI[1]. The clinical presentation of ALI may range from pallor, rest pain, poikilothermia with loss of motor and/or sensory function all the way to frank necrosis depending upon the time from symptom onset to presentation and the presence of collateral blood supply.

In patients with symptomatic femoropopliteal (FP) peripheral arterial disease (PAD), endovascular intervention is the dominant modality for revascularisation therapy[2], with balloon angioplasty serving as the single most common therapy. Primary stenting as first-line therapy is elected much less commonly; however, "bailout" stenting such as in cases of flow-limiting dissection, inadequate luminal gain due to calcification, recoil or perforation is common. Stenting in the FP segment, either as primary or bailout therapy, is associated with modest rates of stent thrombosis above and beyond those which are seen with balloon angioplasty alone and can result in ALI. Thus, in every case, operators weigh the risks and benefits of stenting in the FP segment.

In this issue of EuroIntervention, Nakao et al report the results of a retrospective multicentre study of 499 patients with ALI identified between 2011 and 2023 in Japan[3]. The authors compared clinical characteristics, treatment, and differences in the primary endpoint of amputation free survival (AFS) between patients with stent thrombosis associated ALI (ST-ALI; n=108) and those without ST-ALI (*de novo* ALI; n=391). The ST-ALI cohort was younger, with more atherosclerotic risk factors including hypertension, diabetes, and haemodialysis dependence. On the other hand, the *de novo* ALI group was older with significantly higher rates of atrial fibrillation. Although the *de novo* ALI group suffered higher rates of primary amputation, the ST-ALI group had worse 1-year AFS compared to the *de novo* ALI group (51% vs 76%; p<0.001) with ST, haemodialysis, atrial fibrillation, ischaemic wounds, peak C-reactive protein, and non-ambulatory status predicting worse AFS on multivariable Cox regression analysis. The secondary outcomes of freedom from major adverse limb events (MALE) and occlusion at 12 months were both lower in the ST-ALI cohort.

Article, see page e1163

The authors are to be commended on this important analysis of an understudied population. While there is literature on both ALI as well as ST, this is a unique study comparing the differences in clinical characteristics and "hard" outcomes including major amputation and mortality between what amounts to a PAD cohort and a mostly non-PAD cohort. The between-group differences are stark but not altogether surprising. The high rates of ischaemic wounds in the ST-ALI group speak to an underlying chronic ischaemic burden of atherosclerosis predisposing this population to worse limb outcomes and mortality rates. Thus, we would expect that the ST-ALI group would fare worse with respect to AFS. Notably, the *de novo* ALI cohort required more primary amputation than the ST-ALI cohort, despite presenting earlier to medical care, possibly because of the absence of a robust collateral circulation as we might find in patients with obstructive FP-PAD.

The analysis suggests that avoidance of stenting would naturally abrogate the risk of ST, and therefore should be a dominant strategy in FP intervention. However, given that stenting is so common, even in bailout applications, one wonders if the data corroborate concerns about different stent types having greater risk for ST-ALI. In the present study,

bare metal stents (BMS) were used roughly twice as often as drug-eluting stents (DES) or SG, but ST rates could not be compared. Previous studies have shown higher ST rates with SG. In an analysis of the XLPAD (Excellence in Peripheral Artery Disease) registry of 604 patients who underwent FP stenting, 4.3% had an ST, and 50% of these ST patients developed ALI. Compared to BMS or DES patients, SG patients had ST significantly more often[4]. A subsequent study by Katsanos et al found SG placement also to be a significant predictor of ST as well as major amputation[5]. What about DES? A 2024 study by Shimizu et al found that in 288 patients who received DES to the FP segment in a contemporary cohort, 8.6% of patients had ST, a 1-year patency rate of 22.9% and AFS of 55.1%[6]. However, a more recent study also from Japan suggests rates of DES ST of 3.3% at 1 year, similar to reported data on BMS[7].

The 2020 VOYAGER PAD trial demonstrated the efficacy of low-dose rivaroxaban (2.5 mg twice daily) added to low-dose aspirin in preventing a composite endpoint of both major adverse cardiovascular events and MALE in patients who had undergone PAD intervention, driven by a substantial reduction in ALI[8]. Low-dose aspirin+low-dose rivaroxaban is now given a Class Ia recommendation for all-comers with symptomatic PAD regardless of revascularisation status. The rates of low-dose rivaroxaban use in the present study's population are not noted but may be informative to understand whether its use or lack of use in the ST-ALI population impacted AFS.

Finally, the peak of the COVID-19 global pandemic occurred during this study period, with inflammatory thrombophilia having previously been described[1], marked by dramatic elevations in C-reactive protein and both arterial and venous thrombotic and thromboembolic events. There is little mention of this phenomenon in the present study and how it may have affected both incidence of ALI and outcomes, particularly in the vulnerable population of patients with symptomatic PAD. One wonders if COVID-19 skewed the results.

The present study highlights the dire consequences of ST-ALI compared to *de novo* ALI and the need to minimise stenting in the FP segment where feasible, optimise stenting when used, and ensure adequate platelet inhibition and antithrombotic therapy following stent placement. The morbidity and mortality of ST-ALI and sequelae reflect both bad luck and bad protoplasm.

Authors' affiliation

Columbia University Irving Medical Center, New York, NY, USA

Conflict of interest statement

S.A. Parikh receives institutional research funding from Abbott, Boston Scientific, Surmodics, TriReme Medical, Shockwave Medical, Acotec, Concept Medical, Reflow Medical, Veryan Medical, and Philips; is an advisor to Abbott, Boston Scientific, Medtronic, Cordis, and Philips; has received honoraria from Abiomed, Terumo, Inari, Penumbra, and Canon; and has equity in Encompass Vascular, Advanced NanoTherapies, and Efemoral. R.S. Zilinyi has no conflicts of interest to declare.

References

1. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quéré I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2020;75:2950-73.

2. Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, Chandra V, Drachman DE, Eaves JM, Ehrman JK, Evans JN, Getchius TSD, Gutiérrez JA, Hawkins BM, Hess CN, Ho KJ, Jones WS, Kim ESH, Kinlay S, Kirksey L, Kohlman-Trigoboff D, Long CA, Pollak AW, Sabri SS, Sadwin LB, Secemsky EA, Serhal M, Shishehbor MH, Treat-Jacobson D, Wilkins LR. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2024;149:e1313-410.

3. Nakao S, Iida O, Takahara M, Suematsu N, Yamaoka T, Matsuda D, Nakama T, Fujihara M, Tobita K, Koyama E, Haraguchi T, Ogata K, Mano T. Clinical outcomes of acute limb ischaemia caused by femoropopliteal stent thrombosis. *EuroIntervention.* 2024;20:e1163-72.

4. Banerjee S, Sarode K, Mohammad A, Gigliotti O, Baig MS, Tsai S, Shammas NW, Prasad A, Abu-Fadel M, Klein A, Armstrong EJ, Jeon-Slaughter H, Brilakis ES, Bhatt DL. Femoropopliteal Artery Stent Thrombosis: Report From the Excellence in Peripheral Artery Disease Registry. *Circ Cardiovasc Interv.* 2016;9:e002730.

5. Katsanos K, Al-Lamki SA, Parthipun A, Spiliopoulos S, Patel SD, Paraskevopoulos I, Zayed H, Diamantopoulos A. Peripheral Stent Thrombosis Leading to Acute Limb Ischemia and Major Amputation: Incidence and Risk Factors in the Aortoiliac and Femoropopliteal Arteries. *Cardiovasc Intervent Radiol.* 2017;40:351-9.

6. Shimizu H, Kobayashi T, Okazaki T, Mochizuki S, Maeda K, Sato T, Emura S, Arai Y, Kato Y, Takahashi S. Clinical impact of fluoropolymer-based drug-eluting stent thrombosis in femoropopliteal artery occlusive lesions. *Vascular.* 2024 May 29. [Epub ahead of print].

7. Iida O, Takahara M, Soga Y, Yamaoka T, Fujihara M, Kawasaki D, Ichihashi S, Kozuki A, Nanto S, Sakata Y, Mano T; CAPSICUM Investigators. 1-Year Outcomes of Fluoropolymer-Based Drug-Eluting Stent in Femoropopliteal Practice: Predictors of Restenosis and Aneurysmal Degeneration. *JACC Cardiovasc Interv.* 2022;15:630-8.

8. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, Hess CN, Pap AF, Kittelson JM, Gudz I, Mátyás L, Krievins DK, Diaz R, Brodmann M, Muehlhofer E, Haskell LP, Berkowitz SD, Hiatt WR. Rivaroxaban in Peripheral Artery Disease after Revascularization. *N Engl J Med.* 2020;382:1994-2004.