

## Review Article

# Is Angiosome-Guided Endovascular Therapy Worthwhile?

Yosuke Hata, MD, Osamu Iida, MD, and Toshiaki Mano, MD, PhD

Endovascular therapy (EVT) plays a major role in the treatment of critical limb ischemia (CLI). The latest guidelines state that the angiosome concept should be considered when performing revascularization of infrapopliteal lesions in patients with CLI. There have been several reports both of favorable and unfavorable results of angiosome-guided EVT. Based on previous reports, angiosome-guided EVT tends to improve wound healing (WH) rather than amputation-free survival and overall survival. In addition, indirect revascularization based on the angiosome concept with a good collateral flow may achieve good WH comparable to that achieved by direct revascularization. In the future, rather than just debating the effectiveness/ineffectiveness of the angiosome concept, it will be desirable to investigate the patient and lesion characteristics that may have significant influences on WH after angiosome-guided EVT and to apply the results to clinical practice.


**Keywords:** critical limb ischemia, angiosome concept, wound care, endovascular therapy

## Background

Endovascular therapy (EVT) plays a major role in the treatment of critical limb ischemia (CLI). In the latest guidelines published by the European Society of Cardiology and the European Society for Vascular Surgery,<sup>1)</sup> EVT was recommended as a class IIa treatment for patients with CLI with a high surgical risk. The guidelines also state that the angiosome concept should be considered

*Kansai Rosai Hospital Cardiovascular Center, Amagasaki, Hyogo, Japan*

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Corresponding author: Yosuke Hata, MD, Kansai Rosai Hospital Cardiovascular Center, 3-1-69 Inabaso, Amagasaki, Hyogo 660-8511, Japan  
Tel: +81-6-6416-1221, Fax: +81-6-6419-1870  
E-mail: hata.yosuke@gmail.com

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when performing revascularization of infrapopliteal lesions in patients with CLI. On the other hand, it is also mentioned that the angiosome concept should not be considered as the only strategy and that well-structured research is still needed, and the angiosome concept has some limitations. This chapter discusses the effectiveness and limitations of the angiosome concept for EVT on the basis of previous reports.

## Favorable Results of Angiosome-Guided EVT

There have been several reports of favorable results of angiosome-guided EVT, and the key findings are shown in **Table 1**. The first report on the angiosome concept was published in 2008 by Alexandrescu et al.<sup>2)</sup> In this study, EVT was performed in 85 patients with CLI (102 limbs) with popliteal lesions. A comparison between direct revascularization (DR) and indirect revascularization (IR) based on the angiosome concept was conducted. As a result, it was found that the wound healing (WH) rate was significantly better in the DR group than in the IR group. In addition, in 2012, our group carried out a retrospective analysis of 369 patients with CLI with isolated popliteal lesions. After propensity score matching to adjust the baseline characteristics in 236 patients (DR group: 118 patients, IR group: 118 patients), we found that the DR group had better amputation-free survival (AFS) than the IR group.<sup>3)</sup> Söderström et al.<sup>4)</sup> also used propensity score matching to analyze 250 patients with CLI in 2013 and found that the one-year WH rate was significantly better in the DR group than in the IR group. In 2015, our group reported the results of a retrospective multicenter analysis of 734 consecutive patients with CLI with isolated popliteal lesions, which revealed that IR was an independent predictor of delayed WH.<sup>5)</sup> In 2018, a prospective study of 212 patients with CLI was reported by Elbadawy et al.<sup>6)</sup> While the one-year WH rate was better in the DR group than in the IR group, there were no significant differences in major amputation or AFS between the groups. In some meta-analyses,<sup>7,8)</sup> it was revealed that the prognosis of the limb (WH rate and major amputation rate) is better in the DR group than in the IR group. On the other hand, the

**Table 1** Clinical outcomes of previous studies favorable for the angiosome concept

Author, year	Study design	Propensity score matching	DR	IR	Outcomes	DR vs IR (p-value)	DM (%)	CKD (%)
Alexandrescu, 2008 <sup>1)</sup>	Retrospective	No	85	17	Completion of WH	83% vs 59% (NA)	124 (100)	27 (22)
Alexandrescu, 2011 <sup>15)</sup>	Retrospective	No	134	98	One-year survival Completion of WH	93% vs 90% (p=0.545) 79% vs 55% (p<0.05)	232 (100)	42 (18)
Iida, 2012 <sup>3)</sup>	Retrospective	Yes	200	169	One-year AFS	61% vs 44% (p=0.002)	172 (73)	149 (63)
Söderström, 2013 <sup>4)</sup>	Retrospective	Yes	121	129	One-year WH	72% vs 46% (p<0.001)	250 (100)	39 (16)
Fossaceca, 2013 <sup>16)</sup>	Retrospective	No	167	34	One-year WH One-year LS	57% vs 32% (NA) 90.4% vs 91.2% (NA)	201 (100)	15 (7.4)
Acín, 2014 <sup>14)</sup>	Retrospective	No	46	39	One-year WH	66% (DR) vs 68% (IR with collaterals) vs 7% (IR without collaterals)	101 (100)	0 (0)
Iida, 2014 <sup>17)</sup>	Retrospective	Yes	182	182	One-year WH Two-year MALE Two-year AFS	75% vs 64% (p=0.01) 55% vs 54% (p=0.99) 60% vs 59% (p=0.17)	249 (68)	245 (67)
Elbadawy, 2018 <sup>6)</sup>	Prospective	Yes	117	95	One-year WH One-year LS One-year AFS	81% vs 63% (p=0.02) 90% vs 82% (p=0.148) 73% vs 62% (p=0.164)	162 (76)	22 (10)

DR: direct revascularization; IR: indirect revascularization; DM: diabetes mellitus; CKD: chronic kidney disease; WH: wound healing; AFS: amputation-free survival; LS: limb salvage; NA: not available; MALE: major adverse limb event

**Table 2** Clinical outcomes of previous studies unfavorable for the angiosome concept

Author, year	Study design	Propensity score matching	DR	IR	Outcomes	DR vs IR (p-value)	DM (%)	CKD (%)
Špillarová, 2017 <sup>18)</sup>	Retrospective	No	171	145	One-year WH One-year LS One-year AFS	52% vs 52% (NA) 79% vs 68% (NA) 60% vs 51% (NA)	NA	NA
Weaver, 2018 <sup>9)</sup>	Retrospective	No	154 (wounds)	71 (wounds)	One-year WH	66.9% vs 54.9% (p=0.08)	99 (100)	19 (19.2)

DR: direct revascularization; IR: indirect revascularization; DM: diabetes mellitus; CKD: chronic kidney disease; WH: wound healing; LS: limb salvage; AFS: amputation-free survival; NA: not available

mortality rates were not different between the two groups in these analyses.

The majority of the studies indicating the effectiveness of angiosome-guided EVT are retrospective. Additionally, angiography, for the purpose of classifying patients as DR or IR in these studies, was not evaluated by an independent observer, such as a core laboratory; thus, bias may have occurred.

## Unfavorable Results of Angiosome-Guided EVT

Several negative reports have also been published, as summarized in Table 2. In 2018, Weaver et al.<sup>9)</sup> reported the results of a retrospective analysis of WH after endovascular or open revascularization in 99 patients with CLI with diabetes, but they found no difference between the DR and the IR groups. It has also been reported that clinical stages 3 and 4 of the Wound, Ischemia, and foot Infection

(WIFI) classification system suggested by the Society for Vascular Surgery<sup>10)</sup> predict delayed WH. In this study, the presence or absence of the pedal arch did not affect the prognosis.

In 2018, Biagioni et al.<sup>11)</sup> reported on the clinical outcomes of 80 patients with CLI with popliteal lesions randomized into two groups: a multivessel treatment group and a single-vessel treatment group. The first artery to treat was selected on the basis of good outflow below the ankle, which made EVT feasible. If the severity of the lesions was comparable, the artery was selected in accordance with the angiosome concept. There was no difference in the major amputation rate between the two groups, but the WH rate was higher and the WH time was shorter in the multivessel group than in the single-vessel group. Additionally, subanalyses demonstrated that the treatment of three vessels resulted in a better WH rate compared with two vessels, suggesting the effectiveness of complete revascularization.

In 2014, Kawarada et al.<sup>12)</sup> reported on patients with CLI treated with only one anterior tibial artery or posterior tibial artery. The skin perfusion pressure of these patients was evaluated at the dorsum of the foot (angiosome of the anterior tibial artery) and the sole (angiosome of the posterior tibial artery). Only 40–58% of the patients demonstrated significant elevation of skin perfusion pressure in the regions supplied by the treated artery compared to the regions not supplied. Although no additional analysis of collateral circulation was conducted, it seems that blood flow may be improved after IR based on the angiosome concept.

The sample size was small in all studies. Accordingly, interactions with the patients' backgrounds and demographic factors were not evaluated, which is a major limitation.

### **Efficacy of Angiosome-Guided EVT with Regard to Patient and Lesion Background**

It has been reported that the effectiveness of angiosome-guided EVT depends on various patient and lesion backgrounds. We have conducted various analyses and are currently performing EVT according to the angiosome concept whenever possible; the rationale for this approach is based on two findings. First, in 2013, we reported that IR was associated with a higher incidence of major adverse limb events (MALEs) than DR in patients with CLI with diabetes and infection (C-reactive protein: >3.0 mg/dL).<sup>13)</sup> However, the same study did not show a significant difference among patients with CLI without diabetes or infection. Based on this result, in patients requiring more blood flow because of microangiopathy caused by diabetes or wound infection, blood flow after revascularization significantly influences limb prognosis, suggesting the usefulness of the angiosome concept. Second, when additional analyses were performed to compare the WH rate between the DR and the IR groups of patients without diabetes or infection, the DR group still demonstrated a better WH rate. These findings suggest that the angiosome concept should be applied to all patients with CLI in order to achieve WH and to avoid MALEs.

It has been reported that collateral blood flow is important. In a study by Acín et al.,<sup>14)</sup> patients in the IR group with good collateral flow had better clinical outcomes than those without good collateral flow, and the outcomes were not significantly different from those of patients in the DR group. Based on this result, when evaluating the effectiveness of angiosome-guided EVT, it is important to consider the patient and lesion characteristics and the anatomical features, including collateral flow, in addition to simple comparisons of DR and IR. Furthermore, it has been reported that there are no differences in the clinical outcomes between the DR and IR groups after bypass

surgeries, possibly because surgeries achieve more blood flow than EVT.<sup>8)</sup>

### **Discussion Points for the Angiosome Concept in EVT**

In order to clarify the role of the angiosome concept in EVT, a randomized study is needed; however, this is not practical. Previous reports indicated that the importance of using the angiosome concept may vary depending on (1) the patient factors/limb factors and (2) the endpoints (death, amputation and MALEs, or WH). This dependence is a major limitation of the angiosome concept.

The following points should be noted: (1) the majority of previous studies had a retrospective design, (2) core laboratories were not employed in previous studies to assess the angiography and WH, and (3) bias among assessors is an undeniable problem. These are the major weak points of previous studies on the angiosome concept. In addition, it is difficult to confirm whether or not the plan of an operator was based on the angiosome concept. In short, some patients may have received IR, although DR was planned, whereas others may have received planned IR, possibly introducing bias. In future studies, rather than just focusing on DR or IR, it will be necessary to clarify whether the patients received IR because planned DR was too difficult or because of a good collateral blood flow. Furthermore, the influences of vascular anomalies and collateral blood flow on local perfusion should be carefully evaluated in individual patients. Finally, it is necessary to evaluate the effectiveness of the angiosome concept using a wound severity index, such as the recently introduced WIfI classification.

### **Conclusion**

According to previous reports, angiosome-guided EVT tends to improve WH rather than AFS and overall survival. In addition, IR with good collateral flow may achieve good WH comparable to that achieved by DR. In the future, rather than just debating the effectiveness/ineffectiveness of the angiosome concept, it will be beneficial to investigate the patient and lesion characteristics that may have significant influences on WH after angiosome-guided EVT and to apply the results to clinical practice.

### **Disclosure Statement**

None.

### **Author Contributions**

Study conception: OI

Data collection: YH

Writing: YH, OI

Critical review and revision: all authors

Final approval of the article: all authors

Accountability for all aspects of the work: all authors

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