SAS Journal of Surgery
Abbreviated Key Title: SAS J Surg
ISSN 2454-5104
Journal homepage: https://www.saspublishers.com

OPEN ACCESS

Vascular Surgery

Management of Critical Limb Ischemia Prognostic Factors

Dr. Samir El Youbi[1*], Dr. Bright Benfor[1], Pr Hamza Naouli[1], Pr Hamid Jiber[1], Pr Abdellatif Bouarhroum[1]

[1]Vascular Surgery Department, UHC Hassan II Fez, Morocco

DOI: 10.36347/sasjs.2023.v09i04.015 | **Received:** 05.03.2023 | **Accepted:** 16.04.2023 | **Published:** 25.04.2023

***Corresponding author:** Samir El Youbi
Vascular Surgery Department, UHC Hassan II Fez, Morocco

Abstract **Original Research Article**

Introduction*:** Critical limb ischemia (CLI) represents the most severe form of Peripheral artery disease (PAD). Its prevalence is estimated to be between 0.5% and 2.3% of the population over 40 years old. Despite its importance, epidemiological studies on CLI remain patchy. In Morocco, few studies have been carried out on this subject, and we have no epidemiological data on the morbimortality of chronic critical ischemia of the lower limbs on a national scale. ***Objective: The objective of our study was to evaluate the results of surgical treatment of critical limb ischemia and to identify the factors associated with the medium-term evolution. ***Methods:*** We conducted a retrospective cohort study of all patients admitted to the vascular surgery department of the Hassan II University Hospital for the management of critical ischemia of the lower limbs, who underwent revascularization surgery between 01/01/2013 and 31/12/2019. Patients who underwent a major amputation of the affected limb and those for whom the revascularization procedure was a revision were subsequently excluded. The follow-up period was 2 years and the events of major interest were the occurrence of a major limb amputation and 30-day mortality. ***Results:*** The cohort included 232 patients with critical ischemia. The mean age was 62 years with a clear male predominance of 84.5%. The most common comorbidities were diabetes (65.8%), active smoking (42.5%), and hypertension (31.2%). The majority of patients (62%) benefited from endovascular procedures. The primary technical success was 94.1%, the major amputation rate was 19.7%, and the 30-day mortality was 4.3%. In multivariate analysis, factors independently associated with a high postoperative complication rate were preoperative hyperglycemia, concomitant ischemic heart disease, female sex, young age, and intensive care unit stay. ***Conclusion:*** Our study highlights several risk factors for the occurrence of postoperative complications of CLI. These results encourage the optimization of preoperative management of critically ischemic patients to reduce postoperative morbidity and improve their prognosis.

Keywords: Critical limb ischemia, multivariate analysis, Prognostic factors, medium-term evolution.

Copyright © 2023 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

Peripheral artery disease (PAD) is one of the main modes of expression of atherosclerosis. It affects approximately 200 million people worldwide. The prevalence of this disease has increased by 25% between 2000 and 2010(Fowkes *et al.*, 2013). Its most severe form is chronic critical ischemia (CCI) or critical limb ischemia (CLI), the prevalence of which is estimated to be between 0.5% and 2.3% of the general population, according to American and European studies (Fowkes *et al.*, 2013; "Épidémiologie de l'artériopathie Des Membres Inférieurs - ScienceDirect" n.d.).

Critical ischemia of the lower limbs is a pathology with heavy consequences, burdened with a very important morbimortality because of its frequent association with coronary and cerebrovascular diseases, and by its natural evolution: It is estimated that after one year of follow-up, 50% of the patients suffering from CLI will end up either with a major amputation of the lower limbs, or will die of cardiovascular causes (Sampson *et al.*, 2014)).

In Morocco, critical ischemia remains a frequent reason for hospitalization in vascular surgery departments and units. In our daily practice in the vascular surgery department of the Hassan II University Hospital in Fez, the majority of patients with PAD only consult at this very advanced stage of PAD. Thus, critical ischemia remains the first indication for revascularization surgery of the lower limbs in our context. However, the dynamics of postoperative survival of these patients with critical ischemia are not sufficiently known. In fact, no epidemiological study on a national scale has yet addressed the question of what

happens to patients with critical ischemia after revascularization.

The question of the impact of different factors on the medium-term outcome of management is a crucial subject to elucidate in order to establish a causal link between them and the poor postoperative prognosis.

Through this study, we will try to identify the modifiable prognostic factors in order to determine different measures to adhere within our management to circumscribe the adverse consequences and thus improve the quality of life of patients.

METHODOLOGY

This is an observational study, retrospective cohort type with prognostic aim, carried out in the vascular surgery department of the Hassan II University Hospital and covering a sample of patients admitted for the management of critical ischemia of the lower limbs between January 2013 and December 2019.

Perioperative clinical data and follow-up data of patients admitted to the vascular surgery department of the Hassan II University Hospital are prospectively collected and recorded in the electronic database of the Hospital (Hosix.net). The patients' diagnoses and surgical procedures are coded according to the International Classification of Diseases (ICD-10).

We included in our study all patients who underwent revascularization surgery for critical ischemia of the lower limbs during the recruitment period.

We excluded:

- Subjects who initially or immediately underwent major amputation of the affected limb.
- Subjects for whom the surgical indication was the management of a complication of a previous revascularization: bypass thrombosis, restenosis or stent thrombosis, etc.
- Arteriopathy of non-atheromatous origin: leo-beurger, vasculitis, emboligenic, ...
- Insufficient data in medical record.
- Patients lost to follow-up before the 6th month.

Data collection from medical observations, results of complementary check-ups and surgical reports available on Hosix.net, was retrospective and carried out with the help of an exploitation form. The follow-up period was set at 2 years for each patient included.

Our major endpoints were:

- Major amputation of the revascularized limb at 2 years.
- Mortality at 30 days.

Secondary endpoints:

- Technical success.
- Patency at 2 years.
- Surgical revision.
- Major local complication (MLC).
- Major cardiac and cerebrovascular complications (MCCC).
- Postoperative hospital length of stay, ICU stay, inpatient readmission, and number of surgical procedures.

Descriptive and permeability analyses were performed in collaboration with the epidemiology department at the Hassan II University Hospital of Fez.

The statistical study included a descriptive and a bi-variate analytical study. The descriptive study concerned the general characteristics of the patients, the clinical and paraclinical characteristics. The results were expressed as frequency, mean and standard deviation. Univariate and multivariate analyses were performed to determine the predictive factors of morbimortality. We investigated the association between the end points and explanatory variables such as; sex, age, cardiovascular comorbidities, lesion characteristics and preoperative blood glucose. Any variable with a $p < 0.20$ in the univariate analysis was then entered into a Cox model in a stepwise top-down procedure. We used Student's t-test and chi-square for statistical comparisons of groups. The accepted confidence interval was 95%, and the threshold of $p < 0.05$ was considered significant. Data were entered using Excel 2010 and analyzed using SPSS version 27.

RESULTS

In sum, 232 patients meeting the eligibility criteria were included in our study, The male sex marks a great predominance in our study with a sex ratio of 8H/1F. The average age was 62 years (45 years-74 years) and women were significantly older than men, with an average age of 69.8 years. The cardiovascular risk factors that predisposed to the occurrence of PAD were dominated by: type II diabetes (65.8%), chronic smoking (42.5%) and hypertension (32.2%).

In patients operated on for critical ischemia, the incidence of ischemic heart disease was 9.6%, or 22 patients; and that of heart failure was 9.8%. The incidence of valvular disease was 2.9%, with 4 cases of mitral insufficiency, 1 case of mitral disease, and 2 cases of aortic stenosis (Table 1).

Table 1: Patient characteristics

	Number (n=232)	%
Age		
45 - 55	28	12
55 - 65	92	39.6
≥ 66 Sex, n (%)	112	48.7
H	195	84
F	36	16
Tobacco, n (%)	98	42.2
Diabetes, n (%)	152	65.5
high blood pressure, n (%)	71	30.6
Heart failure, n (%)	23	9.8
Ischemic heart disease, n (%)	22	9.6
Ischemic stroke, n (%)	14	6.1
Decubitus pain	143	62
Trophic disorders	152	66
Lesion mapping:		
Isolated supra-inguinal	39	16.8
Isolated femoropopliteus	76	32.7
Isolated infrapopliteal	72	31
Supra-inguinal and FP	19	8
FP and infrapopliteal	26	11
Nature of the lesions		
Isolated stenoses	39	17
Isolated occlusions	123	53
Mixed lesions	70	30
Classification TASC		
Aorto-iliaque:		
TASC A	21	9
TASC B	13	5.6
TASC C	15	6.5
TASC D	9	3.9
Femoropopliteal:		
TASC A	50	21.5
TASC B	24	10.3
TASC C	19	8.2
TASC D	9	4
Endovascular treatment		
ATL	76	53
ATL + stenting	68	47
Conventional surgery		
Anatomical bypass	58	25
Femoropopliteal	31	13.3
Aorto-femoral	16	6.8
Distal bypass	11	4.7
Extra-anatomical bypass	5	2
femoral femoral crossover	3	1.2
Axillofemoral	2	0.8
Endarterectomy	4	1.7
Hybrid surgery	21	9

A history of ischemic stroke was found in 14 patients (6.1%), including 1 patient with a history of carotid thromboendarterectomy for asymptomatic stenosis.

The majority of our patients (84.5%) had never undergone vascular surgery before. Patients admitted for critical ischemia tended to have more history of revascularization and/or major amputation of the contralateral limb, of which 25 patients had undergone contralateral revascularization and 15 patients had undergone major amputation of the contralateral limb (Table 1).

143 patients or 62% had decubitus pain for more than 15 days, and 152 patients or 66% had trophic disorders on admission (Table 1).

Angioscan of the aorta and lower limbs was the most frequently performed examination. A total of 210 patients or 91% underwent angioscan, and 14% of cases or 32 patients underwent diagnostic arteriography (Table 1).

Lesion mapping (Table 1):

Patients with critical ischemia tended to have multistage lesions, and less frequently had lesions at the suprainguinal level (17%). Femoro-popliteal lesions constituted 52% of the lesions treated in patients with critical ischemia. In addition, 30.2% of the critically ill patients had damage to at least 2 leg arteries.

Regarding the nature of the lesions treated, isolated occlusions were found in 53.2% of the patients treated for critical ischemia, isolated stenoses were found in 17% of the cases and mixed lesions in 29.8% of the cases.

According to the TASC classification of aorto-iliac lesions, 21 patients presented lesions classified as TASC A, whereas 15 patients presented lesions classified as TASC C.

According to the TASC classification of aortoiliac lesions, 5 patients had lesions classifying as TASC A, whereas 19 patients had lesions classifying as TASC C (Table 1).

All patients admitted for critical ischemia in our department were put on aspirin, statin, curative dose heparin, and an analgesic.

Endovascular treatment was the most commonly used technique in our patients, with 62% receiving it. 53% of patients treated by endovascular techniques had benefited from transluminal angioplasty without stenting, whereas 47% of patients had benefited from angioplasty with stenting (Table 1).

Conventional surgery was used in 67 patients, i.e., 28.8% of all patients. Anatomic bypass surgery was the most commonly used technique (86% of conventional surgeries), of which femoropopliteal bypass surgery was the most commonly used, accounting for 53.4% of the patients treated by bypass surgery. Of the 67 procedures performed for critical ischemia by conventional surgery, 63 cases required the placement of various vascular devices. In total, Polytetrafluoroethylene stents were the most used material in 35% of the cases, followed by Dacron stents which were found in 21 cases. Venous allografts were used in 19 cases (Table 1).

Hybrid techniques were used in 9% of patients admitted for critical ischemia of the lower limbs.

In addition to revascularization techniques, 46% of the patients required minor amputation, and 30.4% of the cases had transmetatarsal or Chopart amputation.

The technical success rate in cases of critical ischemia was 94.1%. The primary patency rate at 1 and 2 years in patients operated for critical ischemia was 75.5% and 71.6%, respectively.

Postoperatively, 30.4% of patients operated on for critical ischemia required intensive care, with a median length of stay of 2 days [1-5 days]. In addition, 11.6% of these patients required transfusion of at least 1 packed red blood cell. The frequency and length of stay in the intensive care unit, as well as the transfusion requirements, were identical in both groups.

The median postoperative hospital stay for critical ischemia was 7 days [1-15 days]. Moreover, 38% of the patients operated on for critical ischemia were readmitted to hospital and 13% of the patients required a revascularization surgery.

34 patients presented an immediate postoperative local complication, of which 20 patients (8.8% of cases) presented a local infection. 20.5% of the cases presented a late postoperative complication, of which 8.1% presented a thrombosis and/or restenosis and 6.94% of the patients presented cardiac and cerebrovascular complications at 2 years.

We recorded 10 deaths in our study series. The causes of death were myocardial infarction in 6 patients and ischemic stroke in 4 patients.

The limb salvage rate of patients who underwent revascularization surgery was 81.3%, whereas the major amputation rate was estimated at 19.7%.

In multivariate analysis, preoperative hyperglycemia (RR= 2.34 [95% CI: 1.06-5.17]), young age (RR= 2.28 [95% CI: 1.16-4.46]), and preexisting heart disease (RR= 1.92 [95% CI: 1.04-6.30]) were factors independently associated with the occurrence of major amputation at 2 years (Table 2).

Table 2: Predictive factors for major amputation at 2 years after revascularization for critical ischemia

Covariables	Univariate analysis			Multivariate analysis		
	RRc	CI à 95%	p-value	RRa	CI à 95%	p-value
Glycemia > 1.50g/L	2.31	[1.01-5.25]	0.043	2.34	[1.06-5.17]	0.036
Age <60ans	2.12	[1.01-4.47]	0.045	2.28	[1.16-4.46]	0.016
Ischemic heart disease	2.44	[0.84-7.11]	0.095	2.56	[1.04-6.30]	0.041
Multi-stage lesions	1.85	[0.79-4.31]	0.152	1.92	[0.91-4.04]	0.085
Female sex	1.33	[0.49-3.61]	NS	-	-	NS
Leg arteries	0.95	[0.43-2.09]	NS	-	-	NS

RRc: Crude relative risk; CI: confidence interval; NS:Not significant;
RRa: Relative risk adjusted for age, sex, preoperative glucose level, preexisting ischemic heart disease, and target lesion site

Five predictors of cardiac and cerebrovascular complications at 2 years were determined: preexisting heart disease (RR=9.8; p<0.0001), ICU stay (RR=8.06; p=0.002), revision surgery (RR=5.40; p=0.004), and female sex (RR=4.96; p=0.023) were all factors independently associated with a high risk of postoperative cardiac and cerebrovascular complications (Table 3).

Table 3: Predictive factors for cardiac and cerebrovascular complications at 2 years after revascularization for critical ischemia

Covariables	Univariate analysis			Multivariate analysis		
	RRc	CI à 95%	p-value	RRa	CI à 95%	p-value
Female sex	3.11	[0.9-11.0]	0.085	4.96	[1.2-20.0]	0.023
Intensive care unit stay	5.97	[1.8-20.3]	0.003	8.06	[2.2-29.4]	0.002
Ischemic heart disease	8.13	[2.3-28.7]	0.003	9.80	[2.9- 32.3]	<0.0001
Surgical resumption	7.14	[2.2-23.6]	0.003	5.40	[1.7-16.0]	0.004
Glycemia >1.80g/l	2.42	[0.7- 8.2]	0.144	4.10	[1.7 -15.4]	0.038
Treatment with IEC	4.80	[1.5-15.8]	0.012	-	-	NS
Open surgery	7.04	[1.9-26.6]	0.002	-	-	NS

DISCUSSION

The patients with critical ischemia in our series had cardiovascular risk factors that were for the vast majority comparable to those of other studies in the literature.

Clinically, 66% of our patients had trophic disorders on admission, which is in line with other results reported in the literature. This proportion was 72.5% for Tsuchiya (Tsuchiya *et al.,* 2015) and 73% in the study by Perlanda *et al.,* (Perlander *et al.,* 2020). Indeed, the existence of trophic disorders adds a risk of postoperative local infections and implies the performance of adjuvant detersion, trimming or minor amputation procedures, hence the large number of surgical interventions and postoperative readmissions in our series.

On the other hand, we note that the technical success and major amputation rates in our series compare favorably with other series. Also, we observed a 30-day mortality rate of 4.4%, which is close to that reported for the BASIL randomized trial but remains high compared with that reported in the LIBERTY study (Mustapha *et al.,* 2019) and the Tsuchiya study (Tsuchiya *et al.,* 2015), which studied only endovascular techniques.

Several factors associated with the occurrence of postoperative complications were identified in this study:

A significant association between age and the occurrence of major amputation at 2 years was found in this study. Subjects <60 years of age had twice the risk of progression to major amputation. This result is unexpected because given the acquired systemic dysfunction and frailty associated with advanced age, it was normal to hypothesize that postoperative outcomes would be rather less reassuring in older subjects. However, other authors have reported similar results in the literature. Uhl *et al.,* (Uhl *et al.,* 2017) reported a 95% limb salvage rate in octogenarians versus 90% in younger subjects (RR= 2.61; p= 0.01); and a higher rate of major local complications in non-octogenarians. The explanation for this seemingly paradoxical association is not clear enough, but we believe that this result is related to some demographic and clinical differences between the two patient subgroups. The role of chronic smoking, which is more prevalent in young subjects, and the continuation of smoking in the postoperative period in this subgroup of patients, cannot be ruled out (8). Indeed, in Uhl's study, non-octogenarians tended to have certain

comorbidities more than octogenarians; notably active smoking, diabetes, obesity and chronic hemodialysis (Sonny *et al.,* 2014). All these factors are generally associated with a poor prognosis postoperatively (Ballotta *et al.,* 2005). This result remains interesting and incites to optimize the modalities of follow-up and perioperative management of comorbidities in young subjects who have a better life expectancy, in order to improve their postoperative survival.

In our study, women were 3 times more likely to develop cardiac and cerebrovascular complications than men, independent of other factors (RR =3.11 [95% CI:0.90-11.0]. P-value=0.085). The association of female sex and high postoperative morbidity in critical ischemia has been demonstrated by several contemporary authors. In a cohort study, McCoach *et al.,* (McCoach *et al.,* 2013) reported a 2-fold higher risk of postoperative cardiovascular complications in women, with a limb salvage rate that was comparable to that of the male sex. The impact of sex on postoperative outcomes of critical ischemia remains contested in the literature, however. Notably, in the randomized BASIL-1 trial (Benson *et al.,* 2019), short-term postoperative morbimortality was comparable in both sexes. In addition, women had a higher limb salvage rate and overall survival than men. However, this particular study is old and has several limitations. In particular, women were less likely to be smokers and more likely to have a high rate of survival (Jackson *et al.,* 2014).

Ischemic heart disease was associated with a relatively higher risk of major amputation and cardiac and cerebrovascular complications at 2 years, respectively (RR=2.56 [95 CI: 1.04-6.30] P-value=0.041) and (RR=9.80 [95 CI: 2.9-32.30] P-value=0.0001). This result agrees with other studies that found a significant association between preexisting ischemic heart disease and postoperative outcome in patients revascularized for critical ischemia. Indeed, the existence of ischemic heart disease concomitant with an PAD indicates a severe and particularly aggressive form of atherosclerosis in these patients who become more susceptible to major cardiovascular events such as myocardial infarction, stroke and cardiovascular death or even progression to major amputation postoperatively (Cho *et al.,* 2015).

In order to minimize the risk of postoperative complications related to this comorbidity, patients should receive adequate specialized management perioperatively.

In our study, patients with a blood glucose level >1.80g/l had twice the risk of progression to major amputation at 2 years after revascularization (RR=2.34 [95% CI: 1.06-5.17] P-value=0.036). Similarly, patients with preoperative hyperglycemia had an elevated risk of major cardiac and cerebrovascular complications (RR=4.10 [95% CI: 1.7-15.4] P-value=0.0038). This association was independent of patients' diabetic status. These data are consistent with other results reported in the literature. To explain this result, some authors have suggested that preoperative hyperglycemia is a marker of the degree of severity of the pathology for which surgery was indicated or a marker of the perioperative stress state (Bradbury *et al.,* 2010). Other studies have shown that hyperglycemia is responsible for endothelial dysfunction and oxidative stress; these phenomena are all the more important in non-diabetic subjects. Therefore, the high risk of cardiovascular complications in subjects with higher blood glucose levels may reflect underlying myocardial damage due to oxidative stress and acute inflammatory reactions (Baril *et al.,* 2013; Feringa *et al.,* 2008). Therefore, glycemic control by insulin therapy or other adequate hypoglycemic treatment in both diabetics and non-diabetics during the perioperative period to reduce the risk of major postoperative complications.

In our series, patients with an ICU stay had an 8-fold increased risk of cardiac and cerebrovascular complications at 2 years (RR=8.06 [95% CI: 2.2-29.4] P-value=0.002).

Although no study has yet demonstrated an influence between a stay in the ICU and cardiac and cerebrovascular complications, it is important to note that several studies have suggested a strong association between a longer ICU stay and a poorer short- and long-term prognosis (Mahesh *et al.,* 2012; Carpentier, Beduneau, and Girault 2015).

This result remains relevant in order to reduce the risk of occurrence of major postoperative complications. This result raises the need for future prospective studies to better investigate the influence of ICU stay on postoperative outcomes in this context of critical ischemia.

CONCLUSION

Critical ischemia represents the most severe form of obliterative arteriopathy of the lower limbs and remains one of the most frequent reasons for hospitalization in vascular surgery departments. This disease represents an even greater challenge because of the aging population and the high frequency of cardiovascular risk factors.

Our study revealed several factors associated with postoperative morbidity and mortality, including: preoperative hyperglycemia, concomitant ischemic heart disease, female gender, young age, and intensive care unit stay.

Knowledge of the impact of these different factors on the medium-term outcome of management allows prediction of the postoperative evolution of

patients with critical ischemia and thus the identification of high-risk surgical patients who should benefit from adequate specialized management during the perioperative period, particularly the management of modifiable factors.

REFERENCES

- Fowkes, F. G. R., Rudan, D., Rudan, I., Aboyans, V., Denenberg, J. O., McDermott, M. M., ... & Criqui, M. H. (2013). Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *The lancet*, *382*(9901), 1329-1340.
- Épidémiologie de l'artériopathie des membres inférieurs - ScienceDirect [Internet]. [cité 12 mars 2023]. Disponible sur: https://www.sciencedirect.com/science/article/abs/pii/S0755498218300137
- Sampson, U. K., Fowkes, F. G. R., McDermott, M. M., Criqui, M. H., Aboyans, V., Norman, P. E., ... & Murray, C. (2014). Global and regional burden of death and disability from peripheral artery disease: 21 world regions, 1990 to 2010. *Global heart*, *9*(1), 145-158.
- Tsuchiya, T., Iida, O., Shiraki, T., Soga, Y., Hirano, K., Suzuki, K., ... & Kajinami, K. (2015). Clinical characteristics of patients with Rutherford category IV, compared with V and VI. *SAGE Open Medicine*, *3*, 2050312115597087.
- Perlander, A., Jivegård, L., Nordanstig, J., Svensson, M., & Österberg, K. (2020). Amputation-free survival, limb symptom alleviation, and reintervention rates after open and endovascular revascularization of femoropopliteal lesions in patients with chronic limb-threatening ischemia. *Journal of Vascular Surgery*, *72*(6), 1987-1995.
- Mustapha, J., Gray, W., Martinsen, B. J., Bolduan, R. W., Adams, G. L., Ansel, G., & Jaff, M. R. (2019). One-year results of the LIBERTY 360 study: evaluation of acute and midterm clinical outcomes of peripheral endovascular device interventions. *Journal of Endovascular Therapy*, *26*(2), 143-154.
- Uhl, C., Steinbauer, M., Torsello, G., Bisdas, T., & CRITISCH collaborators. (2017). Outcomes after endovascular revascularization in octogenarians and non-octogenarians with critical limb ischemia. *Journal of Endovascular Therapy*, *24*(4), 471-477.
- Masson, E. Tabagisme au Maroc : connaissances des risques liés au tabac en fonction du revenu [Internet]. EM-Consulte. [cité 12 mars 2023]. Disponible sur: https://www.em-consulte.com/article/211612/tabagisme-au-maroc-connaissances-des-risques-lies-
- Sonny, A., Gornik, H. L., Yang, D., Mascha, E. J., & Sessler, D. I. (2014). Lack of association between carotid artery stenosis and stroke or myocardial injury after noncardiac surgery in high-risk patients. *Anesthesiology*, *121*(5), 922-929.
- Ballotta, E., Renon, L., Da Giau, G., Barbon, B., De Rossi, A., & Baracchini, C. (2005). Prospective randomized study on asymptomatic severe carotid stenosis and perioperative stroke risk in patients undergoing major vascular surgery: prophylactic or deferred carotid endarterectomy?. *Annals of vascular surgery*, *19*(6), 876-881.
- McCoach, C. E., Armstrong, E. J., Singh, S., Javed, U., Anderson, D., Yeo, K. K., ... & Laird, J. R. (2013). Gender-related variation in the clinical presentation and outcomes of critical limb ischemia. *Vascular Medicine*, *18*(1), 19-26.
- Benson, R. A., Meecham, L. A., Hewitt, C. A., & Bradbury, A. W. (2019). Comparison of immediate and long-term outcomes in men and women undergoing revascularisation for chronic limb threatening ischaemia in the bypass vs. angioplasty in severe ischaemia of the leg (BASIL-1) trial. *European Journal of Vascular and Endovascular Surgery*, *58*(2), 224-228.
- Jackson, E. A., Munir, K., Schreiber, T., Rubin, J. R., Cuff, R., Gallagher, K. A., ... & Grossman, P. M. (2014). Impact of sex on morbidity and mortality rates after lower extremity interventions for peripheral arterial disease: observations from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *Journal of the American College of Cardiology*, *63*(23), 2525-2530.
- Cho, S. W., Kim, B. G., Kim, D. H., Kim, B. O., Byun, Y. S., Rhee, K. J., ... & Goh, C. W. (2015). Prediction of coronary artery disease in patients with lower extremity peripheral artery disease. *International Heart Journal*, *56*(2), 209-212.
- Bradbury, A. W., Adam, D. J., Bell, J., Forbes, J. F., Fowkes, F. G. R., Gillespie, I., ... & trial Participants, B. A. S. I. L. (2010). Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: analysis of amputation free and overall survival by treatment received. *Journal of vascular surgery*, *51*(5), 18S-31S.
- Baril, D. T., Patel, V. I., Judelson, D. R., Goodney, P. P., McPhee, J. T., Hevelone, N. D., ... & Vascular Study Group of New England. (2013). Outcomes of lower extremity bypass performed for acute limb ischemia. *Journal of vascular surgery*, *58*(4), 949-956.
- Feringa, H. H. H., Vidakovic, R., Karagiannis, S. E., Dunkelgrun, M., Elhendy, A., Boersma, E., ... & Poldermans, D. (2008). Impaired glucose regulation, elevated glycated haemoglobin and cardiac ischaemic events in vascular surgery patients. *Diabetic medicine*, *25*(3), 314-319.
- Mahesh, B., Choong, C. K., Goldsmith, K., Gerrard, C., Nashef, S. A., & Vuylsteke, A. (2012). Prolonged stay in intensive care unit is a powerful predictor of adverse outcomes after cardiac operations. *The Annals of thoracic surgery*, *94*(1), 109-116.
- Carpentier, D., Beduneau, G., & Girault, C. (2015). Séjour prolongé en réanimation. *Médecine Intensive Réanimation*, 24(4), 379-88.