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Below-the-ankle arterial disease severely impairs the outcomes of diabetic patients with ischemic foot ulcers

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ABSTRACT

Aim: To evaluate the impact of below-the-ankle (BTA) arterial disease in people with ischemic diabetic foot ulcers (DFUs).

Methods: Patients with ischemic DFUs treated by a pre-set limb salvage protocol including peripheral revascularization were included. They were divided in two groups according to the involvement of BTA arteries (BTA+) or not (BTA−). Not healing, minor amputation, major amputation and mortality have been evaluated as primary outcome. Revascularization failure has been evaluated as secondary outcome.

Results: The study group was composed of 272 patients, 120 (44.1%) belonging to BTA+ group and 152 (55.9%) to BTA−. After 1 year of follow-up the outcomes for BTA+ and BTA− were respectively: not healing (40.8 vs 17.8%, $p < 0.0001$), minor amputation (80.8 vs 20.4%, $p < 0.0001$), major amputation (18.3 vs 6.6%, $p = 0.002$), mortality (16.7% vs 10.5%, $p = 0.001$). The rate of revascularization failure was respectively 38.3 vs 11.2%, $p < 0.0001$. At the multivariate analysis BTA arterial disease resulted an independent predictor of not healing [OR 3.5 (CI 95% 2.3–6.1) $p = 0.0001$], minor amputation [OR 3.1 (1.5–5.9) $p < 0.0001$] and revascularization failure [OR 3.5 (1.9–6.3) $p = 0.0001$]. BTA+ patients with successful BTA revascularization showed lower rate of not healing (37.8 vs 89.1%) $p < 0.0001$, minor amputation (74.3 vs 91.3%) $p = 0.002$ and major amputation (8.1 vs 34.8%) $p = 0.0003$ in comparison to patients with unsuccessful BTA revascularization.

Conclusion: BTA arterial disease severely impairs the outcomes of diabetics with ischemic foot ulcers. BTA revascularization reduces the rate of not healing, minor and major amputation.

1. Introduction

Peripheral arterial disease (PAD) is a severe complication of diabetes and can be found approximately in 50% of people with diabetic foot ulcers (DFUs) [1,2]. PAD in diabetics is usually bilateral, mainly distal and rapidly progressive [3,4]. In comparison to those without diabetes, the specific pattern of PAD in people with diabetes is the higher involvement of infra-popliteal vessels (anterior tibial artery, posterior tibial artery, peroneal artery) [5,6].

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PAD is a well known marker of outcome in patients with DFUs, predicting negatively the possibility of healing [7]. Based on anatomical findings and outcomes, it has been documented that diabetic patients show worse PAD below-the-knee and higher risk of lower extremity amputation than non-diabetic patients [5].

Until now it was believed that diabetic patients were less likely to have occlusive arterial disease in foot arteries than non-diabetics [8]. Even though there are few data about the prevalence of below-the-ankle (BTA) arterial disease in people with ischemic DFUs and CLI, in a recent paper Ferraresi et al found that the subgroup of diabetic patients showed BTA arterial disease in 48% of cases. Furthermore, they found that people with diabetes had a significantly higher involvement of BTA arteries than non-diabetics [9].

Anyway, in the majority of studies, the involvement of foot arteries was not evaluated and PAD in diabetic patients with ischemic DFUs has been until now defined as a specific infrapopliteal arterial disease.

In our experience, angiographies of patients with ischemic DFUs often show the involvement of BTA vessels (plantar and pedal arteries) and we retain that foot arteries may play a key role in the healing process of foot ulcers.

The aim of this study is to evaluate the outcomes of patients with DFUs in patients with or without BTA arterial disease.

2. Subjects, materials and methods

The study group was composed of inpatients with ischemic DFUs who consecutively referred to a tertiary care diabetic foot clinic from January 2015 to December 2017. Baseline demographic and clinical data were recorded. Ischemic heart disease (IHD) was considered in case of previous acute coronary syndrome or coronary revascularization, evidence of angina, significant changes on electrocardiography (above or under-leveling ST, q wave, inversion of T wave, new left bundle branch block). Hypertension was considered in case of blood pressure >130/80 mmHg or current antihypertensive therapy, hypercholesterolemia in case of low density lipoproteins (LDL) >70 mg/dl or statin therapy. Patients were considered smokers only in case of smoke habit at the time of treatment [10].

Heart failure (HF) was considered in case of typical symptoms and signs of HF: reduced left ventricular ejection fraction (LVEF) (<40%) or normal or only mildly reduced LVEF and elevated levels of brain natriuretic peptides (BNP > 35 pg/ml and/or NT-proBNP > 125 pg/ml) with not dilated left ventricle (LV) associated to relevant structural heart disease (LV hypertrophy/left atrial enlargement) and/or diastolic dysfunction [11].

All patients have been managed by a pre-set limb salvage protocol based on the Guidance of International Working Group on the Diabetic Foot (IWGDF) including surgical debridement, antibiotic therapy in case of infection, offloading and revascularization [12].

Baseline ulcers characteristic have been reported. The ulcer size is the one recorded at the first evaluation at our diabetic foot unit. Ulcer duration has been reported in weeks. Deep ulcers have been considered in case of full thickness lesion of the skin extended through the subcutis until tendons, muscles or bones. Diagnosis of infection has been done according to clinical signs (redness, warmth, swelling, induration, tenderness, pain, purulent secretion) and treated by broad spectrum antibiotic therapy at the beginning and then based on culture results if required [12]. Diagnosis of critical limb ischemia (CLI) has been performed according to clinical signs (ulceration or gangrene) and TcPO2 (<30 mmhg) [13]. According to Guidance on PAD in diabetic subjects, patients with CLI and foot lesion underwent lower limb revascularization for allowing restoration of foot perfusion [14]. The revascularization procedure has been defined in respect of foot condition, vessels affected and patient's general conditions [14]. Before revascularization, all patients underwent lower limbs ultrasound color duplex to identify the affected vessels. All revascularization procedures have been performed by endovascular approach. The main aim of revascularization was to open all occluded arteries or, if technically not possible, the revascularization of targeted artery (wound related artery) was aimed. Patients were treated by dual antiplatelet therapy (acetylsalicylic acid 100 mg and clopidogrel 75 mg once a day) before the procedure and for at least one month after [14]. In case of intolerance to aspirin or clopidogrel, ticlopidine was administered. After hospitalization, patients were regularly followed in our diabetic foot clinic.

All angiograms recorded during revascularization procedure have been blindly evaluated and described by two expert interventional radiologists. Arterial lesions have been considered in case of stenosis or occlusion. Stenosis has been defined in case of reduction of lumen diameter between 50% and 99%; occlusion was defined in case of complete obliteration. BTA arterial disease has been considered by the presence of stenosis and/or occlusion, single or multiple, of pedal artery and/or plantar arteries (common, medial and lateral) and/or plantar arch. The patients have been divided in two groups according to the involvement of BTA arteries (BTA+) or not (BTA−).

2.1. *Outcomes*

The primary outcome measures were: not healing, minor amputation, major amputation, mortality. The first outcome achieved was the only outcome considered. The same outcomes have compared between BTA+ and BTA−. Not healing was considered in case of not complete epithelialization of target wound not requiring major amputation; minor amputation was considered in case of any amputation below-the-ankle; major amputation was considered in case of any amputation above-the-ankle. Secondary outcome was the evaluation of technical failure of revascularization procedure, measured as technical recanalization failure of occluded vessels (defined as impossibility to overcome the obstruction) and/or absence of arterial flow to the foot. This was considered as an immediate outcome.

In patients with BTA arterial disease, we evaluated also the effectiveness of successful BTA revascularization in comparison to unsuccessful BTA revascularization. All potential predictors of outcome have been analysed.

2.2. Statistical analysis

Statistical analysis was performed by SAS (JMP12; SAS Institute, Cary, NC) for personal computer. Data are expressed as means ± SD. Comparison between groups were reported by a X2 test (frequency data) or Student's *t* test (continuous data). Univariable logistic regression analysis was performed for all potential predictor variables with the outcome of interest (not healing, minor and major amputation, revascularization failure) with values presented as univariable odds ratios (ORs) along with the respective 95% CI. Then, all potential predictors were entered simultaneously in a multivariate logistic regression model. These models yielded a set of variables that best predict outcome. $P < 0.05$ was considered statistically significant.

3. Results

A total of 272 patients have been recruited. BTA+ patients were 120/272 (44.1%) while BTA− were 152/272 (55.9%). BTA+ reported more cases of dialysis, IHD and HF than BTA−. Baseline data were reported in Table 1. Outcomes of whole cohort, BTA+ and BTA− have been evaluated after 1 year of follow-up and reported in Fig. 1.

3.1. Not healing

Overall 76/272 (27.9%) patients did not heal. The rate of not healing for BTA+ and BTA− was respectively 49/120 (40.8%) and 27/152 (17.8%) ($p < 0.0001$). Fig. 1.

At univariate analysis IHD [OR 1.9 (CI 95% 1.3–3.6) $p = 0.0001$], dialysis [1.6 (CI 95% 1.2–2.7) $p = 0.002$], HF [1.8 (CI 95% 1.4–4.2) $p = 0.001$], ulcer size (>5 cm^2) [1.3 (CI 95% 1.05–1.7) $p = 0.04$], heel ulcer [1.3 (CI 95% 1.08–1.9) $p = 0.02$], BTA arterial disease [2.5 (CI 95% 1.4–6.4) $p = 0.0001$], revascularization failure [2.3 (CI 95% 1.8–6.2) $p = 0.0001$] were independent predictors of outcome.

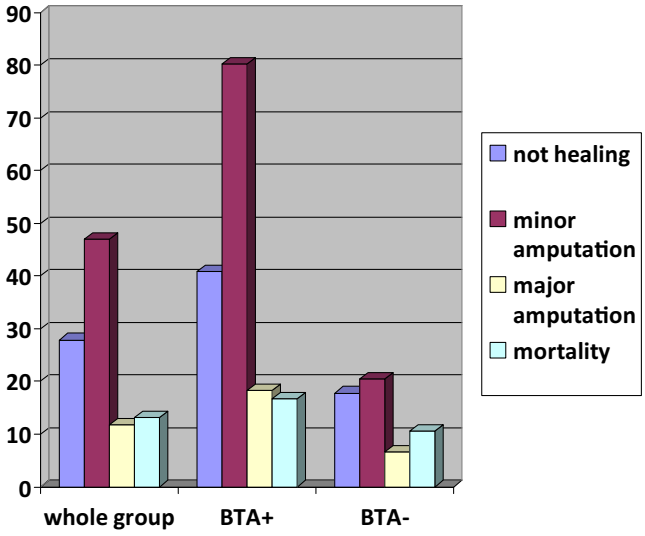

Fig. 1 – Outcomes for whole cohort, BTA+ and BTA− groups. BTA: below-the-ankle.

At the multivariate analysis of all predictors found at univariate analysis, BTA arterial disease and revascularization failure were independent predictors of not healing Table 2.

3.2. Minor amputation

Overall 128/272 (47%) patients had minor amputation. The rate of minor amputation for BTA+ and BTA− was respectively 97/120 (80.8%) and 31/152 (20.4%) ($p < 0.0001$) Fig. 1.

At the univariate analysis ulcer size (>5 cm^2) [OR 1.6 (CI 95% 1.4–2.6) $p = 0.004$), infection [3.3 (CI 95% 1.7–6.1)

Table 1 – Baseline characteristic of whole population, group with below-the-ankle arterial disease (BTA+) and group without below-the-ankle arterial disease (BTA−). LDL-cholesterol: low density protein-cholesterol. CRP: c-reactive protein. TcPO2: transcutaneous oxygen pressure.

Variables	Whole population	BTA+	BTA−	P value
Age (years)	69 ± 9	70 ± 10	68 ± 9	0.1
Sex (men) n (%)	199/272 (73.1%)	82/120 (68.3%)	116/152 (77%)	0.1
Type 2 diabetes n (%)	245/252 (90%)	104/120 (86.7%)	141/152 (92.7%)	0.05
Diabetes duration (years)	21 ± 11	22 ± 12	20 ± 11	0.2
HbA1c (mmol/mol) (%)	62 ± 22 (7.8 ± 4.2)	61 ± 20 (7.7 ± 4)	63 ± 23 (7.9 ± 4.3)	0.7
Hypertension (%)	234/252 (86%)	94/120 (78.3%)	140/152 (92.1%)	0.0004
LDL-cholesterol (mmol/L)	1.7 ± 0.4	1.6 ± 0.6	1.7 ± 0.4	0.3
Smokers n (%)	33/272 (12.1%)	11/120 (9.1%)	22/152 (14.5%)	0.1
Ischemic heart disease n (%)	171/272 (62.9%)	90/120 (75%)	81/152 (53.2%)	0.0003
Heart failure n(%)	88/272 (32.3%)	48/120 (40%)	40/152 (26.3%)	0.001
Dialysis n (%)	84/272 (31%)	60/120 (50%)	24/152 (15.8%)	<0.0001
CRP (mg/dl)	67 ± 52	75 ± 56	59 ± 47	0.02
Ulcer size (>5 cm^2) n (%)	180/272 (66%)	86/120 (71.7%)	94/152 (61.8%)	0.06
Ulcer duration (weeks)	9.6 ± 4	10.1 ± 3	9.2 ± 4	0.3
Deep Ulcers n (%)	180/272 (66.2%)	75/120 (62.5%)	105/152 (69.1%)	0.08
Gangrene (yes) n (%)	75/272 (27.6%)	35/120 (29.2%)	40/152 (26.3%)	0.2
Ulcer infection (yes) n (%)	184/272 (67.6%)	80/120 (66.7%)	104/152 (68.4%)	0.8
TcPO2 values (mmHg)	15 ± 8	11 ± 9	18 ± 8	0.002

Table 2 – Multivariate analysis of independent predictors of outcomes (not healing, minor amputation, major amputation) found at univariate analysis.

Variables	Not Healing			Minor Amputation			Major amputation		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Ischemic heart disease	1.2	0.8–1.6	0.07						
Dialysis	1.1	0.5–1.3	0.1				0.9	0.7–1.2	0.08
Heart failure	0.8	0.6–1.4	0.7						
Ulcer size (>5 cm^2)	1.2	0.8–1.8	0.06	1.5	0.6–1.9	0.2			
Infection	0.9	0.3–1.5	0.6	2.5	1.6–3.7	0.0002	2.6	1.8–3.2	0.002
Heel ulcer	1.1	0.6–1.2	0.3						
BTA arterial disease	3.5	2.3–6.1	0.0001	3.1	1.5–5.9	<0.0001	1.2	0.8–1.7	0.06
Revascularization failure	1.9	1.4–4.0	0.003				5.3	3.1–9.2	<0.0001

p = 0.0001], BTA arterial disease [4.2 (CI 95% 1.5–8.5) p < 0.0001] were independent predictors of outcome. At the multivariate analysis of all predictors found at univariate analysis, BTA arterial disease and foot infection were independent predictors of minor amputation Table 2.

3.3. *Major amputation*

Major amputation was performed in 32/272 (11.7%) patients. The rate of major amputation for BTA+ and BTA− were respectively 22/120 (18.3%) and 10/152 (6.6%) (p = 0.002) Fig. 1.

At the univariate analysis, dialysis [OR 1.9 (CI 95% 1.1–3.0) p = 0.005], infection [4.3 (CI 95% 2.1–7.5) p = 0.0001], BTA arterial disease [2.0 (CI 95% 1.6–3.2) p = 0.001], revascularization failure [7.5 (CI 95% 2.5–11.6) p < 0.0001] were independent predictors of outcome.

At the multivariate analysis of all predictors found at univariate analysis, revascularization failure and foot infection were independent predictors of major amputation Table 2.

3.4. *Mortality*

A total of 36/272 (13.2%) patient died. The rate of death for BTA+ and BTA− were respectively 20/120 (16.7%) and 16/152 (10.5%) (p = 0.001) Fig. 1.

Dialysis [OR 6.6 (CI 95% 2.1–9.5) P < 0.0001], heart failure [9.4 (CI 95% 3.1–12.5) p = 0.0001], foot infection [2.4 (CI 95% 1.7–3.0) p = 0.002] were independent predictors of outcome.

At the multivariate analysis of all predictors found at univariate analysis, heart failure and dialysis were independent predictor of mortality Table 3.

Table 3 – Multivariate analysis of independent predictors of outcome (mortality) found at univariate analysis.

Variables	Mortality		
	OR	95% CI	p value
Dialysis	3.9	1.8–6.8	0.0001
Heart failure	5.1	2.0–12.1	0.0001
Foot infection	0.7	0.4–1.8	0.6

3.5. *Revascularization failure*

Revascularization failure has been evaluated as secondary and immediate outcome. Unsuccessful revascularization was recorded in 63/272 (23.1%) patients. The rate of PTA failure for BTA+ and BTA− were respectively 46/120 (38.3%) and 17/152 (11.2%) (p < 0.0001). IHD [OR 1.7 (CI 95% 1.4–2.6) p = 0.04], dialysis [2.9 (CI 95% 1.1–5.4) p = 0.0001], HF [2.6 (CI 95% 1.6–5.4) p = 0.0002], BTA arterial disease [1.3 (CI 95% 1.05–1.8)] p = 0.03] were independent predictors of outcome.

At the multivariate analysis of all predictors found at univariate analysis, BTA arterial disease [OR 3.5 (CI 95% 1.9–6.3) p = 0.0001], dialysis [2.3 (CI 95% 1.1–2.8) p = 0.0005] and HF [1.8 (CI 95% 1.4–3.6) p = 0.002] were independent predictors of revascularization failure.

TcPO2 1 month after revascularization procedure has been evaluated and compared between the study groups. TcPO values for BTA+ and BTA− were respectively 38 ± 13 mmHg and 47 ± 11 mmHg (p < 0.0001).

3.6. *BTA revascularization*

To better highlight the influence of foot arteries revascularization on the outcomes of patients with BTA arterial disease, a further analysis was performed. In relation to this aim, we have evaluated the impact of successful revascularization in BTA+ group and we found that 74/120 (61.7%) of BTA+ patients had successful revascularization. Patients with successful BTA revascularization showed lower rate of not healing 28/74 (37.8%) vs 41/46 (89.1%) p < 0.0001, minor amputation 55/74 (74.3%) vs 42/46 (91.3%) p = 0.002 and major amputation 6/74 (8.1%) vs 16/46 (34.8%) p = 0.0003 in comparison to patients with unsuccessful BTA revascularization.

Dialysis [OR 3.6 (CI 95% 1.4–5.5) p = 0.0001] and previous revascularization [1.8 (CI 95% 1.4–2.8) p = 0.002] were independent predictor of unsuccessful BTA revascularization at univariate analysis. At the multivariate analysis of all predictors found at univariate analysis, only dialysis [OR 4.1 (CI 95% 1.9–6.3) p = 0.0001] was an independent predictor of unsuccessful BTA revascularization.

In the majority of cases, BTA revascularization has been achieved through antegrade approach while in patients not approachable by traditional technique, pedal-plantar loop, transcollateral recanalization, retrograde percutaneous

access and distal plantar vein arterialization (DPVA) techniques has been used. Only 2/74 (2.7%) patients reported technical complications related to revascularization procedure: one patient had local hematoma after antegrade approach and another a plantar fissuring after pedal-plantar loop procedure.

4. Discussion

This study confirmed that BTA arterial disease is a frequent pattern of PAD in people with diabetes and CLI (approximately 44%). BTA+ patients were in more cases affected by dialysis, IHD and HF in comparison to BTA− patients. Beyond the high incidence of BTA arterial disease in diabetic patients as recently documented also by Ferraresi et al. [8], it seems probably that other specific cardiovascular risk factors as renal failure, IHD and HF could influence the distal involvement of foot arteries in patients with PAD.

To the best of our knowledge, there are no publication about the impact of BTA arterial disease in patients with ischemic DFUs and our study is the first one to evaluate the prevalence of BTA arterial disease and its impact on outcomes in patients with DFUs and CLI. In our cohort, BTA+ patients reported higher rate of not healing, minor amputation, major amputation, mortality and revascularization failure in comparison to BTA−. Furthermore, BTA arterial disease resulted an independent predictor of not healing, minor amputation and revascularization failure.

Even if BTA arterial disease should be considered a dramatic pattern of PAD showing high risk of revascularization failure (approximately 38%), we found that a successful revascularization of foot arteries reduced significantly the probability of not healing (37.8 vs 89.1%) and the rate of major amputation (8.1% vs 34.8%) in comparison to unsuccessful BTA revascularization. In our cohort of BTA+ patients, traditional and new revascularization techniques have been used with low risk of local complications. Nevertheless, the rate of successful revascularization in case of BTA arterial disease was not so high (approximately 62%), mainly in presence of concomitant dialysis which resulted an independent marker of revascularization failure. This element confirms as dialysis increases the severity of PAD in diabetic patients impairing the outcomes of ischemic DFUs as reported in previous papers [15,16].

Wound healing in ischemic patients is a blood-flow related process and the main principle of limb salvage protocol is to restore an adequate blood supply to the foot, particularly in the wound area [12]. Revascularization is the first-line therapy in diabetic patients with ischemic DFUs and the extensive use of percutaneous angioplasty has improved the rate of limb salvage [14]. This requirement should be even more evident in patients with extremely distal DFUs and BTA arterial disease, where the revascularization of foot arteries is mandatory.

Nevertheless, there are few data regarding the angioplasty of foot arteries in diabetic patients. BTA arterial disease is a new frontier for clinicians, vascular surgeons, interventional cardiologist and radiologists. Some studies have validated different strategy to recanalize pedal and plantar arteries [17]. In addition to traditional procedures, new techniques have been proposed to treat BTA arterial disease: pedal-plantar loop, transcollateral recanalization, retrograde percutaneous access, DPVR. Those are useful and extreme options in patients who cannot be treated by traditional antegrade access [18–26]. Plain old balloon angioplasty should be considered the standard technique in foot vessel angioplasty while stenting is contraindicated due to the high burden of mechanical trauma [18,23,26].

These studies have provided principles, feasibility and safety of new techniques for achieving limb salvage in extremely severe case of CLI involving foot arteries. Particularly, the use of pedal-plantar technique has provided high rate of successful recanalization without periprocedural complications in patients with below-the-knee and BTA atherosclerotic disease (immediate revascularization success in 85% of cases) [22]. The use of DPVR is a new extreme technique developed by skilled Professionals for treating CLI patients not manageable by traditional techniques. In a recent paper, our group has reported good early and middle term outcome in no-option dialyzed patients with ischemic heel DFUs and severely below-the-knee calcifications involving foot arteries treated by DPVR (78% of technical successful revascularization and 67% of wound healing after 21 weeks of follow-up) [24].

Despite the lack of published data, BTA revascularization should be the new challenge for improving clinical outcomes in people with BTA arterial disease and ischemic DFUs. The knowledge of anatomical and pathological findings of BTA arterial disease is mandatory for improving foot revascularization and first results are promising for clinicians involved in diabetic foot care.

4.1. *Study limitations*

This study has some limitations. Data are collected from one single diabetic foot center and outcomes are accordingly related to our comprehensive limb salvage protocol including revascularization performed by expert interventional radiologists.

The long-term patency after BTA revascularization has not been evaluated and the impact of BTA restenosis on outcomes is not known.

The pathological characteristics of atherosclerotic plaques in BTA arterial disease have not been reported; future researches could be useful for understanding if a different atherosclerotic disease could affect foot arteries and influence the success of revascularization procedures.

There are not similar studies in literature to compare our results. Additional studies are required to determine whether extreme revascularization of foot arteries may improve wound healing and limb salvage.

4.2. *Conclusions*

In conclusion, this study is the first one to compare the outcomes of diabetic foot patients with or without BTA arterial disease. The study highlights as BTA arterial disease should be considered a frequent and extremely aggressive pattern of PAD in patients with ischemic DFUs significantly influenc-

ing the possibility of wound healing and limb salvage. This pattern is highly frequent and severe in patients with concomitant dialysis.

In case of BTA arterial disease, revascularization of foot arteries is needed for improving outcomes. Innovative revascularization techniques managed by expert vascular surgeons, interventional radiologists or cardiologists should be considered for treating BTA arterial disease.

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Declaration of Competing Interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.04.031.

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