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Access to mechanical thrombectomy for cerebral ischaemia: a population-based study in the North-of-France.

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ABSTRACT

Background and purpose. Hospitals admitting acute strokes should offer access to mechanical thrombectomy (MT), but local organisations are still based on facilities available before MT was proven effective. MT rates and outcomes at population levels are needed to adapt organisations. We evaluated rates of MT and outcomes in inhabitants from the North-of-France (NoF) area.

Method. We prospectively evaluated rates of MT and outcomes of patients at 3 months, good outcomes being defined as a modified Rankin scale (mRS) 0 to 2 or like the pre-stroke mRS.

Results. During the study period (2016-2017), 666 patients underwent MT (454, 68.1% associated with intravenous thrombolysis [IVT]). Besides, 1,595 other patients received IVT alone. The rate of MT was 81 (95% confidence interval [CI] 72-90) per million inhabitants-year, ranging from 36 to 108 between districts. The rate of IVT was 249 (95% CI 234-264) per million inhabitants-year, ranging from 155 to 268. After 3 months, 279 (41.9%) patients who underwent MT had good outcomes, and 167 (25.1%) had died. Patients living outside the district of Lille where the only MT centre is, were less likely to have good outcomes at 3 months, after adjustment on age, sex, baseline severity, and delay.

Conclusion. The rate of MT is one of the highest reported up to now, even in low-rate districts, but outcomes were significantly worse in patients living outside the district of Lille, and this is not only explained by the delay.

KEY WORDS: Stroke. Cerebral ischaemia. Cerebral infarct. Stroke care. Stroke management. Thrombectomy. Thrombolysis. Population-based study.

INTRODUCTION

Mechanical thrombectomy (MT) is of major importance in the management of patients with acute cerebral ischaemia [1], beside stroke unit care [2], aspirin [3-4], intravenous thrombolysis (IVT) with recombinant tissue-plasminogen activator (rt-PA) [5-7], and decompressive surgery [8].

When performed within 6 hours of symptom onset on top of the best medical care, MT increases the proportion of patients who survive without dependency at 3 months [9-15]. Selected patients with a mismatch between a small core and a large perfusion defect on computed tomography (CT) or magnetic resonance imaging (MRI) [16], or a discrepancy between a small infarct core and a severe clinical deficit [17] may still benefit from MT beyond 6 hours. However, the benefit of MT decreases rapidly over time within the 6-hour time-window [15]. Between 6 and 24 hours the proportion of patients who are eligible decreases also rapidly over time [16-17]. Therefore, time is crucial.

All hospitals admitting acute stroke patients in daily practice should therefore be able to offer access to MT, either on site, or after referral within an acceptable delay to another centre where MT is available [18]. Having access to MT on site in all stroke units would lower the level of experience and increase costs, but referral from a primary to a comprehensive stroke centre where MT is available could increase delays and decrease the probability of good outcome as shown recently in the STRATIS registry [19]. The proof of efficacy of MT being recent [9-15], most countries are organised based on facilities that were already available when MT was proven effective [20], and not necessarily on the needs of the population. Therefore, rates of MT at the population level and patients' outcomes need to be evaluated to properly adapt future organisations to populations' needs.

The proportion of patients who undergo MT in a hospital reflects what happens in the stroke unit where MT is available, not how patients are treated at the population level. Three studies found rates of MT between 30 and 40 per million inhabitants-year [21-23], and one found higher rates at 68 per million inhabitants-year [20]. However, these 4 studies were conducted before the results of the trials [9-15] and practices may have changed. Moreover, one of these studies was based on declarative data without monitoring [21], and another extrapolated data from a part of the population [21] that is not necessarily representative of the whole country. In the North-of-France (NoF) area there is no possibility for patients who experience a stroke to be treated by IVT or MT outside the Stroke Network 59-62, allowing a quasi-population-based evaluation of the rates of MT and IVT as explained below.

The aim of our study was to evaluate, over a 2-year period, rates of MT and patients' outcomes in inhabitants from the NoF area.

PATIENTS AND METHODS

We conducted this study in 2016 and 2017, in consecutive subjects who (i) had their main residence in the NoF area as defined below, (ii) developed an acute cerebral ischaemia, and (iii) were admitted in one of the hospitals of the Stroke Network 59-62.

Setting and standard protocols.

The French territory is divided into 101 departments, and departments are divided into districts. The NoF area includes 2 departments (“Nord, *department n° 59*” and “Pas-de-Calais, *department n° 62*”) located in the northern part of the country. The population living in the NoF area was estimated at 4,112,510 inhabitants, with a density of 326 inhabitants per km² (mean for France:

122) [24]. The 2 departments of the NoF area include 13 administrative districts. One of them (district of Lille), accounts for one-third of the total population of the NoF area, and has 4 stroke units (Lille University, Catholic Institute, Roubaix and Tourcoing hospitals). Eight districts have 1 stroke unit (districts of Dunkerque, Calais, Boulogne-sur-mer, Béthune, Lens, Valenciennes, Avesnes-sur-Helpe [stroke unit located in the city of Maubeuge], and Arras). Four districts have no stroke unit but a public hospital with an emergency department included in the stroke network 59-62 (districts of Douai, Cambrai, Montreuil-sur-mer [emergency department located in the city of Rang-du-Fliers], and Saint-Omer). These 4 emergency departments are connected with the closest stroke unit by a telemedicine network and can start rt-PA before referring the patient either to the closest stroke unit (Lens for Douai, Valenciennes for Cambrai, Boulogne-sur-mer for Rang-du-Fliers, and either Calais or Dunkerque for Saint-Omer), or to the Lille university hospital when MT is needed. The only organisational change in the Stroke Network 59-62 introduced after our previous publication [25], are (i) availability of IVT via telemedicine in the emergency departments of Douai, Saint-Omer and Rang-du Fliers, and (ii) the stroke units of Lens, Arras, Valenciennes, and Maubeuge, and the emergency departments of Douai and Cambrai, are now connected by telemedicine with the stroke unit of the Lille University hospital. Besides these 12 hospitals with a stroke unit and the 4 hospitals with an emergency department being part of the Stroke Network 59-62, there are other hospitals in the NoF area that are not part of the network: they are either public hospitals with emergency departments where less than 50 strokes are admitted per year, that are bypassed when emergency regulatory services (SAMU) are contacted, or public or private specialised hospitals (mainly psychiatric hospitals, maternity hospitals, rehabilitation hospitals, and surgery clinics) without general emergency department. These hospitals may admit stroke patients who present themselves spontaneously or have patients

with in-hospital strokes. The rule for these hospitals without stroke unit where IVT is not delivered, is to refer the patient to the closest stroke centre.

The stroke unit of the Lille University Hospital is the only one where MT is available on site. Before the results of the thrombectomy trials, MT was performed only in selected patients or within the THRACE trial [14]. After the publication of the 5 first trials showing the efficacy of MT in the first weeks of 2015 [9-13], we offered access to MT for all patients of the NoF area. All indications of MT are validated by a senior stroke neurologist from the Lille University centre before referral. Interventional neuroradiologists on duty are called only by the stroke neurologist of the University hospital. When the stroke neurologist feels that a technical difficulty is possible, the advice of the interventional neuroradiologist is possible by telemedicine to prevent unnecessary referrals. In patients who are eligible for IVT and referred to the University centre for MT, rt-PA is started in the local hospital and continued during transfer to the University centre by one of the 2 SAMU located in Lille and Arras. To reduce delays, transfers are performed either by ambulance or by helicopter as soon as rt-PA was started in the local hospital and continued in the ambulance or helicopter using the same protocols than those of the stroke units, under the supervision of a specialist of emergency medicine if the patient received IVT, or of an emergency nurse otherwise. The decision to use ambulance or helicopter is under the responsibility of the emergency physician of the SAMU and based on expected delays. At admission in the Lille University centre, patients referred from other hospitals are re-evaluated by the senior neurologist of the Lille University centre in the emergency room. To reduce delays, most patients are immediately sent to the angiographic room for MT without new brain imaging, except when the National Institutes of Health Stroke Scale (NIHSS) [26] score is modified by 4 points or more, compared to the last of the local hospital, or in case of new event during

transportation such as a seizure, or when the delay of transfer was considered too long.

Imaging

In the 16 centres of the Stroke Network 59-62, patients underwent a magnetic resonance imaging (MRI)-scan at admission with diffusion-weighted images (DWI), fluid-attenuated inversion recovery (FLAIR), gradient-echo T2*, and time-of-flight (TOF) sequences, or, in case of contra-indications for MRI, a brain computed tomographic (CT)-scan with angiographic sequences.

Perfusion imaging was used only in selected patients during the study period and was not part of the baseline imaging procedure. The use of first line MRI is in line with the recommendations of the *Haute Autorité de Santé* [27].

Recanalization procedures

Eligibility criteria for MT were: presence of a clinical deficit, presence of large-intracranial vessel occlusion judged accessible for MT, and no or minimal lesion on FLAIR images. Although MT was not yet recommended beyond 6 hours during most of the study period, we considered for MT all patients in whom initiation of MT within 8 hours after symptom onset was possible, knowing that errors on the exact timing are frequent in this context of emergency, as suggested either by new information from a relative, or MRI characteristics. MT was performed as soon as possible after the bolus of i.v. rt-PA or after imaging in patients with contra-indication for i.v. rt-PA. The endovascular procedure used stent retrievers, thrombo-aspiration or both, depending on occlusion type and neuro-interventionalist's preference. The procedure was performed by one of the neuro-interventionalists of the Lille University Hospital, under conscious sedation supervised by an anaesthesiologist, through femoral access.

Before MT, eligible patients received IVT. The main eligibility criteria for IVT were those of the ECASS-2 trial [28], except that we used a time-window of 4.5 hours and did not consider age over 80 years as a non-eligibility criterion, based on the results of ECASS-3 [29] and IST-3 [30]. Patients with an unknown onset-time were treated if they had a DWI/FLAIR mismatch on MRI, *i.e.* a visible acute ischemic lesion on DWI without significant parenchymal hyperintensity on FLAIR images. Patients eligible for IVT were treated according to the revised recommendations of the *European Stroke Organisation* (ESO) [31]. The same protocols were followed in the 12 stroke units, in the 4 emergency departments included in the stroke network, and by the 2 SAMU.

Identification of patients treated with MT in 2016-2017

The French law does not allow interventional neuroradiology in hospitals without neurosurgery. Only 2 hospitals (Lille and Valenciennes) have a neurosurgery department, but the hospital of Valenciennes does not perform MT and refers the patients to the University centre. The closest centres for MT are located in (i) Kortrijk (Belgium) but the insurance system and the language are different, and there is no stroke unit in the NoF area for which Kortrijk is closer than Lille, and (ii) Amiens, but the centre of Amiens is quite far from most stroke units of the NoF area and is not part of the network for the moment. Therefore, we assume that all MT performed in the NoF area were admitted to the Lille university hospital for MT and prospectively recorded.

Inhabitants of the NoF area who were treated outside the NoF area could not be identified, but we have shown in a previous study on IVT comparing hospital-based data and data provided by the population-based Lille stroke registry conducted in a subpopulation of 226, 827 inhabitants that these cases are few, and would have led to a 2.2% underestimation of the proportion of patients treated [25]. Therefore, we considered that the number of patients treated by TBY in other

regions or countries could be neglected. Participating centres prospectively recorded for all patients treated with IVT the date of treatment and the city of residence. The objective for these patients was just to participate in the evaluation of the rate of IVT in the area. We did not record in our database any clinical information for patients who received only IVT and were not referred to the University centre. Hospitals who are not part of the Stroke Network 59-62 are not allowed to perform IVT. Therefore, we assume that all IVT performed in the NoF area were recorded, apart from the 2.2% who received IVT in other regions or countries while travelling [25].

Identification of patients admitted in public or private hospitals for stroke in 2016-2017

To identify patients admitted for a stroke in all hospitals of the NoF area during the study period, we used the methodology of de Peretti et al [32] we extracted from the French national hospital-discharge database for acute care (PMSI) patients residing in the NoF area aged 18 years or more, with stroke codes (ICD-10 categories I60–I64) as the main diagnosis and we excluded survivors discharged within 24 hours.

Data recorded

In patients admitted at the Lille University hospital, primarily or after referral from another hospital of the network, we recorded systematically baseline clinical and imaging characteristics and outcome at 3 months, as previously reported [33-34]. Variables used in the analysis were age, baseline NIHSS score [26], pre-existing level of dependency, discovery-to-groin time and outcome at 3 months with the mRS [35]. We defined a good outcome as a mRS score 0 to 2 at 3 months or like the pre-stroke mRS. In patients who received only IVT without MT, we recorded only the city of residence.

Statistical analysis

We performed statistical analyses with the SPSS 22.0.0.0 package for Windows. We used median values, interquartile ranges (IQR), and percentages. We used the Mann-Whitney U test to compare continuous variables, and the Chi square test with Yates' correction or Fisher's exact test when appropriate to compare categorical variables. We performed the following analyses: (i) we determined the number of patients treated by MT for ischemic stroke in 2016 and 2017 in the NoF area and in each of the 13 districts, presented as a ratio of MT per million inhabitants-year, using governmental estimates of the population by December 31st 2017 [24]; (ii) we performed the same analyses to evaluate the number of patients treated with IVT per million inhabitants-year in the NoF area and in the 13 districts; (iii) we evaluated the proportion of patients treated with MT who had a good outcome at 3 months, in the NoF area and the 13 districts, and (iv) we evaluated the mortality rate at 3 months in patients treated with MT in the NoF area and in the 13 districts. Because of the small population in several districts, for the evaluation of outcomes, we combined districts according to their locations as follows: Sea-side (districts of Dunkerque, Calais, Saint-Omer, Boulogne-sur-mer, and Montreuil-sur-mer; 940,650 inhabitants), Artois (districts of Béthune, Lens, Arras and Douai; 1,165,595 inhabitants), Hainaut (districts of Valenciennes, Cambrai, and Avesnes-sur-Helpe; 756,033 inhabitants); and Lille (district of Lille, 1,250,232 inhabitants). We calculated odds ratios for good outcome and mortality using the district of Lille as reference, and logistic regression analyses with adjustment on age, sex, discovery to groin puncture, and baseline NIHSS.

Registrations and patients' consents.

The thrombolysis and thrombectomy database of the Lille University hospital was declared at the institutional data protection board. The ethical committee (*Comité de Protection des Personnes Nord Ouest IV Lille, France*) approved collection of data by March 9th, 2010 (registration number 10.677). Patients gave informed consent themselves or via a close relative for the follow-up. For other centres, only the city or residence was recorded anonymously without any medical or personal data concerning patients. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

RESULTS

During the study period, 679 patients were treated by MT in the NoF area. Thirteen (1.9%) were excluded because their city of residence was located outside the area. Therefore, the study population consisted of 666 patients (302 in 2016 and 364 in 2017; 454 combined with rt-PA, 68.2%; 212 alone, 31.8%). For the whole NoF area, the annual rate of MT was 81 (95% CI 72-90) per million inhabitants, ranging from 36 to 108 between districts (Fig. 1). During the same period, 2,068 patients were treated by IVT for an ischaemic stroke, of whom 2,049 (99.1%) had their city of residence in the NoF area including the 454 patients who received IVT and underwent MT. For the whole area, the annual rate of IVT per million inhabitants was 249 (95% CI 234-264), ranging from 155 to 268 between districts (Fig. 2).

The median age of patients who underwent MT in the whole area was 72 years (IQR 61-82): 317 (47.6%) were men, the median baseline NIHSS was 16 (IQR 11-21), and 553 patients had a pre-stroke mRS ≤ 2 (83.0%). After 3 months, none of these 666 patients was lost to follow-up, 279 had a good outcome (41.9%) and 167 (25.1%) had died. In the subgroup of 533 patients with a

pre-stroke mRS ≤ 2 (median age 69 years, median NIHSS 16), 248 had a good outcome (37%) and 112 (17%) had died.

During the study period, 14,958 patients were admitted for a stroke, of whom 10,770 met the de Peretti criteria [32] for ischaemic stroke, leading to a rate of IVT of 19.0% of patients admitted for stroke and a rate of MT of 6.2%

Outcomes per groups of districts are detailed in table 1. Patients living outside the district of Lille were less likely to have good outcomes and those leaving in the Hainaut and Sea-side districts were also more likely to die within 3 months even after adjustment on delays. This association was just a non-significant tendency for good outcome in the Hainaut districts. In the subgroup of patients living in the district of Lille, those who were first admitted in one of the 3 stroke units without MT on site (Roubaix, Tourcoing, Catholic institute) had a 2-fold increased risk of death within 3 months and tended to have a lower chance to have good outcomes, compared to those who were directly admitted to the Lille University hospital where MT is available on site (table 2).

DISCUSSION

Our study has shown that (i) for the whole NoF area, the rate of MT was 81 (95% CI 72-90) per million inhabitants-year, with variations from 36 to 108 (*i.e.* 1 to 3) between districts; (ii) the rate of IVT was 249 (95% CI 234-264) per million inhabitants-year, with variations from 155 to 268 between districts (*i.e.* 1 to 1.7); (iii) in inhabitants who underwent MT (median age 72 years, median baseline NIHSS 16), 41.9% had a good outcome at 3 months and 25.1% were dead; (iv) patients living outside the district of Lille were less likely to have good outcomes; (v) patients

from the Sea side and Artois districts were also more likely to die within 3 months; and (vi) differences in outcome persisted after adjustment on delays, suggesting that delays do not account for all factors explaining differences in outcome.

The strength of our study is to have a quasi-population-based design. We did not evaluate the rate of MT at the hospital level, but at the population level: we included only inhabitants living in the NoF area, and excluded those living outside who underwent MT, contrary to other studies [20-23]. Other strengths are (i) the management of patients with similar protocols in all participating centres, and (ii) the absence of patient lost to follow-up 3 months after MT.

Our study has also limitations. Inhabitants who were treated outside the NoF area could not be identified, but in a previous study comparing hospital data in the same area with those of the population-based registry, we found that only 2.2% of inhabitants from the NoF area are treated outside the Stroke Network 59-62 [25]. We can therefore consider that our study is nearly population-based. The use of first line MRI is recommended by the *Haute Autorité de Santé* but may be a limitation for the generalisability of the results, most centres in Europe and North America using CT at baseline to reduce delays.

Four years after publication of the results of the first trial [9], it is still difficult to determine the optimal rate of MT at the population level. Our study was not designed to answer this question, but to evaluate what is feasible in an area of 4 million inhabitants with a stroke network of 16 hospitals and only 1 where MT is available on site. In an Australian population-based study the predicted rate of eligibility for MT ranged from 110 (95% CI 40-180) to 220 (95% CI 130 to 310) per million inhabitants-year, depending on selection criteria [36]. In the NoF area, the annual rate of MT was 81 (95% CI 72-90) per million inhabitants, ranging from 36 to 108 between districts.

We cannot easily compare our results with those of previous studies conducted at different periods. A nationwide German study [20] found a rate of 68 MT per million-inhabitants-year with differences between *Länder* from 50 to 88, and a study conducted in Catalonia found a rate of 40 [24] if we include patients considered as eligible for MT who were randomised in the non-interventional arm of a trial. However, these 2 studies were conducted before proof of efficacy of MT. There were only 2 studies published after the trials; a large European survey that found a rate of 37 (95% CI 27-48) MT per million inhabitants-year [21] and an American study that estimated from Medicare data the number of MT performed in 2015 in the USA at 31 per million inhabitants-year [22].

Of all trials, MR CLEAN [9] is the one where the characteristics of patients were the most comparable to ours. Compared to patients randomised in the intervention arm of MR CLEAN [9], our patients with a prestroke mRS ≤ 2 were slightly less severe (median NIHSS 16 vs. 17) but 3 years older (median 72 years vs. 66). The proportion of patients with good outcomes (37% vs. 33% in MR CLEAN) and death (17% vs. 21% in MR CLEAN) were in the same range.

We found important differences in outcomes between districts: the proportion of patients with good outcomes was lower in patients living outside the district of Lille, while mortality rates were higher except in Hainaut districts. Differences in outcomes may have several explanations: education of the population about symptoms of stroke and how to proceed, pre-existing health status, availability of transportation system, distance to the MT centre, availability of a local primary stroke centre after discharge from the university centre, and availability of rehabilitation facilities may differ between districts and contribute to differences in outcome. Delays are crucial, but they are not the only factors influencing the outcome. What makes the difference

between districts is not only the delay as shown by the adjustment on delays. This needs now to be investigated, to determine what is the best strategy to improve outcomes. Implementation of 1 or 2 other MT centres in the NoF area is the most appropriate solution in areas where delay is the most important factor associated with a worse outcome, but other strategies may be more appropriate in areas where other factors are more prominent.

In conclusion, although the rate of IVT in the NoF area is high compared to available literature, and overall outcomes are in the range of what was found in the MR CLEAN trial, there are differences in both rates of IVT and outcomes within the area. Delays do not explain all the differences, and this study should now be completed by the identification of other factors that could explain these differences and be improved.

DISCLOSURES

Drs Leys, Dequatre-Ponchelle, Ferrigno, Hénon, Moulin, and Cordonnier were investigators of the ECASS 4 trial (honoraria paid to the CHU Lille). Dr Leys was member of the steering committee of ECASS 4 (no honoraria). Dr Goldstein received honorarium and travel fees from Boehringer Ingelheim (speaker at symposia). Drs Casolla, Tortuyaux, Moreau, Chochoi, Girard-Buttaz, Mounier-Vehier, and Pruvo report no disclosure.

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Table 1. Outcome at 3 months of the 666 inhabitants of the North-of-France (NoF) area who were treated by mechanical thrombectomy (MT) in 2016 and 2017. NIHSS: National institutes of Health stroke scale [25]. ^{adj}OR: odds ratio (95% confidence intervals). [†]Adjusted on age, sex, delay (discovery to groin puncture), and baseline NIHSS. Good outcome: modified Rankin scale (mRS) [32] 0 to 2 or like the pre-stroke mRS. Values are median and interquartile ranges unless specified. *Number of persons.

		Lille	Sea-side	Artois	Hainaut
Districts	Whole NoF area	Lille	Dunkerque, Saint-Omer, Calais, Boulogne-sur-mer, Montreuil-sur-mer	Béthune, Lens, Douai, Arras	Valenciennes, Cambrai, Avesnes-sur-Helpe
Inhabitants*	4,112,510	1,250,232	940,650	1,165,595	756,033
MT*	666	245	99	180	142
Age	72 (61-82)	77 (66-85)	69 (55-79)	71 (60-82)	70 (60-79)
NIHSS	16 (11-21)	17 (10-22)	17 (12-19)	17 (12-21)	16 (11-20)
Good outcome	279 (41.8%)	117 (47.8%)	40 (40.4%)	65 (36.1%)	57 (40.1%)
^{adj}OR[†]		1 (ref)	0.59 (0.35-1.01)	0.55 (0.36-0.85)	0.58 (0.38-0.96)
Death	167 (25.1%)	53 (21.6%)	28 (28.3%)	57 (31.7%)	29 (20.4%)
^{adj}OR[†]		1 (ref)	2.07 (1.14-3.77)	1.84 (1.13-2.99)	1.18 (0.68-2.06)

Table 2. Outcome at 3 months of the 245 inhabitants of the district of Lille who were treated by mechanical thrombectomy (MT) in 2016 and 2017. NIHSS: National institutes of Health stroke scale [25]. ^{adj}OR: odds ratio (95% confidence intervals). [†]Adjusted on age, sex, delay (discovery to groin puncture), and baseline NIHSS. Good outcome: modified Rankin scale (mRS) [32] 0 to 2 or like the pre-stroke mRS. Values are median and interquartile ranges unless specified. *Number of persons.

	Patients directly admitted at the Lille university hospital	Patients first admitted at Roubaix, Tourcoing or Catholic Institute hospital
MT*	153	92
Age	77 (63-85)	76 (63-83)
NIHSS	16 (11-21)	17 (11-22)
Good outcome	77 (50.3%)	40 (43.5%)
^{adj}OR[†]	1 (ref)	0.45 (0.13-1.57)
Death	28 (18.3%)	25 (27.2%)
^{adj}OR[†]	1 (ref)	2.08 (1.05-4.11)

Figure legends

Figure 1. Number of mechanical thrombectomy per year and per million inhabitants in the 13 districts of the North-of-France area.

Figure 2. Number of intravenous thrombolysis per year and per million inhabitants in the 13 districts of the North-of-France area.

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