Novel stroke prophylaxis strategies: when should device-based cardiac occlusion therapies be considered?

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A B S T R A C T

Introduction

Oral anticoagulation (OAC) is the established therapy to prevent ischemic stroke in high-risk patients with atrial fibrillation (AF) and it reduces the threat of recurrence in those who had a cardioembolic stroke. However, OAC is associated with a substantial risk of major bleeding. Therefore, device-based occlusion therapies including left atrial appendage occlusion (LAAO) and patent foramen ovale (PFO) closure have been developed to close the pathway for thrombi that potentially embolize to the brain. In this way, adequate prevention against ischemic stroke may be provided without significantly increasing the bleeding risk. Clinical evidence from randomized controlled trials and a large multicenter registry supports the efficacy of LAAO to prevent ischemic stroke in AF patients for whom OAC is less suitable. Observational data suggest that LAAO may be more beneficial than medical therapy in the treatment of AF patients after an intracerebral hemorrhage (ICH), and initiatives are undertaken to further explore the effect of LAAO in this population. Long-term follow-up of patients who had a cryptogenic stroke and underwent PFO closure shows the beneficial effect of this strategy to prevent recurrent ischemic stroke. While device-based therapies are inevitably associated with the risk of acute, peri-procedural safety events, their relative benefits over medical treatment may become increasingly important at longer-term follow-up, given the steadily accumulating lifetime bleeding risk of long-term anticoagulation. Overall, device-based cardiac occlusion therapies may be justified for the prevention of ischemic stroke in AF patients with a high bleeding risk and relatively young cryptogenic stroke patients with evidence of a PFO.

Keywords: Ischemic stroke, atrial fibrillation, left atrial appendage occlusion, patent foramen ovale closure, percutaneous technique.

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INTRODUCTION

Each year, stroke affects the lives of almost 2 million patients in Europe and the USA [1,2]. The vast majority of these strokes (85%) is ischemic [3]. Besides atherosclerotic cerebrovascular disease and small vessel disease as primary causes of stroke, the heart plays a prominent role in 50% of ischemic strokes. As such, it may be either the origin of thrombi (cardioembolism) or act as the pathway for thrombi traveling from a venous source to the brain (paradoxical embolism).

The role of the heart in embolic stroke is an expression of the heart-brain axis. Conditions in the brain may affect cardiac function, and vice versa, cardiac conditions may have an effect on the brain, with potentially devastating outcome in the case of embolic stroke. While many details of these heart-brain interactions are still to be clarified, important progress has been made in understanding the role of atrial fibrillation and the PFO in embolic stroke.

Cardioembolism accounts for 20% of all ischemic strokes [3], and of all cardiac pathologies, non-valvular atrial fibrillation (referred to as AF in this article) is associated with half of these cases [4]. Anticipating a substantial increase in AF prevalence [5], the absolute increase in the number of associated strokes will put a huge challenge on the healthcare system. While AF is a risk factor for ischemic stroke, the actual stroke risk depends on the presence of additional risk factors. This is expressed in the $CHADS_2$ [6] and the more recent CHA_2DS_2-VASc [7] risk stratification schemes (Table 1). The risk of ischemic stroke may range from 0.6% per year for a patient with a single risk factor to as high as 3 to 5% per year for a patient with three risk factors [8] (Figure 1). These stratification schemes

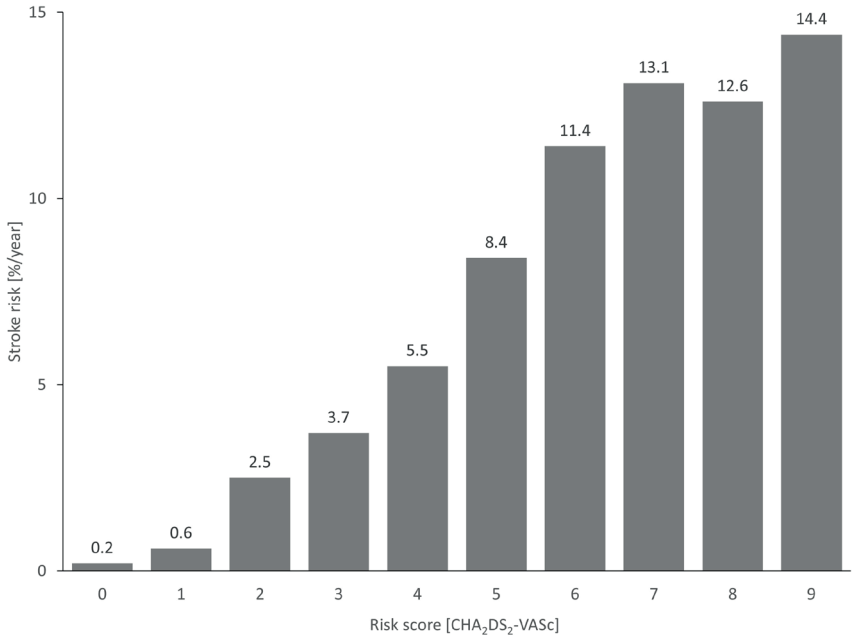

Figure 1.

Stroke risk as a function of the CHA_2DS_2-VASc score for patients not receiving antithrombotic therapy. Based on data from Friberg et al. [8]. Estimations are less reliable for high-risk categories (≥7) due to fewer patients in these categories.

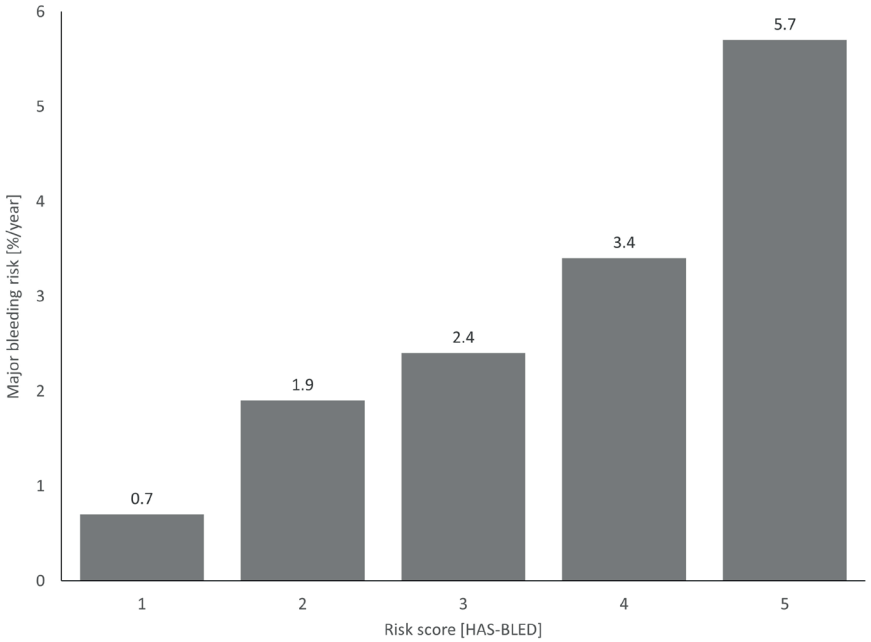

Figure 2.

Risk of major bleeding as a function of the HAS-BLED risk score for patients on oral anticoagulation therapy. Based on data from Friberg et al. [8]. Only shown for risk scores between 1 and 5, as other categories had relatively few patients.

are based on the well-studied population of patients who usually have symptomatic AF in an advanced stage. Little is known about the stroke risk of patients in earlier disease stages who are more often asymptomatic and have a lower AF burden.

Oral anticoagulation (OAC) with warfarin has established its efficacy in preventing AF-related stroke and reduces the stroke risk by two-thirds [9]. However, depending on their risk factors, patients on OAC may face a considerable bleeding risk, as accounted for by the

Table 1: CHA_2DS_2-VASc risk stratification scheme [7]

Risk factor	Score
Congestive heart failure / LV dysfunction	1
History of hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Prior stroke, TIA or TE	2
Vascular disease (MI, PAD, aortic plaque)	1
Age 65 - 74 years	1
Sex category (female gender)	1

LV: left ventricle, TIA: transient ischemic attack, TE: thrombo-embolism, MI: myocardial infarction, PAD: peripheral artery disease

Table 2: HAS-BLED risk stratification scheme [10]

Risk factor	Score
Hypertension (systolic BP > 160 mmHg)	1
Abnormal renal function / hepatic function	1 for each
Stroke	1
Bleeding	1
Labile INR	1
Age > 65 years	1
Drugs (APT, NSAID) / alcohol (>8 units per week)	1 for each

BP: blood pressure, INR: international normalized ratio, APT: antiplatelet therapy, NSAID: non-steroidal anti-inflammatory drug

HAS-BLED risk stratification scheme (Table 2, Figure 2) [8,10]. Given the fact that ischemic stroke and bleeding share a number of common risk factors, the bleeding risk increases with increasing stroke risk, creating a dilemma for pharmacological stroke prophylaxis. This has triggered the interest in non-pharmacological, device-based cardiac occlusion therapies. As the left atrial appendage (LAA) is the prominent source of cardiac thrombi in AF patients, left atrial appendage occlusion (LAAO) has emerged as an alternative stroke prevention method in these patients.

For 30% of ischemic strokes, no clear etiology can be determined. While often referred to as cryptogenic strokes (CS), a more recent concept is the notion of embolic stroke of unknown source (ESUS) [11]. A possible mechanism of these strokes is paradoxical embolism [12] through a PFO, as suggested by the relatively high PFO prevalence in CS patients compared to patients with other strokes [13]. However, a PFO in a patient with stroke from unknown cause may also be an incidental, non-causative finding. The Risk of Paradoxical Embolism (RoPE) score [14] stratifies patients as to the probability that the PFO was involved in the stroke mechanism (high score), as opposed to being an incidental finding (low score). The score accounts for age, cortical strokes on neuroimaging, diabetes, hypertension, smoking and prior stroke or transient ischemic attack (TIA). While antithrombotic therapy may prevent stroke recurrence, device-based alternatives are available for CS patients with evidence of a PFO. The mechanism of action of the involved devices is based on closing the PFO and thereby preventing thrombi to cross the septum and travel to the cerebral circulation.

PHARMACOLOGICAL STROKE PREVENTION IN AF

Patients with AF and a CHA_2DS_2-VASc score ≥1 have an elevated risk for ischemic stroke and are indicated for oral anticoagulation (OAC) therapy [15]. Traditional dose adjusted warfarin therapy is complicated by a narrow therapeutic window [16] in combination with multiple interactions with diet and concomitant medication. As a result, under- or over-anticoagulation may occur, with the associated risks of stroke or bleeding. Moreover, even appropriately anticoagulated patients may have an increased risk of intracranial hemorrhage [17]. Specifically, the risk for intracranial and other major bleeding for patients on OAC is 0.46% and 0.61% per year, respectively, and may be doubled during the first month after initiation of the therapy [18]. However, overall bleeding rates vary between 3 and 24%, with higher rates in patients with higher $CHADS_2$ score [19]. The need for antiplatelet therapy after coronary stenting in anticoagulated AF patients adds to the complexity of OAC therapy. For instance, the risk of gastrointestinal (GI) bleeding for patients on warfarin combined with aspirin or with dual antiplatelet therapy increases five- and seven-fold, respectively, compared with no therapy [20]. Driven by the risk of warfarin-associated bleeding, the drug is severely under-prescribed, leaving approximately 50% of high-risk patients and up to 75% of patients >80 years without protection [21]. While non-vitamin K antagonist oral anticoagulants (NOACs) are partially successful in reducing the bleeding risk, anticoagulation-related bleeding remains a significant issue in clinical practice. Patients on NOACs may face a risk of GI bleeding of 1 to 3% per year and an intracranial bleeding risk between 0.3 and 0.8% per year [22].

PERCUTANEOUS OCCLUSION OF THE LAA

Based on the observation that approximately 90% of cardiac thrombi in AF patients originate from the LAA [23], it appears logical to prevent cardioembolism in these patients by closing or occluding the LAA. While the proof of this concept was provided by surgical LAA ligation [24], the surgical approach is not feasible as a stand-alone treatment. Instead, percutaneous, transcatheter alternatives have been developed, among which are several devices for transcatheter endocardial LAAO. The most commonly applied devices for percutaneous LAAO include the AMPLATZER Cardiac Plug and Amulet devices (both St. Jude Medical, Plymouth, MN, USA) and the WATCHMAN device (Boston Scientific, Natick, MA, USA).

Table 3: Evidence for LAAO from large scale studies

Study	Study type Device	Patients	Key outcome for LAAO
PROTECT AF [25,26]	RCT, LAAO versus warfarin WATCHMAN	AF with $CHADS_2$ ≥1 OAC-tolerant LAAO: n=463 Warfarin: n=244	Non-inferior to warfarin in prevention of all-cause stroke, cardiovascular death and systemic embolism (events/100 patient-years: LAAO: 3.0, warfarin: 4.9). Non-inferior to warfarin in prevention of hemorrhagic stroke (events/100 patient-years: LAAO: 0.1, warfarin: 1.6). Non-inferiority regarding primary efficacy endpoint was maintained at longer-term follow-up (HR: 0.61, p=0.04).
PREVAIL [28]	RCT, LAAO versus warfarin WATCHMAN	AF with $CHADS_2$ ≥2 OAC-tolerant LAAO: n=269 Warfarin: n=138	Similar rates for primary efficacy endpoint events in randomization arms. Non-inferiority not achieved, primarily due to unexpectedly low event rate in warfarin group. Lower rate of peri-procedural complications with increasing operator experience.
International multicenter registry [29]	Prospective single-arm registry AMPLATZER Cardiac Plug	OAC-contraindicated n=1047	Observed versus expected rates: - Reduction in ischemic stroke rate: 59% - Reduction in major bleeding rate: 61%

HR: hazard ratio, LAAO left atrial appendage occlusion, OAC: oral anticoagulation, RCT: randomized controlled trial

An LAAO device is implanted during a catheterization procedure, using standard cardiac catheterization techniques and obtaining access to the LAA by transseptal puncture. Implantation is usually guided by transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE). The device is implanted using a dedicated delivery system and released after confirmation of a stable position and appropriate closure of the LAA. Endothelialization of the device is typically complete in three months, after which antithrombotic therapy is no longer required.

EVIDENCE FOR LAAO

A number of large scale studies have provided evidence for the safety and efficacy of LAAO (Table 3). The randomized controlled PROTECT AF trial (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) compared LAA closure using the WATCHMAN device with dose-adjusted warfarin therapy [25]. The study enrolled a total of 707 OAC-tolerant AF patients who were randomized to LAAO (n=463) or warfarin therapy (n=244). Results demonstrated the non-inferiority of LAAO compared with warfarin to prevent the primary efficacy endpoint, composed of all-cause stroke, cardiovascular death and systemic embolism (event rates: 3.0 and 4.9 per 100 patient-years for the LAAO and warfarin groups, respectively). LAAO was also non-inferior in the prevention of hemorrhagic stroke (event rates: 0.1 and 1.6 per 100 patient-years). A higher incidence of safety endpoints in the LAAO group was primarily driven by procedure-related complications such as serious pericardial effusion (4.8% of the procedures) and ischemic stroke (1.1%). However, due to a steadily increasing number of events over time among warfarin-treated patients, the groups approached each other at longer follow-up periods with respect to the freedom from safety events [25]. Outcomes from this trial at longer-term (mean follow-up: 3.8 ± 1.7 years) [26,27] continued to show the non-inferiority of LAAO reflected by a lower rate of efficacy endpoints in the device group compared with warfarin (hazard ratio (HR): 0.61, 95% CI: 0.38 – 0.97, p=0.04).

Following the PROTECT AF study, investigators continued implantation of the device in the Continued Access Protocol (CAP) registry. Data from this registry as well as additional analysis of the PROTECT AF data showed that the safety of device implantation significantly improved with increased operator experience [27].

A further randomized evaluation of LAAO in OAC-tolerant patients was undertaken in the PREVAIL study (Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation

Versus Long Term Warfarin Therapy) [28]. The increased implant success rate in this study (95.1%) compared to the CAP (94.3%) and PROTECT AF (90.9%) studies confirmed the learning curve effect of device implantation. While this study showed increased safety with increased operator experience, it did not achieve statistical non-inferiority for the composed primary efficacy endpoint, although the 18-month event rates were similar in both groups. Investigators considered the unexpectedly low rate of ischemic stroke in the warfarin group as the major reason for not achieving non-inferiority (0.7 events per 100 patient-years in PREVAIL versus 1.6 – 2.2 in large trials on pharmacological stroke prevention).

The largest data set published on the AMPLATZER Cardiac Plug was collected in the international Amplatzer registry [29], including data from 1047 patients from 22 centers. This was a non-randomized, single-arm study with the objective to evaluate the acute and long-term safety and effectiveness of the device in real-world clinical practice. Unlike the randomized trials with the WATCHMAN device, patients in this registry were contraindicated or intolerant to OAC. Enrolled patients had mean CHA_2DS_2-VASc and HAS-BLED scores of 4.5 ± 1.6 and 3.1 ± 1.2, respectively, characterizing this cohort as being at high-risk for stroke and bleeding. The most common reasons to consider LAAO for these patients included previous major bleeding (47%) and a high bleeding risk (35%). Device implantation was successful in 97.3% of the patients and major peri-procedural adverse events occurred at a rate of 4.97%. Over a total of 1349 patient-years the observed rate of stroke and TIA was 2.30%. This represented a 59% reduction, compared with the expected rate based on the mean CHA_2DS_2-VASc score of the cohort. Similarly, the incidence of major bleeding was reduced by 61%, compared with the expected incidence for an anticoagulated cohort with the same bleeding risk.

Overall, the available evidence supports the use of LAAO in patients who are contraindicated or intolerant to OAC. For patients without contraindications to OAC, the PROTECT AF trial demonstrated non-inferior effectiveness of LAAO compared with warfarin, while the PREVAIL study substantially contributed to the demonstration of safety of the therapy. The current guidelines of the European Society of Cardiology for the management of AF [15] state that LAAO may be considered for patients with a high stroke risk and contraindications for long-term oral anticoagulation. European guidelines on myocardial revascularization [30] suggest the option of LAAO for AF patients undergoing percutaneous coronary intervention who have a high stroke risk and a contraindication for the combined use of antiplatelets and OAC therapy.

LAAO IN PATIENTS WITH INTRACEREBRAL HEMORRHAGE

To date, there is no consensus as to the optimal therapy for AF patients after they suffered an intracerebral hemorrhage (ICH). Driven by concerns for recurrent ICH and other serious bleeding, these patients are often left without the anticoagulation required to reduce their stroke risk. For instance, >30% of these patients in the Danish Stroke Register appear to have no stroke prevention therapy. To evaluate the role of LAAO in patients who had an ICH, a propensity score matched study was conducted among Nordic centers implanting the AMPLATZER Cardiac Plug and Amulet devices. A cohort of AF patients who underwent LAAO after an ICH were matched with ICH patients receiving standard care. Analysis evaluated the composed primary endpoint of all-cause mortality, acute ischemic stroke and major bleeding. The preliminary outcome of this study suggests that LAAO may be a beneficial stroke prevention strategy in AF patients after an ICH. This result triggered the development of the investigator-initiated STROKECLOSE study (Prevention of STROKE by left atrial appendage CLOSurE in atrial fibrillation patients after intracerebral hemorrhage). This randomized controlled trial intends to enroll 750 AF patients with prior ICH who will be randomized to LAAO or standard medical care, with randomization stratified for prognostic variables. The primary composite endpoint includes ischemic and hemorrhagic stroke, systemic embolism, life-threatening or major bleeding and all-cause mortality and will be evaluated over a minimum follow-up duration of two years. The STROKECLOSE study is scheduled to start in 2016.

PFO CLOSURE IN CS PATIENTS: LONG-TERM RESULTS OF THE RESPECT TRIAL

Percutaneous catheter-based PFO closure is a treatment option to prevent recurrent stroke in CS patients with a PFO. The safety and effectiveness of percutaneous PFO closure has been evaluated in three large randomized controlled trials. Among these studies, the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) [31] was the largest study with the most extensive follow-up. This study enrolled 980 patients aged between 18 and 60 years who had a CS within 270 days prior to enrollment and with evidence of a PFO. Patients were randomized to PFO closure with the AMPLATZER PFO Occluder (n=499) or medical treatment (n=481). The primary efficacy endpoint was the composite of ischemic stroke or early death after randomization. Initial analysis was performed after a pre-defined number of 25 events, which occurred after a mean follow-up period of 2.6 ± 2.0 years (median: 2.1 years). Although this analysis showed a higher freedom of primary endpoint events in the PFO closure group compared to the controls, the difference was not significant in the intention-to-treat (ITT) analysis (HR: 0.49, 95% CI: 0.22 – 1.11, p=0.08). In the as-treated cohort, PFO closure was associated with a significantly higher freedom from primary endpoint events (HR: 0.27, 95% CI: 0.10 – 0.75, p=0.007) [31].

Long-term results of the RESPECT trial were presented at the TCT2015 conference [32], covering a follow-up period of 5.5 and 4.9 years for the closure group and medical treatment group, respectively (Table 4). During this period, 42 endpoint events occurred, all of which were ischemic strokes. In the ITT analysis no significant difference between the groups was found (p=0.16). This analysis was considered to be confounded by strokes

Table 4: RESPECT long-term results

Analysis population Endpoint	Relative risk reduction	p-value	Analysis conclusion
ITT All-cause stroke	N/A*	0.16	Confounded by strokes of known mechanism
ITT Cryptogenic stroke	54%	0.042	Efficacy for cryptogenic stroke prevention
ITT: <60 years old All-cause stroke	52%	0.035	Supportive analysis
ITT: ASA/SS subgroup Cryptogenic stroke	75%	0.007	Additional benefit in patients with ASA or SS

*: non-proportional hazards (not appropriate to estimate)
ASA: atrial septal aneurysm, ITT: intention-to-treat, SS: substantial shunt

of known etiology, i.e. non-cryptogenic strokes not associated with PFO-mediated paradoxical embolism. With the original patients enrolled in the period between 2003 and 2011 at a mean age of 46 years, more than 20% of these patients was aged >60 years at the time of the long-term follow-up analysis, increasing the probability of non-cryptogenic strokes in this cohort. Indeed, blinded evaluation identified 13 of the 42 strokes to be non-cryptogenic and probably not PFO-related. With the inclusion of CS only, PFO closure was associated with a significantly better event-free survival compared with medical management (HR: 0.46, p=0.042). Similarly, in the subgroup of patients <60 years, in whom stroke is more likely to be PFO-mediated due to a higher number of cryptogenic events, PFO closure achieved a significantly higher event-free survival (HR: 0.476, p=0.035). Moreover, in patients with an ASA or a substantial shunt a relative risk reduction of 75% was observed (p=0.007). With regard to safety, similar rates of AF, major bleeding and all-cause mortality were found in the treatment groups. Compared with medical management, deep venous thrombosis and pulmonary embolism occurred at a higher rate in the PFO closure group (0.61 vs. 0.12 per 100 patient-years), which, to some extent, may be explained by the use of OAC in the medical treatment arm.

In conclusion, results from the RESPECT trial support the procedural safety of PFO closure with the AMPLATZER PFO Occluder. Long-term outcome showed that PFO closure is superior to medical management in the prevention of recurrent paradoxical embolism and associated CS. By definition, the therapy is not able to prevent non-cryptogenic strokes, which are more likely to occur in older patients with traditional stroke risk factors. This underlines the particular benefits of PFO closure for relatively young patients and the crucial importance of an appropriate patient selection.

CONCLUDING SUMMARY

Device-based cardiac occlusion therapies appear to be effective in the prevention of ischemic stroke in AF patients and recurrent CS in patients with a PFO. This effectiveness seems to be achieved with considerably lower risk of systemic and intracranial bleeding than with oral anticoagulation therapies. Complication rates associated with device implantation decrease with increasing operator experience. Compared with pharmacological treatment, beneficial effects of device-based therapies are likely to become increasingly obvious at longer-term follow-up, given the accumulating lifetime bleeding risk of long-term anticoagulation. This justifies the application of LAAO in AF patients at risk of ischemic stroke and bleeding, and PFO closure in relatively young CS patients.

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