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## Stroke and Dementia in Atrial Fibrillation

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### 1. Introduction

#### 1.1 Incidence and prevalence

Atrial fibrillation (AF) and its consequences are today's main epidemiologic concerns. Two most important population based studies, the Framingham Study and the Rotterdam Study, report a lifetime risk of developing AF as one in four people after the age of 40 years. This is opposed to breast cancer which affects one in eight women, or heart failure affecting every fifth individual. (Lloyd-Jones et al., 2004, Mattace-Raso et al., 2006) With aging population, both AF prevalence and incidence are also increasing. (Lakatta & Levy, 2003b) AF represents the most common, highly prevalent cardiac arrhythmia which is the strongest risk factor for ischemic stroke, currently affecting 4,5 to 6 million Europeans and 2,3 to 5,1 million Americans. The prevalence of AF ranges from 2,5% in individuals over 40 yrs of age, 6% in those older than 65, to 12-16% in those over 75 yrs. (Lloyd-Jones et al., 2004; Stewart et al., 2002; Wolf et al., 1991; Kannell et al., 2008; Miyasaka et al., 2006) AF affects more than 1% of the population in total, and 70% of AF patients are aged between 65 and 85 yrs. (Phillips et al., 1990) This number is expected to double in the next 30 years. (Miyasaka et al., 2006; Savelieva & Camm, 2001; Go et al., 2008).

#### 1.2 AF burden

AF also represents a great burden both for the patient and the society. AF symptoms (palpitations, fatigue, chest pain, dizziness, light headedness, syncope and dyspnoea) have a strong negative impact on patients' quality of life, regardless of their frequency or duration. (Fuster et al., 2006; Van den Berg et al., 2005) Studies have shown that 68% of patients find AF symptoms disruptive, and 30% suffer an associated anxiety or depression. (Hamer et al., 1994; Thrall et al., 2007) AF accounts for more hospitalizations than any other arrhythmia. Society wise, AF represents a great public health issue which is expected to increase over the next decades due to aging population and improved cardiac disease management. In 1995, there were more than 1,6 million consultations, and more than 59000 hospitalizations due to AF. (Stewart et al., 2002) In Denmark alone, this number has increased by 60% in the last 20 years. (Friberg et al., 2003).

### 2. AF – risk for stroke and dementia occurrence

AF is the commonest sustained cardiac rhythm disorder, and is encountered in everyday clinical practice. Irrespective of whether we use a rate-control or rhythm-control strategy, stroke prevention with appropriate thromboprophylaxis still remains central to the

management of this common arrhythmia. When strokes occur in AF patients, the risk of mortality and disability, as well as recurrent stroke is substantially much higher. (Lip & Halperin, 2010)

Additionally, AF as the most common arrhythmia in the elderly is becoming more frequently evaluated in various studies. Furthermore, Leibovitch has pointed out, in his review article, that the most important issues to treat in the very elderly are hypertension and AF. (2008)

AF is a potentially dangerous condition for the development of two very serious neurological conditions: stroke and dementia. Those two conditions are the leading causes of mortality and disability in the developed countries and also in the developing world as estimated in 2010 by World Health Organizations. (Shirwany et Zou, 2010)

The risk of stroke is increased five-fold in individuals with AF. (Wolf et al., 1991) However, it often passes on unnoticed until its gloomy consequences are discovered. Apparently, about 20% of ischemic stroke patients have AF, based on their admission electrocardiogram (ECG). (Kimura et al., 2004; Liao et al., 2007) Additionally, AF seems to be even more important than hypertension in stroke aetiology of the very old. (Marengoni et al., 2009; Ratcliffe et Wilcock, 1985) And, silent or asymptomatic AF unfortunately carries the same long-term risk for stroke, just like for symptomatic patients. (Page et al., 2003) Continuous ECG monitoring can register up to 40% of cases, where a pacemaker reading can reveal as much as 88% of cases. Namely, a Scottish population study showed that for both women and men, there was a significant increase in all-cause mortality, cardiovascular events, fatal or nonfatal stroke, and heart failure. (Stewart et al., 2002; Benjamin et al., 1998) Regardless whether it is paroxysmal or persistent AF, risk of stroke is similar (Atrial Fibrillation Investigators, 1994) since there is a high risk of recurrence and conversion of paroxysmal to persistent AF. (Allessie et al., 2001) The increasing risk of fatal AF consequences comes from the fact that AF is asymptomatic in more than one third of the patients. (Israel et al., 2004)

The presence of AF worsens the prognosis in patients with cardiovascular comorbidities, increasing their risk for cardiovascular events, stroke, and hospitalization due to heart failure (RR 1,88-4,96). (Wachtel et al., 2005; Pizzetti et al., 2001; Wang et al., 2003) New onset AF has shown to be an independent predictor of in-hospital mortality, longer intensive care unit stay, and longer overall hospital stay. (Rivero-Ayerza et al., 2008) Additionally, in a hospital setting, AF as a comorbidity indicates worse metabolic status and poor clinical outcome for patients with dementia, stroke or heart failure. (Fumagalli et al., 2010)

The road from AF to cognitive impairment and dementia can be either direct or via stroke as an intermediate. Silent or asymptomatic strokes are valuable predictors for clinical strokes and dementia, as well. The Rotterdam study showed a 3 fold risk increase for stroke, and 2,3 fold risk increase for dementia with a steeper decline in cognitive function. (Vermeer et al, 2003a; Vermeer et al., 2003b) Concerning pre and post stroke dementia burden, it was analyzed recently by Pendlebury and Rothwell in a meta-analysis that there are 10% of demented patients before first stroke, 10% of dementia occurred soon after first stroke and more that 30% after recurrent stroke. (2009)

Lastly, it is thought that other often underdiagnosed vascular conditions like hypertension and ischemic heart disease or depression in the elderly will eventually lead to dementia development, as well. (Collerton et al., 2009).

### **3. AF and stroke**

#### **3.1 AF and increase in stroke risk**

Non-valvular atrial fibrillation (NVAf) is associated with a prothrombotic state which carries an increased risk for thromboembolic events. Studies show that levels of coagulation markers

are still elevated even during anticoagulation therapy. Patients with chronic AF were found to have a higher prevalence of chronic heart failure and history of stroke, but the prevalence of high D-dimer levels of these patients was comparable to those with paroxysmal AF. (Sadanaga et al., 2010) Recent data also link the hypercoagulability of AF with decreased renal function in NVAf patients. By yet unclear mechanism, the reduction in residual renal function enhances hypercoagulability in NVAf patients. (Tanaka et al., 2009) Predictors for thromboembolic events in NVAf are established, and they include recent heart failure, hypertension, advanced age, diabetes mellitus, previous thromboembolic events, echocardiographic evidence of left ventricular dysfunction and left atrial enlargement. (Stroke Prevention in Atrial Fibrillation Investigators, 1992) Increased concentrations of hemostatic markers TAT and D-dimer were found in patients with NVAf, linking hypercoagulability and AF. Both of these markers have high molecular weights, ensuring very limited excretion from the kidneys. Therefore, their concentrations accurately reflect intravascular fibrin formation and lysis, and not accumulation as a result of renal failure. Several recent studies have established a relationship between elevation of these markers and subsequent thromboembolic events in patients with NVAf. (Enata et al., 2004; Nozawa et al., 2006) Therefore, elevation of D-dimer levels despite proper anticoagulant treatment can predict thromboembolic and cardiovascular events in patients with AF. Whether these events can be prevented by increasing anticoagulant intensity still needs to be discovered. (Sadanaga et al., 2010)

The risk for thromboembolic events is present even during the non-paroxysmal period in patients with paroxysmal AF. Plasma markers of thrombin activity (thrombin-antithrombin III complex-TAT), active fibrinolysis (plasmin-alpha 2-plasmin inhibitor complex-PIC), and platelet activity (platelet factor 4-PF4) were evaluated in the left atria (LA) of patients with paroxysmal AF (pAF) during the non-paroxysmal period. The results of this study showed elevated coagulation activity in LA of patients with pAF, even during the non-paroxysmal period. This is the first study to report hypercoagulability in the LA of pAF patients during sinus rhythm. (Motoki et al., 2009) Experiments demonstrated two coagulation mechanisms, one being endothelial dysfunction caused by AF, (Fukuchi et al., 2001) and oxidative stress induced in the LA by AF. (Dudley et al., 2005; Kim et al., 2005) This study also has clinical relevance since it showed increased coagulation activity in LA in pAF patients, but without increased platelet activity, making anticoagulation, rather than antiplatelet, a therapy of choice.

### **3.2 AF and stroke – the studies and surveys**

Stroke is probably the most devastating complication of AF. AF is the cause of 15-20% of all ischemic strokes, (Go, 2005) and it increases the risk for stroke fivefold. (Wolf et al., 2001) Cardioembolic stroke, most of which is due to AF, is the most lethal subtype of ischemic stroke and has a higher risk of disability than other stroke subtypes. (Simpson et al., 2010)

AF is also an independent risk factor for stroke severity and recurrence. (Penado et al., 2003) Not only do AF patients have increased post-stroke mortality and stroke recurrence, but they also suffer more severe strokes than their age-matched counterparts suffering strokes due to other aetiologies. (Marini et al., 2005; Dulli et al., 2003) AF should be considered when assessing cryptogenic strokes, which account for about one third of first ever ischemic strokes. Most likely 25% to 50% of cryptogenic strokes could be attributed to undetected AF, and therefore are of cardioembolic origin. (Petty et al., 1999) Unrecognized AF can also cause cryptogenic transient ischemic attack (TIA). (Malik et al., 2011) Namely, following prolonged monitoring of asymptomatic patients, 85% of AF episodes lasted less than 30 seconds. (Tayal et al., 2008) To support this thesis, a magnetic resonance (MR) study was

performed on more than 2000 asymptomatic subjects. In 10,7% of participants at least one silent cerebral infarction could be detected; the risk for silent brain infarct is doubled in subjects with AF in comparison to those without AF. The Framingham Offspring Study of prevalence and correlates of silent cerebral infarcts (SCI) was the first one to demonstrate a significant relationship between AF and SCI, which has been associated with increased risk of incident stroke and cognitive impairment. (Das et al., 2008) As previously mentioned, silent strokes are, also, predictors of less favourable cognitive outcome and dementia occurrence. (Vermeer et al., 2003a; Vermeer et al., 2003b) For all the above mentioned reasons, it seems wise to develop a risk score, such as that derived from the Framingham Heart Study, that could help to identify risk of atrial fibrillation for individuals in the community, assess technologies or markers for improvement of risk prediction, and target high-risk individuals for preventive measures. (Schnabel et al., 2009)

When a stroke occurs in patients with AF, the severity of the stroke is generally much greater, as is mortality and disability compared to those patients in sinus rhythm. Additionally, it seems that arrhythmia progression in isolated AF is a marker of increased risk for adverse cardiovascular events. (Potpara et al., 2011) Unsurprisingly, the biggest challenge facing physicians caring for patients with AF is the prevention of stroke and thromboembolism, whether as primary or secondary prevention.

In the Euro Heart Survey, prescription of antithrombotic therapy was based on the type of AF and availability of warfarin monitoring clinics, rather than the stroke risk profile per se. (Nieuwlaat et al., 2007) However, the type of AF should not be taken into consideration, given that paroxysmal AF has a similar stroke risk to persistent or permanent AF in the presence of risk factors - therefore such patients would derive much benefit from anticoagulation prescription. (Tay et al., 2009)

The National Acute Israeli Stroke Survey (NASIS) examined the potential effect of preadmission anticoagulation on stroke severity and outcome in patients with AF. Data showed that effective anticoagulation therapy is associated with decreased stroke severity, improved functional outcome, and better survival in patients with AF admitted with acute brain ischemia. Another important finding of this study showed that the effective anticoagulation was not associated with an increased risk of symptomatic hemorrhagic transformation during hospitalization. (Schwammenthal et al., 2010) Rietbrock et al. evaluate stroke incidence by examining the United Kingdom General Practice Research Database from 1987 onwards in routine clinical practice among >51,000 chronic AF patients aged 40 years who were taking either aspirin or warfarin. Virtually all the patients had been treated with warfarin or aspirin, and almost 10,000 patients had received both: concomitantly or separately. Compared to no warfarin use, current and past use were both associated with a significant reduction in stroke rate, by 67% (RR 0,33, 95% CI 0,30-0,35) and 44% (RR 0,56, 95% CI 0,50-0,63), respectively. The benefits were more evident amongst the elderly, whereby the risk of stroke was reduced by 45% in elderly warfarin users (aged 75 years or older) and by 14% in younger users. In contrast, there was no difference in the stroke rate between current and past aspirin use (RR 1,04, 95% CI 0,94 - 1,15). Thus, all AF patients with one or more risk factors (that is, the "moderate risk" and "high risk" categories) should all be seriously considered for warfarin, whilst those with no risk factors at all (essentially, the "low risk" category) could be considered for aspirin or no antithrombotic therapy. Another interesting observation from the study is that the stroke-risk reduction was only apparent after 6-12 months of treatment, possibly reflecting poor INR control in the first six months. (2009)

Further important issue concerning AF and acute ischemic stroke is the destiny of patients who are causally treated with rtPA (recombinant tissue plasminogen activator) intravenous thrombolysis within the first 3 hours after the acute stroke onset. Previous results showed poor rate of early recanalization with a low rate of early major neurological improvement after rtPA administration. (Kimura et al., 2008) In contrast, recent encouraging results were reported by the Czeck multidisciplinary medical researchers. It appears that no initial statistical differences existed between the treated versus non-treated groups when 24 hour and 7 day clinical improvement or rate of achieved recanalizations were compared. However, AF patients had significantly poorer 90-day clinical outcome than non-AF patients using modified Rankin scale for comparison (median mRS 2,5 vs. 1,0). It is speculated that this is most likely due to more severe baseline neurological deficits or the greater number of arterial occlusions witnessed by the MRA before the use of intravenous thrombolysis. The other explanation is the physiology of clot dissolution, which depends on size, site of occlusion, clot composition, surface area of the clot exposed to the blood flow, and penetration of rtPA into the clot structure. Fresh and old clots form in the left atrium, but old and large thrombi may be more resistant to thrombolytic therapy than fresh and small ones. Therefore, it appears that AF stroke patients are more likely to have old and large thrombi, which are resistant to thrombolytic therapy. (Sanak et al., 2011)

#### **4. When to treat AF patients in order to prevent future neurological complications?**

The size of expected AF affected TIA and stroke patients is 15%. It seems that the most important factors that need to be evaluated in these patients regarding AF screening are age and left atrial diameter. Using this protocol about 47% of TIA and stroke patients can be excluded from further protocol. (Malik et al., 2011)

Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation. Absolute increases in major extracranial hemorrhage associated with antithrombotic therapy were less than the absolute reductions in stroke. Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation. Warfarin is substantially more efficacious (by approximately 40%) than antiplatelet therapy. (Hart et al., 2007)

##### **4.1 Patient selection**

Over the last 15 years or so, the various published stroke risk schema only have modest predictive value for thromboembolism, with no improvement in predictive ability over the years. (Lip & Halperin, 2010) Many stroke risk assessment schema classify a large proportion of subjects into the 'moderate risk' category where treatment guidelines recommend either warfarin or aspirin, and risk stratification schema that result in classification of a large proportion of AF subjects into the 'moderate risk' category could potentially be less useful in everyday clinical practice, since current treatment guidelines recommend the use of either warfarin or aspirin in such patients, causing confusion over which therapy should really be prescribed. Alternatively, classification as 'moderate risk' is often used as an excuse not to give anticoagulation, since the guidelines 'allow' aspirin.

Given the modest predictive ability for identifying 'high risk' subjects and the availability of new oral anticoagulant drugs that overcome the shortcomings of warfarin, stroke risk

stratification schema perhaps need to focus more on identifying the 'truly low risk' category of patients where no antithrombotic therapy may even be an option, given the increasing debate over the effectiveness of aspirin and potential for harm. (Sato et al., 2006) This concept was first proposed by van Walraven et al. and more recently revisited by Lip and Halperin. (van Walraven et al., 2003; Lip & Halperin, 2010)

In selecting the appropriate strategy to prevent stroke in an individual patient with AF, clinicians must consider the patients' risk of stroke, their risk of bleeding, concomitant indications for either anti-platelet medications or oral anticoagulants (OAC), anticipated challenges with INR control and patient preference. One of the most frequently used assessment tools by American Cardiologists is the CHADS<sub>2</sub> score grouping the patients into low- (score 0 to 1), intermediate- (score 2 to 3), or high- (score 4 to 6) risk category. However, European Society of Cardiology prefers the use of CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Its components are as follows: C - congestive heart failure/LV dysfunction, H - hypertension, A - age ≥ 75 years, D - diabetes mellitus, S - stroke (TIA/ thromboembolism - TE), V - vascular disease, A - age 65-74 years and S - sex (female); and lower case numbers representing items with greater weight. The second score is more sensitive to a greater number of vascular risk factors and lowers the cut off value for treatment initiation making it therefore a future strategy for more refined stroke risk lowering schema: those at truly low risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc = 0) who need not be prescribed any antithrombotic therapy, while all others (CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥1) can be considered for anticoagulation.(Table 1.)

CHADS <sub>2</sub>	Score	CHA <sub>2</sub> DS <sub>2</sub> -VASc	Score
Congestive heart failure	1	Congestive heart failure/LV dysfunction	1
Hypertension	1	Hypertension	1
Aged ≥75 years	1	Aged ≥75 years	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
Maximum score	6	Vascular disease (prior MI, PAD, or aortic plaque)	1
		Aged 65-74 years	1
		Sex category (i.e. female gender)	1
		Maximum score	10

Table 1. The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc score table

Not less important, is the need to select those patients who are truly at low bleeding risk, and therefore a HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ration, Elderly, Drugs/alcohol concomitantly) simple risk assessment score was proposed where score over 3 points indicates „high risk“ requiring regular and more frequent check-ups. (Lip, 2011)

#### 4.2 Oral anticoagulation therapy

Weighing all of these, anti-platelet therapy is the most appropriate strategy for many patients. Using either of the two aforementioned scales, OAC are advised if the score is ≥ 2. Furthermore, recent study reported that significantly elevated plasma C-reactive protein levels were noted in the high-risk group compared to those in the intermediate- and low-

risk groups; and the use of transoesophageal echocardiography, the incidence of left atrial spontaneous echo contrast and left atrial thrombus increased with an increasing CHADS<sub>2</sub> score. (Maehama et al., 2010)

As for AF treatment and stroke, strokes due to AF are largely preventable with warfarin therapy, and that results in a 64% relative risk reduction. (Hart et al., 2007) Furthermore, recent observational study found out that it is even more beneficial if the INR was maintained at 1,8 (range 1,5-2,0) than at the standard target of 2,5. (Pengo et al., 2010) In addition to its established benefit for stroke prevention, effective anticoagulation therapy is associated with decreased stroke severity and better functional outcome and survival in patients with AF presenting with acute brain ischemia. (Schwammenthal et al., 2010) Sadly, many times anticoagulation for stroke prevention was found underused in general for patients with AF, and even in such high-risk groups as patients with stroke. However, participation in special quality improvement programs, like Get-With-The-Guidelines-Stroke (GWTG-S) was associated with improved adherence for patients with ECG-documented AF; still patients with a history of AF alone were largely untreated. (Lewis et al., 2009)

Additional oral treatment choices may soon be available for patients with AF, which would be particularly useful for patients in whom OAC is not used because of poor INR control, inability to comply with INR monitoring or drug-interactions. Both oral direct thrombin inhibitors and factor Xa inhibitors, like endoxaban, overcome these limitations of warfarin and may find a role in stroke prevention among these groups of patients, who are typically treated with anti-platelet agents. (Healy, 2009) The advent of novel oral direct-thrombin inhibitors and Factor Xa inhibitors with their more stable pharmacokinetic profiles, removal of the need for INR monitoring, and fewer patient-related barriers (diet, alcohol and drug interactions, INR control, etc.) that currently limit prescription of anticoagulation, may increase the unmet need of anticoagulation and make anticoagulation available and safe to those patients who may stand to derive benefit from it, including those with a CHADS<sub>2</sub> score of 1. (Lane & Lip, 2010)

#### **4.3 Antiplatelet therapy**

For the 22% of AF patients with a CHADS<sub>2</sub> score of 0, the low observed risk of stroke makes aspirin the preferred treatment option. (Lee et al., 2010) Given the slightly higher stroke risk among the 32% of AF patients with a CHADS<sub>2</sub> score of 1, aspirin, the combination of aspirin plus clopidogrel and OAC are all appropriate options, with the ultimate choice between therapies hinging on patient preference, bleeding risk and concomitant indications for one of these therapies. For patients who are at higher risk of stroke, but who cannot or will not take OAC; the combination of aspirin plus clopidogrel has now been shown to provide greater protection against stroke than aspirin alone. Finally, for OAC-treated patients who cannot achieve good INR control, combination anti-platelet therapy may be a safer and equally effective alternative to OAC. (Lee et al., 2010)

#### **4.4 Mechanical devices**

Recently, Ohara et al. have shown that the severity of blood stasis in the left atrium was greater in chronic AF patients than in paroxysmal AF patients at the comparable risk level and that severity of blood stasis in the LA and aortic atherosclerosis correlates with an accumulation of clinical risk factors for thromboembolism in non-valvular AF patients.



(2010) Furthermore, enhanced coagulation activation appears to be related to a reduction in residual renal function in patients with non-valvular AF patients which suggests that decreased renal function might be a candidate predictor of thromboembolic events in those patients. (Tanaka et al, 2009)

However, since more than 90% of atrial thrombi originate from the left atrial appendage (LAA), the devices that can isolate this structure from the systemic circulation perhaps may obviate the need for long-term anticoagulation therapy. Namely, the PLAATO device (Percutaneous Left Atrial Appendage Transcatheter Occlusion; Appriva Medical, CA, USA), later withdrawn by the manufacturer in 2006 or the WATCHMAN system (Aritech Inc, MN, USA), which is a self-expanding nitinol frame structure. Newer oral anticoagulants (eg, the oral direct thrombin inhibitors) or even the isolated use of antiplatelet therapy is necessary after device implantation, in addition to refinements in stroke and bleeding risk stratification. Still, not all thrombi originate from the LAA, with up to a quarter of strokes in patients with atrial fibrillation caused by cerebrovascular disease and complex atheromatous plaques involving the aorta and carotid arteries, or other cardiac sites. (Wrigley & Lip, 2009) Another important concern is the development of cardioembolic stroke, a serious periprocedural complication of radiofrequency catheter ablation and it may cause long-term neurocognitive and functional impairment resulting in significant disability or mortality on its own. Most periprocedural clinical events occur during or within 48 hours of the procedure with the incidence of 1–6% for focal ablations and up to 7% for linear AF ablations depending on the implemented anticoagulation strategy and the method of assessment. However, once successfully implemented, at 1 year follow-up interval, complete functional and neurocognitive recovery is expected. (Patel et al., 2010)

#### **4.5 Hypertension treatment**

Blockade of the renin-angiotensin system is an important approach in managing high blood pressure, and has increasingly been shown to affect cardiovascular disease processes mediated by angiotensin II throughout the cardiovascular and renal continua. It seems that new-onset AF and associated stroke were significantly reduced by losartan- compared to atenolol-based antihypertensive treatment with similar blood pressure reduction in the LIFE study. (Wachtel et al., 2005) Additionally, clinical evidence was found in favor of telmisartan and reduction of left ventricular hypertrophy, arterial stiffness and the recurrence of atrial fibrillation, as well as renoprotection. (Galzerano et al., 2010)

#### **4.6 Inflammation**

In recent years data to support the notion that inflammation plays a role in the pathogenesis of AF are increasing. Many ongoing studies are attempting to attenuate these inflammatory processes in patients with AF by novel therapeutic strategies, such as the use of glucocorticoids. However, systemic glucocorticoid use itself has been linked to increased risk of AF. Therefore, more research is necessary to determine whether these drugs are a potential treatment or risk factor for AF. (Rienstra & Van Gelder, 2010)

#### **4.7 Quality of life surveys**

Lastly, but not least important is, side to side with therapeutic effects, the health-related quality of life considered by the patient (HRQoL) at baseline and after potential therapeutic intervention. Most often this is achieved with the use of Short-Form health survey-36 items that does not seem to be proficient enough and formation of standardized AF-specific

questionnaires is warranted. So far, two main therapeutic options follow either rate-control or rhythm-control and neither has been proven significantly better than the other, yet both improve HRQoL, so the choice of which pharmacologic agent to prefer could be personally tailored to each patient by such questionnaire. (Fuster & Mearns, 2010)

## 5. AF and dementia

Dementia prevalence increases with age, from 5-8% over 65 years of age to 25-50% over the age of 85 years. (Collerton et al., 2009; Luchsinger, 2010) The Rotterdam Study showed that dementia occurred twice as common in subjects with AF (more so if subject age was less than 75 years of age and if they were women), and a significant positive association between cognitive impairment and AF was confirmed (no age association was discovered). And, even though AF proved to be commonly discovered in AD and VAD patients, it is more strongly associated with AD incidence. (Ettore et al., 2009) The greatest reason for missing AF diagnosis is that a single ECG is usually ordered for acute stroke patients, thereby causing those with paroxysmal AF to elude from screening and diagnosis. (Kamel et al., 2009). There is no evidence of putative mechanisms of direct relation between dementia and AF, because AF is found in all types of dementia-vascular, Alzheimer and mixed types of dementia which are results of different pathomorphological and pathophysiological mechanisms.

The onset of dementia goes unnoticed in the early stages, sometimes symptoms such as cognitive and intellectual impairment as well as carrying out everyday activities may become apparent only in the mid-to-late stages. Symptoms of dementia include: memory loss, confusion, forgetfulness, poor concentration, inability to cope with everyday activities, language impairment, slurred speech, inability to follow simple instructions, inappropriate laughing and crying, behavioral changes, impaired social skills, eating problems, a shuffling or jerky gait, incontinence and/or lack of bowel control. Lateralizing signs such as hemiparesis, bradykinesia, hyperreflexia, ataxia, pseudobulbar palsy, and gait and swallowing difficulties may also be observed. (Vermeer et al., 2003; Velandai et al., 2006)

Several specific diagnostic criteria can be used to diagnose vascular dementia: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, International Classification of Diseases, Tenth Edition criteria, National Institute of Neurological Disorders and Stroke- Association International pour la Recherche & L'Enseignement en Neurosciences (NINDS-AIREN) criteria, The Alzheimer's Disease Diagnostic and Treatment Center criteria, The Hachinski ischemic score. In evaluation of dementia patients neuroimaging methods should, also, be included as well as evaluation of specific serum and cerebrospinal fluid markers for AD. A number of neuroimaging candidate markers are promising, such as hippocampal and entorhinal cortex volumetry, basal forebrain nuclei assessment, cortical thickness, deformation based and voxel based morphometry, diffusion tensor imaging tractography and functional magnetic resonance imaging. For example, combined measurements of the cerebrospinal fluid (CSF) t-tau, A $\beta$ 42 and p-tau profile and regional flow or mediotemporal lobe atrophy demonstrate higher predictive power than either diagnostic approach alone in cognitive impairment evaluation. Differential diagnosis between AD and vascular dementia seems promising by using the ratio of A $\beta$ 42 and p-tau, between AD and Lewy bodies dementia by using the ratio of A $\beta$  peptides of varying lengths (A $\beta$ 42/ A $\beta$ 38 and A $\beta$ 42/ A $\beta$ 37) and tau protein. Other interesting novel biomarker candidates derived from blood and CSF are being currently proposed (phase I or II of multicenter studies).

Magnetic resonance imaging (MRI) can provide a detailed image of the brain and cerebrovascular system. However, the structural changes detected with MRI as well as the biomarkers do not accurately predict the clinical manifestation of cognitive impairment so cognitive testing is imperative. (Rockwood et al., 2009)

### 5.1 Dementia syndromes

Progression of Alzheimer dementia (AD) is highly variable. Most estimates derive from convenience samples from dementia clinics or research centers where there is substantial potential for survival bias and other distortions. Nowadays, there is a growing rise in public health concern due to lack of effective curative treatment and raising prevalence with variable survival rate of the two most frequent dementia syndromes (gloomy results report survival rate for men with AD 4,1 years and for women 4,6 years; while five year survival rate for VAD is 39%). (Tschantz et al., 2011)

AF in connection with dementia is usually analyzed through most common types of dementia: Alzheimer's disease (AD), vascular dementia (VAD) and mixed dementia (MD). When AF is regarded in the pathophysiology of stroke or dementia, it must be said that AF can result in either cardiac thromboembolism or reduced cardiac output and cerebral hypoperfusion with main neuroradiological manifestation such as white matter lesions (WML). WML are a frequent finding in patients with vascular cognitive impairment, AD and VAD. WML are reported to be up to three-fold more prevalent in patients with AD. (Vermeer et al., 2003a) Furthermore, lacunar state, in which numerous lacunae indicate the presence of severe widespread small vessel disease, is another observed manifestation in AF patients. (Vermeer et al., 2003b)

By far, the most common type of dementia is AD accounting for 60-80% of all dementia patients, and having the greatest prevalence among all neurological diseases. AD is defined by the World Health Organization (WHO) as a degenerative brain syndrome characterized by progressive decline in memory, thinking, comprehension, calculation, language, learning capacity and judgment sufficient to impair personal activities of daily living. Today, it is believed to be associated with excessive extracellular beta-amyloid and intracellular hyperphosphorylated tau protein accumulation eventually leading to the loss of cholinergic neurons and relative glutamate excess. (Rocchi et al., 2009)

VAD, accounting for 10-20% of all dementia patients, is characterized by a stepwise deteriorating course and a patchy distribution of neurologic deficits (affecting some functions and not others) caused by cerebrovascular disease. It is not a single disease, but rather a group of syndromes relating to different vascular mechanisms. Common risk factors for VAD are the ones already recognized for cerebrovascular disease – non-modifiable risk factors such as age, gender, race/ethnicity, genotype, previous myocardial infarction, and TIA or stroke; and modifiable risk factors like diabetes, hyperlipidemia, arterial hypertension, atrial fibrillation, coronary and or peripheral artery disease, obesity, physical inactivity, stress, alcohol consumption, and smoking. (Luchsinger, 2010; Llewellyn et al., 2008)

Subtypes of vascular dementia include: mild cognitive impairment, multi-infarct dementia (MID), strategic infarct dementia, subcortical ischemic dementia, ischemic-hypoxic dementia, and haemorrhagic dementia. (Grand et al., 2011)

The term mild cognitive impairment (MCI) refers to a transitional stage between cognitive changes of normal aging and vascular dementia. At this stage, cognitive decline is not severe enough to constitute dementia, but also it is beyond the cognitive functioning deficit which is expected in normal aging. Patients with MCI have subjective memory complaints

which are relative to age and education norms, but essentially normal general function as well as activities of daily living. Patients with MCI progress to dementia at a rate of 10-15% per year, far higher than the baseline rate of 1-2% per year in normal elderly. In cases of MCI an elderly patient will come in complaining of memory lapses, and will want to know if they have "normal" age related memory loss or something more serious. In everyday evaluation of cognitive changes most neurologists and psychiatrists rely on the Folstein Mini Mental State Exam (MMSE). But the MMSE has some serious limitations- it is quite sensitive at picking up moderate to severe dementia, it is very poor at screening for patients with MCI. Both, normal and MCI patients will typically score 26 or above, the usual cut-off point for cognitive impairment. The Montreal Cognitive Assessment (MoCA) appears to work much better in such cases. The test was developed specifically to better diagnose MCI, it is a more challenging version of the MMSE. It is quick to administer (about 10 minutes) and has a maximum of 30 points. In a study comparing the MMSE with the MoCA, the MMSE had a sensitivity of only 18% to detect MCI (meaning it missed 82%, while the MoCA detected 90% of MCI subjects). As always, though, high sensitivity comes at the price of somewhat lower specificity- the specificity for MCI was 87%, meaning that 13% of actually normal people will be falsely labeled as impaired -- still quite accurate. (Nasreddine ZS, 2005; Dong Y et al., 2010)

MD is dementia consisting of features proving the coexistence of AD and VAD either clinically or based on neuroimaging evidence of cerebral ischemic lesions. It is thought that vascular processes in both disorders mutually induce each other. To support such thesis, the following shared risk factors are secluded: hypertension, adult onset diabetes mellitus, atherosclerosis, AF and smoking. Lastly, MD is more common among the old elderly (85+), and can be definitely proven solely on autopsy. (Ferri et al., 2005; Collerton et al., 2009)

### **5.2 Vascular cognitive impairment**

Apart from the three previously mentioned dementia syndromes, newly arising topic concerning dementia is vascular cognitive impairment (VCI) that inclines toward substituting "Alzheimerized" dementia concept in the setting of cerebrovascular disease with a spectrum of cognitive deficits that are all of vascular origin. The pyramid of cognitive decline in this setting initiates with condition known as the "brain at risk", perisymptomatic changes, VCI, white matter lesions (WML) and lacunae, and, lastly, VAD. It is important to acknowledge that vascular diseases can cause focal (usually due to thrombosis or embolism) or diffuse (usually due to hypertension) effects on the brain that may eventually lead to cognitive decline. However, both mechanisms are frequently present in the same patient.

Unfortunately, up to date there are no resolute clinical criteria for VCI, still the common clinical finding is progressive gait alteration and incontinence. (Battistin & Cagnin, 2010) And recently, there is a growing interest in the clinical and scientific area involving the elderly community in investigation of elderly fallers. Interestingly, recurrent fallers had lower MMSE scores than single fallers or non-fallers. (Vassalo et al., 2002) Areas of higher cortical function that showed the most deterioration were: attention and calculation, registration (short term memory), recall and praxis (visuospatial perception). (Chen et al., 2010) Chen et al. have isolated independent factors to be history of dementia, stroke or AF or prolonged hospital stay (> 5 weeks). (2010)

### **5.3 AF, stroke and dementia**

Reported estimates of the prevalence of dementia are consistent: 10% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and more

than a third had dementia after recurrent stroke. The strong association of post-stroke dementia with multiple strokes and the prognostic value of other stroke characteristics highlight the central causal role of stroke itself as opposed to the underlying vascular risk factors and, thus, the likely effect of optimum acute stroke care and secondary prevention in reducing the burden of dementia. (Pendlebury & Rothwel, 2009)

Pendlebury and Rothwel, stated that stroke characteristics determined patient's predisposition towards dementia rather than the underlying vascular risk factors. Namely, most important risk factors in prestroke dementia were medial temporal lobe atrophy, female sex and family history of dementia; while in poststroke dementia the most important was the presence of multiple cerebral lesions in time and place. (2009) Vascular risk factors for AD include stroke, hypertension, diabetes, homocysteine, smoking, hypercholesterolemia, heart failure and AF; it is possible that these can trigger cerebrovascular dysfunction and AD pathology. Explanations for these associations include the coincidence of common disorders in the elderly where vascular and cerebrovascular disease can precipitate AD, implying that the onset of dementia disease is determined by a synergistic combination of risk factors. (de Toledo Ferraz Alves et al., 2010) Additionally, many vascular risk factors for AD, such as atherosclerosis, stroke and cardiac disease in the aging individual, could result in cerebrovascular dysfunction and trigger AD pathology. A major vascular susceptibility factor gene is the apolipoprotein E gene, found to be associated with sporadic late-onset AD cases. Another interesting vascular susceptibility gene is angiotensin converting enzyme (ACE). Other possible genes include VLDL-R, LRP, NOS3, CST3, OLR1, MTHFR, PON1 and VEGF, but many of the related studies have shown conflicting results. (Rocchi et al., 2009)

Some strokes are clinically detected, while others go undetected. Silent strokes are, also, associated with higher age, elevated blood pressure and AF. (Vermeer et al., 2003a) It is important to stress that apart from silent strokes, AF itself can, also, occur silently thus posing great threat to our aging society. (Aliot, 2009) The presence of AF increases the risk for stroke, about 20% of all embolic strokes are associated with it. (Ratcliffe & Wilcock, 1985) There is increasing evidence that AF is associated with an increased risk of asymptomatic or silent cerebral infarction and as a result may confer an increased risk of progressive cognitive impairment. Most cases of AF are now of non-rheumatic or non-valvular (NVAf) aetiology. NVAf confers a fivefold increased risk of clinically apparent stroke compared to those patients, still in sinus rhythm. Silent cerebral infarctions are not associated with the nature (chronic/paroxysmal) or duration of atrial fibrillation. This may be so due to the fact that the risk of stroke for people with silent brain infarcts is comparable with the risk of TIA patients, of whom approximately 20% develop stroke within 4 years. (Vemmeer et al., 2003)

Recently, AF was associated with the hazard ratio of 1.8 (95%CI, 1,0-3,4) for first-ever stroke, but not significantly associated with dementia or AD. (Marengoni et al., 2009) However, brain reserve appears to be protective in case of stroke with favourable outcome measures such as younger age, higher premorbid IQ, no AF, no dementia, less apathy and fewer intercurrent cerebrovascular events. (Withall et al., 2009)

#### **5.4 Dementia treatment**

Treatment of dementia rests on a two-pronged approach: modification of the underlying disease (risk factors) and prevention and treatment of dementia symptoms. Goals of pharmacotherapy should be: primary and secondary prevention of cognitive changes in AF patients, reduction of present cognitive changes with acceptable side effects of pharmacotherapy, and restoration/improvement in functional measures and quality of life.

Various potential risk or preventive factors for vascular dementia have been suggested by epidemiologic research: lifestyle changes, including diet, physical activity and stress reduction as well as pharmacological strategies such as antihypertensive drugs, statins, antiplatelet, anticoagulant therapy, antidiabetic drugs, insulin, hormone replacement therapy, NSAID (nonsteroidal drugs), Ginko biloba, ENADPH, donepezil, galantamine, memantine, rivastigmine, cyclandelate, hyderginepentoxifylline, CDP choline. Meta analyses have shown that long-term use of NSAID reduces risk of dementia, and the type of NSAID is important – the best drugs contain acetylsalicylic acid in low concentrations (75-100 mg). Ginko Biloba was proven to be useful in secondary prevention of cognitive decline. Anticoagulant therapy is recommended in patients with atrial fibrillation.

WARIS II (Warfarin-aspirin reinfarction study) has shown that aspirin is better than warfarin in stroke risk reduction in diabetic patients with recurrent strokes. WASPO (Warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation), BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged Study), ACTIVE W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular events-W) have shown that warfarin is still the best in prevention of vascular events in patients with atrial fibrillation (even in age more 75). RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) study has shown that new drug Dabigatran (DTIs) is superior to warfarin with lower number of complication in prevention of CVD. ROCKET AF (Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) study has shown similar results. (Bowler JB, 2007; Rockwood et al., 2009) Nonanticoagulant strategies to prevent CVD in AF patients should include: left atrial appendage surgical excision, left atrial appendage percutaneous occlusion, catheter ablation or treatment with dronedarone (amiodarone). (Patel D et al., 2010)

### **5.5 Use of anticoagulants among the demented**

Anticoagulation for stroke prevention seems to be underused in elderly patients with nonvalvular AF and those with falls and/or early dementia are thought to be at a particular risk for stroke and hemorrhage. Jacobs et al. have performed a retrospective observational study using CHADS<sub>2</sub> score and outcome events at 12 months concluding that geriatric population with chronic AF, including patients with falls and/or dementia, who were prescribed warfarin (85%) and consequently had low rates of stroke, hemorrhage, and death at 12 months despite a low time-in-therapeutic range. However, patients with falls and/or dementia had had a high mortality rate (~45%). (2009)

Additionally, it needs to be said that despite growing evidence linking cognitive impairment to vascular risk factors, only a minority of clinical practice therapeutic guidelines consider cognition as either an adverse outcome or a factor to be considered in their treatment. (Rockwood et al., 2009) Regarding AF treatment, Flaker et al. have recently shown that less effective anticoagulation indicates more vascular events and greater cognitive dysfunction, and that low MMSE scores select those patients that have to apply strict therapeutic regime to improve their outcome. (2010) A study by Ali et al. proved that less than 50% of AD patients taking oral anticoagulation were within therapeutic targets. Furthermore, the presence of AF is associated with poor performance on neuropsychological testing, regardless of the actual duration of AF in a particular patient. Subcutaneous heparin in patients with AF is superior because of its bioavailability, but its mode of administration and long-term risks makes its use non-feasible. Antithrombotic agents such as aspirin or

clopidogrel are not widely used, despite proven clopidogrel's greater efficacy, while the two combined in the ACTIVE study caused its premature cessation due to increased number of vascular events incidence. (Ali et al., 2006) Most promising therapeutic agents today seem to be direct thrombin inhibitors (ximelagatran, argatroban and dabigatran) that appear to be at least as effective as warfarine, but require no monitoring while having great bioavailability. (Spinler, 2010)

## 6. AF and arterial stiffness

Stiffening in the large central arterial system, such as the aortic tree, significantly contributes to cardiovascular diseases in elderly and is positively associated with systolic hypertension, coronary artery disease, stroke, heart failure and AF. ( Shirwany & Zou, 2010) Namely, Mitchell et al. have published that increased pulse pressure (reflection of aortic stiffness) increases cardiac pressure load and thus may lead to an increase new-onset AF risk. (2007) It is becoming clear that we need to address the problem of AF detection among patients with transient ischemic attack (TIA) or stroke in order to prevent further clinical events from occurring. The expected size of affected population is about 15% according to Malik et al. (2011) The most important factors that need to be evaluated are: left atrial diameter, age and diagnosis of stroke, while history of smoking seems to be inversely related. Sensitivity of testing was high (85,5%) and specificity rather low (53,1%), but still about 47% of TIA and stroke can be excluded from further AF screening examination using this protocol. (Malik et al., 2011)

Arterial stiffness (AS) as a measurement of altered vascular mechanics is considered to play a key role in the pathophysiology of the cardiovascular system. Clinical conditions mostly predisposing to AS increase are hypertension, dyslipidemia and diabetes with metabolic syndrome that engulfs all of the three mentioned conditions. (Lakatta & Levy, 2003a) There is, also, evidence that elevated homocysteine in hypertensive individuals or those with isolated office hypertension plays an important role; and that aortic stiffness is associated with estrogen receptors alpha (ESR1) and beta (ESR 2), and not with estrogen aromatase (CYP19A1). (Vyssoulis et al., 2010; Peter et al., 2009) Finally, a study by Midei and Matthews discovered that adolescents with higher attachment anxiety and total hostility have greater pulse wave velocity, which is even more apparent among black individuals. (2009)

Important information can be gained through brain CT imaging in which the presence of cortical infarction suggests the presence of severe ipsilateral carotid stenosis or atrial fibrillation thereby modifying clinical classification, patient investigation and prognosis. (Mead et al., 1999) It seems that small striatal infarct and the presence of high levels of brain amyloid will point to those most prone for the development of cognitive impairment and AD dementia development compared to individuals with just one or the other. This increased risk is supported clinically by adult onset of diabetes mellitus, hypertension, atherosclerosis and atrial fibrillation. (Cechetto et al., 2008) Still, severe age related changes in white matter independently and strongly predict rapid global functional decline. (Inzitari et al., 2009)

### 6.1 Arterial stiffness (AS) indexes

Most repeatedly mentioned indexes of arterial stiffness in the literature are: beta stiffness index, pulse wave velocity, augmentation index and analysis of characteristics of central blood pressure waveform. And, it seems that two most important factors affecting arterial stiffness increase, such as increasing age and blood pressure, affect the fibrotic components

of the extracellular matrix, such as elastin, collagen and fibronectin. (Lakatta & Levy, 2003a) Lately, even tissue Doppler measuring left ventricular systolic dysfunction is used to indicate increased arterial wave reflection. (Russo et al., 2011)

Carotid artery stiffness was found not to be an independent risk factor or predictor of vascular events in patients with manifest arterial disease, but it may prove useful for selection of those patients with lesser risk when evaluated together with low systolic blood pressure. (Dijk et al., 2005) A recent study indicated that central arterial stiffness, usually represented by descendent thoracic aorta stiffness and atheroma presence as expressed by beta stiffness index, can be correlated to and represented by radial augmentation index. (Sako et al, 2009) Lastly, vascular stiffness was found to be inversely related to cognitive function, and greater in VaD compared with AD. Using pulse wave velocity may be useful in identifying VaD. (Rabkin & Jarvie, 2011)

Mitchell et al. have recently published that increased pulse pressure (reflection of aortic stiffness) increases cardiac pressure load and may increase AF risk. The association between pulse pressure and AF persisted in models that adjusted for baseline left atrial dimension, left ventricular mass, and left ventricular fractional shortening. Interestingly, in models adjusted for age, sex, and clinical risk factors for AF (elevated body mass index, history of smoking, valvular disease, diabetes mellitus, left ventricular hypertrophy, hypertension treatment, and myocardial infarction or heart failure), mean arterial pressure was unrelated to incident AF.

It seems that ultrasonographic measurement of AS can be chosen as sensitive for detection of vascular damage prior to IMT (intima-media thickness) increase at all ages. (Nunez et al., 2010) Additionally, glycemic status appears to be independently associated with impaired endothelial function and increased arterial stiffness using multivariate analysis, among sensitive population leading to abnormal vessel wall characteristics and more small vessel disease-related cerebrovascular events in stroke survivors. (Gunarathne et al., 2009)

AS indexes may be regarded as quick, undemanding, and bed-side premorbid diagnostic tools, used as markers or predictors, for the assessment of life and disability threatening neurological conditions such as stroke or dementia in the setting of altered vascular mechanics and AF. Furthermore, perfusion enhancement, monitored by AS parameters, seems to produce a favourable and consistent response in AD patients, unlike other more often used dementia therapeutic regimes, offering a new and powerful window for AD treatment. (London et al., 2004; Hirata et al., 2005; Williams et al., 2006)

## **6.2 Is there treatment for altered arterial stiffness?**

Recently, in order to influence cerebral perfusion and consequently arterial stiffness, the most favourable treatments were mentioned: calcium channel blockers, diuretics and ACE inhibitors. (London et al., 2004; Hirata et al., 2005; Williams et al., 2006) Additionally, newer beta blockers, with supplementary vasodilating properties, showing favourable effects on carbohydrate and lipid metabolism, endothelial function and on oxidative stress, also, indicated substantial positive therapeutic effect. (Agabiti-Rosei et al., 2009)

It is important to acknowledge that beta-blockers and diuretics act mostly on macrovasculature, while ACE inhibitors and calcium entry blockers show microvascular favourable actions along with improvement of large artery mechanics and reduction of central wave reflections. (Rizzoni et al., 2009)

Opposed to this, statins were not proven to have any beneficial effects outside the treatment of hyperlipidemia and atherosclerosis. Sex difference of AD incidences between men and



women may be attributed to better pharmacological treatment of men versus women. (Beri et al., 2009)

## 7. Conclusion

Since vascular disorders are regarded as being preventable, early detection and accurate diagnosis of such conditions are very important clinical issues. AF plays an important role in future stroke risk and dementia risk. Namely, consistent evidence supports an association between AF and increased incidence of dementia in patients with stroke. Still, potential association between AF and incident dementia in mild cognitive impairment requires further investigation. AS provides a tool for vascular mechanics assessment and thus offers a window of opportunity for early treatment and diversion of overt clinical vascular events.

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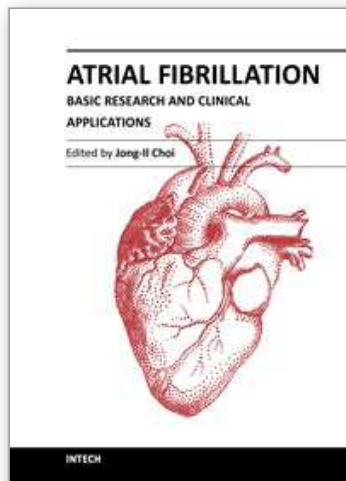
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