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## The strategies of treatment of atrial fibrillation in the elderly

### Leczenie migotania przedsionków u pacjentów w podeszłym wieku

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#### S u m m a r y

Atrial fibrillation (AF) is the most common arrhythmia in elderly people. AF is associated with high risk of stroke, congestive heart failure and with increased mortality. Elderly patients have the highest incidence of thrombotic complications as well as the highest risk of anticoagulant-associated bleeding. CHADS<sub>2</sub> score is the simplest scheme to assess the risk of stroke, and HAS-BLED score is the scale to define the risk of bleeding during treatment with oral anticoagulants. The management of AF focuses on rate or rhythm control and the prevention of stroke with antithrombotic drugs. In case the antithrombotic therapy is recommended, new oral anticoagulants should be considered rather than warfarin concerning their greater clinical benefit. Antiarrhythmic drugs should be used carefully in elderly patients because of the frequency of metabolic abnormalities and higher risk of drug interactions and bradycardia. A rate-control rather than a rhythm-control strategy is the treatment of choice for AF in almost all elderly patients, especially if they are paucisymptomatic.

#### S t r e s z c z e n i e

Migotanie przedsionków jest najczęściej występującą arytmia u osób w podeszłym wieku. Jego konsekwencją jest zwiększone ryzyko udaru mózgu, zastoinowej niewydolności serca i zwiększona śmiertelność. Osoby w podeszłym wieku są bardziej narażone na występowanie powikłań zakrzepowych, ale również na krwawienia związane z przyjmowaniem doustnych antykoagulantów. CHADS<sub>2</sub> jest najprostszą skalą oceniającą ryzyko udaru mózgu, a HAS-BLED skalą oceniającą ryzyko krwawienia podczas leczenia doustnymi antykoagulantami. Leczenie migotania przedsionków koncentruje się na kontroli częstotliwości rytmu komór bądź utrzymywaniu rytmu zatokowego oraz na zapobieganiu udarowi mózgu za pomocą leków przeciwkrzepliwych. W przypadku zalecania terapii przeciwkrzepliwiej należy rozważyć włączenie nowych doustnych antykoagulantów zamiast warfaryny, biorąc pod uwagę korzyści płynące z ich stosowania. Leki antyarytmiczne u osób starszych powinny być zalecane ze szczególną ostrożnością z uwagi na ich zmieniony metabolizm, zwiększone ryzyko interakcji lekowych i bradykardii. Leczeniem z wyboru starszych pacjentów z migotaniem przedsionków, zwłaszcza skąpoobjawowych, jest kontrola częstotliwości rytmu komór, a nie utrzymywanie rytmu zatokowego.

#### INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in older adults with a prevalence increasing from 0.1% among persons younger than 55 years to 9% in people aged 80 years or more. AF can cause various signs and symptoms including palpitations, dizziness, dyspnea, syncope, unstable hemodynamics, tachycardia-induced cardiomyopathy and stroke. Arrhythmia is associated with a five-fold increase in the risk of stroke, a three-fold rise in the incidence of congestive heart

failure, and higher mortality (1). Diagnosing AF before the first complications occur is a well-recognized priority for the prevention of stroke. ESC Guidelines for the management of atrial fibrillation edited in 2012 recommend, in patients aged 65 years or over, an opportunistic screening for AF by pulse palpation, followed by an ECG in those with an irregular pulse to verify diagnosis, and to detect AF prior to the first incident of stroke (2). The management of AF focuses on rate or rhythm control and the prevention of stroke with antithrombotics.

## STROKE RISK EVALUATION

Stroke related to atrial fibrillation is a growing global public health problem. Patients with AF have a variable risk of embolic stroke depending on both comorbid conditions and their age, as most AF patients are above 75 years. Older age is considered an independent risk factor for AF-associated stroke. CHADS<sub>2</sub> score is the simplest scale to assess the risk of stroke (table 1 and 2).

**Table 1.** CHADS<sub>2</sub> score.

Risk factor	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes	1
Stroke or TIA	2
Maximum score	6

**Table 2.** CHADS<sub>2</sub> score and stroke rate.

CHADS <sub>2</sub> score	Adjusted stroke rate (%/year)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

The CHADS<sub>2</sub> score is a simple, practical scale but it does not include many well recognized risk factors for stroke, e.g. vascular diseases. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was found to be better at identifying “truly low-risk” patients with AF while remained as good as CHADS<sub>2</sub> in identifying patients who are at risk for developing thromboembolism and stroke (tab. 3). Its employment is particularly indicated in patients with CHADS<sub>2</sub> score of 0-1 in order to better delineate the truly low-risk patients (2).

**Table 3.** CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age > 75 years	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease (i.e. prior myocardial infarction, peripheral artery disease, aortic plaque)	1
Age 65-74 years	1
Sex category (i.e. female sex)	1
Maximum score	9

## ANTITHROMBOTIC THERAPY

It was found that oral anticoagulant therapy with vitamin K antagonists (VKA) reduced the risk of isch-

emic stroke by 64% in patients with AF. Due to the significantly higher incidence of stroke in the elderly population, the absolute risk reduction in people aged > 65 years was much more pronounced than in younger individuals (3). Apart from considerably increased incidence of thrombotic complications elderly patients are characterized by the much higher risk of anticoagulant-associated bleeding (2). Because of this the final decision of starting treatment with oral anticoagulants should be preceded by careful assessment of the risk of bleeding. The ESC guidelines recommend to use the HAS-BLED score to determine risk (tab. 4). A score of ≥ 3 is considered to be indicative for high risk of bleeding and suggesting that some caution together with special medical attention and regular reviews of the patient are needed following the initiation of anti-thrombotic therapy.

**Table 4.** Clinical characteristics comprising the HAS-BLED bleeding risk score.

Clinical characteristics	Points
Hypertension	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Elderly (age > 65 years)	1
Drugs or alcohol (1 point each)	1 or 2

Considering their mechanisms of action, oral anticoagulants can be divided into several different groups. The oldest one comprise vitamin K antagonists (e.g. warfarin). The drugs inhibit the synthesis of vitamin K-dependent clotting factors, including factors II, VII, IX, and X as well as the anticoagulant proteins C and S. Vitamin K antagonists are effective and inexpensive medicines, but they are characterized by many food and drug interactions and narrow therapeutic window. Their dosing has to be adjusted to ensure the therapeutic level of INR.

As elderly patients are at increased risk of both embolic stroke as a result of AF, and hemorrhage as a complication of anticoagulant therapy the consequence of this dilemma is often underuse of warfarin in older adults. Vitamin K antagonists can be really dangerous in elderly people because of increased incidence of falls and higher risk of severe bleeding in this age group. When warfarin is used a target INR between 2 and 3 is recommended. The cohort study including large group of 12 202 patients demonstrated that the starting dose of 5 mg was too high in up to 82% of women and 65% of men aged 70 years or more (4). According to the American Geriatric Society guidelines close monitoring of the therapy in older adults is necessary and the INR should be measured 2-4 times per week for the first 1-2 weeks, once weekly for the next 1 month, and monthly thereafter (5).

The new group of oral anticoagulants (NOACs) consists of dabigatran, rivaroxaban and apixaban. Clinical benefits and risks of NOACs have been analyzed in the nationwide Danish study. It was found that all new drugs showed clear clinical advantages over warfarin in people with high risk of bleeding and/or stroke (6). One of important benefits of NOACs in the treatment of elderly individuals is a fixed dose.

The assessment of renal function is necessary in people treated with NOACs as the drugs are not recommended in patients with severe renal impairment (glomerular filtration rate – GFR < 30 ml/min/1.73 m<sup>2</sup>) (2). US Food and Drug Administration considered severe renal impairment as a contraindication for treatment with dabigatran (7, 8). The drug should be used cautiously in adults aged over 75 years as in standard dose it is characterized by greater risk of bleeding than is treatment with warfarin (7). To decrease the risk of major bleeding during therapy with dabigatran to that of warfarin in patients aged > 75 years the dosage 110 mg twice daily should be used. The ESC 2012 guidelines suggest to prefer dabigatran in the dose 110 mg twice daily instead of 150 mg twice daily in patients older than 80 years, in individuals treated with interacting drugs (e.g. verapamil), and in people with a HAS-BLED score of ≥ 3 and moderate renal impairment (2). The possibility of the increased risk of myocardial infarction in patients treated with dabigatran needs to be emphasize as one study showed a significantly higher risk of myocardial infarction and acute coronary syndrome in dabigatran users than in the warfarin, enoxaparin or placebo groups (9). This result, however, was described in one trial only.

The European Society of Cardiology in 2012 updated the recommendations for treatment of atrial fibrillation. The suggested treatment should be dependent of the CHA<sub>2</sub>DS<sub>2</sub>-VASc scale score:

- CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 – no antithrombotic therapy is recommended (IB),
- CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 – warfarin or NOACs should be considered (IIA) except of the females with the score of 1,
- CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2, warfarin or NOACs is recommended (IA) (2).

When the antithrombotic therapy is recommended, NOACs should be considered rather than warfarin (IIA), because of their greater clinical benefit (10). To properly choose the method of treatment the compliance to medicine, much worse in the elderly, and the necessity to maintain INR level if vitamin K antagonists are used, have to be taken into account. If NOACs are chosen for elderly patients, it is obligatory to monitor kidney function (11). In proper doses these novel agents reduce, compared with warfarin, the risk of intracranial hemorrhage, the most devastating complication of anticoagulation therapy in older persons (12). Aspirin is no longer recommended for AF thromboprophylaxis as it has similar bleeding risk to warfarin and shows no positive clinical benefit in

any risk stratification (13, 14). Antiplatelet therapy with aspirin at the dose of 75-100 mg/day plus clopidogrel at a dose 75 mg/day or, less effectively, aspirin alone at a dose of 75-325 mg, should be considered exclusively in patients who refuse any oral anticoagulants, or cannot tolerate these drugs for reasons unrelated to bleeding (2).

## RATE CONTROL VS. RHYTHM CONTROL

One of the basic questions on the AF treatment concerns the dilemma: rate control vs. rhythm control in elderly people? Six major trials: PIAF (2001), AFFIRM (2002), RACE (2002), STAF (2003), HOT CAFÉ (2004) and AF-CHF (2008) have compared clinical outcomes of treatment modalities aimed for rate control or rhythm control in AF patients (15-20). The mean age of trials participants was 60.5-70.0 years, confirming the conviction that elderly persons are often underrepresented in clinical studies. Older people are characterized by lower muscle mass and higher body fat content, as well as altered hepatic drug metabolism. All these physiological changes result in difficulties with prediction of dosage and drug activity.

Rhythm control should be favored in symptomatic patients. Sinus rhythm can be achieved with class Ic or class III antiarrhythmic drugs and/or electrical cardioversion. If structural heart disease is found class Ic agents should be avoided (21, 22).

Current evidence indicates that in people without significant symptoms of AF, clinical outcomes of rate control are equivalent to that of rhythm control (14, 15). Rate control is able to be achieved with β-blockers, calcium channel blockers or digoxin. Previous guidelines recommended “strict rate control” with resting heart rate less than 80 bpm but recent data suggest that a target of less than 110 bpm can be accepted (23, 24).

According to current European guidelines pharmacologic options for rhythm control in AF patients with significant structural heart disease are almost exclusively restricted to amiodarone. The guidelines, however, are based on limited data specifically targeting the elderly (2). Dronedarone was developed as a modification of amiodarone in an attempt to maintain the efficacy and to reduce toxicity of the agent. The results of the ANDROMEDA study showed, however, that dronedarone can increase mortality in patients with heart failure (HF) and the study was stopped early (25). Currently, the use of dronedarone is limited to maintenance of the sinus rhythm in patients with paroxysmal AF and normal systolic function.

Sotalol is an agent with combined effects, as β-blocker and class III antiarrhythmic drug. In the SAFE-T study of patients with persistent AF, both amiodarone and sotalol revealed similar effectiveness in converting AF to sinus rhythm, although amiodarone was superior in maintaining sinus rhythm following electrical cardioversion (26). Sotalol may cause significant QT prolongation and increase therefore the risk of arrhythmia in elderly patients. Unlike other β-blockers,

sotalol shows no proven benefits in individuals with heart failure so it is not recommended for use in AF patients with cardiac insufficiency (2).

As distinct from rhythm control, there are several groups of drugs able to control the heart rate.  $\beta$ -blockers, e.g. carvedilol or metoprolol, are recommended for the treatment of cardiac insufficiency because of their proven prognostic and clinical benefits (27). The results of the COMET study revealed, that atrial fibrillation was a poor prognostic factor in patients with heart failure and showed a significant benefit of carvedilol compared to metoprolol in patients with AF and heart failure (28).

Digoxin is recognized a second-line therapy for AF rate control and it is used in heart failure individuals as a weak inotrope. Advanced age of patients can increase the risk for digoxin toxicity because of the impaired renal function and low body mass. The clinical trial (DIG study) did not confirm, however, any association between advanced age and increased risk for digoxin side effects (29).

Calcium channel blockers make another option for rate control in patients with AF if  $\beta$ -blockers are contraindicated. A recent study that compared effectiveness and safety of four different single-drug regimens for rate control in AF patients, with a mean age of 71 years, showed that diltiazem at the dose of 360 mg daily was superior in both rate control and symptoms improvement (30).

To summarize the therapeutic dilemma, many trials that included patients with AF were consistent and showed no difference in mortality rate between patients assigned to one strategy or another. Nevertheless, the analysis of the AFFIRM study revealed that in patients

aged > 65 years rate-control strategy was superior to the rhythm-control strategy for reduction of risk of stroke and mortality. Ancillary studies suggested that increased stroke incidence in the rhythm-control group was probably related to the underuse of oral anticoagulants. Taking into account additional factors e.g. diminished tolerance of antiarrhythmic drugs, it has to be concluded that a rate-control strategy is the treatment of choice for AF in almost all elderly patients (31).

## CONCLUSIONS

The objectives of the AF treatment in the elderly are to prevent AF complications, particularly stroke, and to improve the quality of life. Specific precautions must be taken in older people because of the co-morbidities and age-related changes in pharmacokinetics or pharmacodynamics of drugs. Preventing of AF complications relies mainly on anticoagulant therapy. Novel oral anticoagulants make promising treatment modalities, because of lower risk of intracerebral hemorrhage compared with vitamin K antagonists. Current treatment of elderly patients with AF involves the therapy of underlying cardiomyopathy and heart rate-control rather than a rhythm-control as a first-line therapy, especially if the patients are paucisymptomatic. Antiarrhythmic drugs should be used carefully in elderly patients because of the high frequency of metabolic abnormalities and increased risk of drug interactions and bradycardia. There are only few randomized controlled trials aimed to determine optimal management of atrial fibrillation in elderly patients. Next studies are ongoing and they give hope to improve treatment strategies in older people with AF.

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