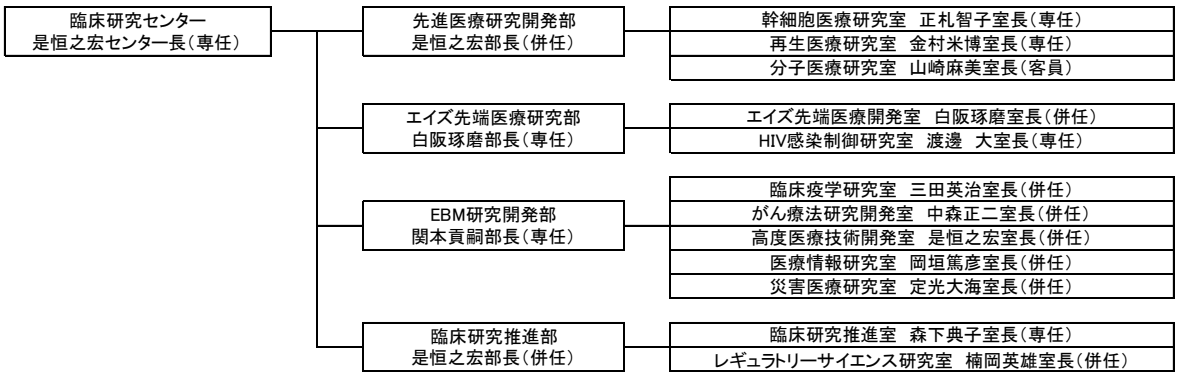
臨床研究センター

センター長　是恒之宏

当臨床研究センターもセンターとなって 7 年目を迎えた。国立病院機構では平成 17 年度より新たな研究業績評価が開始されたが、当院は平成 18 年度 2 位以外は常に 1 位を獲得している。この業績評価は、治験、臨床研究プロトコール作成、特許の取得、競争的研究費の獲得、論文著書、国内外の学会発表などの総合力で分析される。日常臨床が多忙を極める中で、治験を含めた臨床研究への積極的な大阪医療センターの取り組みが評価されたものと考える。平成 20 年度より、当院および九州医療センターはその業績を認められ、臨床研究部から臨床研究センターへランクアップとなった。それにともない、組織は 1 部 5 室から 2 部 9 室と改変し、それまで治験管理センターとして病院内の組織であった治験管理部門を新たに臨床研究も含めた支援室、臨床研究推進室として研究センターの元におくこととなった。平成 23 年度からは、新たに高度医療技術開発室、レギュラトリーサイエンス研究室を開設し、3 部 11 室となった。これまでと同様、文部科研に応募を希望する医師については、併任発令を行い、これに対応した。また、院内の多くの医師が臨床研究に携わっていること、本部からの研究助成金を研究業績に応じて一部分配することにより研究推進を図る目的で、平成 18 年度より医長以上の併任、英文論文筆頭著者併任をおこなうこととしている。平成 25 年度 DMAT 西日本拠点に指定されたのに伴い、平成 26 年度から災害医療研究室を加え 4 部 12 室となった。平成 26 年度の構成は以下のとおりである。



※専任室員
山本篤世室員（幹細胞医療研究室）
隅田美穂室員（再生医療研究室）
兼松大介室員（再生医療研究室）

2014.4.1

先進医療研究開発部

幹細胞医療研究室

幹細胞医療研究室では、ヒト iPS 細胞（人工多能性幹細胞）を用いて、再生医療の実現化に向けた技術開発研究を実施している。神経疾患の再生医療実現を目指し、iPS 細胞から臨床グレードの神経幹細胞（ニューロンやグリア細胞を供給する能力を持った幹細胞）へと誘導する方法の開発を進めている。また、神経疾患患者の検体から iPS 細胞を樹立し、神経幹細胞の誘導及び神経系細胞への分化を行い、疾患発症機序の解明にも取り組んでいる。

再生医療研究室

再生医療研究室では、各種幹細胞および免疫細胞等のヒト細胞を応用した「細胞治療」を新しい先進的な医療として確立させることを目標に、治療に使用する各種ヒト細胞の培養・加工プロセスの開発、治療用ヒト細胞の品質管理並びに安全性評価に関する技術開発などの研究を行なっている。また、ヒト幹細胞を応用した薬剤毒性評価系の開発と新規治療薬候補化合物の探索を目指した基礎的研究を実施している。さらに悪性脳腫瘍の分子診断体制を構築するための多施設共同研究体制の構築を実施した。

分子医療研究室

分子医療研究室の主な研究課題は、難治性脳形成障害症（Fetal Brain Malformation; FBM）の胎児診断における診断基準の作成と患者由来検体の収集とその遺伝子解析及び臨床像解析の多施設共同研究の体制強化である。現在までに FBM 約 350 例が登録されている。従来の遺伝子解析に加え標的遺伝子検索システム（target sequencing system ）と次世代シークエンサーを用いた遺伝子解析（whole exome sequencing ；WES)を施行し、新規遺伝子変異を同定してきた。①脳室拡大が主な所見の水頭症群②全前脳胞症の群③小頭症群④細胞移動障害を呈する群④骨系統疾患の群⑤後頭蓋窩フリーエコー病変⑥大頭症群⑦二分脊椎症群⑧胎内頭蓋内出血あるいは水無脳症・裂脳症・孔脳症群。⑨脳梁欠損群において解析遺伝子のパネル化作成にむけて準備をしている。

エイズ先端医療研究部

エイズ先端医療開発室

HIV 感染制御研究室

海外同様、わが国、特に大阪でも HIV 感染症患者数は増え続けており、毎年、新規 HIV 感染者、エイズ患者数は増加の傾向にある。治療の進歩によって HIV 感染症の予後は大きく改善されたが、エイズ医療では多くの課題が未だ残されている。約 20 年以上前に血液製剤で感染した患者の多くは C 型肝炎との重複感染であり治療が困難な例が多い。その後、増えている性感染症としての HIV 感染症患者では 20 歳代、30 歳代が多く、社会的、経済的に不安定な者も少なくなく、セクシャリティーなどマイノリティーでの課題も抱えている。当研究室では、この様な多くの課題の中で、HIV 感染症治療、エイズ医療の分野を中心とした研究を進め、主に厚生労働科学研究費補助金エイズ対策

事業、財団法人友愛福祉財団の調査研究事業、独立行政法人国立病院機構の共同研究等に取り組んできた。エイズ先端医療研究部はエイズ先端医療開発室（白阪が室長を兼務）と HIV 感染制御研究室（渡邊大室長）から成り、前者は医療についての研究、後者は基礎的研究を主に行っている。服薬アドヒアランスの向上に関する研究班、HIV 感染症及びその合併症の課題を克服する研究班では分担研究者と共に HIV 感染症のチーム医療の在り方、エイズ看護の在り方、長期療養の問題等と取り組んで来た。今後もエイズの治療と医療に付き研究を進める。

EBM 研究開発部

臨床疫学研究室

臨床疫学研究室では、臨床疫学・アウトカムリサーチの実施基盤を確立し、データの集積・解析を行いつつエビデンスを形成し、コストベネフィットを解析する形態の臨床研究を行っている。特に消化器疾患診療に関する薬剤・機器臨床試験の他、当院の政策医療である肝臓病の診療に役立つ臨床研究を推進している。平成 26 年度も厚生労働科研、国立病院機構共同研究などの公的助成や民間助成を得て、1) C 型肝炎治療の効果予測因子、2) B 型肝炎に対する核酸アナログの耐性変異の解析、3) アデホビル・テノホビルの腎機能障害の検討を行い、成果をあげている。

がん療法研究開発室

現在、がん治療においては、オーダーメード医療という語に代表されるように、各個人のがんの種類や病態の特徴に応じた医療が積極的に進められている。病気や病態の違いは分子異常の違いによって生じており、それを利用した遺伝子診断や分子標的治療もさかんに行われるようになってきた。本研究室では、がん患者から得られた血液や組織を利用してがんにおける分子異常を探り、それに基づいた新たながんの診断や治療戦略の開発をめざした translational　research とその臨床応用めざしている。具体的には、国立がん研究センターをはじめ企業の研究期間を含めた専門組織との共同研究により、1）臨床材料を用いた網羅的遺伝子解析や網羅的ペプチド蛋白解析、糖鎖解析を利用した発がん、増殖、転移に関わる責任分子の抽出、同定と治療応用可能標的分子の確認。2）分子異常に基づいた新たな腫瘍マーカーの開発。3）抗がん剤や放射線治療の感受性や耐性に関与する分子の分離とその臨床応用。4）実臨床における全国規模の大規模多施設共同臨床試験に積極的に参加するとともに自主的臨床試験研究の企画を行っている。

高度医療技術開発室

近年における医療を取り巻く情報処理や画像処理の技術革新により、診断、治療における医用画像診断装置の利用範囲は拡大しており、著しいイノベーションを引き起こしている。医用画像診断装置の技術開発により低侵襲化、従来視覚化困難であった部位や現象の画像化が可能になりつつあり、そこから新たな治療が生まれる可能性がある。これらの技術開発には医工連携すなわち病院、大学、企業との連携体制の構築が必要であるが、米国における産学連携の仕組みや組織と比較すると本邦ではまだまだ発展の余地が多いと言える。病院における医療現場のニーズを企

業が保有している技術開発力や大学の基礎医学研究 能力に結び付けながら、常に新しい高度医療技術の開発に取り組んでゆくことが、病院に付属する本研究室の最も重要な役割である。平成24 年度より循環器系研究室員を配置し、医用画像診断装置の技術開発を大阪大学大学院医学系研究科保健学専攻機能診断科学講座とともに推進している。

医療情報研究室

医療情報研究室では、医療への IT 応用に関するソフト、ハードの両側面の研究を行っている。整形外科領域におけるシミュレーションを用いた研究、病院において実稼働している病院情報統合システムを用いた研究、病院情報システム本体の機能拡張に関する独自の研究を実施する一方、治験・臨床研究や医療安全に関するシステム的検討、シミュレーションや統計などの情報科学の医療応用に関する研究を行っている。また、ネットワーク技術や画像処理技術の応用・改良など、情報処理の基盤技術に関連した研究も行っている。最近では南海トラフ巨大地震、首都直下型地震の医療機関被災状況シミュレーションや DMAT 配置計画等、国の災害対策の元となるデータの供給も行なっている。

災害医療研究室

平成 25 年 10 月より厚生労働省医政局災害医療対策室 DMAT 事務局が開設された。それに合わせて、臨床研究センターに災害医療研究室を新設し、災害医療に関する調査研究を行っている。平成 25 年度は厚生労働科学研究費補助金（H25-特別-指定-023）による「南海トラフ巨大地震の被害想定に対する DMAT による急性期医療対応に関する研究」を実施した。さらに平成 26 年度からは、厚生労働科学研究費補助金地域医療基盤開発推進研究事業（H26-医療-指定-023 ）による「首都直下地震に対応した DMAT の戦略的医療活動に必要な医療支援の定量的評価に関する研究」を 2 年計画で実施中である。また、厚生労働科学研究費補助金地域医療開発推進研究事業の「東日本大震災からみた今後の災害医療体制のあり方に関する研究」、さらに健康安全・危機管理対策総合研究事業の「災害時における医療チームと関係機関との連携に関する研究」の分担研究として災害時に用いる標準的災害診療記録票の作成に関する研究を実施し、平成 27 年度も継続予定である。平成 26 年度 NHO 共同研究「障害者病棟を持つ病院の災害対策マニュアル整備に関する研究」にも参画している。今後、DMAT だけでなく国立病院機構の災害医療における役割や消防あるいは警察機関との連携に関する継続的な研究も計画している。

臨床研究推進部

臨床研究推進室

臨床研究推進室は、治験や臨床研究の円滑な実施とその質を保証することを目的として平成 11 年 4 月に「治験管理センター」として開設され、本年度で 16 年目を迎えている。平成 20 年度からは臨床研究部が臨床研究センターに昇格したのを機に、「治験管理センター」から「臨床研究推進室」へと組織および名称変更を行った。

臨床研究推進室には「治験管理部門」「臨床試験支援部門」があるが、治験管理部門が、治験以外の臨床研究支援も含め、活動の中心となっている。主な活動として、治験の全体的なコーディネーションを担うとともに、治験の契約前から終了まで迅速かつ質の高い治験実施を支援している他、受託研究審査委員会（IRB）事務局機能も併せ持っている。

平成 26 年度には、厚生労働省より「質の高い倫理審査が行える委員会（認定倫理審査委員会)」として認定を受けることができた（平成 27 年 3 月 31 日付)。

レギュラトリーサイエンス研究室

レギュラトリーサイエンスは、平成 23 年 8 月の科学技術基本計画では「科学技術の成果を人と社会に役立てることを目的に、根拠に基づき的確な予測、評価、判断を行い、科学技術の成果を人と社会とも調査の上で最も望ましい姿に調整するための科学」と定義されている。平成 26 年 11 月には、薬事法が「医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律」に改正され、「再生医療等の安全性の確保等に関する法律」が制定された。いずれも平成 27 年 11 月から施行されている。このようなレギュラトリーサイエンスの対象領域の拡張を踏まえ、当研究室では、医師、医療従事者のみならず、他分野の研究者、知識人との連携・協力により、特に、再生医療・細胞治療・遺伝子治療といった先端医学、ゲノム科学をとりいれた臨床研究、あるいは新たな感染症対策などの分野において、先進医療について、最新の科学的技術・知識に基づく予測・評価を行うとともに、社会との調和を図ることをテーマとしている。

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Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013)

– Digest Version –

JCS Joint Working Group

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JCS Joint Working Group

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Class of Recommendations

Class I: There is evidence and/or general agreement that a given procedure or treatment is effective and/or useful.

Class II: There is no consistent evidence and/or general agreement that a given procedure or treatment is effective and/or useful.

Class IIa: Weight of evidence and opinion is in favor of usefulness and/or effectiveness.

Class IIa': Although evidence is not well established, there is general agreement that a given procedure or treatment is effective and/or useful among specialists in Japan.

Class IIb: Usefulness or effectiveness is not fully established by evidence or opinion.

Class III: There is evidence and/or general agreement that the procedure or treatment is not effective and/or useful or may even be harmful.

Level of Evidence

Level A: Demonstrated with multi-center randomized, controlled studies with 400 patients or more or meta-analyses.

Level B: Demonstrated with multi-center randomized, controlled studies with less than 400 patients, well-designed comparative studies, or large-scale cohort studies.

Level C: Only consensus opinion of experts, without data of randomized, controlled studies.

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Introduction of the Revised Guidelines

The present guidelines are a revision of the 2008 version of Guidelines for Pharmacotherapy of Atrial Fibrillation,[1] which were originally published in 2001,[2] and reflect new findings obtained during the past five years since the publication of the 2008 revision.

Treatment strategies for atrial fibrillation (AF) consist of rate control, rhythm control (treatment to restore sinus rhythm and prevent recurrences), and antithrombotic therapy. Recent findings have indicated that there is no significant difference between strict and lenient rate control in outcome after several years. On the other hand, no drastic changes have occurred in pharmacotherapy to restore sinus rhythm and prevent AF recurrences. Although upstream therapy was highly anticipated as an important preventive strategy, several prospective clinical trials reported negative results. Catheter ablation has become prevalent in Japan, and the results superior to pharmacotherapy have been reported. In the present revision, catheter ablation is described as an essential technique for the treatment of AF.

Major changes made for the present revision are as follows.

New Oral Anticoagulants: The first is the inclusion of new oral anticoagulants (NOACs) in the guidelines. An oral direct thrombin inhibitor and factor Xa (FXa) inhibitors, which were developed to overcome the drawbacks of warfarin, have not been widely used in Japan yet, and further clinical experience must be accumulated. The level of evidence for individual NOACs is based on data obtained as of December 2013. Readers should be alert for new information about these drugs as new findings are being uncovered one after another.

Target PT-INR: Information on optimal anticoagulation intensity with warfarin was obtained in the J-RHYTHM Registry, a prospective study in more than 7,000 Japanese patients, which indicated that the target range of prothrombin time international normalized ratio (PT-INR) would be 1.6~2.6 for Japanese patients, especially those over 70 years of age. The difference in optimal PT-INR levels between Japanese and Western patients was confirmed.

Risk Assessment: The $CHADS_2$ score was used to stratify the risk of cardiogenic embolism in the previous revision, and has also been used in prospective clinical trials conducted following the publication of the previous guidelines. We therefore use the $CHADS_2$ score, rather than the newer score CHA_2DS_2-VASc, in the present revision that was written on the basis of the results of clinical trials using the $CHADS_2$ score.

Changing Definitions of Some Terms: In the present guidelines, "valvular AF" is defined as AF in patients with prosthetic valve replacement using mechanical valves or bioprosthetic valves, or those with AF and rheumatic mitral disease (mitral stenosis in most cases). In this revision, AF in patients after mitral valve plasty is no longer included in "valvular AF". AF associated with non-rheumatic mitral regurgitation is classified into non-valvular AF. The definition of "lone" AF differs among specialists, and has changed over time. A strict definition of "lone" AF may cause confusion in selecting treatment in the clinical setting. In the present revision, we avoid using the term "lone" as much as possible, and describe it as AF "with no clinically significant structural heart disease". Structural heart diseases include cardiac hypertrophy, cardiac dysfunction, and cardiac ischemia.

The above-mentioned new findings were included in the present revision to provide guidelines suitable for patients with AF in Japan. As with any guidelines, the present ones provide "guidance" for selection of treatment options by practitioners, who must understand the pathophysiological characteristics of AF in each patient and determine the optimal treatment strategy for him or her accordingly. It should be noted that determination of treatment by attending physicians based on the specific conditions and circumstances of their patients should take precedence over the guidelines, and that the present guidelines provide no grounds for argument in cases of legal prosecution.

I Epidemiology of AF

The prevalence of AF increases with age. Epidemiological surveys in North America and Western Europe[3–7] have indicated that the prevalence of AF increases very slowly with age in people under 60 years of age, and that it is less than 2% in people in their early 60s. The prevalence then increases significantly in more elderly people to 9~14% of the general population over 80 years of age. Although some surveys have reported no difference between sexes, many studies have reported that the prevalence of AF is higher in men than in women. In Japan, the results of a national survey[8] of randomly sampled populations in different areas in Japan and an epidemiological survey[9] conducted by the Japanese Circulation Society indicated that the prevalence of AF increases slowly up to 60 years of age to approximately 1% of the general population, and that the increase beyond 70 years of age is slower than in Western countries. The prevalence of AF is only around 3% of the general population over 80 years of age in Japan. Male patients are strongly predominant in Japan. Studies in Korea[10] and Taiwan[11] have reported prevalences similar to Japan.

The types and prevalences of diseases underlying AF differ between Japan and Western countries, as well. Recent studies[12] in Western countries have reported that hypertension is observed in about 60% of patients, and ischemic heart diseases in 25~33% of patients with AF, while valvular heart disease is uncommon. In Japan,[13,14] the prevalences of hypertension, ischemic heart disease, and valvular heart diseases in patients with AF are about 60%, 10%, and 10~20%, respectively, and the prevalence of ischemic heart disease is substantially lower than in Western countries. Risk factors for the development of AF that have been identified in Western studies[15] include aging, diabetes mellitus, hypertension, cardiac diseases (ischemic and valvular heart diseases), heart failure, excessive alcohol consumption, and obesity, while those specified in the Hisayama Study,[16] an epidemiological survey in Hisayama town, Kyushu, Japan include aging, heart diseases (ischemic and valvular heart diseases), and alcohol consumption. Recent studies[17] in Japan have revealed that metabolic syndrome is a risk factor for the development of AF. Recent studies have revealed that chronic kidney disease[18] and smoking[19] increase the risk of the development of AF.

II Pathophysiology of AF

1. Pathophysiology of AF

AF is characterized by unorganized and rapid irregular atrial activation with loss of the contribution of atrial contraction to ventricular filling, resulting in decrease in cardiac output. This causes hemodynamic impairment and exacerbation of heart failure. A persistently rapid ventricular rate during AF may cause tachycardia-induced cardiomyopathy.[20] In addition, AF decreases atrial blood flow velocity, which may cause intra-atrial thrombogenesis.

2. Underlying Diseases

Some diseases are frequently associated with AF. Generally, at the onset of AF, (1) mechanical load on the left atrium, (2) autonomic nervous system activity, and (3) changes in ion channels in the atrial myocardium are involved simultaneously or in sequence as substrates for the development of AF.[21,22] Hypertension is one of the most prevalent major risk factors for the development of AF, and it has been demonstrated that appropriate antihypertensive treatment decreases the incidence of new-onset AF.[23] In patients with hyperthyroidism[24] and those with familial AF,[25] altered or abnormal expression of potassium channel-related genes promotes the development of AF. Lone AF, which is defined as AF with no structural heart diseases, has recently been pointed out to relate to several forms of familial AF associated with genetic alterations, and also to single nucleotide polymorphisms.[26]

3. Types and Clinical Significance of AF

AF is classified by its duration of continuation, into paroxysmal, persistent, and permanent AF (See Section IV. "Clinical Picture"). AF may progress from paroxysmal to persistent AF, and then eventually to permanent AF. During AF, a decrease in cardiac output may occur due to loss of atrial contraction. Patients with AF thus experience easy fatigability during effort including exercise in addition to palpitation. In patients with poor cardiac function or those with hypertrophic cardiomyopathy, AF may significantly exacerbate heart failure and induce pulmonary congestion. In some patients, persistently rapid ventricular rate during AF causes cardiomyopathy-like symptoms. In patients with Wolff-Parkinson-White (WPW) syndrome, a condition characterized by accessory pathways in the heart, AF may in rare cases lead to ventricular fibrillation.[27]

As AF may cause low blood flow velocity in the atrium, atrial endothelial dysfunction, or changes of coagulation activity, left atrial thrombus may occur and result in cerebral embolism. Patients with AF are treated according to the type and pathophysiology of AF.

III Electrophysiological Mechanism of AF

1. Mechanism of Onset of AF

When atrial electrogram is recorded during AF, irregular, very fast, and unorganized activation is observed in many segments. It has been demonstrated in animals and humans that these abnormal activations are caused by a focal mechanism, i.e., abnormal focal excitability (automaticity), and random reentry of multiple wavelets.

1.1 Focal Mechanism

The focal mechanism is characterized by rapidly firing atrial foci and fibrillatory conduction in the atria. Electrophysiologically, it is similar to ectopic atrial tachycardia. On clinical grounds, AF originating from localized area in the atrium or vena cava is believed to be due to a focal mechanism.[28] On the other hand, about 90% of frequent atrial premature contractions observed in patients with paroxysmal AF originate in the pulmonary veins.[29,30] Short runs of atrial premature contractions may lead to a rapidly firing driver, which can cause fibrillatory conduction and eventually AF. In addition, premature contractions originating in the pulmonary veins may trigger reentry in the atrium, causing AF. It has been suggested that the development of premature atrial contractions originating in the pulmonary veins and a rapidly firing driver result from triggered activity in the pulmonary veins or reentry in the region of the junction of the left atrium and pulmonary vein.[31,32]

1.2 Reentry of Multiple Wavelets

In an experiment using Langendorff-perfused hearts in which AF was induced under infusion of acetylcholine, focal activations were observed simultaneously at least 3~6 foci in the atrium. Some of these simultaneously circulating wavelets may disappear and the others split into branches, causing random reentry, which continues to maintain AF.[33] Reentry of multiple wavelets has also been observed during AF induced in a model of sterile pericarditis.[34] The role of reentry in the development of AF is still unclear anatomically, and reentry may result from functional barriers such as refractory period and anisotropic conduction. Various types of reentry such as leading circle reentry,[35] anisotropic reentry,[36] and spiral reentry[37] have been experimentally identified.

2. Electrical and Structural Remodeling

Reentry of multiple wavelets will occur only when the excitation wavelength is short enough or the atria are large enough.[38] Since the excitation wavelength is determined by the product of conduction velocity and refractory period, the conduction velocity must be slow or the refractory period must be short enough to maintain AF. The concept of "atrial fibrillation begets atrial fibrillation",[39] where AF (tachycardia) shortens the atrial refractory period (this change is referred to as electrical remodeling), making possible the reentry of multiple wavelets, is an important factor in the induction of permanent AF. It has been proposed that electrical remodeling develops through the accumulation of intracellular calcium ions, a decrease in calcium current, and shortened duration of the action potential.[40,41] When tachycardia persists, the excitation wavelength

decreases further due to down-regulation of ion channels and a decrease in conduction velocity due to a decrease in sodium current.

When AF persists for a long period of time, structural changes such as hypertrophy and fibrosis of the atrial myocardium and altered gap junctions may occur (these changes are referred to as structural remodeling).[40,41] Fibrosis will decrease conduction velocity and increase the heterogeneity of conduction, making the atria susceptible to reentry.[42] In patients with AF complicated by structural heart disease, atrial structural remodeling tends to progress further, and AF tends to develop more frequently and to persist for long periods of time.

3. Genetic Risk and Electrophysiological Changes

Youths with lone AF often have a family history of AF (in 15~30%).[25] In a prospective cohort study within the Framingham Heart Study, the presence of AF in at least one parent increased the risk of offspring AF with an odds ratio of 1.85. When age at onset of AF was limited to younger than 75 years in both parents and offspring, the odds ratio increased to 3.23.[43] Families with an autosomal dominant form of AF have been reported, and a mutation in the *KCNQ1* gene (S140G) was suspected as a cause of the familial AF.[44] Mutations in the cardiac sodium channel gene *SCN5A*,[45] the gap junction protein gene (*GJA5*),[46] and the natriuretic peptide precursor A gene (*NPPA*)[47] have been detected in families with AF. It has been found that a strong association is present between two sequence variants (rs220073 and rs10033464) on chromosome 4q25 and AF, and the risk of AF increases by 1.71 and 1.42 per copy, respectively.[48] Chromosome 4q25 variants have been suggested to modulate clinical expression of latent mutations in *SCN5A*, *KCNQ1*, *NPPA*, and *NKX2.5* genes in familial AF.[49]

IV Clinical Picture

1. Classification of AF

Since AF is a chronic progressive disease with a variety of clinical pictures and there is uncertainty regarding diagnosis of AF due to methodological and time-dependent factors, accurate classification of AF may not be clinically useful. Given the long-term natural history of AF,[50] in which episodes terminate spontaneously in the early stages, increase in duration and incidence over time, as they repeat and eventually become permanent, the following classification of AF[51] is proposed in the present guidelines.

First-Detected AF: First episode of AF with electrocardiographic documentation, regardless of how long the AF episode has continued.
Paroxysmal AF: Episodes that return to sinus rhythm within 7 days after onset.
Persistent AF: Episodes that last longer than 7 days.
Long-Term Persistent AF: Persistent AF lasting ≥one year.
Permanent AF: Episodes that cannot be terminated with electrical or pharmacological cardioversion.

The duration of AF should be comprehensively determined by clinicians based on the history and symptoms of AF and ECG findings.

2. First-Detected AF

First-detected AF is defined as the first episode of AF documented electrocardiographically, regardless of whether it is truly the first episode of AF in the patient. It is important to reclassify first-detected AF according to the history, symptoms, and ECG findings in the past and present and the clinical course after the diagnosis of AF.

When the first-detected AF episode is transient and terminates spontaneously, AF does not recur for several years in about 50% of such patients.[52] Patients with AF that occurs during the acute phase of myocardial infarction or the early postoperative period after heart surgery and patients with AF associated with underlying conditions such as hyperthyroidism, where the cause or contributor can be removed or corrected, do not require continuous administration of antiarrhythmic drugs. In patients in whom the first-detected AF lasts longer than 7 days, AF does not terminate spontaneously. Whether cardioversion is required should be determined by overall consideration of the background characteristics and quality of life (QOL) of individual patients.

3. Paroxysmal AF

Paroxysmal AF returns to sinus rhythm within 7 days (within 48 hours in many cases) with or without pharmacotherapy or non-pharmacotherapy, and is observed during the early phases of persistent/permanent AF. Although many patients with AF respond well to pharmacotherapy early after onset, they tend to become unresponsive to pharmacotherapy later. In a long-term observational study[53] in Japan in which patients with AF were followed for 15 years on average, paroxysmal AF progressed to persistent/permanent AF at an average of 5.5%/year in patients receiving Class I antiarrhythmic drugs. In Japan, age, left atrial diameter, prior myocardial infarction, valvular heart disease, and diabetes mellitus have been reported as independent risk factors for the progression to persistent/permanent AF.[53,54] In Western countries, the HATCH score (hypertension, age [75 years and older], transient ischemic attack or stroke, chronic obstructive pulmonary disease and heart failure) is used to predict the progression to permanent AF.[55]

Patients with poor QOL due to paroxysmal AF should be treated with antiarrhythmic drugs to prevent episodes of AF. However, the duration of pharmacotherapy needed to maintain sinus rhythm should be determined for individual patients based on comprehensive evaluation of the duration of treatment, background characteristics, and feasibility of non-pharmacotherapy with catheter ablation. Patients should continue anticoagulation based on their risk of cerebral infarction regardless of whether the treatment selected is designed to maintain sinus rhythm or to control heart rate.

4. Persistent AF

Persistent AF is defined as an episode of AF lasting longer than 7 days. It is impossible to distinguish persistent AF from permanent AF when neither pharmacological nor electrical cardioversion is performed. Although persistent AF cannot be terminated with pharmacological cardioversion except when certain types of antiarrhythmic drugs are used, patients respond well to electrical cardioversion, and 94% of them return to sinus rhythm.[56] AF frequently recurs after cardioversion: the percentages of patients who remain in sinus rhythm with common pharmacotherapy are about 50% at year 1, 40% at year 2, and 30% at year 3.[56] The rate of recurrence differs depending on patient characteristics, and known risk factors for AF recurrence include advanced age, hypertension, heart failure, and duration of AF episode.[56]

Patients with AF lasting ≥one year, which is generally called long-term persistent AF, are often difficult to maintain sinus rhythm.

Cardioversion followed by maintenance of sinus rhythm is considered appropriate treatment for patients with poor QOL but without known risk factors. For other patients, heart rate control and anticoagulation based on the risk of cerebral infarction are also acceptable options of AF treatment.

5. Permanent AF

Permanent AF is defined as AF not responding to pharmacological or electrical cardioversion. Common policies of treatment for permanent AF aim at preventing possible sequelae of it rather than controlling AF itself, and perform heart rate control and anticoagulation based on the risk of cerebral infarction.

V Treatment

1. How to Develop Treatment Strategies

In the treatment of AF, it is important to target improvement of controllable underlying diseases other than arrhythmia. Patients with cardiac dysfunction and ischemia should thus be treated for such diseases before considering whether antiarrhythmic treatment is necessary. During treatment, control of embolism should be appropriately performed.

Although treatment of AF has been targeted to maintain sinus rhythm, the results of large-scale clinical trials such as the PIAF (Pharmacological Intervention in Atrial Fibrillation).[57] the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management),[58] the RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation),[59] the STAF (Strategies of Treatment of Atrial Fibrillation)[60] published in 2000 or later have indicated that rhythm control therapy to maintain sinus rhythm is not superior to rate control therapy, and these finding substantially affect the use of antiarrhythmic drugs.[61]

In the treatment of AF, physicians should first assess whether anticoagulation therapy is indicated or not, and then select either rhythm control therapy or rate control therapy according to the condition of the patient. Patients with a high risk of embolism should continue anticoagulation therapy for life even if sinus rhythm can be maintained. Rate control therapy does not exacerbate the prognosis of AF, and is rather safe considering the adverse reactions to antiarrhythmic drugs. Antiarrhythmic drugs may cause serious adverse drug reactions (ADRs) that may significantly affect the patient outcome, and rhythm control to maintain sinus rhythm is limited in terms of long-term efficacy. In fact, many patients undergoing rhythm control therapy experience the progression to persistent or permanent AF.[53] In patients with permanent AF, rate control and anticoagulation therapy may often ensure an acceptable QOL. However, many clinicians know that rate control therapy is nearly ineffective for patients who have intolerable symptoms when an AF episode develops.

The results of the J-RHYTHM study[62] have demonstrated that tolerability is important in the treatment of paroxysmal AF, and that rhythm control therapy to maintain sinus rhythm is appropriate for patients with paroxysmal AF especially for relatively young patients with highly symptomatic paroxysmal AF. In this study, the incidence of serious ADRs to antiarrhythmic drugs was very low as compared with that reported in foreign clinical trials. Although the participants were mainly patients with a relatively low risk of thromboembolism, many patients were treated with warfarin and the incidence of cerebral infarction was only 2.3% during the mean follow-up period.

The purpose of antiarrhythmic pharmacotherapy is to improve QOL rather than to decrease mortality or prevent cerebral infarction through maintaining sinus rhythm. It should be noted that participants in the J-RHYTHM study[62] had a mean age of 64 years and normal cardiac function without underlying heart disease. We should conduct further studies to find the best way to treat patients with AF and cardiac dysfunction who cannot use sodium channel blockers.

1.1 Treatment Strategies Specific to Underlying Diseases

1.1.1 Valvular Heart Disease

When AF develops in patients with valvular heart disease, further deterioration of cardiac hemodynamics occurs and embolism develops more frequently. It is thus important to prevent the development of AF in such patients. Physicians should consider surgical treatment of valvular heart diseases such as valve replacement before atrial remodeling progresses. In patients with valvular heart diseases and AF, use of the Maze procedure or Radial incision approach to maintain sinus rhythm is recommended. Long-term treatment with Class I antiarrhythmic drugs is not recommended. Patients should aggressively undergo upstream therapy to prevent atrial remodeling through improvement of cardiac function.

1.1.2 Hypertension

Development of AF may possibly be prevented by early treatment of hypertension to ensure appropriate blood pressure control. Prevention of remodeling of the atria and pulmonary veins due to hypertension is an important upstream therapy in controlling the substrates of AF. Blood pressure control is important in patients with any type of AF, and high blood pressure should not be ignored during treatment of AF. Hypertension may facilitate the development and maintenance of AF and increase the risk of embolism. It is recommended that

hypertensive patients with AF should be treated mainly with angiotensin II receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors, and combinations of different types of antihypertensive drugs may be needed to ensure sufficient antihypertensive efficacy. Prevention of AF recurrence with Class I antiarrhythmic drugs may be effective in patients without cardiac dysfunction.

1.1.3 Coronary Artery Disease

Treatment targeting AF alone is potentially dangerous in patients with coronary artery disease. Basically, improvement of myocardial ischemia should be prioritized. AF complicated by acute coronary syndrome should be treated with cardioversion whenever necessary, though Class I antiarrhythmic drugs are not recommended for this purpose. Although Class III antiarrhythmic drugs such as sotalol and amiodarone are preferable,[51] use of them in patients with acute coronary syndrome is not covered by the National Health Insurance (NHI) in Japan. Particularly in patients with left ventricular dysfunction, ACE inhibitors and ARBs should be used aggressively from the early stage to prevent not only left ventricular remodeling but also left atrial remodeling.[63] Physicians should be aware that the use of antiplatelet drugs will increase the risk of bleeding complications in patients receiving anticoagulants to prevent embolism.

1.1.4 Heart Failure (Left Ventricular Dysfunction)

Although AF may promote further deterioration of cardiac function and is thus an unfavorable condition in patients with cardiac dysfunction, prevention of AF with sodium channel blockers is not recommend, since they may worsen the prognosis of such patients. Since the incidence of embolism is high in patients with AF complicated by heart failure, if not contraindicated, anticoagulation should be promptly initiated and treatment should focus on improving cardiac function. In patients with left ventricular dysfunction, ACE inhibitors and ARBs are expected to be effective in preventing the development of AF.[64,65]

1.1.5 Dilated Cardiomyopathy

AF promotes heart failure, increases the risk of embolism, and worsens the prognosis of dilated cardiomyopathy. In patients with AF and dilated cardiomyopathy, heart rate control should be prioritized to maintain cardiac function and prevent the progression of heart failure. Patients with chronic heart failure require stabilization of hemodynamics and prevention of embolism.

1.1.6 Hypertrophic Cardiomyopathy

In patients with hypertrophic cardiomyopathy complicated by left ventricular outflow tract obstruction, AF may cause an abrupt decrease in cardiac output, which may progress to ventricular fibrillation. Although electrical cardioversion is effective when urgently required, prevention of AF recurrence is also important and effective treatment is thus essential. Amiodarone is indicated for paroxysmal and persistent AF in patients with hypertrophic cardiomyopathy. Although the negative inotropic effect of Class I antiarrhythmic drugs is considered beneficial in preventing the progression of hypertrophic cardiomyopathy,[66,67] the efficacy of these drugs in preventing AF in this patient population has not been investigated in detail.

1.1.7 Chronic Respiratory Disease

Bronchodilators may induce AF. Patients with chronic respiratory disease and AF should be treated to control hypoxemia and acidosis, and undergo rate control therapy using verapamil and diltiazem. β-blockers that may worsen underlying respiratory disease, and theophylline, which may increase the likelihood of development of AF, should be avoided.

1.1.8 Hyperthyroidism

Normalization of thyroid function should be prioritized, and AF should be treated with β-blockers to control heart rate. When β-blockers cannot be used, verapamil and diltiazem should be administered. AF often terminates spontaneously (in about 70% of patients) after normalization of thyroid function.[68] Cardioversion is indicated for patients with a long history of AF who have not returned to sinus rhythm for at least 3 months after normalization of thyroid function.

1.1.9 WPW Syndrome

In patients with WPW syndrome and short anterograde refractory period of the accessory pathway, ventricular fibrillation may develop shortly after the development of AF. The incidence of AF in patients with WPW syndrome is believed to be 15~30%. Patients with a shortest RR interval during AF of ≤250 msec are at high risk of sudden death.[51] Catheter ablation of accessory pathways is the first-line treatment for patients with WPW syndrome and AF. Digitalis and non-dihydropyridine calcium channel blockers should be avoided,[51] since these drugs may speed conduction over the accessory pathway. Class I antiarrhythmic drugs without anticholinergic activity may be used.

1.1.10 Sick Sinus Syndrome

Treatment of bradycardia should in principle be prioritized in such patients, and pacemaker implantation should be performed if required. Treatment of AF as a manifestation of tachycardia may be performed using antiarrhythmic drugs after pacemaker implantation. Appropriate atrial pacing is expected to decrease the incidence of AF. The risk of embolism is high and anticoagulation is required.

1.1.11 AF in Elderly Patients

Aging is an independent major risk factor for embolism and anticoagulation is in principle required for elderly patients.

1.1.12 AF in Children

Although AF is rare in children, it may occur following surgery for congenital heart disease. Since excessive atrial overload is a major factor in inducing AF, management and treatment of primary diseases and cardiac function are necessary.

1.1.13 AF During Pregnancy

No drugs for the treatment of AF have been demonstrated to be safe during pregnancy. Pregnant women with AF complicated by heart failure should be treated to alleviate heart failure and control heart rate for AF. Pregnant women should not receive ACE inhibitors and ARBs for the treatment of heart failure. Although appropriate measures differ by the type of underlying diseases, delivery is generally possible without treatment to prevent recurrence of paroxysmal AF. Careful consideration is necessary for anticoagulation during pregnancy.

1.1.14 Lone AF

Lone AF[69] means AF without clinical or echocardiographic evidence of underlying diseases such as cardiac, pulmonary and thyroid disease and without hypertension, but there is no single definition of lone AF. Although the prognosis of lone AF is generally considered favorable, the risk of cerebrovas-

cular disorder increases especially in patients over 60 years of age.[70] It has been suggested that being up to 60 years of age should be added to the criteria for diagnosing lone AF.[51] Researchers have maintained that the term "lone AF" should not be used since underlying conditions contributing to the development of lone AF may be clarified in the future.[71] In the present revision, the term "lone AF" will not basically be used as a category of AF in the following sections on treatment strategies, and will be described as "AF with no clinically significant structural heart disease." Structural heart diseases include cardiac hypertrophy, cardiac dysfunction, and cardiac ischemia (See Section V.4 "Indications for and Methods of Sinus Rhythm Restoration and Prevention of AF Recurrence").

1.1.15 Renal and Hepatic Dysfunctions

As many antiarrhythmic drugs have a narrow safety margin, toxic symptoms often develop when renally excreted drugs are given to patients with renal dysfunction and elderly patients in whom renal excretion of these drugs is delayed, and when hepatically excreted drugs are given to patients with hepatic dysfunction in whom drug metabolism in the liver is delayed. In order to avoid such problems, patients with renal dysfunction and elderly patients should be treated with hepatically excreted drugs, and those with hepatic dysfunction with renal excreted drugs. Close observation is necessary to adjust the dose of antiarrhythmic drugs in patients with dysfunction in organs in which drugs are metabolized or excreted.

2. Indications for and Methods of Antithrombotic Therapy

This section was revised on the contents of the Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2008)[1], the Guidelines for Management of Anticoagulant and Antiplatelet Therapy in Cardiovascular Disease (JCS 2009),[72] and the Guidelines for Indication and Management of Pregnancy and Delivery in Women with Heart Disease (JCS 2010)[73] published by the Japanese Circulation Society, as well as guideline documents published in Western countries from 2006~2012,[51,74-77] and the results of relevant studies in and outside Japan.

2.1 Risk Assessment for Cerebral Infarction and Antithrombotic Therapy in Patients With AF

Class I

- Anticoagulation therapy based on risk assessment for cerebral infarction and bleeding is recommended. (**Level of Evidence: A**)
- NOACs should be considered, whenever indicated, as the first line therapy in patients with a $CHADS_2$ score of ≥2. (**Level of Evidence: A**)
- Anticoagulation therapy with dabigatran (**Level of Evidence: B**), rivaroxaban (**Level of Evidence: A**), apixaban (**Level of Evidence: A**), edoxaban*1 (**Level of Evidence: A**), or warfarin (**Level of Evidence: A**) should be performed in high-risk patients with a $CHADS_2$ score of ≥2.
- Anticoagulation therapy with dabigatran (**Level of Evidence: B**) or apixaban (**Level of Evidence: A**) should be performed in intermediate-risk patients with a $CHADS_2$ score of 1.
- During warfarin therapy, a PT-INR of 2.0~3.0 should be maintained. (**Level of Evidence: A**)
- During warfarin therapy in patients aged ≥70 years with non-valvular AF, a PT-INR of 1.6~2.6 should be maintained. (**Level of Evidence: B**)
- The dose of NOACs should be adjusted in patients with moderate renal dysfunction. (**Level of Evidence: A**)
- The PT-INR should be monitored periodically during warfarin therapy. (**Level of Evidence: A**)

Class IIa

- Anticoagulation therapy with rivaroxaban, edoxaban*1 or warfarin should be considered for intermediate-risk patients with a $CHADS_2$ score of 1. (**Level of evidence: B**)
- Anticoagulation therapy should be considered for patients with cardiomyopathy, those aged 65~74 years, or those at a risk of cardiovascular disease (e.g., prior myocardial infarction, aortic plaque, and peripheral arterial disease). (**Level of Evidence: B**)
- A regular review of the necessity to continue anticoagulation therapy should be considered. (**Level of Evidence: A**)
- Anticoagulation therapy according to the guidelines for AF should be considered for patients with atrial flutter. (**Level of Evidence: B**)

Class IIb

- A combination of antiplatelet and anticoagulant drugs may be considered for patients with coronary artery disease who undergo percutaneous coronary intervention (PCI) or surgical revascularization. (**Level of Evidence: C**)
- Antithrombotic therapy may be considered for patients with lone AF*2 aged <60 years. (**Level of Evidence: C**)
- Adding antiplatelet drugs or increasing the target PT-INR to 2.5~3.5 may be considered for patients who develop ischemic stroke or systemic embolism during anticoagulation therapy at PT-INR 2.0~3.0. (**Level of Evidence: C**)
- Antiplatelet drugs may be considered for patients who cannot use oral anticoagulants. (**Level of Evidence: C**)

Class III

- Dabigatran should not be administered to patients using mechanical heart valves. (**Level of Evidence: B**)

*1: Not covered by the NHI in Japan as of December 2013.
*2: Defined as AF with no clinically significant structural heart disease (cardiac hypertrophy, cardiac dysfunction, or cardiac ischemia) (See Section V.1.1.14 "Lone AF" for detail).

2.1.1 Risk Assessment for the Development of Cerebral Infarction

It is recommended that appropriate antithrombotic therapy be performed on the basis of assessment of risk of cerebral infarction in patients with non-valvular AF (Figure 1). Patients with "valvular" AF are defined as AF patients with rheumatic mitral valve disease (mainly stenosis), and those after prosthetic valve replacement (using mechanical or bioprosthetic valves),[72] while patients with non-valvular AF include those following mitral valve plasty and those with non-rheumatic mitral regurgitation. As lone AF is defined differently by different researchers,[51] the present guideline use "AF with no clinically significant structural heart disease" to describe lone AF. Structural heart disease includes cardiac hypertrophy, cardiac dysfunction, and cardiac ischemia. Based on the finding that the incidence of cerebral infarction is high in patients with multiple risk factors, use of the $CHADS_2$ score (0~6 points) has been proposed (Table 1).[78] This straightforward and useful score should be used first to assess the risk of cerebral infarction in patients with AF. Higher $CHADS_2$ scores represent higher risk of the development of cerebral infarction,

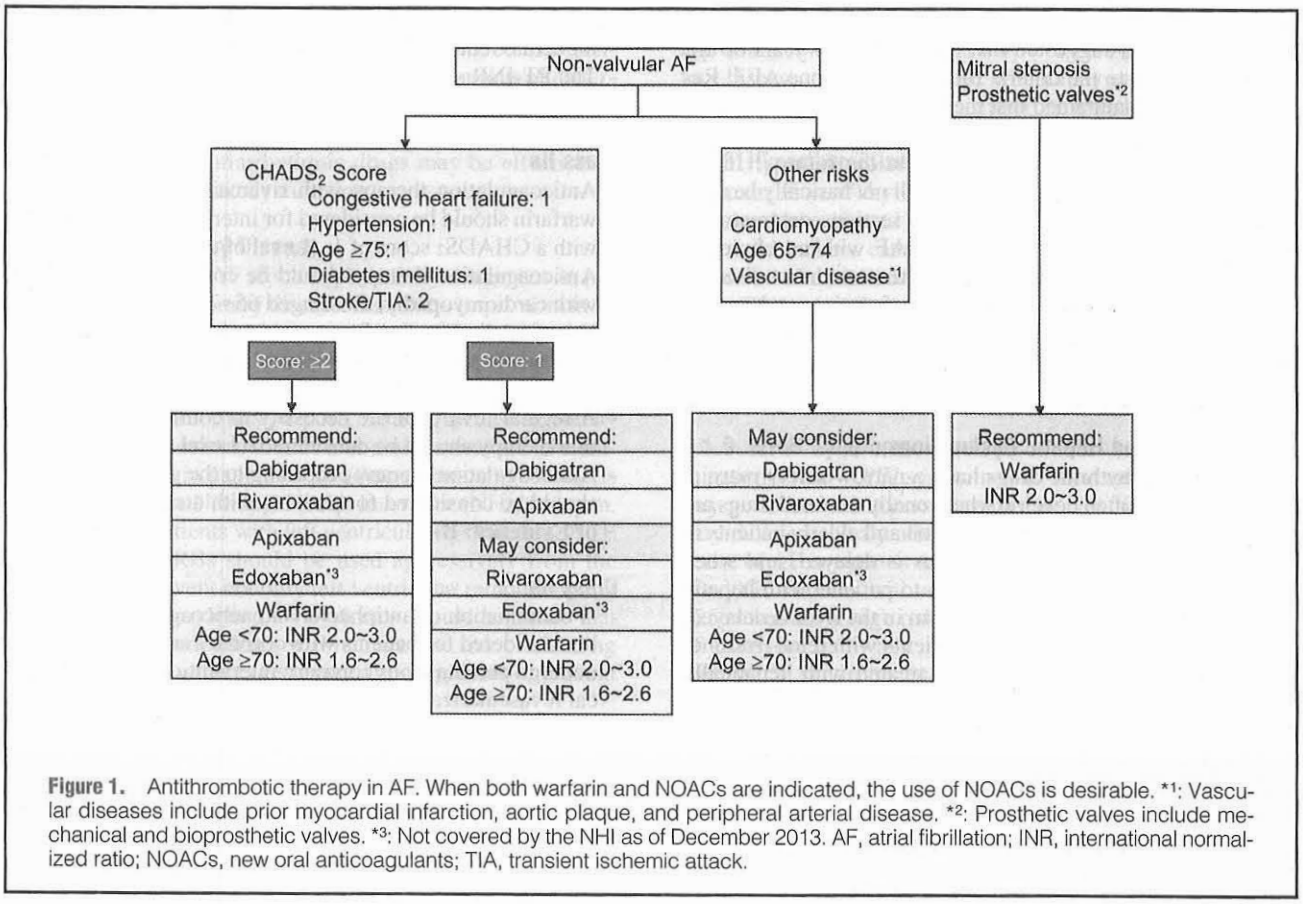

Figure 1. Antithrombotic therapy in AF. When both warfarin and NOACs are indicated, the use of NOACs is desirable. *1: Vascular diseases include prior myocardial infarction, aortic plaque, and peripheral arterial disease. *2: Prosthetic valves include mechanical and bioprosthetic valves. *3: Not covered by the NHI as of December 2013. AF, atrial fibrillation; INR, international normalized ratio; NOACs, new oral anticoagulants; TIA, transient ischemic attack.

Table 1. $CHADS_2$ Score

	Risk factors	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A	Age ≥75y	1
D	Diabetes mellitus	1
S_2	Stroke/TIA	2
	Total	0~6

LV, left ventricular; TIA, transient ischemic attack.
Source: Gage BF, et al. *JAMA* 2001; **285:** 2864–2870,[78] with modification.

and the annual incidence of cerebral infarction is ≥4% among patients with a $CHADS_2$ score of ≥2. Warfarin therapy is thus recommended for patients with a $CHADS_2$ score of ≥2. Warfarin therapy may be considered for patients with a $CHADS_2$ score of 1, but it is unclear whether the effect of warfarin therapy in the prevention of cerebral infarction outweighs the risk of bleeding complication. NOACs (e.g., dabigatran, rivaroxaban and apixaban) are recommended for patients with a $CHADS_2$ score of ≥2 as in the case of warfarin since phase III clinical studies have demonstrated that NOACs are similar or superior to warfarin in terms of the prevention of cerebral infarction; that the incidence of major bleeding events was not higher in patients receiving NOACs than in those receiving warfarin; and the incidence of intracranial hemorrhage was substantially lower in patients receiving NOACs.[79–82] Patients who have no renal dysfunction and are indicated for anticoagulation should be treated with NOACs rather than warfarin. On the basis of sub-analyses of phase III studies, the present guidelines recommend dabigatran and apixaban as drugs that are recommended for patients with a $CHADS_2$ score of 1.[83,84] Rivaroxaban and edoxaban are described as drugs that may be considered for this patient population as phase III studies of these drugs did not include patients with a $CHADS_2$ score of 1.

Risk factors for cerebral infarction that are not incorporated into the $CHADS_2$ score include cardiomyopathy,[85,86] advanced age (65~74 years),[87] prior myocardial infarction, aortic plaque, and vascular diseases including peripheral arterial disease.[75,87,88] Since the benefits of anticoagulation has not been fully evaluated in patients with these risk factors, the present guidelines describe that anticoagulation may be considered for these patients. Although "female" was listed as a risk factor for cerebral infarction in the previous revision of this guideline document, being female is not an independent risk factor in patients aged <65 years with no significant structural heart disease,[89,90] and anticoagulation may be considered for patients aged 65~74 years regardless of sex. In the present revision, female is not listed as a risk factor. Thyroid disease is not described as a risk factor because this has not been fully investigated as a risk factor for cerebral infarction.

Patients with paroxysmal AF should receive anticoagulation as recommended for those with persistent or permanent AF.[91]

Patients with mitral stenosis and patients using mechanical or bioprosthetic heart valves are at a high risk of embolism, and are recommended to undergo warfarin therapy with a tar-

get PT-INR of 2.0~3.0.[72] At the time of writing, NOACs are not indicated for patients with valvular AF. In the RE-ALIGN (Randomized, phase II study to Evaluate the sAfety and pharmacokinetics of oraL dabIGatran etexilate in patients after heart valve replacemeNt)[92] in patients after mechanical valve replacement, dabigatran was inferior to warfarin in terms of efficacy and safety. No studies have reported the efficacy of NOACs in AF patients using bioprosthetic heart valves.

2.1.2 The $CHADS_2$ and CHA_2DS_2-VASc Scores

Patients with a $CHADS_2$ score of 0 or 1, in whom the efficacy of warfarin therapy has not been established, account for about 50% of patients with non-valvular AF.[89] Although the incidence of cerebral infarction in patients with a $CHADS_2$ score of ≤1 is lower than in those with a $CHADS_2$ score of ≥2, the number of patients developing cerebral infarction is substantially large as this patient population is large in size. The $CHADS_2$ score is appropriate in identifying high-risk patients who need warfarin therapy, but cannot specify low-risk patients accurately.

The CHA_2DS_2-VASc score[75,92a] was developed in order to classify patients with a $CHADS_2$ score of ≤1 into those with relatively higher risk and those with very low risk of cerebral infarction. The CHA_2DS_2-VASc score (0~9 points) considers over 65 years of age, vascular disease such as prior myocardial infarction, and sex category as additional risk factors, and over 75 years of age as a higher risk factor (**Table 2**). Higher CHA_2DS_2-VASc scores mean higher risk of cerebral infarction. Physicians should be aware that being female does not increase the risk when they are under 65 years of age and have no significant structural heart disease.[74]

Patients with a CHA_2DS_2-VASc of 0 (low risk patients) should basically not receive anticoagulation as the incidence of embolic events is too low to justify the risk of intracranial hemorrhage associated with warfarin therapy. Anticoagulation therapy should be administered to patients with a CHA_2DS_2-VASc of ≥2, and may be considered for those with a CHA_2DS_2-VASc of 1.

Although the CHA_2DS_2-VASc score is accurate and especially useful in specifying patients with a low risk of cerebral infarction, it is rarely used by clinicians due to the complexity of assessment. Even the $CHADS_2$ score has not become popular in the clinical setting, but it has been used in sub-analyses of clinical trials of NOACs. Accordingly, the present guidelines mainly use the $CHADS_2$ score and consider other risk factors used in the CHA_2DS_2-VASc score to develop recommendations on antithrombotic therapy for patients with AF (**Figure 1**). Although the CHA_2DS_2-VASc score does not include cardiomyopathy, several studies[85,86] in Japan have reported the disease as a risk factor for cerebral infarction. The present guidelines include cardiomyopathy as a risk factor that should be considered in addition to the $CHADS_2$ score.

Table 2. CHA_2DS_2-VASc Score

	Risk factors	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75y	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE	2
V	Vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque)	1
A	Age 65~74y	1
Sc	Sex category (i.e., female gender)	1
	Total	0~9*

Note: Maximum score is 9 since age may contribute 0, 1, or 2 points.
LV, left ventricular; TE, thromboembolisim; TIA, transient ischemic attack.
Adapted from Lip GY, et al. *Chest* 2010; **137:** 263–272,[92a] with permission from American College of Chest Physicians.

2.2 Assessment of the Risk of Bleeding During Anticoagulation and Measures to Be Taken

2.2.1 The HAS-BLED Score

In the HAS-BLED score (0~9 points, **Table 3**),[93] patients with

Table 3. HAS-BLED Score

Letter	Clinical characteristic	Point awarded
H	Hypertension*1	1
A	Abnormal renal and liver function (1 point each)*2	2
S	Stroke	1
B	Bleeding*3	1
L	Labile INRs*4	1
E	Elderly (i.e., age >65 y)	1
D	Drugs or alcohol (1 point each)*5	2
	Total	Maximum 9 points

*1: Hypertension is defined as systolic blood pressure >160 mmHg.
*2: Abnormal renal function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L (2.26 mg/dL).
Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2×upper limit of normal, in association with AST/ALT/ALP >3×upper limit normal).
*3: Bleeding refers to previous bleeding history and/or predisposition to bleeding (e.g., bleeding diathesis, anemia).
*4: Labile INRs refers to unstable/high INRs or poor time in therapeutic range (i.e., <60%).
*5: Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.
Adapted from Pisters R, et al. *Chest* 2010; **138:** 1093–1100,[93] with permission from American College of Chest Physicians.

a score of 0 are considered to have low risk of bleeding (annual incidence of major bleeding: 1%), those with a score of 1~2 have intermediate risk (2~4%), and those with a score of ≥3 have high risk (4~6%). Patients with higher risk of bleeding need careful risk management.

2.2.2 Major Risk Factors for Bleeding

Over 75 years of age, low body weight (≤50 kg), renal dysfunction (creatinine clearance ≤50 mL/min), and use of antiplatelet drugs have been pointed out as major risk factors for bleeding during anticoagulation.[82,94]

2.2.3 Factors Related to Intracranial Hemorrhage

Studies have pointed out hypertension, smoking, excessive alcohol consumption, East Asian ethnicity, hypocholesterolemia, hepatitis/cirrhosis, advanced age, prior cerebral infarction, cerebral microbleeds on MRI as factors related to the development of intracranial hemorrhage; and hypertension, prior cerebral infarction, hepatitis/cirrhosis, hyperglycemia, and antithrombotic therapy as predisposing factors to enlargement of intracerebral hematoma.[95-98] In a sub-analysis of the RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) trial, age, previous stroke/transient ischemic attack (TIA), aspirin use, warfarin therapy, and non-white race were pointed out as risk factors for intracranial hemorrhage.[99]

In order to prevent the development of intracranial hemorrhage, patients should receive NOACs with a low risk of inducing intracranial hemorrhage, adequately control blood pressure and glucose level, refrain from smoking and excessive alcohol intake, and avoid antiplatelet drugs whenever possible.[100,101]

2.3 Dose Adjustment and Management of Warfarin Therapy

Warfarin therapy is recommended with a target PT-INR range of 2.0~3.0. The target PT-INR range should be 1.6~2.6 for patients aged ≥70 years.[102] PT-INR should be monitored carefully during the induction phase of warfarin therapy, and then periodically during the maintenance phase to ensure maintaining the therapeutic range of anticoagulation. In order to obtain maximum benefit from warfarin therapy, the time in therapeutic range,[103] the percentage of time in which the PT-INR remained within the target range, should be kept above 60%.

2.4 Positioning of Antiplatelet Drugs

As antiplatelet drugs cannot prevent large infarction in patients with paroxysmal AF and those with persistent AF, and are expected to prevent only lacunar infarction and minor infarction associated with atherothrombotic infarction, they are not recommended as the first-line therapy for patients with AF.[104] Antiplatelet therapy should be considered only when anticoagulation cannot be used.

2.5 Antithrombotic Therapy During Cardioversion

Class I

- For patients with AF lasting ≥48 hours or of unknown duration, warfarin therapy (PT-INR 2.0~3.0 for patients aged <70 years, or 1.6~2.6 for patients aged ≥70 years) is recommended for 3 weeks before and 4 weeks after cardioversion (**Level of Evidence: B**). Cardioversion may be performed either electrically or pharmacologically.
- For patients with AF lasting ≥48 hours accompanied by hemodynamic instability who require immediate cardioversion, intravenous heparin is recommended (following an initial intravenous bolus injection, continuous infusion is performed at a dose adjusted to prolong the activated partial thromboplastin time [APTT] to 1.5~2 times the reference control value) (**Level of Evidence: C**): Following cardioversion, warfarin (PT-INR 2.0~3.0 for patients aged <70 years, or 1.6~2.6 for patients aged ≥70 years) should be administered for at least 4 weeks in the same fashion as patients undergoing elective cardioversion.
- For patients with AF lasting <48 hours accompanied by hemodynamic instability resulting in angina attack, acute myocardial infarction, shock, pulmonary edema, or other conditions, immediate cardioversion is recommended without waiting for prior anticoagulation. (**Level of Evidence: C**)

Class IIa

- For patients with AF lasting <48 hours, anticoagulation therapy before and after cardioversion should be considered according to the assessment of risk of thromboembolism. (**Level of Evidence: C**)
- Screening for the presence of thrombus in the left atrial appendage and left atrium by transesophageal echocardiography (TEE) should be considered before cardioversion. (**Level of Evidence: B**)
- In patients with no thrombus detected: Prompt cardioversion under intravenous heparin (following an initial intravenous bolus injection, continuous infusion is performed at a dose adjusted to prolong the APTT to 1.5~2 times the reference control value) (**Level of Evidence: B**). Administer warfarin for at least 4 weeks after cardioversion according to the recommendation for patients undergoing elective cardioversion (PT-INR 2.0~3.0 for patients aged <70 years, or 1.6~2.6 for patients aged ≥70 years). (**Level of Evidence: C**)
- In patients in whom thrombus is detected: Administer warfarin (PT-INR 2.0~3.0 for patients aged <70 years, or 1.6~2.6 for patients aged ≥70 years) for at least 3 weeks before cardioversion and at least 4 weeks after recovery to sinus rhythm (**Level of Evidence: C**). Warfarin therapy may be continued for a long period of time even in patients who appear to maintain sinus rhythm, depending on assessment of risk of thromboembolism.
- For patients with AF lasting ≥48 hours or of unknown duration, anticoagulation therapy with dabigatran for 3 weeks before and 4 weeks after cardioversion should be considered (**Level of evidence: C**). Cardioversion may be performed either electrically or pharmacologically.
- Anticoagulation should be considered for patients with atrial flutter to prepare for cardioversion to sinus rhythm in the same fashion as patients with AF. (**Level of Evidence: C**)

Class IIb

- None.

Class III

- None.

Case-control studies on the risk of thromboembolism associated with cardioversion have reported that the incidence rates of thromboembolic events after cardioversion were 1~5%,[105,106] and the risk may be decreased by warfarin therapy (target PT-INR 2.0~3.0) for 3 weeks before and 4 weeks after cardioversion.[107,108] In the clinical setting, this measure is given to patients with AF lasting ≥48 hours or of unknown duration. Left atrial thrombus or embolism may develop in patients with AF not lasting for 48 hours, but the necessity of antithrombotic therapy in this patient population is unclear. Prior to cardioversion, warfarin therapy should be given to maintain anticoagulation in the therapeutic range for 3 weeks, and thus should

be initiated early enough. As NOACs exert their anticoagulation effects from the first day of treatment on, patients may take NOACs for 3 weeks before cardioversion to ensure appropriate anticoagulation. Patients with AF lasting for ≥48 hours may undergo TEE to determine further treatment strategies. Specifically, patients with no thrombus detected by TEE may undergo prompt cardioversion under intravenous heparin and then receive warfarin therapy for 4 weeks. Patients with thrombus detected by TEE may receive warfarin for 3 weeks before another TEE, and those without thrombus undergo cardioversion and receive warfarin for 4 weeks.[109]

2.6 Treatment During Tooth Extraction and Surgery

Class I

- None.

Class IIa

- Warfarin therapy should be considered to maintain PT-INR within the optimal therapeutic range during tooth extraction (**Level of Evidence: A**) or cataract surgery. (**Level of Evidence: C**)
- Antiplatelet therapy should be considered to continue during tooth extraction (**Level of Evidence: A**) or cataract surgery. (**Level of Evidence: C**)

Class IIa'

- Continuation of NOACs during tooth extraction or cataract surgery should be considered. (**Level of Evidence: C**)
- Continuation of anticoagulants or antiplatelets during gastrointestinal endoscopic procedure should be considered. (**Level of Evidence: C**)
- In patients who are receiving a single antithrombotic drug and undergo gastrointestinal endoscopic procedure with a low risk of bleeding, continuation of the antithrombotic therapy during the procedure should be considered. In patients receiving warfarin, ensure that warfarin therapy is maintained within the optimal therapeutic range before endoscopy. (**Level of Evidence: C**)
- In patients who are receiving a single antithrombotic drug and undergo gastrointestinal endoscopic procedure with a high risk of bleeding, physicians should consider continuing aspirin or suspending it for 3~5 days; replacing thienopyridines by aspirin or cilostazol and then following the recommendations for these drugs or suspending them for 5~7 days; suspending antiplatelet drugs other than aspirin and thienopyridines for 1 day; and replacing warfarin or NOACs by heparin. (**Level of Evidence: C**)
- In patients who are receiving multiple antithrombotic drugs and undergo gastrointestinal endoscopic procedure, physicians should consider continuing aspirin or replacing it by cilostazol; replacing thienopyridines by aspirin or cilostazol or suspending them for 5~7 days; suspending antiplatelet drugs other than thienopyridines for 1 day or replacing them by cilostazol (**Level of Evidence: C**); and replacing warfarin and NOACs by heparin. (**Level of Evidence: C**)
- For patients for whom postoperative bleeding can readily be treated, continuation of anticoagulants or antiplatelets during minor body surface surgery (including pacemaker implantation) should be considered. (**Level of Evidence: C**)
- For patients undergoing minor body surface surgery for whom bleeding complications cannot be readily treated, treatment in the same fashion as patients undergoing major surgery should be considered. (**Level of Evidence: C**)
- Prior to major surgery, physicians should consider discontinuing warfarin for 3~5 days, dabigatran for 24 hours ~ 4 days, rivaroxaban for ≥24 hours, apixaban for 24~48 hours, and replacing them by heparin. (**Level of Evidence: C**)
- Prior to major surgery, physicians should consider discontinuing aspirin, ticlopidine and clopidogrel for 7~14 days, and cilostazol for 3 days (**Level of Evidence: C**). Following discontinuation, avoidance of dehydration, fluid therapy, and heparin therapy should be considered for patients at high risk of thromboembolism. (**Level of Evidence: C**)
- For patients undergoing urgent surgery, treatment in the same fashion as patients with bleeding complications should be considered. (**Level of Evidence: C**)

Class III

- Oral antithrombotic therapy should not be discontinued (**Level of Evidence: B**). When antithrombotic therapy must be discontinued, consider alternative treatments such as heparin therapy, avoidance of dehydration, and fluid therapy. (**Level of Evidence: C**)

Physicians should not discontinue antithrombotic therapy during tooth extraction[110] or cataract surgery[111] without careful consideration, and should be aware that the Japan Gastroenterological Endoscopy Society has recommended that single-agent antithrombotic therapy should not be discontinued during endoscopic biopsy in the recently revised guidelines of gastrointestinal endoscopy for patients receiving antithrombotic therapy.[112] When antithrombotic therapy must be discontinued, physicians should consider heparin therapy and obtain informed consent from the patient. When antithrombotic therapy is replaced by heparin, heparin should be administered intravenously or subcutaneously at a dose of about 10,000~25,000 U/day. In high-risk patients, the dose of heparin should be adjusted to prolong the APTT to 1.5~2.5 times the reference control value. Heparin should be discontinued 4~6 hours before surgery or be neutralized with protamine just before surgery. In either case, APTT should be confirmed just before surgery. After surgery, heparin therapy should be resumed as soon as possible, and warfarin therapy should be restarted when patient condition is stable. Heparin therapy should be discontinued when PT-INR reaches the therapeutic range.

2.7 Treatment of Bleeding Complications

Class I

- Conventional emergency treatment is recommended. (**Level of Evidence: C**)
- The warfarin dosage should be reduced or warfarin should be discontinued depending on the severity of the bleeding complication (moderate or severe) occurring during warfarin therapy and vitamin K should be administered whenever necessary. (**Level of Evidence: C**)
- Heparin dosage should be reduced, or heparin should be discontinued and neutralized with protamine, depending on the severity of bleeding complications occurring during heparin therapy. (**Level of Evidence: C**)

Class IIa

- Treatment with fresh frozen plasma or freeze-dried human blood coagulation factor IX complex should be considered for patients who require prompt control of the effects of warfarin (**Level of Evidence: C**). Although the control effect of freeze-dried human blood coagulation factor IX complex is much stronger, the use of it in this case is not covered by the NHI in Japan.
- After controlling the effect of warfarin, treatment with freeze-dried human blood coagulation factor IX complex (not cov-

ered by the NHI) and vitamin K should be considered to prevent recurrence of increase in PT-INR controlled by freeze-dried human blood coagulation factor IX complex. (**Level of Evidence: C**)
- Discontinuation of NOACs should be considered depending on the severity of bleeding complications occurring during treatment with NOACs, and conduct appropriate fluid therapy to promote diuresis and urinary excretion of the drugs. (**Level of Evidence: C**)

Class IIb
- Treatment with recombinant coagulation factor VII (not covered by the NHI) may be considered for patients who require prompt inhibition of the effects of warfarin. (**Level of Evidence: C**)
- Treatment with freeze-dried human blood coagulation factor IX complex (not covered by the NHI), recombinant coagulation factor VII (not covered by the NHI) or fresh frozen plasma should be considered for patients who require prompt inhibition of the effects of NOACs. (**Level of Evidence: C**)
- Dialysis therapy should be considered for patients receiving dabigatran. (**Level of Evidence: C**)
- Gastric lavage and treatment with activated charcoal immediately after taking NOACs should be considered. (**Level of Evidence: C**)

Class III
- None.

For patients with minor bleeding, physicians should not discontinue antithrombotic therapy easily and should consider continuing appropriate antithrombotic therapy. Although the treatment of bleeding during treatment with NOACs has not been established, the above-listed measures are considered effective.

2.8 Pregnancy and Childbirth

Class I
- None.

Class IIa
- None.

Class IIa'
- Physicians should consider avoiding warfarin therapy and replacing it with subcutaneous heparin during the first 13 weeks of pregnancy. (**Level of Evidence: C**)
- Physicians should consider administering warfarin during weeks 14~33 of pregnancy. (**Level of Evidence: C**)
- Physicians should consider reducing warfarin dose and administering intravenous heparin in hospital to prevent the development of intracranial hemorrhage in the fetus during weeks 34~36 of pregnancy or later. (**Level of Evidence: C**)
- Physicians should consider early delivery after discontinuation of heparin therapy and early restarting intravenous infusion of heparin to prevent the development of thrombi in the mother due to enhancement of coagulation in weeks 34~36 of pregnancy or later. (**Level of Evidence: C**)

Class III
- Women should avoid pregnancy and childbirth during anticoagulation therapy. (**Level of Evidence: C**)

It is most important that women of childbearing age who are undergoing antithrombotic therapy receive an explanation in detail, preferably before pregnancy and childbirth, of the facts that mothers are at risk of thromboembolism even when their cardiac function and general body function are good under appropriate antithrombotic therapy, that oral warfarin may be teratogenic and may cause intracranial hemorrhage in fetuses, and that optimal management of antithrombotic therapy during pregnancy and childbirth has not been established.[73] No clinical trials of NOACs such as dabigatran and rivaroxaban have been conducted in pregnant women and lactating mothers, and the safety of these drugs during pregnancy and lactation has not been established. In animal studies, NOACs were excreted into the milk.

2.9 NOACs

In Japan, dabigatran, an oral direct thrombin inhibitor, and rivaroxaban and apixaban, oral direct FXa inhibitors have been approved by the Ministry of Health, Labour and Welfare (MHLW), and are available in the clinical setting. The efficacy of edoxaban was investigated in the ENGAGE AF-TIMI 48 (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48), an international double-blind study versus warfarin, and the results have been published.[113] Edoxaban has been approved in Japan for the prevention of deep vein thrombosis and pulmonary thromboembolism in patients after hip joint or knee joint surgery. NOACs are superior to warfarin because NOACs do not require periodical blood sampling for efficacy monitoring, may be administered at the same dose to different patients, are far less likely to induce intracranial hemorrhage, are not affected by meals, and do not interact with other drugs. As NOACs exert their effects rapidly and the half-lives are generally short, the drugs may not be replaced by heparin before surgery in many patients. Even if heparin therapy is needed before surgery, it may be initiated immediately before surgery. The demerits are that NOACs cannot be administered to patients with severe renal dysfunction; efficacy decreases rapidly due to their short half-lives when doses are skipped; treatment measures for major bleeding due to NOACs have not been established; and patients may have to pay more health care fees when using NOACs. Readers should be alert for new information about these drugs as new findings are being uncovered one after another.

3. Indications for and Methods of Heart Rate Control

Class I
- β-blockers (e.g., metoprolol, bisoprolol, and propranolol) or non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) are recommended for patients with persistent or permanent AF in the absence of an accessory pathway. (**Level of Evidence: B**)
- Digoxin, amiodarone (oral or intravenous*), landiolol, carvedilol, or bisoprolol for the treatment of AF in the absence of an accessory pathway are recommended for patients with heart failure. (**Level of Evidence: B**)
- Oral digoxin is recommended for patients with heart failure or long-term bedridden patients. (**Level of Evidence: C**)

Class IIa
- Digoxin with either β-blockers or non-dihydropyridine calcium channel blockers should be considered to control heart rate at rest and during exercise. (**Level of Evidence: B**)
- Ablation of the atrioventricular (AV) node or accessory path-

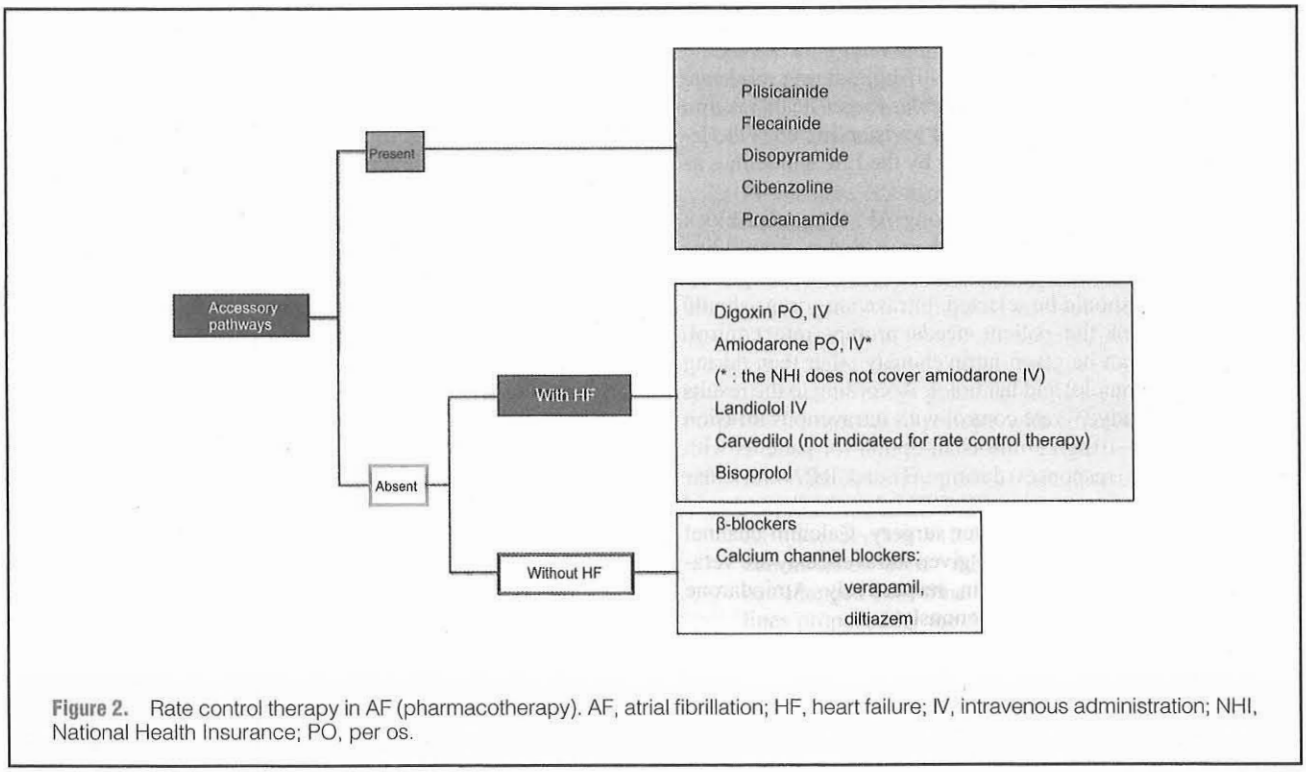

Figure 2. Rate control therapy in AF (pharmacotherapy). AF, atrial fibrillation; HF, heart failure; IV, intravenous administration; NHI, National Health Insurance; PO, per os.

way should be considered for patients with AF in whom heart rate cannot be controlled sufficiently with pharmacotherapy or those who cannot receive it due to ADRs. (**Level of Evidence: B**)
- Intravenous amiodarone should be considered for patients who did not respond to other treatment or are contraindicated for other treatment. (**Level of Evidence: B**)
- Intravenous administration of Class Ia (procainamide, cibenzoline, or disopyramide) or Class Ic (pilsicainide or flecainide) antiarrhythmic drugs should be considered for patients who have an accessory pathway but do not require electrical cardioversion. (**Level of Evidence: C**)
- Physicians should consider starting rate control therapy with a lenient target (resting heart rate <110 bpm) and then setting a more strict goal (heart rate at rest <80bpm, and during modest exercise <110bpm) when the patient shows no improvement in symptoms and cardiac function. (**Level of Evidence: A**)

Class IIb

- Oral amiodarone may be considered for patients in whom digoxin, β-blockers, and non-dihydropyridine calcium channel blockers alone or in combination with other drugs cannot effectively control heart rate at rest and during exercise. (**Level of Evidence: C**)
- Ablation of the AV node may be considered for patients in whom pharmacotherapy cannot control heart rate and those who are suspected to have tachycardia-induced cardiomyopathy. (**Level of Evidence: C**)

Class III

- Digitalis is not effective in controlling heart rate during the acute stage of paroxysmal AF. (**Level of Evidence: B**)
- AV node ablation for rate control should not be performed before trying pharmacotherapy. (**Level of Evidence: C**)
- Patients with uncompensated heart failure should not be treated with intravenous non-dihydropyridine calcium channel blockers, which may worsen hemodynamics. (**Level of Evidence: C**)
- Patients with accessory pathways should not be treated with intravenous digitalis or non-dihydropyridine calcium channel blockers. (**Level of Evidence: C**)

* The use of intravenous amiodarone is not covered by the NHI in Japan.

Persistent elevation of heart rate above 130 bpm during AF may induce congestive heart failure even in patients without structural heart disease. In order to prevent the development of congestive heart failure, it is important to control the heart rate during AF to ≤130 bpm.[114] In the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II) study, the incidence rates of symptoms and adverse events and the severity of heart failure did not differ between patients receiving lenient rate control with a target resting heart rate of <110 bpm and those receiving strict rate control with a target resting heart rate of <80 bpm and a target heart rate of <110 bpm during moderate exercise.[115] However, this finding does not mean that a target resting heart rate of 100~109 bpm is sufficient. Heart rate should be decreased to the level where symptoms are alleviated.

The guidelines for the management of atrial fibrillation proposed by the European Society of Cardiology (ESC)[75] in 2010 recommend the above-mentioned lenient rate control protocol aimed at a resting heart rate of <110 bpm as a **Class IIa** recommendation, while the guidelines for the management of patients with atrial fibrillation proposed by the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the Heart Rhythm Society (HRS)[116]

describe that "Criteria for rate control vary with patient age but usually involve achieving ventricular rates between 60 and 80 bpm at rest and between 90 and 115 bpm during moderate exercise" but do not indicate particular target heart rates in their recommendations. The present revision includes the lenient rate control protocol proposed by the ESC guidelines as a **Class IIa** recommendation.

In order to control heart rate during AF, drugs that block AV nodal conduction such as β-blockers, non-dihydropyridine calcium channel blockers (verapamil and diltiazem), digitalis, and amiodarone should be selected. Intravenous drugs should be selected when the patient needs prompt rate control. β-blockers that can be given intravenously other than during surgery are propranolol and landiolol. According to the results of the J-Land Study,[117] rate control with intravenous infusion of landiolol at 1~10 μg/kg/min is an option for patients with rapid ventricular responses during AF and left ventricular dysfunction (ejection fraction 25~50%), but the dose should be lower than the dose used after surgery. Calcium channel blockers and digitalis that can be given intravenously are verapamil and diltiazem, and digoxin, respectively. Amiodarone may also be administered intravenously.

Oral β-blockers include metoprolol, bisoprolol,[118] atenolol, carteolol, propranolol, and carvedilol (physicians should refer to the prescribing information of each drug as some drugs are not indicated for particular conditions). Verapamil and diltiazem (calcium channel blockers), digoxin (a digitalis glycoside), and amiodarone may be given orally.

Drugs should be selected according to the presence/absence of accessory pathways and heart failure (Figure 2). AF patients who have accessory pathways, are hemodynamically stable, and do not require electrical cardioversion should be treated with intravenous Class Ia (procainamide, cibenzoline, and disopyramide) or Class Ic (pilsicainide and flecainide) antiarrhythmic drugs. AF patients who have no accessory pathways and have cardiac dysfunction should be treated with digitalis, carvedilol, bisoprolol or oral amiodarone. Amiodarone, bepridil, and sotalol may inhibit conduction in the AV node and decrease heart rate even if AF persists.[119]

As digitalis decreases resting heart rate but does not decrease heart rate during exercise, patients who require rate control during exercise should receive digitalis with β-blockers or calcium channel blockers, or receive β-blockers, calcium channel blockers or both instead of digitalis. It has been suggested that rate control with digoxin may increase mortality.[120] When sufficient rate control cannot be achieved with more than one drug or when sinus rhythm cannot be maintained with antiarrhythmic drugs or pulmonary vein isolation, rate control through catheter ablation of the AV node and pacemaker implantation may be considered.

Patients with atrial flutter should be treated in the same manner. However, care is needed when Class I antiarrhythmic drugs are used: when such drugs are administered, atrial rate is decreased, which may permit 1:1 AV conduction and increase ventricular rate.

4. Indications for and Methods of Sinus Rhythm Restoration and Prevention of AF Recurrence

4.1 Sinus Rhythm Restoration and Prevention of AF Recurrence

4.1.1 Sinus Rhythm Restoration (Cardioversion)

It is important to confirm the absence of atrial thrombi or ensure sufficient anticoagulation before performing cardioversion of AF. Treatment to minimize the risk of thromboembolism before performing cardioversion is required especially for patients with AF lasting ≥48 hours or of unknown duration, unless urgent cardioversion is necessary.

a. Electrical Cardioversion

Class I

- R-wave synchronized direct-current cardioversion is recommended for AF patients with life-threatening conditions such as prolonged myocardial ischemia, angina, symptomatic hypotension, and worsening heart failure, and patients in whom a rapid ventricular rate does not respond promptly to pharmacotherapy and hemodynamic collapse is present. (**Level of Evidence: C**)
- Prompt direct-current cardioversion is recommended for patients with AF involving preexcitation when rapid ventricular rate or hemodynamic instability is present. (**Level of Evidence: C**)
- Direct-current cardioversion for the treatment of AF is recommended for patients with structural heart disease when unacceptable symptoms are present and the presence of atrial thrombus has been ruled out. (**Level of Evidence: C**)

Class IIa

- Direct-current cardioversion should be considered to terminate AF refractory to antiarrhythmic drugs within 48 hours. (**Level of Evidence: C**)
- Direct-current cardioversion should be considered for patients with symptomatic AF lasting ≥48 hours or of unknown duration after the presence of atrial thrombus has been ruled out by TEE or after effective and adequate anticoagulation therapy for ≥3 weeks. (**Level of Evidence: C**)
- Repeat direct-current cardioversion should be considered for patients in whom AF recurs with unacceptable symptoms shortly after direct-current cardioversion. (**Level of Evidence: C**)
- Direct-current cardioversion should be considered for patients in whom AF persists after control of hyperthyroidism or in patients with new-onset AF after cardiac surgery in whom pharmacological cardioversion with antiarrhythmic drugs is ineffective or cannot be performed. (**Level of Evidence: C**)

Class IIb

- Elective direct-current cardioversion may be considered for patients with asymptomatic AF lasting <1 year without significant left atrial enlargement. (**Level of Evidence: C**)
- Repeat direct-current cardioversion may be considered for patients in whom AF recurs shortly after return to sinus rhythm even with prophylactic antiarrhythmic drugs and multiple direct-current cardioversions. (**Level of Evidence: C**)

Class III

- Direct-current cardioversion should not be performed in patients with digitalis intoxication or hypokalemia. (**Level of Evidence: C**)
- Direct-current cardioversion without support with pacing therapy should not be performed in patients in whom advanced AV block or sick sinus syndrome has been confirmed present. (**Level of Evidence: C**)
- Elective direct-current cardioversion should not be performed in patients with AF lasting ≥48 hours in whom anticoagulation therapy has not been performed and the presence of atrial thrombus has not been ruled out by TEE or other measures. (**Level of Evidence: C**)

In emergency patients with acute hemodynamic collapse, QRS-synchronized direct-current cardioversion with ≥100 J under general anesthesia is a prompt and effective method (Figure 3).

In addition to patients who require emergency electrical cardioversion, electrical cardioversion is selected when the patient prefers the procedure, when pharmacological cardioversion with antiarrhythmic drugs is difficult, or when electrical cardioversion is considered safer than pharmacological cardioversion. Antiarrhythmic drugs are not effective and may even exert a proarrhythmic effect in patients with AF associated with structural heart disease such as cardiac hypertrophy, cardiac dysfunction and cardiac ischemia. Electrical cardioversion is therefore recommended for patients with AF associated with structural heart disease as this method is safer and reliable, and may lead to prompt improvement of symptoms and hemodynamic condition in this patient population (Figure 3).

b. Pharmacological Cardioversion

Class I

- Sodium channel blockers[*1] are recommended for patients with paroxysmal AF lasting <48 hours with no clinically significant structural heart disease. (**Level of Evidence: A**)

Class IIa

- Potent sodium channel blockers[*1] should be considered for patients with AF lasting 48 hours ~ 7 days who are undergoing anticoagulation therapy or in whom the presence of atrial thrombus has been ruled out. (**Level of Evidence: C**)
- Bepridil should be considered for patients with AF lasting >7 days with normal cardiac function and a normal QT interval. (**Level of Evidence: B**)
- Single doses of pilsicainide, flecainide, propafenone, or cibenzoline should be considered for the treatment of symptomatic paroxysmal AF that developed outside hospitals in patients without sinus dysfunction, AV conduction disturbance, bundle branch block, Brugada syndrome, structural heart disease or a history of atrial flutter (physicians should confirm the efficacy and safety of single-dose treatment with these drugs before prescribing the drugs for the alleviation of symptomatic AF). (**Level of Evidence: B**)

Class IIb

- Addition of aprindine may be considered for patients with AF lasting >7 days who have not responded to bepridil. (**Level Evidence: C**)
- Bepridil may be considered for patients with persistent AF and cardiac dysfunction. (**Level of Evidence: C**)
- Amiodarone may be considered for patients with persistent AF associated with structural heart disease. (**Level of Evidence: B**)

Class III

- Potent sodium channel blockers[*1] should not be administered to patients with cardiac dysfunction. (**Level of Evidence: C**)
- Pharmacological cardioversion without support with pacing therapy should not be performed in patients in whom advanced AV block or sick sinus syndrome has been confirmed present. (**Level of Evidence: C**)
- Sodium channel blockers[*1] should not be administered to patients with AF and Brugada syndrome. (**Level of Evidence: C**)
- Bepridil should not be administered to patients with persistent AF and a long QT interval. (**Level of Evidence: C**)
- Pharmacological cardioversion should not be performed in patients with AF lasting ≥48 hours in whom anticoagulation therapy has not been performed and the presence of atrial thrombus has not been ruled out by TEE or other measures. (**Level of Evidence: C**)

[*1]: Pilsicainide, cibenzoline, propafenone, disopyramide, and flecainide.

As safety is prioritized, pharmacological cardioversion is usually tried to treat AF in patients without structural heart disease.[*2] The efficacy of pharmacological cardioversion is closely related to the persistency of AF. Special consideration should be made whether or not pharmacological cardioversion is appropriate for individual patients with structural heart disease.

[*2]: **AF Without Structural Heart Disease**
AF without structural heart disease is referred to as lone AF (See Section V.1.1.14 "Lone AF"). However, the definition of "lone" AF differs among specialists, and has changed over time. For example, in Western guidelines proposed by the AHA and the ESC, AF in hypertensive patients without left ventricular hypertrophy is handled similarly to lone AF in terms of recommendations other than that for the prevention of embolism. In this revision, we avoid using the term "lone", and describe as AF "with no clinically significant structural heart disease". Structural heart diseases include cardiac hypertrophy, cardiac dysfunction, and cardiac ischemia.

i. Paroxysmal AF

Although paroxysmal AF is defined as AF that terminates spontaneously, cardioversion may be tried in some patients with paroxysmal AF lasting <48 hours when symptoms are severe or when the risk of embolism during cardioversion of more persistent AF should be avoided. In patients with AF not associated with clinically significant structural heart disease, the shorter the duration of AF, the more effective are sodium channel blockers. Patients with AF lasting ≤7 days may receive sodium channel blockers for this purpose. Intravenous treatment is often selected to ensure prompt termination of AF, but in some cases physicians instruct patients to take oral antiarrhythmic drugs when AF occurs ("pill-in-the-pocket" therapy; See Section V.4.2 "Single-Dose Treatment with Antiarrhythmic Drugs [Pill-in-the-Pocket Approach[121]]").

Sodium channel blockers with slow kinetics are more potent and effective in terminating AF, and are thus selected as the first-line drug for AF without structural heart disease, as also recommended in Western guidelines (Figure 3).[51]

Among potent sodium channel blockers available in Japan, pilsicainide, cibenzoline, propafenone, disopyramide, and flecainide are used as the first-line drugs to terminate paroxysmal AF in patients with no clinically significant structural heart disease (Figure 3). However, careful monitoring is necessary during treatment as they may facilitate the progression of AF to atrial flutter with significant tachycardia by permitting 1:1 AV conduction,[122] worsen sinus node dysfunction, or may cause fatal arrhythmia in patients with Brugada syndrome by augmenting ST elevation.[123]

ii. Persistent AF

Rate control therapy is the treatment of choice for patients with persistent AF. A combination of cardioversion and sinus rhythm maintenance may be considered for patients in whom rate control therapy is difficult, those with persistent symp-

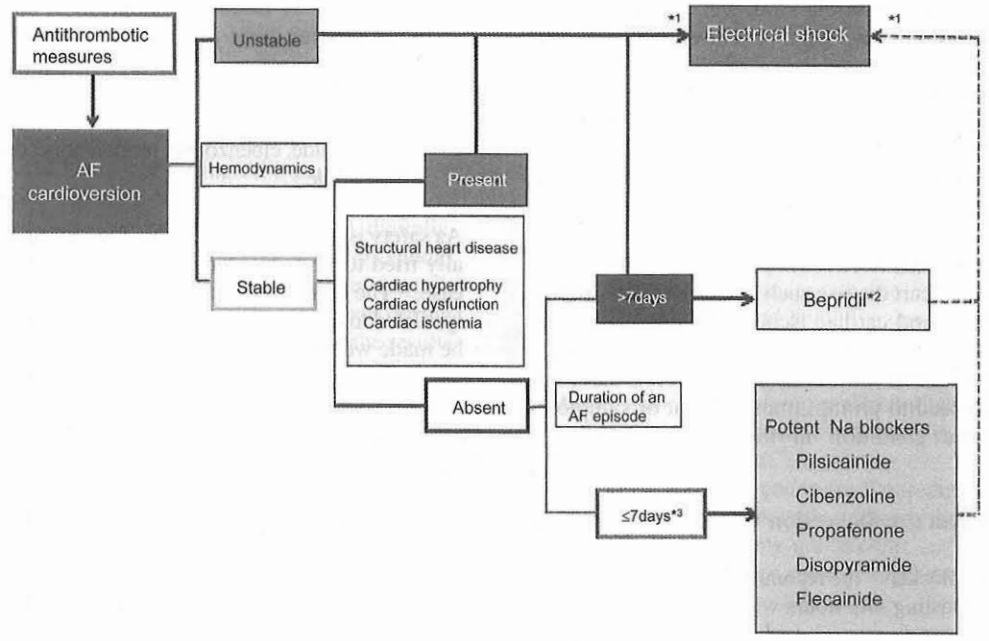

Figure 3. Cardioversion of AF. Dotted lines indicate the need for careful consideration. AF, atrial fibrillation; Na blockers, sodium channel blockers. *1: Amiodarone is a treatment option for the following conditions in foreign countries, but may not be covered by the National Health Insurance in Japan. (1) Pharmacological cardioversion in patients with structural heart disease. (2) Treatment to increase the success rate of electrical cardioversion and prevent AF recurrence after cardioversion. *2: Patients not responding to bepridil monotherapy may respond to a combination of bepridil with aprindine or other Class Ic antiarrhythmic drugs. Aprindine monotherapy may also be effective. *3: In order to ensure efficacy and prevent thromboembolic complications, the duration of an AF episode should be limited to ≤48 hours.

toms after rate control therapy, and those who require ablation before AF becomes permanent. Pharmacological cardioversion is inferior to electrical cardioversion in terms of success rate and time to return to sinus rhythm in patients with persistent AF, and antiarrhythmic drugs may exert a proarrhythmic effect. Physicians should carefully consider the conditions of individual patients to determine whether or not pharmacological cardioversion should be attempted.

Antiarrhythmic drugs that are effective in the acute phase of AF may not always be effective in the treatment of patients with AF lasting ≥7 days and advanced atrial remodeling. Amiodarone and bepridil may terminate persistent AF, and bepridil is indicated for this purpose in Japan. On the basis of the results of clinical trials[124] in Japan, the present guidelines recommend bepridil for pharmacological cardioversion of persistent AF without structural heart disease (Figure 3). However, physicians should carefully monitor QT interval as bepridil may exert a fatal proarrhythmic effect by prolonging QT interval to induce torsades de pointes.

4.1.2 Prevention of AF Recurrence

Class I

- Antiarrhythmic drugs are recommended for patients with highly symptomatic paroxysmal AF. (**Level of Evidence: A**)
- Sodium channel blockers* are recommended for the treatment of recurrent symptomatic AF in patients with no clinically significant structural heart disease. (**Level of Evidence: A**)
- Amiodarone is recommended for the treatment of AF in patients with cardiac dysfunction or hypertrophic cardiomyopathy. (**Level of Evidence: B**)

Class IIa

- Drugs that were effective in terminating persistent AF should be considered to prevent AF recurrence. (**Level of Evidence: C**)
- Amiodarone or sotalol should be considered to prevent AF recurrence in patients with structural heart disease (other than hypertrophic cardiomyopathy) without cardiac dysfunction. (**Level of Evidence: B**)

Class IIb

- Sodium channel blockers* may be considered for asymptomatic or mildly symptomatic patients with recurrent AF. (**Level of Evidence: C**)
- Potent sodium channel blockers* may be considered for patients with AF complicated with atrial flutter. (**Level of Evidence: C**)
- Antiarrhythmic drugs other than β-blockers may be considered to prevent AF recurrence in patients with new-onset AF, alcoholic AF or postoperative AF following cardiac surgery. (**Level of Evidence: C**)
- Oral amiodarone may be considered for the treatment of paroxysmal AF not responding to sodium channel blockers* in patients with no clinically significant structural heart diseases. (**Level of Evidence: B**)

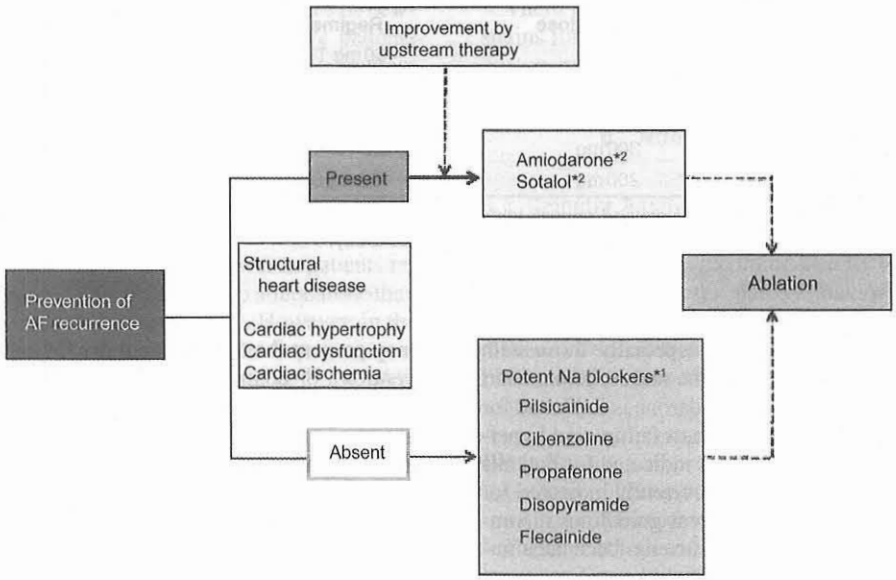

Figure 4. Prevention of AF recurrence. Dotted lines indicate the need for careful consideration. AF, atrial fibrillation; Na blockers, sodium channel blockers. *1: When cardioversion with bepridil was effective in terminating persistent AF, the patient may be treated with bepridil. Amiodarone and sotalol may be effective in preventing recurrent persistent AF after cardioversion. *2: In Japan, amiodarone is indicated only for the treatment of AF associated with hypertrophic cardiomyopathy or heart failure. Sotalol is effective in preventing AF recurrence associated with ischemic heart disease, but is not covered by the National Health Insurance in Japan. It has been reported that bepridil and aprindine are effective for patients with cardiac dysfunction.

Class III

- Antiarrhythmic drugs should not be administered to patients with bradycardia-tachycardia syndrome without pacemaker implantation. (**Level of Evidence: C**)
- Potent sodium channel blockers* should not be administered to patients with clinically significant structural heart disease. (**Level of Evidence: C**)
- Treatment with antiarrhythmic drugs should not be continued in patients who repeatedly have AF recurrence despite antiarrhythmic drug treatment, and does not show symptomatic improvement nor decrease in the duration of each AF episode. (**Level of Evidence: C**)
- Sodium channel blockers* should not be used for the treatment of AF associated with Brugada syndrome. (**Level of Evidence: C**)
- Potassium-channel blocking antiarrhythmic drugs should not be used for the treatment of AF associated with long QT syndrome. (**Level of Evidence: C**)

*: Pilsicainide, cibenzoline, propafenone, disopyramide, and flecainide.

Pharmacotherapy is typically initiated when the patient has frequent AF episodes. Catheter ablation should also be considered for patients with recurrent symptomatic AF not responding to pharmacotherapy.

a. AF Without Clinically Significant Structural Heart Disease

Drugs listed in Figure 4 should be used. The effect of these drugs in preventing AF recurrence may differ by the time of a day when AF episodes typically occur and the duration of each AF episode. As long-term maintenance therapy is often required to prevent AF recurrence, physicians should adjust the dose of each drug considering the age, renal function and hepatic function of the patient (Table 4). Careful consideration must be given whether or not the preventive treatment should be continued for a long period of time.

The efficacy of bepridil in preventing AF recurrence is considered limited.[125,126] In Europe and the United States, the efficacy of amiodarone has been fully established,[127] and the drug is widely used to prevent AF recurrence in patients with different types of underlying disease and also in patients with intractable AF without structural heart disease. In Japan, the use of sotalol for this purpose is not covered by the NHI, and amiodarone as a drug to prevent AF is indicated only for patients with hypertrophic cardiomyopathy and those with heart failure.

b. AF in Patients With Underlying Disease

As AF may cause severe symptoms and significantly affect hemodynamics in patients with cardiac hypertrophy, cardiac dysfunction, and cardiac ischemia, preventing AF recurrence is important. Antiarrhythmic drugs, especially sodium channel blockers are not fully effective in preventing AF recurrence, and may exert a proarrhythmic effect and negative inotropic action.

Patients with an underlying disease should undergo "upstream therapies" to control the underlying cause of AF. Patients with ischemic heart disease must first be treated to alleviate ischemia, while patients with cardiac hypertrophy and cardiac dysfunction should be considered for treatment with ACE inhibitors, ARBs and/or β-blockers.[63,128–131]

Only a few drugs are available for the treatment of AF in

Table 4. Drugs and Dosage Regimens for Patients Without Clinically Significant Structural Heart Disease

	Oral daily dose	Regimen	IV
Pilsicainide	150 mg	50 mg TID	1 mg/kg/10 min
Cibenzoline	300 mg	100 mg TID	1.4 mg/kg/2~5 min
Propafenone	450 mg	150 mg TID	–
Disopyramide	300 mg	150 mg BID* or 100 mg TID	1~2 mg/kg/5 min
Flecainide	200 mg	100 mg BID	1~2 mg/kg/10 min

*: When using Rythmodan® R (sustained-release tablets).
BID, twice a day; IV, intravenous administration; TID, three times a day.

patients with structural heart disease, especially those with cardiac hypertrophy, cardiac dysfunction, and ischemic heart disease in Japan. Specifically, oral amiodarone is indicated for the prevention of AF in patients with heart failure and hypertrophic cardiomyopathy, and bepridil is indicated for patients with persistent AF. No other drugs are currently indicated for AF in this patient population. The present guidelines recommend amiodarone of which ample evidence has been accumulated (Figure 4). However, amiodarone is known to cause serious pulmonary complications and other extracardiac ADRs in the liver, thyroid, eyes, and skin among other organs, and physicians should monitor their patients carefully for a long period of time. As amiodarone may interact with other drugs, and may potentiate the effects of digitalis, warfarin and NOACs during management of AF, careful monitoring is important.

Although evidence for sotalol and bepridil is less abundant than amiodarone, they are expected to be effective as these drugs block potassium channels. Both drugs may slow heart rate and prolong the QT interval further in patients with a long QT interval, and physicians should carefully monitor their patients during treatment for the development of torsades de pointes.

4.2 Single-Dose Treatment With Antiarrhythmic Drugs (Pill-in-the-Pocket Approach)

When physicians prescribe drugs proven to be safe and effective in individual patients in the treatment of AF episodes when taken as a single dose as required, patients may take their drugs in the early stages of episodes of AF to ensure efficacy and may thus control AF by themselves at night or outside the home without seeking emergency care. This method is referred to as the "pill-in-the-pocket" approach.[121]

For this approach, drugs should be rapidly absorbable from the gastrointestinal tract after oral intake to achieve peak blood concentrations promptly and reach sufficient effective blood concentrations after a single administration. Pilsicainide,[132] flecainide,[133,134] propafenone,[133,134] and cibenzoline[135] are used in this approach. It should be noted that the first administration of antiarrhythmic drugs should be performed under ECG monitoring to confirm that the treatment is effective and safe, i.e., that the drugs neither induce sinus arrest or conduction disturbance, induce excessive prolongation of the QT interval, nor lead to Brugada-type ECG findings. Patients should be able to understand the pharmacological characteristics of drugs and refrain from inappropriate additional intake of their drugs even when expected effects are not obtained.

5. Upstream Therapy

Upstream therapy to prevent or delay myocardial remodeling associated with hypertension, heart failure, or inflammation may prevent the development of new-onset AF (primary prevention), or control AF recurrence or progression to permanent AF (secondary prevention).

Primary Prevention

Class I

- None.

Class IIa

- ACE inhibitors or ARBs should be considered to prevent the development of new-onset AF in patients with heart failure and cardiac dysfunction. (**Level of Evidence: A**)
- ACE inhibitors or ARBs should be considered to prevent the development of new-onset AF in patients with hypertension associated with left ventricular hypertrophy. (**Level of Evidence: B**)
- Statins should be considered to prevent the development of new-onset AF after cardiac surgery. (**Level of Evidence: B**)

Class IIb

- Statins may be considered to prevent the development of new-onset AF in patients with structural heart disease such as heart failure. (**Level of Evidence: B**)

Class III

- ACE inhibitors, ARBs, or statins should not be used to prevent the development of new-onset AF in patients without cardiac disease. (**Level of Evidence: C**)

Secondary Prevention

Class IIb

- ACE inhibitors or ARBs may be considered to prevent AF recurrence. (**Level of Evidence: B**)

5.1 ACE Inhibitors and ARBs

ACE inhibitors and ARBs inhibit the arrhythmogenic effects of angiotensin II which include atrial fibrosis and hypertrophy, uncoupling gap junctions, abnormal calcium handling, alteration of ion channels, oxidative stress, and promotion of inflammation.[128,136,137]

5.1.1 Primary Prevention

In randomized clinical trials such as the Val-HeFT (Valsartan Heart Failure Trial)[130] and the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity)[64] in patients with heart failure, ACE inhibitors and ARBs decrease the risk of new-onset AF, and meta-analysis of these studies have reported that these drugs decreased the risk of new-onset AF by 30~48%. In the LIFE (Losartan Intervention For End Point Reduction in Hypertension) study[128] in hypertensive patients with left ventricular hypertrophy, the incidence of new-onset AF was 33% lower in patients receiving losartan

than in those receiving atenolol. Meta-analyses have indicated that ACE inhibitors and ARBs decrease the incidence of new-onset AF by 25%. In other studies in hypertensive patients receiving antihypertensive drugs, the risk of the development of new-onset AF is significantly lower in patients receiving ACE inhibitors and ARBs than in those receiving calcium channel blockers and diuretics.[138,139]

5.1.2 Secondary Prevention

It has been reported that the incidence of AF recurrence after electrical cardioversion was significantly lower in patients receiving ACE inhibitors or ARBs in addition to amiodarone than in those receiving amiodarone monotherapy. However, in the GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation) trial,[140] the addition of valsartan to conventional therapies could not reduce the rate of AF recurrence over the 1-year follow up period in AF patients with cardiovascular disease, diabetes mellitus, or left atrial enlargement.

In the J-RHYTHM II study[141] in patients with hypertension and paroxysmal AF, blood pressure was significantly lower in patients in the amlodipine group than in those in the candesartan group. Both drugs decreased the number of days with AF episodes and the incidence of symptomatic AF, but no significant difference was observed between the two groups. The incidence of persistent AF did not differ significantly between the two groups. These findings indicate that sufficient blood pressure control rather than the type of antihypertensive drugs is important for successful upstream therapy for patients with AF.

In the ACTIVE I (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events)[142] in patients with AF and a systolic blood pressure of ≥110 mmHg, the addition of irbesartan to the conventional therapy did not prevent thrombotic events in AF patients with a risk of cardiovascular events.

These findings indicate that ACE inhibitors and ARBs may prevent the development of new-onset AF in patients with underlying heart disease such as left ventricular dysfunction and left ventricular hypertrophy, but there is limited evidence that these drugs can prevent AF recurrence in patients with mild structural heart disease.

5.2 HMG-CoA Reductase Inhibitors (Statins)

Statins may prevent AF through various mechanisms including anti-inflammatory and anti-oxidant actions, and reduction of endothelial dysfunction.[143,144]

5.2.1 Primary Prevention

Although it has been reported that statins decreased the incidence of new-onset AF in patients with left ventricular dysfunction and heart failure by 20~50%,[144] consistent results have not been obtained in studies in patients with hypertension, coronary artery disease, and acute coronary syndrome. In retrospective studies including the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study,[145] statins decreased the incidence of postoperative AF.

5.2.2 Secondary Prevention

It has been reported that the effect of statins in preventing AF is more pronounced for paroxysmal AF than for persistent AF.[144] Randomized control studies have not demonstrated the benefit of statins in preventing AF recurrence in patients after electrical cardioversion.[146] Meta-analyses have not resulted in consistent conclusions about the benefits of statins in the secondary prevention of AF.[147]

There is only insufficient evidence in support of the use of statins for primary or secondary prevention of AF, except for postoperative AF.

6. Non-Pharmacotherapy of AF

6.1 Catheter Ablation in the Atrium

Class I

- Catheter ablation is recommended for the treatment of drug-resistant symptomatic paroxysmal AF in patients without severe left atrial enlargement, severe left ventricular dysfunction or severe pulmonary disease in medical institutions where ≥50 cases of catheter ablation of AF are conducted annually.

Class IIa

- Catheter ablation should be considered for patients with drug-resistant symptomatic paroxysmal or persistent AF.
- Catheter ablation should be considered for patients who are engaged in occupations such as airline pilots and mass transit drivers with a risk of accidents if an episode occurs.
- Catheter ablation should be considered for patients who respond to pharmacotherapy but prefer ablation of AF.
- Maze operation should be considered as an additional procedure during open chest surgery.

Class IIb

- Catheter ablation may be considered for patients with drug-resistant symptomatic paroxysmal or persistent AF associated with severe left atrial enlargement and severe left ventricular dysfunction.
- Catheter ablation may be considered for patients with asymptomatic paroxysmal or persistent AF with no significant deterioration of QOL.

Class III

- Catheter ablation should not be performed in patients suspected to have left atrial thrombus.
- Catheter ablation should not be performed in patients who are contraindicated for anticoagulation therapy.

Catheter ablation for AF has evolved rapidly following a report that AF is triggered by focal firing originating at the ostium of the pulmonary veins and that catheter ablation targeting the focal source may terminate AF. Currently, anatomical isolation techniques to eliminate the electric connection between the superior and inferior pulmonary veins and the left atrium (such as circumferential pulmonary vein ablation) using three-dimensional navigation systems such as the CARTO system are often used in Europe and the United States.[148–150] In addition to the above technique, ablations targeting complex fractionated atrial electrogram (CFAE)[151] and autonomic ganglionated plexuses,[152] linear ablation at the roofline joining the right/left pulmonary veins,[153] and linear ablation at the mitral isthmus are also performed. AF frequently recurs after ablation. It has been reported that recurrence of paroxysmal AF could be avoided after the first and second ablations in 50~80% and 80~90% of patients with paroxysmal AF, respectively.[154–156] On the other hand, it is more difficult to obtain complete cure of persistent AF compared to paroxysmal AF, and various additional techniques are often required for this. The rate of success after repeated circumferential pulmonary vein ablation has been reported to be 60~75%.[150,157]

It has been reported that major complications such as cerebral infarction, cardiac tamponade, pulmonary vein stenosis/occlusion, phrenic nerve/vagal nerve injury, and left atrial-esophageal fistula develop in 2~6% of patients undergoing ablation for AF.[158–162] Care is needed to avoid such complications, especially left atrial-esophageal fistula, which though low in incidence is usually fatal when it occurs.

In the present guidelines, catheter ablation is recommended as a **Class I** option for the treatment of patients with drug-resistant, symptomatic paroxysmal AF when this procedure is conducted in medical institutions with extensive experience. It is of course quite important to appropriately provide detailed information on the pathophysiology, prognosis, and treatment of AF to eligible patients before obtaining informed consent.

6.2 AV Nodal Ablation

AV nodal ablation may be effective in patients for whom ablation in the left atrium is difficult or has not been successful, who have high ventricular rates or severe symptoms associated with AF, and who do not respond well to pharmacotherapy.[163]

6.3 Pacemaker Therapy

Information on pacing techniques and algorithms for the prevention or treatment of AF is limited, and no reliable data are available on pacemaker therapy for patients with AF without bradycardia.

6.4 Antithrombotic Drugs

Since the long-term prognosis following ablation has not yet been established, no conclusion has been reached regarding how long patients should continue anticoagulation following ablation. Anticoagulation therapy should not be discontinued in patients with a $CHADS_2$ score of ≥2 even after successful ablation of AF.[75,158]

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Appendix 1 JCS Joint Working Group

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Independent Assessment Committee:
- Itsuo Kodama, Nagoya University
- Satoshi Ogawa, International University of Health and Welfare, Mita Hospital
- Tohru Ohe, The Sakakibara Heart Institute of Okayama
- Hiroyuki Tsutsui, Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine

(The affiliations of the members are as of June 2013)

Appendix 2 Disclosure of Potential Conflicts of Interest (COI): Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013)

Author	Employer/ leadership position (private company)	Stake-holder	Patent royalty	Honorarium	Payment for manu-scripts	Research grant	Scholarship (educational) grant/endowed chair	Other rewards	Potential COI of the marital partner, first-degree family members, or those who share income and property
Chair: Hiroshi Inoue				Otsuka Pharmaceutical, Daiichi Sankyo, Dainippon Sumitomo Pharma, Nippon Boehringer Ingelheim, Bayer Yakuhin			Nippon Boehringer Ingelheim, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Dainippon Sumitomo Pharma		
Members: Hirotsugu Atarashi				Daiichi Sankyo, Nippon Boehringer Ingelheim, Bayer Yakuhin, Otsuka Pharmaceutical, Eisai, Teijin Pharma			Nippon Boehringer Ingelheim		

(Appendix 2 continued the next page.)

Author	Employer/ leadership position (private company)	Stake-holder	Patent royalty	Honorarium	Payment for manu-scripts	Research grant	Scholarship (educational) grant/endowed chair	Other rewards	Potential COI of the marital partner, first-degree family members, or those who share income and property
Members: Ken Okumura				Nippon Boehringer Ingelheim, Bayer Yakuhin, Daiichi Sankyo, Pfizer Japan, Mitsubishi Tanabe Pharma, Johnson & Johnson, Medtronic Japan					
Members: Shiro Kamakura				Nippon Boehringer Ingelheim, Bayer Yakuhin					
Members: Koichiro Kumagai				Nippon Boehringer Ingelheim, Bayer Yakuhin, Daiichi Sankyo, Mitsubishi Tanabe Pharma, MSD			Nippon Boehringer Ingelheim, Daiichi Sankyo		
Members: Yukihiro Koretsune				Nippon Boehringer Ingelheim, Bayer Yakuhin, Daiichi Sankyo		Daiichi Sankyo	Nippon Boehringer Ingelheim		
Members: Kaoru Sugi				Bayer Yakuhin, Nippon Boehringer Ingelheim			Sanofi, Mochida Pharmaceutical, Daiichi Sankyo, Dainippon Sumitomo Pharma		
Members: Hideo Mitamura				Nippon Boehringer Ingelheim, Daiichi Sankyo					
Members: Masahiro Yasaka				Nippon Boehringer Ingelheim, Bayer Yakuhin, Bristol-Myers Squibb, Otsuka Pharmaceutical, Daiichi Sankyo					
Members: Takeshi Yamashita				Nippon Boehringer Ingelheim, Pfizer Japan, Bayer Yakuhin, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Eisai, Bristol-Myers Squibb, Ono Pharmaceutical		Novartis Pharma	Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Daiichi Sankyo		
Collaborators: Kazuhiro Satomi				St. Jude Medical Japan, Johnson & Johnson					

Companies are listed only by name.

Benefit of Cilostazol in Patients with High Risk of Bleeding: Subanalysis of Cilostazol Stroke Prevention Study 2

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Key Words
Secondary prevention · Hemorrhagic stroke · Cilostazol · Aspirin · Lacunar stroke · Blood pressure

Abstract
Background: The Cilostazol Stroke Prevention Study 2 (CSPS 2) showed that cilostazol significantly reduced the risk of stroke by 25.7% relative to aspirin, with significantly fewer hemorrhagic events, in patients with prior ischemic stroke, excluding cardioembolic stroke. However, whether the benefit of cilostazol is sustained in patients with a high risk of bleeding has not been examined. ***Methods:*** We conducted a subanalysis of CSPS 2 to examine whether known risk factors for hemorrhagic stroke, such as stroke subtype and systolic blood pressure (SBP), influence the efficacy of the study drugs on hemorrhagic stroke. The relative risk reduction of hemorrhagic stroke was determined from the incidences calculated by the person-year method. The cumulative incidence rates of ischemic stroke and hemorrhagic stroke were estimated and plotted using the Kaplan-Meier method. Incidences of serious hemorrhage and hemorrhage requiring hospital admission were also evaluated in the two treatment groups. Hazard ratios (HR) and 95% confidence intervals (95% CI) calculated by the Cox proportion hazard model for

Results of the present study were presented at the International Stroke Conference 2012 in New Orleans, La., USA, and published in an abstract form in Stroke, vol. 43, issue 2.

cilostazol versus aspirin were assessed, and a log-rank test was used for the comparison between treatments. ***Results:*** The incidence of hemorrhagic stroke was significantly lower in the cilostazol group than in the aspirin group among patients with prior lacunar stroke (0.36 vs. 1.20% in person-year, HR 0.35, 95% CI 0.18–0.70, p < 0.01), but not among those with prior atherothrombotic stroke (0.31 vs. 0.59% in person-year, HR 0.53, 95% CI 0.14–2.0, p = 0.34). The incidence of hemorrhagic stroke was significantly lower in the cilostazol group than in the aspirin group throughout all SBP categories (Poisson regression model including time-dependent covariates, p < 0.01) including SBP above 140 mm Hg (cilostazol 0.45% vs. aspirin 1.44% in person-year; Poisson regression model including time-dependent covariates, p = 0.02). Cilostazol, compared with aspirin, significantly reduced the incidence of cerebral hemorrhage (HR 0.36, 95% CI 0.19–0.70, p < 0.01), overall hemorrhage requiring hospital admission (HR 0.53, 95% CI 0.29–0.97, p = 0.04), and gastrointestinal (GI) bleeding requiring hospital admission (HR 0.44, 95% CI 0.21–0.90, p = 0.03). ***Conclusions:*** Hemorrhagic stroke was less frequent in the cilostazol group than in the aspirin group among patients with lacunar stroke as well as those with increased blood pressure levels. As for extracranial hemorrhage requiring hospitalization, GI bleeding was also less frequent in the cilostazol than in the aspirin group. Cilostazol is supposed to be a therapeutic option to replace aspirin for secondary stroke prevention, especially in these subgroups with high risks for hemorrhagic events.

Introduction

Survivors of ischemic stroke have an increased risk of recurrence of stroke. Platelets play an important role in the development of ischemic stroke, and antiplatelet therapy has been reported to be effective in many clinical trials for secondary prevention of stroke in high-risk patients [1]. However, aspirin is known to be associated with increased hemorrhagic risk, e.g. approximately a twofold increase in gastrointestinal (GI) bleeding [2, 3] or more prevalent intracranial hemorrhage [4, 5]. Recently, efforts have been made to identify antiplatelet agents which have stronger preventive effects on the occurrence of stroke without an increased hemorrhagic risk.

Cilostazol, a phosphodiesterase-3 inhibitor, reduced recurrent stroke, with no increase in cerebral hemorrhage in patients with ischemic stroke, including those with risk factors for hemorrhagic stroke such as lacunar stroke, hypertension or older age [6–9]. In a randomized, double-blind, controlled trial, the Cilostazol Stroke Prevention Study 2 (CSPS 2) conducted in Japanese patients with noncardioembolic ischemic stroke, cilostazol significantly reduced the risk of stroke by 25.7% relative to aspirin, with significantly fewer hemorrhagic events [10]. The results were supported by a meta-analysis of randomized controlled trials comparing cilostazol with aspirin [11]. However, whether the benefit of cilostazol is sustained in patients with a high risk of bleeding has not been examined.

In the present study, data from the CSPS 2 were reexamined, and a subanalysis was conducted to verify whether or not known risk factors for hemorrhagic stroke, such as stroke subtype and blood pressure level, influence the safety of cilostazol in comparison with aspirin. Risks of hemorrhagic events other than hemorrhagic stroke were also analyzed and compared between the two treatment groups.

Methods

Patients

All patients included for analyses in the CSPS 2 (Clinical Trials.gov, No. NCT00234065) were examined in the present study. The study design and results of CSPS 2 have been reported elsewhere [10]. In summary, 2,672 patients with a previous ischemic stroke, excluding cardioembolic stroke, whose onset of event was within 6 months prior to registration, were randomly assigned to treatment with either cilostazol (100 mg twice daily) or aspirin (81 mg once daily). The mean duration of follow-up was 29 months.

Procedures and Statistical Analysis

Incidences of ischemic stroke and hemorrhagic stroke during treatment with cilostazol or aspirin were calculated using the person-year method, according to prior stroke subtype (atherothrombotic or lacunar). Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. Their relative risk reduction (RRR) was determined from the incidences calculated by the person-year method. The cumulative incidence rates of ischemic stroke and hemorrhagic stroke were estimated and plotted using the Kaplan-Meier method. Incidences of serious hemorrhages, including cerebral hemorrhage, subarachnoid hemorrhage and hemorrhage requiring hospital admission, were also evaluated in the two treatment groups. Hazard ratios (HR) and 95% confidence intervals (95% CI) calculated by the Cox proportion hazard model for cilostazol versus aspirin were assessed for hemorrhagic stroke by stroke subtypes and serious hemorrhage/hemorrhage requiring hospital admission, and a log-rank test was used for the comparison between treatments.

A predictability of the incidence of hemorrhagic stroke was examined from systolic blood pressure (SBP) during the study period. This analysis was based on the individual SBP measurements at each time point and analyzed using the Poisson regression model (SBP levels by treatments were treated as time-dependent covariates [12]). A probability level <0.05 was considered to indicate significance.

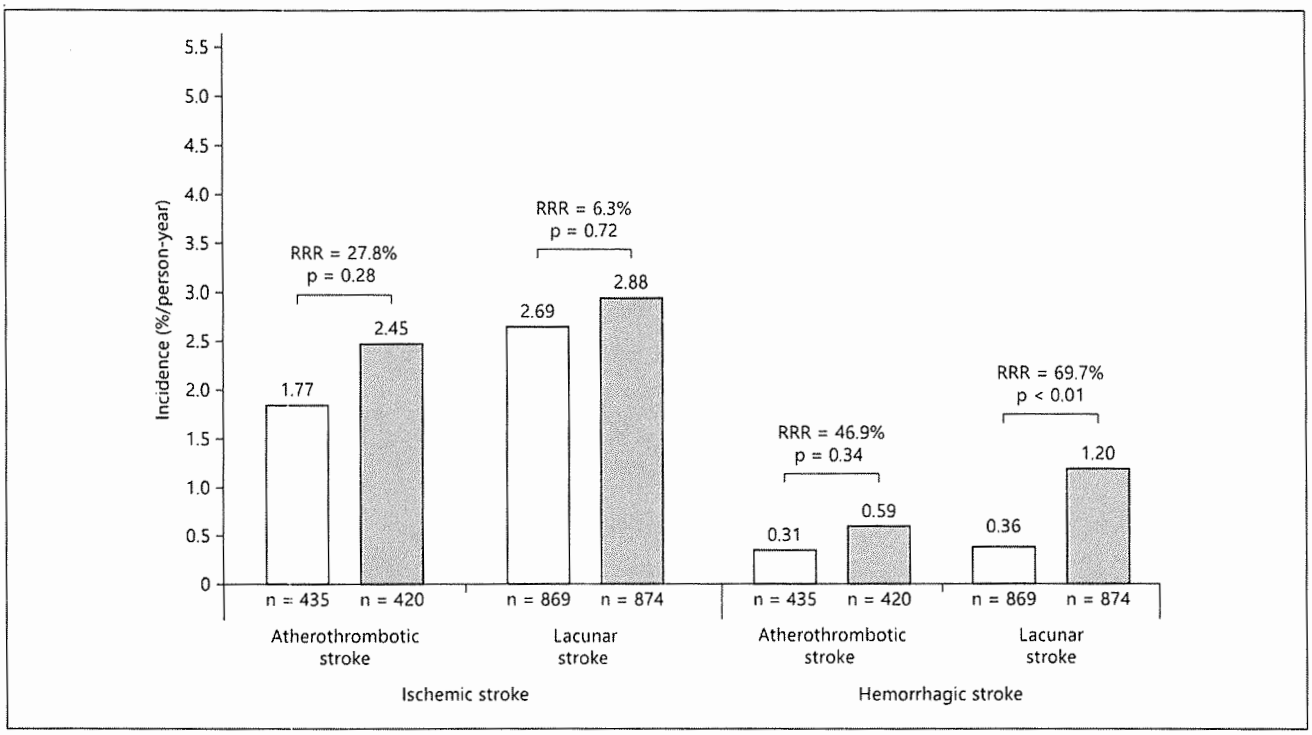


Fig. 1. Incidence of ischemic stroke and hemorrhagic stroke in patients with a prior history of atherothrombotic or lacunar stroke. White bars indicate cilostazol and dark bars aspirin.

In order to identify risk factors for hemorrhagic stroke, factorial analysis of the data using the Cox proportional hazard model was performed. Univariate analysis was first conducted, and variables identified significant ($p < 0.02$) in the univariate analysis were further assessed by multivariate analysis with the stepwise method using 2 independent variables at each step.

All analyses were performed using SAS version 9.2 software (SAS Institute).

Results

Incidence of Hemorrhagic Stroke by Stroke Subtypes

Figure 1 shows the incidence of ischemic and hemorrhagic strokes and RRR for cilostazol compared with aspirin, by baseline stroke subtype. The incidence of ischemic stroke was numerically lower for cilostazol compared with aspirin treatment, both in patients with atherothrombotic stroke (1.77 vs. 2.45% in person-year, RRR 27.8%) and lacunar stroke (2.69 vs. 2.88% in person-year, RRR 6.3%), although the differences were not statistically significant. A significant difference between the cilostazol and aspirin groups was observed for the incidence of hemorrhagic stroke in patients with lacunar stroke (0.36 vs. 1.20% in person-year, RRR 69.7%, $p < 0.01$), but not in those with atherothrombotic stroke. No interaction was observed between the ischemic stroke subtypes and the treatment effect for prevention of ischemic stroke ($p = 0.46$) or hemorrhagic stroke ($p = 0.58$).

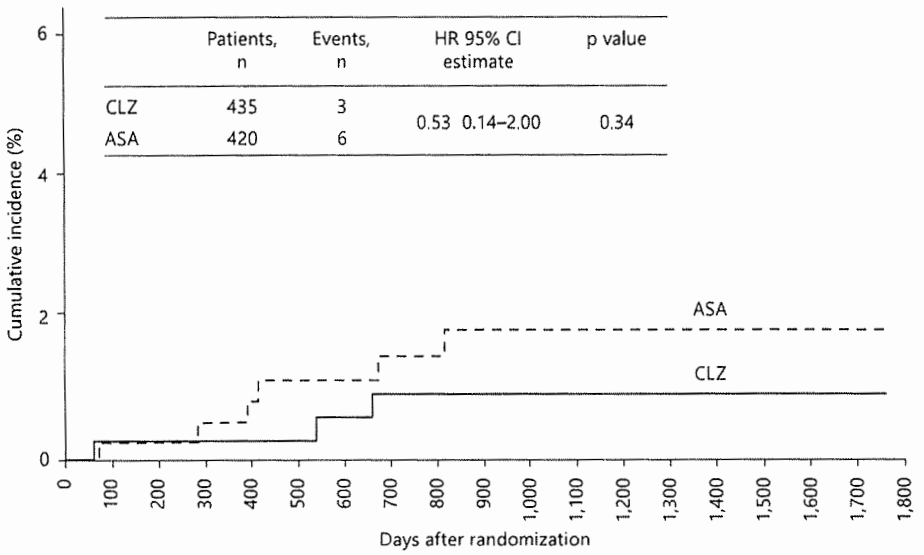
Cumulative Incidence of Hemorrhagic Stroke

Figure 2 shows the cumulative incidence of hemorrhagic stroke in patients with atherothrombotic stroke or lacunar stroke. The HR for cilostazol compared with aspirin showed a significant reduction of hemorrhagic stroke in patients with lacunar stroke (HR 0.35, 95% CI 0.18–0.70, $p < 0.01$; fig. 2b), while the difference between the treatment groups was not significant in patients with atherothrombotic stroke (HR 0.53, 95% CI 0.14–2.0, $p = 0.34$; fig. 2a).

Incidence of Hemorrhagic Stroke by SBP Levels

A significantly lower incidence of hemorrhagic stroke was observed in the cilostazol group compared with the aspirin group throughout all SBP categories ($p < 0.01$) including SBP above 140 mm Hg (0.45 vs. 1.44% per per-

a

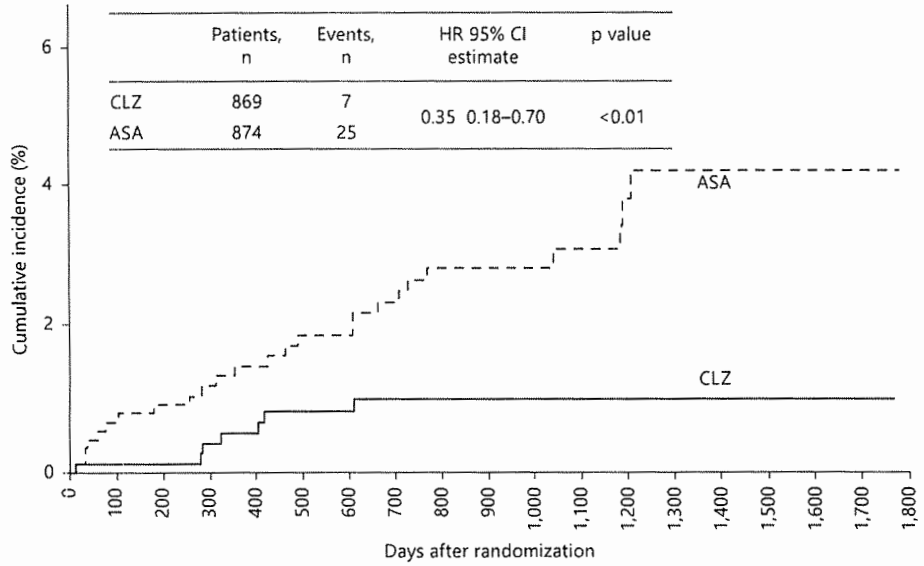


	Patients, n	Events, n	HR 95% CI estimate	p value
CLZ	435	3	0.53 0.14–2.00	0.34
ASA	420	6		

Number at risk

	Days after randomization																	
	0	100	200	300	400	500	600	700	800	900	1,000	1,100	1,200	1,300	1,400	1,500	1,600	1,700	1,800
CLZ	435	367	341	331	317	310	296	286	262	225	182	141	105	71	41	25	13	4	0
ASA	420	389	365	348	328	318	306	290	265	239	197	166	125	87	56	27	13	3	0

b



	Patients, n	Events, n	HR 95% CI estimate	p value
CLZ	869	7	0.35 0.18–0.70	<0.01
ASA	874	25		

Number at risk

	Days after randomization																	
	0	100	200	300	400	500	600	700	800	900	1,000	1,100	1,200	1,300	1,400	1,500	1,600	1,700	1,800
CLZ	869	741	694	674	648	608	578	558	508	443	373	298	215	151	93	42	15	3	0
ASA	874	804	753	710	689	658	632	610	545	488	410	326	242	162	92	46	19	4	0

Fig. 2. Cumulative incidence of hemorrhagic stroke (cerebral hemorrhage or subarachnoid hemorrhage) in patients with a history of atherothrombotic stroke (**a**) or lacunar stroke (**b**). CLZ = Cilostazol; ASA = aspirin; p values assessed by the log-rank test.

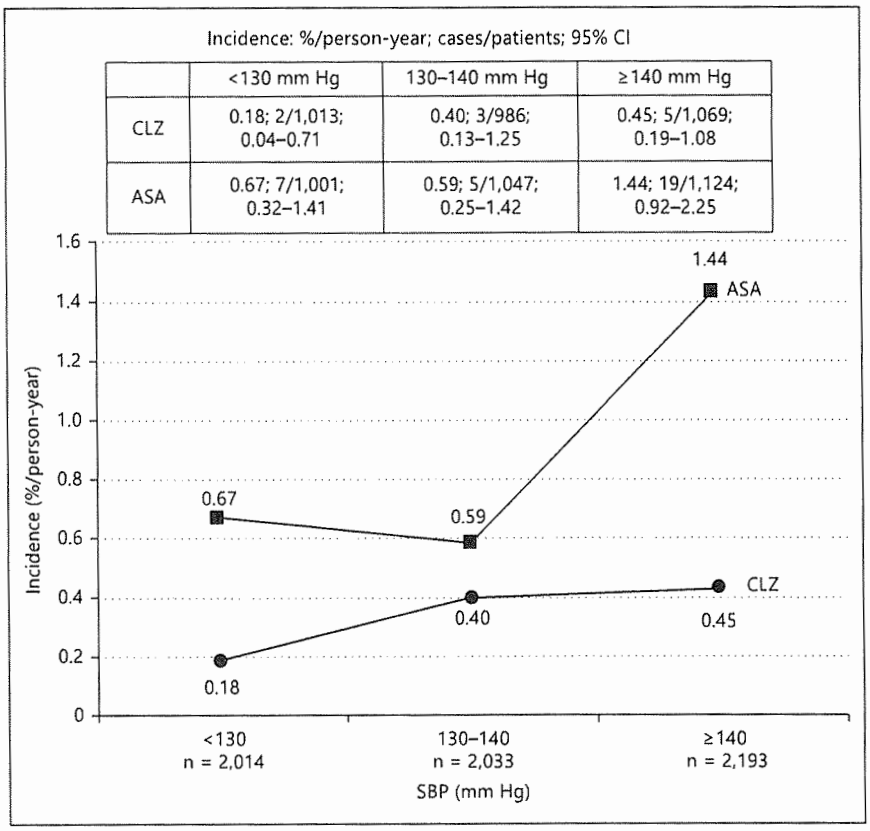


Fig. 3. Incidence of hemorrhagic stroke according to SBP. p = 0.61 for interaction; p < 0.01 for treatment. In this figure, 'patients' shows number of patients who showed the classified value at least once; ASA = Aspirin; CLZ = cilostazol.

son-year; p = 0.02; fig. 3). No interaction was observed between SBP levels and the treatment effect for prevention of hemorrhagic stroke (p = 0.61).

Risk Factors for Hemorrhagic Stroke

Univariate analysis found that age, body mass index, recurrent (versus first) stroke, modified Rankin Scale, stroke subtype, localization (e.g. cortex, subcortical white matter), vascular territory (e.g. vertebrobasilar artery, middle cerebral artery), SBP, diastolic blood pressure, triglyceride, concomitant use of angiotensin receptor blockers, Ca antagonists, lipid-lowering agents and statins were significant risk factors for hemorrhagic stroke. The multivariate analysis identified SBP as a significant factor.

Incidence of Serious Hemorrhagic Events

Incidences of intracranial hemorrhage and hemorrhage requiring hospital admission are shown in figure 4. Cilostazol, compared with aspirin, significantly reduced the incidence of cerebral hemorrhage (HR 0.36, 95% CI 0.19–0.70, p < 0.01), overall hemorrhage requiring hospital admission (HR 0.53, 95% CI 0.29–0.97, p = 0.04) and GI bleeding requiring hospital admission (HR 0.44, 95% CI 0.21–0.90, p = 0.03). No significant between-group differences were observed for incidence of subarachnoid hemorrhage, subdural hematoma, epistaxis or other hemorrhage requiring hospital admission.

Discussion

In the present study, the incidence of hemorrhagic stroke was similar in patients with prior atherothrombotic stroke (0.31% in person-year) and lacunar stroke (0.36% in person-year) among patients in the cilostazol group. On the other hand, in the aspirin group, the incidence of hemorrhagic stroke was twofold higher in patients with prior lacunar stroke than in those with prior atherothrombotic stroke (1.20 vs. 0.59% in person-year).

In a 10-year follow-up by the Hisayama study, patients with lacunar stroke had a higher incidence of hemorrhagic stroke than patients with atherothrombotic stroke [13]. Lacunar stroke was also reported to be associated with a

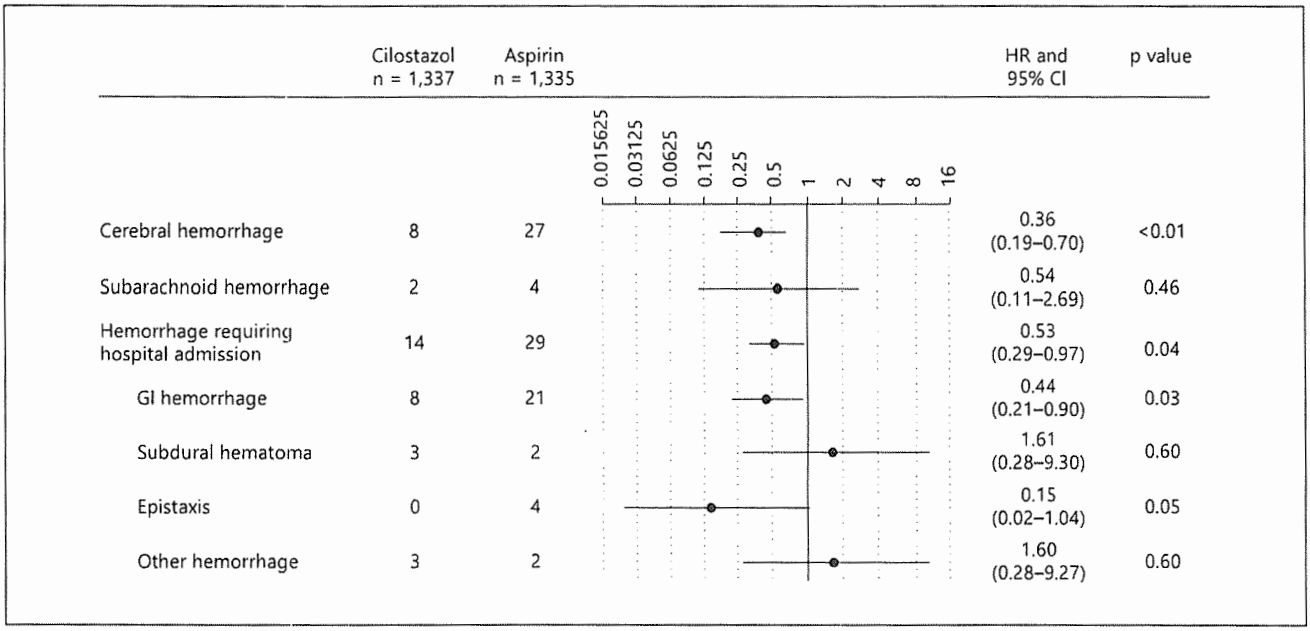


Fig. 4. Incidence of serious hemorrhage and hemorrhage requiring hospital admission. p values assessed by the log-rank test.

significant increase in asymptomatic hemorrhagic transformation of infarction, defined by follow-up CT [14], suggesting a close relationship between lacunar stroke and intracerebral hemorrhage.

The multivariate analysis to identify risk factors for hemorrhagic stroke identified SBP as a significant factor. Though stroke subtype was not included, we conducted the present subanalysis including stroke subtype based on the above-mentioned findings.

Endothelial dysfunction rather than chronic platelet activation is reported to play a central role in the pathophysiology of lacunar stroke [15], and also, acute ischemic stroke is considered associated with endothelial dysfunction of the peripheral vascular beds [16], suggesting that treatment which can improve endothelial dysfunction might be necessary for the prevention of lacunar stroke and hemorrhagic stroke. Aspirin therapy is known to be associated with increased hemorrhagic risk, and dual antiplatelet therapy with clopidogrel and aspirin was reported to add no benefit, but increased the bleeding risk in patients with lacunar stroke for long-time treatment [17, 18]. As far as we are aware, this is the first report to demonstrate a higher risk of hemorrhagic stroke in patients with lacunar stroke than in those with atherothrombotic stroke among patients on aspirin. However, the number of atherothrombotic stroke patients was half of that of lacunar stroke, suggesting that the lack of findings of significant differences between the study drugs in the atherothrombotic group may be attributable to the smaller sample size compared to the lacunar stroke group.

A relationship between the incidence of hemorrhagic stroke and blood pressure level has been reported in several studies. For example, Toyoda et al. [19] reported a relationship between increased blood pressure level and incidence of hemorrhagic stroke during antithrombotic treatment. The SPS 3 study also demonstrated that the incidence of stroke was reduced in the lower target SBP group (<130 mm Hg, mean 127 mm Hg) compared with the higher target SBP group (130–149 mm Hg, mean 138 mm Hg) in patients with lacunar stroke, and the difference was significant when limited to the reduction of hemorrhagic stroke, suggesting that the use of an SBP target less than 130 mm Hg might be beneficial for the reduction of hemorrhagic stroke in patients with lacunar stroke [20]. The present study demonstrated that the risk of hemorrhagic stroke was lower in patients on cilostazol than in those on aspirin in all the SBP categories including patients with SBP level over 140 mm Hg, demonstrating usefulness of cilostazol in patients with a high risk of bleeding such as lacunar stroke or high SBP.

Cilostazol exerts an antiplatelet action by inhibiting phosphodiesterase-3 and increasing cyclic adenosine monophosphate levels in platelets. It can also increase blood flow by vasodilation mediated through improvement of vascular endothelial cell function with increased nitric oxide production and barrier function, reducing the expression of adhesion molecules or preventing vascular smooth muscle cell proliferation [21–23]. In addition, cilostazol inhibits the expression of matrix metalloproteinase-9, which is one of the proteases associated with fragility of small vessels [24], and inhibits degeneration of small penetrating arteries in the brains of hypertensive rats [25]. Based on the findings, it could be speculated that endothelial dysfunction induced by high blood pressure was partly reversed by cilostazol.

It has been reported that the incidence of GI bleeding was significantly increased even with low-dose aspirin [2], and the odds ratio for GI bleeding with aspirin was 8.2 in a Japanese case-control study [26]. In the present study, the incidence of GI bleeding was significantly higher in the aspirin group than in the cilostazol group. Unlike aspirin, cilostazol does not induce damage to the gastric mucosa, which might explain the difference in the incidence of GI bleeding between the two study drugs. The limitation of the present study was that CSPS 2 was conducted in a Japanese population, and confirmatory studies in other ethnic groups are required. Additionally, this analysis may have been underpowered to demonstrate significant treatment differences for some factors.

Conclusion

Cilostazol was associated with fewer hemorrhagic strokes in patients with a high risk of hemorrhagic stroke, such as those with lacunar stroke and high SBP levels, and was also associated with less GI bleeding than aspirin.

Cilostazol is supposed to be a therapeutic option to replace aspirin for secondary stroke prevention, especially in these high-risk subgroups for hemorrhagic events. Further comprehensive analyses on larger numbers of patients, including other ethnic subpopulations, are required to obtain conclusive results.

Disclosure Statement

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The funding source had a role in the study design, data collection, and data analysis, but not in data interpretation or writing of the report. Data were collected by the sponsor, and statistical analyses were entrusted to a contract research organization (EPS). The contract research organization did statistical analyses under the supervision of the trial statistician (C.H.), who was independent from the sponsor. Both the corresponding author and C.H. had full access to all the data in the study, and the corresponding author had the final responsibility for the decision to submit this paper for publication.

Shinichiro Uchiyama's institution has received grants and honoraria for lecture from Otsuka Pharmaceutical, Sanofi-Aventis, Boehringer Ingelheim, Daiichi-Sankyo and Bayer Health Care.

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Yasuo Katayama, Shunnosuke Handa, Kempei Matsuoka, Chokoh Genka, Hideo Kusuoka, Motoo Tsushima, Tohru Sawada and Chikuma Hamada declare that they have no conflicts of interest.

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Original Article

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$CHADS_2$ and CHA_2DS_2-VASc scores as bleeding risk indices for patients with atrial fibrillation: the Bleeding with Antithrombotic Therapy Study

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The $CHADS_2$ and CHA_2DS_2-VASc scores, that is, ischemic stroke risk indices for patients having atrial fibrillation (AF), may also be useful as bleeding risk indices. Japanese patients with AF, who routinely took oral antithrombotic agents were enrolled from a prospective, multicenter study. The $CHADS_2$ and CHA_2DS_2-VASc scores were assessed based on information at entry. Scores of 0, 1 and ≥2 were defined as the low, intermediate and high ischemic risk categories, respectively, for each index. Of 1221 patients, 873 took warfarin, 114 took antiplatelet agents and 234 took both. The annual incidence of ischemic stroke was 0.76% in the low-risk category, 1.46% in the intermediate-risk category and 2.90% in the high-risk category by $CHADS_2$ scores, and 1.44, 0.42 and 2.50%, respectively, by

CHA_2DS_2-VASc scores. The annual incidence of major bleeding in each category was 1.52, 2.19 and 2.25% by $CHADS_2$, and 1.44, 1.69 and 2.24% by CHA_2DS_2-VASc. After multivariate adjustment, the $CHADS_2$ was associated with ischemia (odds ratio 1.76, 95% confidence interval 1.03–3.38 per 1-category increase) and the CHA_2DS_2-VASc tended to be associated with ischemia (2.18, 0.89–8.43). On the other hand, associations of the indices with bleeding were weak. In conclusion, bleeding risk increased gradually as the $CHADS_2$ and CHA_2DS_2-VASc scores increased in Japanese antithrombotic users, although the statistical impact was rather weak compared with their predictive power for ischemic stroke.

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