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Atrial Fibrillation-Related Stroke across Europe: A Preventable Problem

Working Group Recommendations

Dr Alastair Benbow
Fondation Universitaire,
Brussels, Belgium

Professor Dr Paulus Kirchhof
University of Birmingham,
Birmingham, United Kingdom

Professor Dr Karl-Heinz Ladwig
Technical University of Munich,
Munich, Germany

Trudie Lobban MBE
Arrhythmia Alliance;
AF Association

Dr Xavier Viñolas
Hospital Sant Pau,
Barcelona, Spain

Professor Shinya Goto
Tokai University,
Kanagawa, Japan

Professor Han-Hwa Hu
Taipei Veterans General Hospital,
Taipei, Taiwan

Dr David KL Quek
Pantai Hospital Kuala Lumpur,
Kuala Lumpur, Malaysia

Professor Dr Kui-Hian Sim
Sarawak General Hospital,
Sarawak, Malaysia

Professor Hung-Fat Tse
The University of Hong Kong,
Hong Kong, China

Professor Shu Zhang
Fu Wai Cardiovascular Hospital,
Beijing, China

Dr Carlos Cantú
National Institute of Medical Services
and Nutrition Salvador Zubirán,
Mexico City, Mexico

Mellanie True Hills
StopAfib.org and the American
Foundation for Women's Health

Dr Ayrton Massaro
Past-President of Ibero-American
Stroke Society, Brazil

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Strike Out Stroke in Atrial Fibrillation
Action for Stroke Prevention

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The recommendations in this document are endorsed by the organizations shown below.

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Authors

Writing group

Dr Alastair Benbow
Executive Director, European Brain Council, (Brussels Office), Fondation Universitaire,Brussels, Belgium

Professor Dr Paulus Kirchhof
Chair in Cardiovascular Medicine, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, United Kingdom; Senior Consultant, Department of Cardiology and Angiology, University Hospital Münster, Germany

Professor Dr Karl-Heinz Ladwig
Professor of Psychosomatic Medicine and Psychological Medicine, Technical University of Munich; Deputy Director of the Chronic Disease Epidemiology Department of the Institute of Epidemiology at the Helmholtz Zentrum München, German Research Centre for Environmental Health, Neuherberg, Germany

Trudie Lobban MBE
Founder and Trustee, Arrhythmia Alliance; Founder and Chief Executive Officer, AF Association

Dr Xavier Viñolas
Director, Arrhythmia Unit, Hospital Sant Pau, Barcelona, Spain

Professor Shinya Goto
Professor of Medicine, Department of Medicine (Cardiology) and the Metabolic Disease Center, and the Department of Metabolic Systems Medicine, Institute of Medical Science, Tokai University, Kanagawa, Japan

Professor Han-Hwa Hu
Professor of Neurology, National Yang-Ming University, Taipei, Taiwan; Emeritus Chief of the Neurovascular Section, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan; President of the Taiwan Stroke Association

Dr David KL Quek
Consultant Cardiologist, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; President of the Malaysia Medical Association and Elected Member of the Malaysian Medical Council

Professor Dr Kui-Hian Sim
Head of the Department of Cardiology and Head of Clinical Research Centre (CRC), Sarawak General Hospital, Sarawak, Malaysia; President of the National Heart Association of Malaysia

Professor Hung-Fat Tse
Professor of Medicine, Cardiology Division, Department of Medicine, The University of Hong Kong, Hong Kong, China

Professor Shu Zhang
Professor of Medicine, Chief of Department of Cardiology, Director of Arrhythmia Center; National Center for Cardiovascular Disease, Fu Wai Cardiovascular Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; President of Chinese Society of Pacing and Electrophysiology, Beijing, China

Dr Carlos Cantú
Chair, Department of Neurology, National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico; Professor of Stroke Program, National Autonomous University of Mexico, Mexico; Founding Member of the Mexican Stroke Association

Mellanie True Hills
Founder and Chief Executive Officer, StopAfib.org and the American Foundation for Women's Health

Dr Ayrton Massaro
Past-President of Ibero-American Stroke Society; Co-chair of the 2012 World Stroke Conference, Brazil

Working group

Dr Felicita Andreotti
Certified Professor, Department of Cardiovascular Sciences, Catholic University, Rome, Italy

Professor John Camm
Professor of Clinical Cardiologym St George's University, London, United Kingdom

Professor László Csiba
Professor and Head of the Department of Neurology, University of Debrecen, Hungary; President of the European Society of Neurosonology and Cerebral Hemodynamics

Professor Antonio Dávalos
Director, Department of Neurosciences, Hospital Universitari Germans Trias i Pujol, Barcelona; Associated Professor of Neurology, Universitat Autònoma de Barcelona, Barcelona, Spain

Professor Dr Werner Hacke
Professor and Chairman, Department of Neurology, University of Heidelberg, Heidelberg, Germany; Honorary President, European Stroke Organisation

Professor Michael G Hennerici
Professor and Chairman of Neurology, Department of Neurology, University of Heidelberg, Universitätsklinikum Mannheim, Germany; Chairman, European Stroke Conference

Professor Richard Hobbs
Professor and Head, Department of Primary Care Health Sciences, University of Oxford; National Director, NIHR School for Primary Care Research, United Kingdom; Chairman, European Primary Care Cardiovascular Society

Dr Torsten Hoppe-Tichy
Chief Pharmacist, Pharmacy Department, University Hospital of Heidelberg, Germany; President of ADKA (The German Society of Hospital Pharmacists)

Eve Knight
Chief Executive and Co-founder, AntiCoagulation Europe

Joe Korner
Director of Communications, The UK Stroke Association, London, United Kingdom; Representative for the Stroke Alliance For Europe (SAFE)

Professor Antoine Leenhardt
Professor of Cardiology, Paris 7 University; Head of the Arrhythmia Department, Bichat Hospital, Paris, France; Past-President the French Working Group of Cardiac Arrhythmias and Pacing

Dr Maddalena Lettino
Chief of the Clinical Cardiology Unit, Istituto Clinico Humanitas, Rozzano (Milano), Italy; Past-Chair, Italian Atherosclerosis, Thrombosis and Vascular Biology (ATBV) Working Group; Chair of the Italian Working Group on Acute Cardiac Care; Board member of the ESC Acute Cardiovascular Care Assocciation

Professor Gregory YH Lip
Consultant Cardiologist and Professor of Cardiovascular Medicine, University of Birmingham Center for Cardiovascular Sciences; Director, Haemostasis Thrombosis & Vascular Sciences Biology Unit; City Hospital, Birmingham, United Kingdom

Professor Lorenzo Mantovani
Professor, Faculty of Pharmacy, Federico II University of Naples, Naples, Italy

Rod Mitchell
Patient Advocate, Board Member, European Platform for Patients' Organisations, Science and Industry (Epposi) and the European Genetics Alliance Network (EGAN); Past Board member, International Alliance of Patients' Organizations

Professor Bo Norrving
Professor of Neurology, Department of Clinical Neurosciences, Section of Neurology, Lund University, Lund, Sweden; Past-President of the World Stroke Organization (2008–2012)

Professor Panos Vardas
President Elect of the European Society of Cardiology; Professor of Cardiology, University of Crete; Head of Cardiology Department, Heraklion University Hospital, Crete, Greece; President, European Heart Rhythm Association; Founder member of the Hellenic Cardiovascular Research Society and the Society's first President

Professor Graeme J Hankey
Head of Stroke Unit, Royal Perth Hospital, Perth, Western Australia; Clinical Professor, School of Medicine and Pharmacology, University of Western Australia, Nedlands, Australia

Professor Dayi Hu
Chief of the Cardiology Division of Peking University's People's Hospital, Dean of the Medical College of Shanghai at Tongji University; Dean of the Cardiology Department of Capital University of Medical Science, Beijing, China; President of the Chinese Society of Cardiology; President of the Chinese College of Cardiovascular Physicians

Professor Norio Tanahashi
Professor of Neurology, Saitama International Medical Center, Saitama Medical University, Hidaka City, Japan

Professor Byung-Woo Yoon
Department of Neurology, Seoul National University Hospital; Director of Clinical Research Center for Stroke, Korea; Current President of the Korean Society of Stroke

Dr Álvaro Avezum
Director, Research Division, Dante Pazzanese Institute of Cardiology, São Paulo, Brazil

Dr Jorge Gonzalez-Zuelgaray
Director of the Center of Cardiac Arrhythmias and of the Career of Specialists in Arrhythmias and Clinical Electrophysiology, University of Buenos Aires; Chief of Service of Arrhythmias and Electrophysiology (Sanatorio de la Trinidad San Isidro, Buenos Aires, Argentina); President of Arrhythmia Alliance and AF Association, Argentina

Dr Walter Reyes-Caorsi
Chief, Electrophysiology Service, Casa de Galicia Hospital, Montevideo, Uruguay; Member, Continuing Medical Committee, Uruguayan Society of Cardiology; Member, Editorial Committee, Uruguayan Journal of Cardiology; Board Member, Honorary Commission for Cardiovascular Health; Director, Arrhythmia Council, South American Society of Cardiology

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Endorsements

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The International FH Foundation	www.fh-foundation.org
World Heart Federation	www.world-heart-federation.org
World Stroke Organization (WSO)	www.world-stroke.org

Atrial fibrillation-related stroke: a global but preventable problem

- A stroke occurs when a blood vessel becomes blocked and the supply of blood to the brain becomes interrupted (ischaemic stroke), or when blood from a ruptured vessel leaks into the brain (haemorrhagic stroke). Both can cause significant brain damage
- Approximately 15% of all strokes are associated with atrial fibrillation (AF),[1] an abnormal heart rhythm. The condition occurs with increasing frequency as people get older and is the most common heart rhythm disorder[2]
- AF causes a stroke when the abnormal heart rhythm leads to the formation of a blood clot in the heart that is then transported to the brain. Patients with AF are *five times* more likely to experience a stroke than those without AF,[3] and AF-related strokes are more severe than strokes unrelated to AF[4,5]
- Globally, approximately 15 million people suffer a stroke each year.[6] In Europe, 1.3 million people suffered a stroke in 2010,[7] and approximately one-third of this number were left permanently disabled.[8] The costs associated with stroke are also considerable, and have been estimated previously at approximately 3% of total healthcare expenditure for some countries[9]
- In this booklet, we look at key facts concerning the human and economic cost of this preventable type of stroke in Europe, and how best to prevent it

AF-related stroke is a major problem in Europe today. However, it is a problem that can be overcome

Atrial fibrillation-related stroke in Europe: the avoidable burden

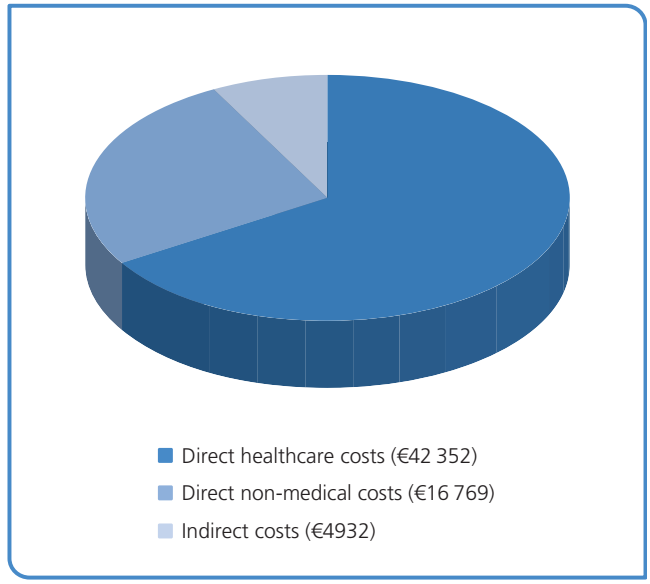
The clinical burden

- In 2010, there were more than 8 million people in Europe who were affected by stroke, with 1.3 million newly diagnosed stroke cases occurring in that same year[7]
- Stroke survivors often have permanent physical and cognitive disabilities; family members can also experience depression and a loss of independence[10,11]
- AF is the most common sustained abnormal heart rhythm (arrhythmia) and occurs with increasing frequency as people get older[2]
- AF currently affects approximately 10 million Europeans.[12] However, an increasingly ageing population means that the number of Europeans affected is expected to rise to 25–30 million by the year 2050
- Because of the larger size of the clot, AF-related stroke is more severe than non-AF-related stroke. It is associated with a higher risk of in-hospital death, greater disability, longer hospital stays, a reduced likelihood of patients returning to their own home and increased risk of recurrent stroke[4,5]
- As a result, AF-related stroke imposes a much greater burden on patients and their families than non-AF-related stroke

The financial burden

- The financial burden placed on European countries by stroke is huge. For 2010, the estimated cost of stroke in Europe was €64 billion.[7] Assuming that 15% of these strokes were caused by AF[1] and that AF-related strokes are generally more severe,[4,5] the cost of AF-related stroke could be at least ~€10 billion each year
  - Approximately two-thirds (66%) of stroke costs were direct healthcare costs; 26% were direct non-medical costs (such as informal care) and approximately 8% were indirect costs (loss of productivity or early retirement) (Figure 1)

Figure 1. Cost of stroke (millions) across Europe in 2010.[7]



- Stroke costs are also higher in patients with AF compared with costs in patients without AF
  - In the Berlin Acute Stroke Study,[13] the average direct cost of stroke for patients with AF hospitalized for acute stroke (followed up for 1 year) was considerably higher than for patients without AF (€11 799 versus €8817, respectively)
  - In a Swedish study of >6500 patients with first-ever stroke,[14] patients with AF had an average 3-year inpatient cost of €10 192, which was €818 higher than the average 3-year cost for patients without AF (€9374)

Improving stroke prevention: diagnosing atrial fibrillation earlier

- Although AF itself can be simple to diagnose, in many cases it goes undetected
- One major problem with AF is that it is often asymptomatic.[15] As a result, many patients are not diagnosed and do not receive the anticoagulation that they need
- In recent years, strategies have been developed to improve detection of AF: a first step towards providing therapy for the prevention of AF-related stroke
- Checking patients aged ≥65 years for an irregular pulse at their next visit and referring them for an electrocardiogram was an effective way of screening patients for AF in one UK-based primary care study.[16] The annual detection rate for new cases of AF in centres where patients were screened in this way was 1.64% per year, compared with 1.04% peryear in centres that did not have an activescreening programme
- Based on these figures, if such a screening programme was adopted in a primary care centre that previously had none, the centre could expect to see an approximate increase of 60% in the annual detection rate (e.g. approximately 1600 vs 1000 new cases per 100 000 patients per year), i.e. a 60% increase in the number of patients who could receive therapy for prevention of AF-related stroke

Preventing stroke in patients with atrial fibrillation: feasible and cost-effective, but underutilized

- For many years, oral anticoagulation with vitamin K antagonists (VKAs), such as warfarin, has been the 'gold standard' therapy for long-term stroke prevention in patients with moderate to high risk of stroke. In clinical studies, VKAs reduce stroke risk by an average of 64% compared with no therapy and by 38% versus aspirin[17]
- However, clinical trials are 'controlled' environments with strict trial conditions and careful anticoagulation monitoring.[18,19] In real life, VKAs are underused; several studies report anticoagulant use in <50% of AF patients who are at high risk of stroke (Figure 2)[20]
- Patients on VKAs may also spend much of their time (perhaps 45% on average) outside the 'target' therapeutic range for optimal therapy (referred to as the 'international normalized ratio' [INR] of 2.0–3.0).[21] Based on these numbers, perhaps 25–30% of patients with AF receive optimal VKA therapy at any one time
- Low time in therapeutic range (TTR) means that, for much of the time, a patient's INR is either too low, increasing the risk of ischaemic stroke, or too high, resulting in an increased risk of bleeding, especially intracranial haemorrhage (ICH). Because of this, low TTR (poor INR control) is associated with increased event rates and higher costs

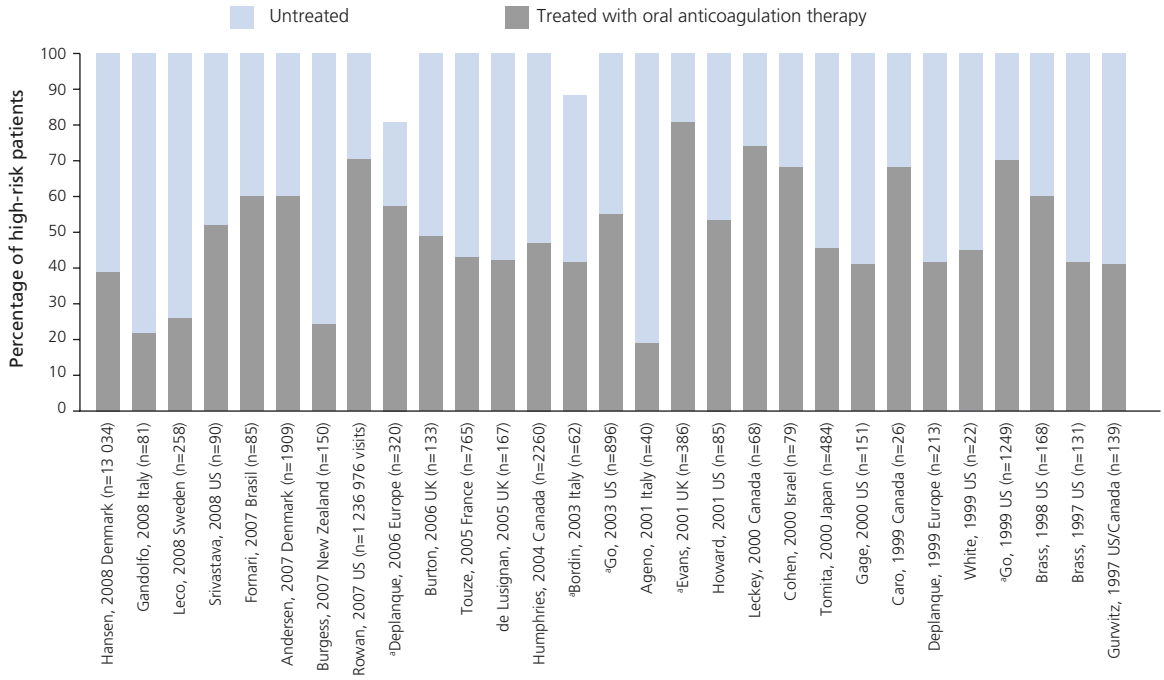
Why is optimal prevention not achieved in practice?

- Successful VKA therapy requires frequent monitoring and dose adjustment to keep the patient within the INR range of 2.0–3.0.[22] VKAs also have an unpredictable and variable dose-response and interact with many different foods, alcohol and drug classes[23]
- Many physicians overestimate the bleeding risk associated with VKAs and underestimate their benefits, particularly in the elderly.[24] Patients themselves may also be unwilling to use them because of fears of side-effects[25]
- Physicians are often concerned about a patient's ability to comply with VKA therapy because of the requirement for regular monitoring and dose adjustment, especially if the patient is elderly, lives alone or has cognitive impairment[26,27]

Suboptimal use of VKAs increases costs

- VKA therapy can be cost-effective for the prevention of AF-related stroke, even in elderly patients;[28] however, this depends on how well it is managed
- The cost of stroke per patient with AF in those who were anticoagulated in routine medical care

Figure 2. Patients with atrial fibrillation and prior stroke/transient ischaemic attack: oral anticoagulation levels as a proportion of patients eligible for oral anticoagulation therapy.



Adapted from *Am J Med*, vol. 123, Ogilvie IM *et al*. Underuse of oral anticoagulants in atrial fibrillation: a systematic review, 638–645.e4, copyright 2012, with permission from Elsevier.[20]

[a]Contraindications taken into account

(approximately 70% of patients) was more than double that for patients attending specialized anticoagulation clinics (approximately 30% of patients) ($3710 vs $1485 per patient with AF) in one US model (Figure 3).[29] Much of this extra cost stemmed from managing complications associated with VKA therapy, such as bleeding. It is likely that further strokes resulting from underuse also increased costs

Cost of VKA monitoring[a]

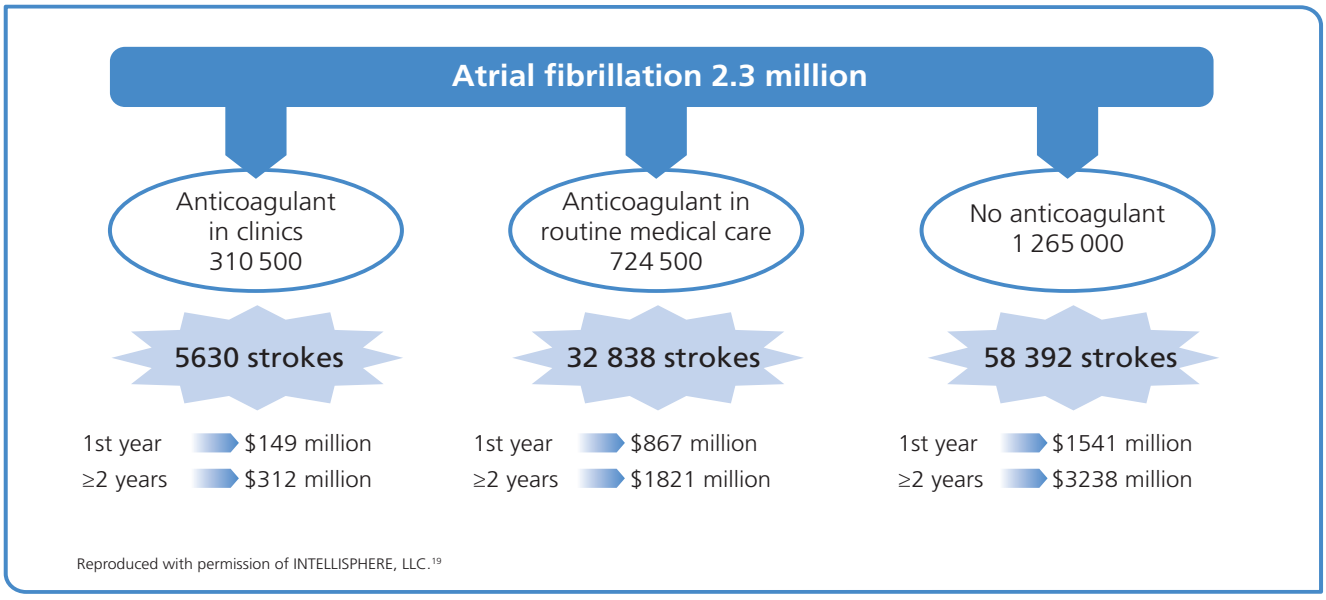
- The direct cost of routine INR monitoring has been estimated to be approximately €519 in the UK[30] and €513 in Denmark,[31] but can vary substantially depending on country and healthcare system.[32] For example, considerably higher annual costs of ~€1787 for the first year and ~€980 for the second year have been estimated for Swedish primary care[33]
- Cost estimates often do not take into account the indirect costs incurred by the patient and their family (e.g. lost productivity and transport to clinic). A questionnaire-based study of patients in the SPORTIF trial found that the average cost to patients of attending an anticoagulation clinic varied from €6.90 (France) to €20.50 (Portugal) per visit.[34] Over the course of many years, this can translate into substantial costs

Recent advances in prevention of atrial fibrillation-related stroke: non-vitamin K antagonist oral anticoagulants

- VKAs have their limitations, which contribute to their underuse
- In recent years, the efficacy and safety of the non-VKA oral anticoagulants (OACs) rivaroxaban, dabigatran and apixaban have been tested in large-scale global trials: ROCKET AF, RELY and ARISTOTLE[35–37]
  - Rivaroxaban (Xarelto®, Bayer HealthCare) and dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) have been approved for use and have reimbursement approval for the prevention of AF-related stroke in many European countries[38,39]

[a]Costs have been converted to Euros based on exchange rates at the time the study was carried out.

Figure 3. Results of a 2004 economic model showing projected costs of stroke across three different clinical practice patterns in patients with atrial fibrillation in the US.



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- These non-VKA OACs have distinct advantages over VKAs in that they:
  - Have predictable pharmacokinetics/ pharmacodynamics. This means that, unlike the VKAs, a given dose of a non-VKA OAC always achieves the same degree of anticoagulation
  - Have few food or drug interactions, in contrast to VKAs
  - Are taken as fixed once-daily (rivaroxaban) or twice-daily (dabigatran) doses
  - Require no routine coagulation monitoring
- The ROCKET AF and RE-LY trials with rivaroxaban and dabigatran, respectively, have shown that these agents are at least as effective as VKAs for the prevention of AF-related stroke. They are also associated with significant reductions in ICH compared with VKA therapy – a particularly feared complication among physicians[35,37]
- Both rivaroxaban and dabigatran were also found to be cost-effective by the UK's National Institute for Health and Clinical Excellence (NICE) 'within the range normally considered a cost-effective use of National Health Service resources'.[40,41] In addition, both anticoagulants have now received reimbursement approval in many countries, including Sweden, France, UK, Canada and Germany, among others
- Although the introduction of agents such as the non-VKA OACs are associated with increased drug costs relative to VKAs, the overall impact on the healthcare budget may be offset to some extent by the introduction of 'generics' for some key cardiovascular drugs. Furthermore, the improved safety profile of the non-VKA OACs can also be expected to further offset costs versus the VKAs

What can be done: action steps

- Huge numbers of strokes that are attributable to AF occur each year in the EU at an estimated annual cost of at least €10 billion. The associated clinical, social and human burdens are tremendous
- The critical challenge is for key parties – healthcare professionals, policy-makers, medical societies, patient advocacy groups and industry alike – to work together to reduce the burden of AF-related stroke across Europe

Actions for policy-makers

- Raise public awareness and understanding of AF, the signs and symptoms of AF, how AF can be detected via health checks, and the risk of AF-related stroke
- Implement and support effective practice standards and targets for healthcare professionals; for example, targets for AF screening and availability of a choice of therapeutic options that meets patient needs
- Implement national strategies for the early diagnosis of AF; these might include identifying patients who are at high risk of AF (owing to age, heart disease, alcohol consumption, high blood pressure orother chronic conditions), or by promotingroutine screening

- Ensure equal and timely access to the best available care (such as anticoagulation clinics and newer therapies) for all patients with AF across Europe, regardless of where they live or their background
- Ensure that stroke prevention is addressed in national healthcare plans and that AF is recognized as a serious and significant risk factor for stroke

Actions for medical societies and healthcare professionals

- Maintain a good working knowledge of the most recent clinical guidelines and educate practising physicians to help ensure that patients with AF receive the best possible care available to them[42,43]
- Inform colleagues in the healthcare profession of the importance of diagnostic checks for AF and of the benefit–risk of anticoagulation in patients with AF
- Ensure colleagues are aware of advances in development of new therapeutic options, and of their potential benefits
- Ensure colleagues in the healthcare profession are trained on the appropriate use of approved non-VKA OACs
- Educate patients on why they are receiving treatment and the importance of taking their anticoagulation therapy as prescribed
- Ensure that healthcare payers understand the clinical and economic advantages of having access to new, alternative therapeutic options and how this will help to reduce the number of at-risk patients receiving sub-optimal treatment through increased efficiency of treatment, thereby increasing prevention of AF-related stroke

Actions for patient advocacy groups

- Improve public awareness and understanding of AF and the risk of AF-related stroke. Campaigns such as the global 'Know Your Pulse' campaign and the 'Sign Against Stroke in Atrial Fibrillation' campaign both increase patient understanding and provide a collective means for patients to call on local policy-makers to improve care[44,45]
- Help patients to understand the benefits and risks of different therapies and to make informed choices regarding their own therapy. In addition, help patients to understand why they always need to take their therapy according to the prescribed schedule
- Ensure healthcare payers not only consider robust clinical data but also listen to the patient voice to ensure their decisions reflect patient need

AF-related stroke is a major burden that will continue to grow, and urgent action to tackle the problem is needed. However, the solution is in our hands – earlier diagnosis and better treatment will allow us to dramatically limit the impact of this devastating but preventable condition

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Conflicts of Interest

Dr Felicita Andreotti
Speaker/consultant: AstraZeneca, Bayer, BMS-Pfizer, Daiichi Sankyo, Eli Lilly

Dr Álvaro Avezum
Research contract: Boehringer Ingelheim, GSK; ACTIVE-W, ACTIVE-A. Consultant: Boehringer Ingelheim, GSK, BMS, Pfizer, AstraZeneca. National Coordinator/Steering Committee member: ACTIVE W, ACTIVE A, RE-LY, ARISTOTLE, AVERROES, ROCKET AF

Dr Alastair Benbow
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Professor John Camm
Advisor/speaker: AstraZeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson & Johnson, Mitsubishi, Novartis, Takeda

Dr Carlos Cantú
Advisory board member: Bayer Co. Speaker: Ferrer, Bayer Co.

Professor László Csiba
None

Professor Antonio Dávalos
Consultant: Bayer, Boehringer Ingelheim

Dr Jorge Gonzalez-Zuelgaray
Speaker: Bayer, Medtronic

Professor Shinya Goto
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Professor Dr Werner Hacke
Consultant: Boehringer Ingelheim, Bayer. Speaker: Boehringer Ingelheim, Bayer. Research support: Boehringer Ingelheim, unrestricted grant for ECASS 4 (an IIT)

Professor Graeme J Hankey
Honoraria: Executive Committees – AMADEUS (Sanofi-Aventis), ROCKET AF (Johnson & Johnson), BOREALIS (Sanofi-Aventis); Steering Committee – TRA 20P TIMI 50; Stroke Outcome Adjudication Committees – RE-LY, AVERROES. Speaker/Consultant: Bayer, Boehringer Ingelheim, Pfizer Australia

Professor Michael G Hennerici
None

Mellanie True Hills
None

Professor Richard Hobbs
Speaker fees/sponsorship: AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Merck, Novartis, Pfizer, Roche

Dr Torsten Hoppe-Tichy
None

Professor Dayi Hu
None

Professor Han-Hwa Hu
None

Professor Dr Paulus Kirchhof
Consulting fees/honoraria: 3M Medica, MEDA Pharma, AstraZeneca, Bayer Healthcare, Biosense Webster, Boehringer Ingelheim, Daiichi Sankyo, German Cardiac Society, MEDA Pharma, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer/BMS, Sanofi, Servier, Siemens, TAKEDA. Research grants: 3M Medica/MEDA Pharma, Cardiovascular Therapeutics, Medtronic, OMRON, Sanofi, St. Jude Medical, German Federal Ministry for Education and Research (BMBF), Fondation Leducq, German Research Foundation (DFG), European Union (EU). Travel support: ESC, EHRA, AFNET

Eve Knight
None

Joe Korner
None

Professor Dr Karl-Heinz Ladwig
None

Professor Antoine Leenhardt
Board member/conference speaker: Sanofi, Bayer, Daiichi Sankyo, Boehringer Ingelheim, Meda Pharma, Pfizer, MSD, St. Jude Medical, Boston, Servier

Dr Maddalena Lettino
Speaker: AstraZeneca, BMS, Boehringer, Eli Lilly, Daiichi Sankyo, Bayer, Pfizer, The Medicines Company. Advisory board member: Eli Lilly, The Medicines Company, BMS, Pfizer, MSD

Professor Gregory YH Lip
Consultant: Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi Sankyo, Biotronik, Portola, Boehringer Ingelheim. Speakers bureau: Bayer, BMS/Pfizer, Boehringer Ingelheim, Sanofi-Aventis

Trudie Lobban MBE
None

Professor Lorenzo Mantovani
Research grants: Bayer Research, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb. Consultant/Advisory Board member: Bayer

Dr Ayrton Massaro
None

Rod Mitchell
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Professor Bo Norrving
Advisor/consultant: PhotoThera, SERVIER, SYGNIS Pharma AG. Speaker/member of a speakers bureau: Allergan, Bayer HealthCare Pharmaceuticals. Boehringer Ingelheim Pharmaceuticals

Dr David KL Quek
None

Dr Walter Reyes-Caorsi
Advisory Board member: Bayer Uruguay S.A. Speaker: Bayer Uruguay

Professor Dr Kui-Hian Sim
Ongoing clinical trial and Investigator fees: Sanofi, Roche, Eli Lily

Professor Norio Tanahashi
None

Professor Hung-Fat Tse
Advisor/consultant: Bayer Schering Pharma, Boehringer Ingelheim Pharmaceuticals, Sanofi-Aventis, St. Jude Medical, Cordis Corporation, Medtronic, GlaxoSmithKline, Merck Sharp & Dohme Corp

Professor Panos Vardas
Consultant/honoraria: Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic, Menarini, Servier

Dr Xavier Viñolas
Consultant: Bayer, Medtronic, St. Jude Medical, Boston Scientific

Professor Byung-Woo Yoon
None

Professor Shu Zhang
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