

Atrial Fibrillation-Related Stroke: An Avoidable Burden

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Atrial fibrillation-related stroke: an avoidable burden

- ◆ Atrial fibrillation (AF) – an abnormal heart rhythm – increases the risk of stroke by almost *five times* compared with a normal heart rhythm (sinus rhythm)¹
- ◆ AF is the most common heart rhythm disorder and occurs with increasing frequency as people get older.² AF has been estimated to affect 0.1–4.0% of the population,^{2–4} depending on the country
 - More than 23 million people are affected by AF in Europe, China and the US combined^{4–6}
- ◆ Approximately 15 million people worldwide suffer a stroke each year.⁷ Of this number, approximately one-third die and another third are left permanently disabled. AF is associated with at least 15% of all strokes⁸
- ◆ AF-related strokes are more severe than those not related to AF; they are associated with an increased likelihood of permanent disability requiring institutional care, and also result in greater short- and long-term mortality⁹
- ◆ The annual cost of stroke is approximately €64 billion in Europe¹⁰ and \$34 billion in the US.¹¹ The cost of AF-related stroke is substantially higher than the cost of stroke in patients without AF¹²

The Berlin Acute Stroke Study showed that the average direct costs over the first year after hospitalization for stroke were more than 30% higher for patients with AF (€11 799) than for patients without AF (€8817)¹²

- ◆ Assuming that 15% of strokes are caused by AF and considering that AF-related strokes are generally more severe than strokes unrelated to AF, the cost of AF-related stroke could be at least €10 billion in Europe and \$5 billion in the US each year
- ◆ AF-related stroke is preventable, but many patients currently do not receive optimal prevention therapy. This booklet discusses which patients are not receiving appropriate therapy and the reasons for this. Actions for key parties are outlined to ensure that in future all patients with AF receive optimal therapy to prevent stroke

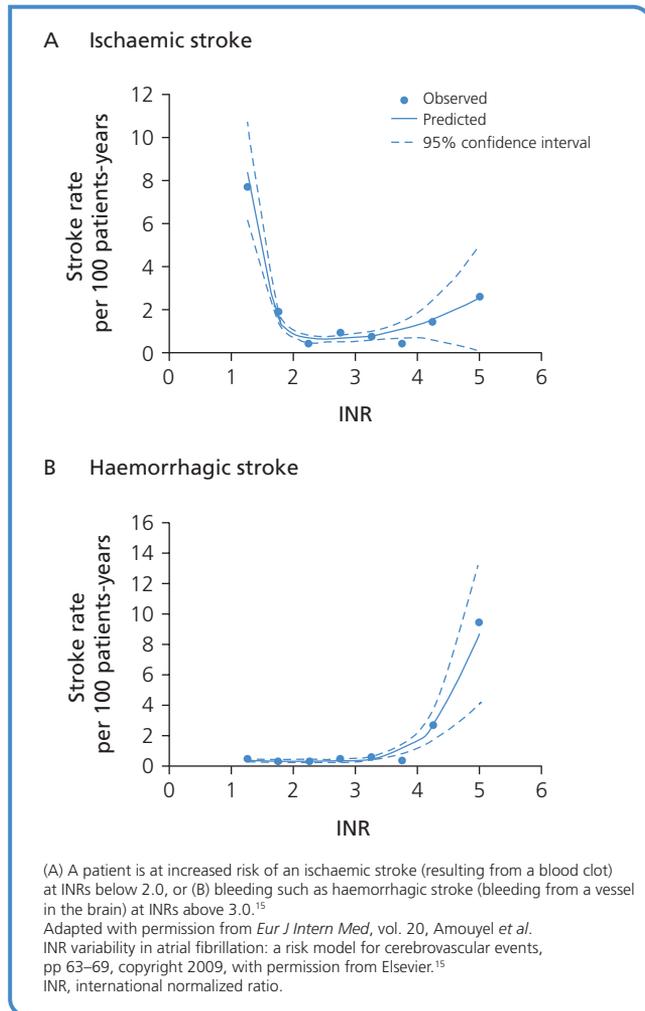
Atrial fibrillation-related stroke is preventable

- ◆ 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
- ◆ AF-related strokes are caused by blood clots that form within the heart and then travel to the brain. Anticoagulant drugs can prevent the formation of blood clots and, therefore, can reduce the risk of AF-related stroke
- ◆ Vitamin K antagonists (VKAs; such as warfarin, acenocoumarol and phenprocoumon) are oral anticoagulant (OAC) drugs that reduce the risk of stroke in patients with AF:¹³
 - By 64% compared with placebo
 - By 38% compared with aspirin (an antiplatelet agent)

For many patients, optimal anticoagulation is not possible

- ◆ Although VKAs can be effective, the anticoagulation effects of these agents are unpredictable, because of the indirect way in which they prevent clotting, and because they interact with many foods and drugs¹⁴
- ◆ Under similar conditions, the amount of anticoagulation a VKA provides varies substantially between patients, and in the same patient on a daily basis, depending on diet, medications and co-existing medical conditions.¹⁴ This means that:
 - The dose of a VKA must be tailored to each and every patient; a fixed-dose regimen is not possible
 - Patients need regular monitoring to ensure that the correct level of anticoagulation is achieved. This is done by measuring the 'international normalized ratio' (INR)
 - The dose of VKA must be adjusted to ensure that patients remain in the recommended safe and effective therapeutic INR range of 2.0–3.0
- ◆ An INR <2.0 is associated with increased risk of ischaemic stroke, and an INR >3.0 diminishes the ability of blood to clot, thus placing patients at risk of anticoagulant-related bleeding, including life-threatening events such as haemorrhagic stroke (Figure 1)¹⁵

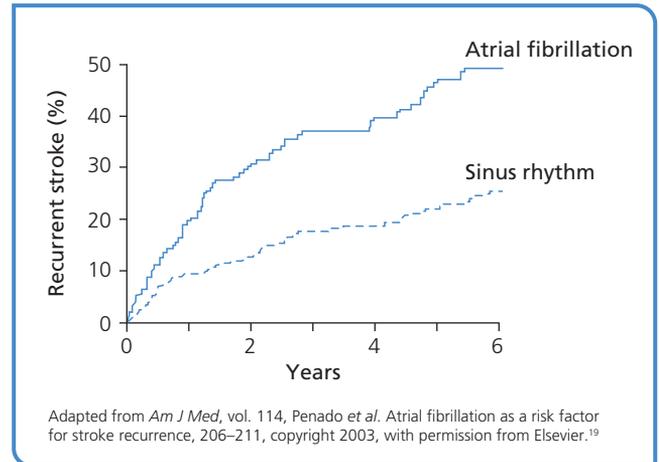
Figure 1. The INR should be maintained in the range 2.0–3.0 for patients receiving warfarin.



- ◆ Patients who have never been previously treated with a VKA may have poor INR control when initiating VKA therapy. In some patients a stable INR, or even a satisfactory amount of time within the therapeutic INR range, is never achieved
- ◆ In addition to diet and medications, co-existing medical conditions such as heart failure and prior stroke can affect an individual's ability to reach a target INR and remain within the therapeutic range^{16,17}
- ◆ The limitations of VKAs mean that, unfortunately, many patients with AF are not adequately treated to prevent stroke. There are certain patient groups in whom anticoagulation with VKAs is particularly difficult

Stroke prevention needs to be improved for all patients with AF

Figure 2. Cumulative stroke recurrence rate in non-anticoagulated patients with atrial fibrillation or in normal sinus rhythm.¹⁹



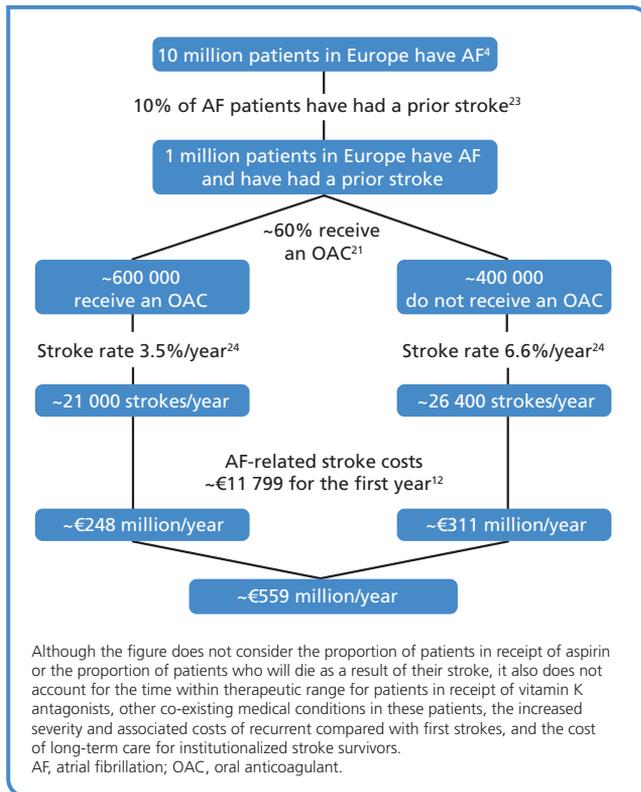
Patients for whom VKAs often fail to provide adequate prevention

- ◆ Patients with AF who have previously had a stroke (ischaemic or haemorrhagic)
- ◆ Prior stroke is a strong additional risk factor for stroke in patients with AF, increasing the risk by 2.5-fold compared with patients with AF and no history of stroke.¹⁸ Furthermore, stroke patients with AF have more than double the risk of recurrent stroke compared with stroke patients without AF (Figure 2)¹⁹
- ◆ Prior stroke also increases the risk of anticoagulant-related bleeding,²⁰ which complicates the management of stroke prevention in this patient group
- ◆ It is of great concern that most studies worldwide report guideline-recommended anticoagulation rates below 60% in this patient group, adding considerably to the clinical and cost burden of AF-related stroke (Figure 3)²¹
- ◆ This patient group is in particular need of effective and safer therapy options
- ◆ Most recurrent AF-related strokes are severe¹⁹ and, compared with a first stroke, are more likely to be fatal.²² This further emphasizes the need for improved treatment options for the prevention of AF-related stroke in this group of patients

Elderly patients with AF

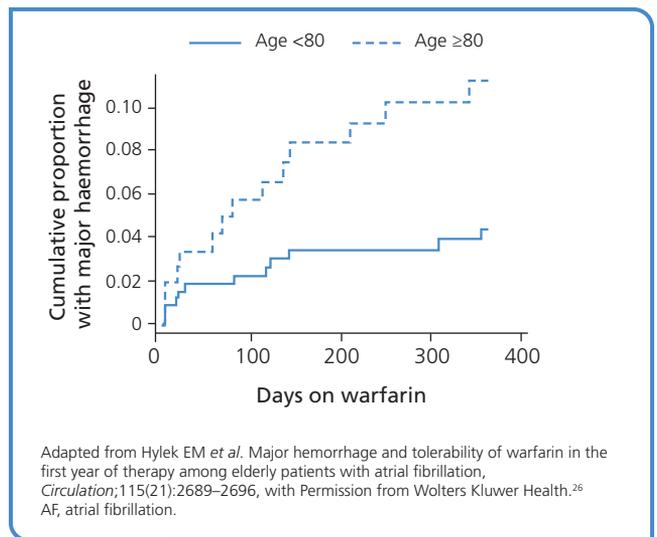
- ◆ AF affects 6–9% of people over 80 years of age.^{2,3} Furthermore, it is estimated that approximately 4% of 85-year-olds may have undiagnosed AF and, therefore, are unknowingly at risk of stroke²⁵

Figure 3. Hypothetical illustration of the excess strokes and economic burden resulting from under-treatment of patients with AF and prior stroke in Europe.^{4,12,21,23,24}



- ◆ The number of elderly people with AF is also predicted to rise as the proportion of elderly people increases worldwide²
- ◆ In patients with AF, the risk of stroke increases by 50% with each advancing decade of age;¹⁸ the annual stroke rate in patients not receiving VKAs rises from 2% for ages 65–74 years to 3% for ages 75–84 years, and to 5% in patients aged 85 years or older²⁴
- ◆ Unfortunately, the risk of major bleeding is also significantly higher in patients aged 80 years or older compared with younger patients (Figure 4)²⁶
- ◆ Physicians are often reluctant to prescribe VKAs to elderly patients because they:^{27,28}
 - Fear causing serious bleeding events (because the risk of bleeding with VKA therapy increases with age)
 - Consider elderly patients to be more prone to falls, which may further increase their risk of bleeding
 - Are concerned that compliance and the ability to attend INR monitoring appointments may be compromised by frailty or dementia

Figure 4. The rate of major bleeding events in patients aged 80 years or older with AF treated with vitamin K antagonists compared with younger patients with AF.²⁶

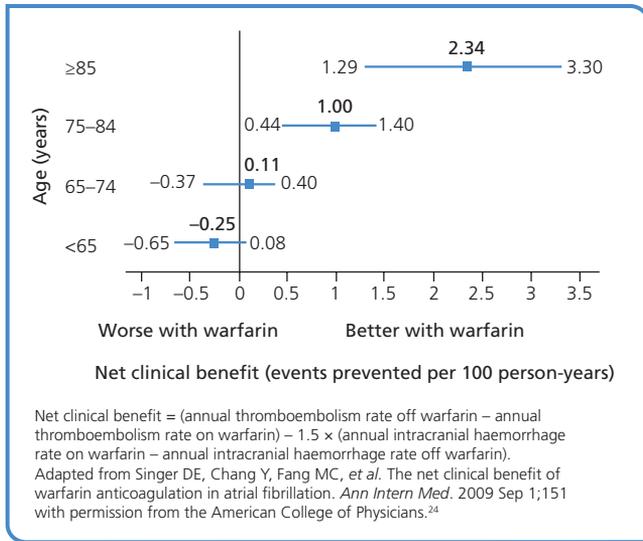


- ◆ These fears are often misplaced; evidence from elderly patients with AF receiving VKA therapy shows that the risk of a serious bleeding event from falling is so small that the benefits of therapy far outweigh the risk.²⁹ It has been reported that anticoagulation with a VKA reduced the incidence of AF-related stroke in patients aged 75 years or older without an increased risk of bleeding, compared with patients taking aspirin³⁰
- ◆ If the risk of serious bleeding, such as intracranial haemorrhage (including haemorrhagic stroke), caused by therapy is weighed against the benefit of stroke risk reduction, the overall benefit of VKA therapy actually increases with age (Figure 5)²⁴
- ◆ Despite the benefits of anticoagulation outweighing the risks in elderly patients with AF, many physicians under-prescribe effective therapy for the prevention of AF-related stroke
- ◆ There is a clear need for an OAC that does not require regular coagulation monitoring and carries a lower risk of intracranial haemorrhage

Patients with poor INR control

- ◆ As shown in Figure 1, an INR <2.0 is associated with increased risk of ischaemic stroke and an INR >3.0 places patients at risk of anticoagulant-related bleeding;¹⁵ therefore, it is important that a patient spends as much time as possible within the target INR range (2.0–3.0)

Figure 5. The net clinical benefit of warfarin by age.²⁴



- ◆ Many elderly patients with AF have one or more co-existing medical conditions for which they take many drugs that may affect the amount of time they are able to remain within the therapeutic INR range.²⁶ Other factors that affect time spent in therapeutic range include hospitalizations and dementia¹⁷
 - ◆ On average, patients on VKAs may be in the therapeutic range only about 60% of the time³¹
 - The quality of anticoagulation care varies considerably. The average amount of time patients spend with an INR within the therapeutic range varies between countries, and may also depend on whether VKAs are managed in specialized clinics or elsewhere³¹
 - ◆ Depending on the country, up to one-third of patients spend less than half of their time in the therapeutic INR range.³¹ It has also been suggested that only 10% of patients receiving VKAs are able to maintain a stable INR within the therapeutic range over the course of 1 year³²
 - ◆ Patients with poor INR control often decide to discontinue VKA therapy altogether,³³ leaving them at risk of AF-related stroke
 - ◆ The substantial number of patients with poor INR control highlights the need for more manageable therapeutic options to reduce the burden of AF-related stroke
- Patients who discontinue VKA therapy*
- ◆ Within 1 year of initiation of VKA therapy, about one-quarter of patients discontinue therapy.³³ The risk of AF-related stroke increases by 65% when a patient stops taking VKA therapy¹³
- ◆ This highlights the urgent need for alternative therapeutic options to reduce the burden of AF-related stroke in patients who are either unable or unwilling to take VKAs
- Suboptimal anticoagulation leads to avoidable strokes and increases costs**
- ◆ Despite being effective, VKAs are underused in practice because of their disadvantages. A recent global registry collecting real-life clinical data³⁴ showed that:
 - Only about 50% of patients with AF at risk of stroke, and for whom guidelines recommended OAC therapy, actually received such therapy
 - Approximately 25% of the patients who should have received an anticoagulant received aspirin, which is not as effective as OAC therapy in reducing the risk of AF related stroke¹³
 - ◆ Of concern, approximately 70% of patients with known AF who had an ischaemic stroke were not receiving anticoagulant therapy to prevent AF-related stroke at the time of the stroke³⁵⁻³⁷
 - ◆ Of 1000 patients with AF at age 70 years, it is predicted that if all patients commence VKA therapy and have perfect adherence to therapy (i.e. only discontinuing for bleeding events) with perfect INR control, these patients would experience about 500 ischaemic strokes collectively within their remaining lifetime (including both primary and recurrent strokes)³⁸
 - However, this does not represent the ‘real world’ situation. When accounting for ‘real-world’ INR control and VKA adherence, based on clinical practice observed in the US, it is predicted that there would be almost 500 additional strokes, collectively, in the same 1000 patients (984 ischaemic strokes in total)
 - If ‘real-world’ prescription of aspirin or nothing (instead of VKAs) to VKA-eligible patients is also considered, in addition to ‘real-world’ INR control and VKA adherence, there could be as many as 670 additional strokes overall in the same 1000 patients (about 1170 ischaemic strokes in total)
 - The remaining lifetime cost, including direct healthcare costs of clinical events such as stroke or bleeding, costs of routine INR monitoring and of long-term care, for one of these patients on VKAs is \$68 039 with perfect INR control versus \$84 518 with ‘real-world’ INR control, and \$87 248 if ‘real-world’ prescribing patterns and INR control are considered

Prevention of AF-related stroke needs to be improved for all patients; new options are urgently needed to increase the proportion of patients with AF who receive appropriate stroke prevention therapy

A solution: more therapy options to prevent more AF-related strokes

- ◆ Non-VKA OACs have been developed to overcome some of the limitations associated with VKAs. These newer agents can provide an important alternative for those patients unable to achieve adequate prevention of AF-related stroke with VKAs
- ◆ The non-VKA OACs rivaroxaban (Xarelto®, Bayer HealthCare) and dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) are currently approved for use for the prevention of AF-related stroke, and have reimbursement approval, in many countries globally, including the US and Europe. Approval of a third non-VKA OAC, apixaban (Eliquis®, Pfizer), is also expected
- ◆ In contrast to VKAs, non-VKA OACs:³⁹⁻⁴²
 - Have a predictable anticoagulation effect: a given dose always achieves the same degree of anticoagulation
 - Have few food or drug interactions
 - Are taken as fixed once-daily (rivaroxaban) or twice-daily (dabigatran, apixaban) doses
 - Require no routine coagulation monitoring
- ◆ The non-VKA OACs rivaroxaban, dabigatran and apixaban have been tested in three large-scale global trials (ROCKET AF, RE-LY and ARISTOTLE, respectively) and were found to be at least as effective as VKAs for stroke prevention in patients with AF, without increasing major bleeding⁴³⁻⁴⁵
- ◆ There were significant increases in gastrointestinal bleeding, compared with VKA therapy, with rivaroxaban and the higher dabigatran dose (150 mg twice daily), but not with apixaban or the lower dabigatran dose (110 mg twice daily)⁴³⁻⁴⁵
- ◆ Importantly though, compared with warfarin, the non-VKA OACs were all associated with significant reductions in serious bleeding events of particular concern:⁴³⁻⁴⁵
 - All significantly reduced intracranial bleeding – the most feared bleeding event
- Rivaroxaban and apixaban reduced fatal bleeding, which reached statistical significance for rivaroxaban, and dabigatran significantly reduced life-threatening bleeding
- ◆ In addition, the efficacy and safety profiles of the non-VKA OACs, compared with warfarin, were consistent in patients with prior stroke compared with the overall trial populations⁴⁶⁻⁴⁸
- ◆ Furthermore, properly managed non-VKA OACs have demonstrated efficacy and an acceptable safety profile in patients with moderate renal impairment, thereby providing an additional option for the prevention of AF-related stroke in this patient group^{44,49-51}
- ◆ Non-VKA OACs can, therefore, offer:
 - Treatment for patients who would be otherwise unlikely to receive any therapy at all
 - An option for patients discontinuing VKAs
 - No concerns over INR control with regard to monitoring or staying within a narrow therapeutic range
 - Simplified patient management with fixed daily dosing and no requirement for periodic dose adjustment
 - Markedly lower risk of intracranial haemorrhage and fatal bleeding
- ◆ Studies in the UK, Canada and the US have concluded that, overall, the non-VKA OACs are cost-effective alternatives to VKAs at the thresholds implemented in these countries, particularly when a patient does not have good INR control on VKAs⁵²⁻⁵⁶
- ◆ The cost of routine monitoring in patients taking VKAs can be substantial, both to healthcare providers⁵⁷ and to patients and their carers.⁵⁸ Because the non-VKA OACs do not require routine coagulation monitoring, expenditure associated with monitoring could be redirected to patient and physician education to improve adherence to therapy and patient management
- ◆ More importantly, the availability of the non-VKA OACs will hopefully increase the proportion of patients with AF receiving therapy to prevent AF-related stroke, thereby reducing the number of AF-related strokes and the huge clinical and economic burden that results

Call to action: how can we prevent more atrial fibrillation-related strokes?

- ◆ The availability of non-VKA OACs means that physicians now have more therapeutic choices, allowing a more patient-centred approach to therapy to prevent AF-related stroke. More treatment options could mean that more eligible patients with AF will receive the necessary therapy for stroke prevention. Prevention of AF-related stroke needs to be improved for all patients with AF, as well as the groups specifically discussed in this booklet
- ◆ Managing VKAs is challenging, especially for certain patients. Physicians need to be informed as to how the non-VKA OACs afford an opportunity to address those challenges. Physicians must also be educated as to the optimal management of the non-VKA OACs, and responsible prescribing of these agents
- ◆ Patient education is also needed to ensure patients know why they are taking an anticoagulant and the importance of complying with therapy. Patients need to be made aware of the educational materials available to them from patient advocacy groups such as the AF Association and StopAfib.org^{59,60}
- ◆ The critical challenge is for key parties – healthcare professionals, policy-makers, medical societies, patient advocacy groups and industry alike – to work together to ensure that all patients with AF at risk of stroke receive optimal therapy for the prevention of AF-related stroke

Actions for policy-makers

- ◆ Improve organizational infrastructure to facilitate delivery of novel therapeutics
- ◆ Ensure equal and timely access to the best available care (such as anticoagulation clinics and newer therapies) for all patients with AF, regardless of where they live or their background
- ◆ Ensure that prevention of AF-related stroke 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^{61–63}

- ◆ Inform colleagues in the healthcare professions 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 the development of new therapeutic options, including the new non-VKA OACs, and of their potential benefits
- ◆ Promote training for colleagues in the healthcare professions on the appropriate use of approved non-VKA OACs
- ◆ Educate patients on why they are receiving anticoagulant 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, thereby increasing prevention of AF-related stroke

Actions for patient advocacy groups

- ◆ 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 – improved treatment options (such as approved non-VKA OACs) will allow us to limit dramatically the impact of this devastating but preventable condition

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Conflicts of Interest

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