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Managing high-risk atrial fibrillation patients with multiple comorbidities

Gregory Y. H. Lip[1,2*]

Abstract

Atrial fibrillation (AF) patients are often high risk being elderly and having multiple comorbidities. Many risk factors are established to be associated with new onset incident AF, as well as AF-related complications such as stroke and hospitalisations. Multimorbidity AF patients are high risk and require a holistic approach to care, which should be proactively managing with an integrated care or holistic approach as per the ABC (atrial fibrillation better care) pathway.

Keywords Atrial fibrillation, ABC pathway, Elderly, Multimorbidity

Introduction

Atrial fibrillation (AF) is the commonest heart rhythm disorder and increasingly so, with an increasingly elderly general population. AF is commonly asymptomatic, yet confers a significant mortality and morbidity from stroke [1–3].

In appropriate management, pathway for such patients requires awareness, detection and evaluation or characterisation of the AF patients, followed by a holistic approach to their treatment, including stroke prevention, rate or rhythm control and the proactive management of comorbidities [4].

In the Asia–Pacific region, the recent Asia–Pacific Heart Rhythm Society (APHRS) AF registry reported that OAC use was reassuringly high at 77% with the majority being prescribed a NOAC, while at one-year follow-up 93% and 88% remained on vitamin K antagonists are NOACs, respectively [5]. Clinical outcomes were worse for patients with permanent and persistent atrial fibrillation.

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Characterisation and evaluation of the AF patient can be summed up using the 4S-AF scheme: stroke risk, symptom severity, severity of AF burden and substrate [6].

The APHRS AF registry also examined the clinical utility and prognostic implications of the 4S-AF scheme [7]. As expected, increasing adverse features by the 4S-AF scheme is associated with worse outcomes, consistent with prior analyses from Europe [8, 9] and China [10]. Nonetheless, if the 4S-AF domains are appropriately treated, for example, for stroke risk, anticoagulation therapy reduces the composite clinical outcome, as does appropriate rate or rhythm control and risk factor management [7]. If all the 4S-AF domains were successfully and appropriately treated, there was a clear beneficial outcome (adjusted odds ratio 0.384, 95% CI 0.229–0.646) [7].

This clearly highlights the importance of appropriate evaluation and characterisation, followed by appropriate treatment.

AF, multimorbidity and frailty

AF commonly coexists with various cardiovascular and non-cardiovascular risk factors, which often occur in clusters. These multiple comorbidities leading to the concept of 'multimorbidity', which is closely related to ageing and frailty. These multimorbidity factors also

change with ageing and incident comorbidities, with implications for AF and stroke risks [11–13].

In a large population-based cohort, where in the non-AF population, the incidence of multimorbidity as reflected by the Charlson comorbidity index (CCI) increases between 2002 and 2014 in a steady manner reflecting the increasingly aged population, whereas in the AF population this increases substantially steeper, with mean CCI 4.49 in AF patients and 1.06 in non-AF patients, by 2014 ($p < 0.001$) [14]. This increase in multimorbidity in AF is related to an increased risk of stroke, major bleeding and all-cause death. Despite these patients being at very high risk, there was an inverse relationship between increasing multimorbidity and the use of oral anticoagulation (OAC)treatment (OR 0.65 (95% CI 0.60–0.70) for CCI ≥ 4 versus score 0–3), leading to suboptimal thromboprophylaxis in this high-risk group (Fig. 1).

Another condition allying closely with AF and age is frailty. In a systematic review and metaanalysis on frailty, its prevalence and the impact on outcomes in subjects with AF, there is a clear increase in the prevalence of frailty with increasing age [15]. Frailty also increases with various comorbidities. For example, as the prevalence of stroke increases in a population, the prevalence of frailty increases. Increasing frailty has major implications for an increased risk of all-cause death (OR 5.56, 95% CI 3.46–8.94), stroke (OR 1.59, 95% CI 1.0–2.52) and major bleeding (OR 1.64, 95% CI 1.11–2.41) in patients with frailty.

The importance of comorbidities and patient-centred management is therefore reflected in contemporary guidelines for the management of AF [16]. Previously, a lot of emphasis has been on OAC for stroke prevention of AF, but now we clearly realise that with ageing, frailty and multimorbidity in AF patients, there is a great need for a more holistic or integrated care approach to managing AF.

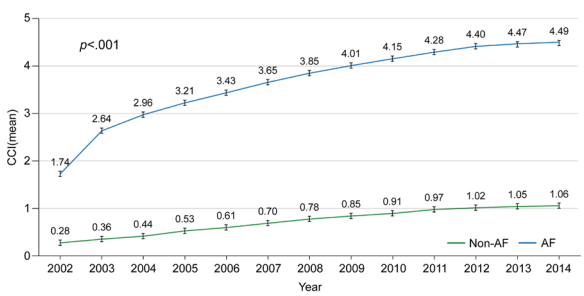

Fig. 1 Carlson comorbidity index trends according to atrial fibrillation diagnosis (Whiskers indicate standard deviation of mean. *AF* Atrial fibrillation, *CCL* Charlson comorbidity index)

The atrial fibrillation better care (ABC) pathway

The ABC pathway aims to promote a holistic approach to AF care, by focus on the main pillars of AF management (Fig. 2) [17]:

- A is for avoid stroke or anticoagulation, where the default is stroke prevention unless the patient is at low risk. Therefore, the first step is to identify the low-risk AF patients who do not require antithrombotic therapy. The second step is to offer stroke prevention to patients in one or more stroke risk factors. Step three is to make a choice about oral anticoagulation which is usually a non-vitamin K antagonist OAC (NOAC).
- B refers to better symptom management with patient-centred symptom directed decisions on rate or rhythm control.
- C is for cardiovascular and comorbidity optimisation, including attention to the patients psychological morbidity, as well as lifestyle changes, including obesity reduction, regular exercise, reduction of alcohol intake, etc.

The ABC pathway has been promoted in recent guidelines internationally [16, 18].

Adherence to the ABC pathway translates to a 58% reduction or cause death 63% reduction in cardiovascular death, 45% reduction in ischaemic stroke and a 31% reduction in major bleeding (Fig. 3) [19].

The ABC pathway has been prospectively tested in the mAFA-II trial which was a prospective cluster randomised trial using mobile health (mHealth intervention compared to usual care clusters [20]. The mHealth intervention used a mobile AF app based on the ABC pathway. In the primary analysis, there was a clear advantage of the mAFA intervention, on the primary composite outcome of stroke/SE, death and rehospitalisation in favour the ABC pathway compared to usual care [21]. This was largely driven by a marked reduction in hospitalisations.

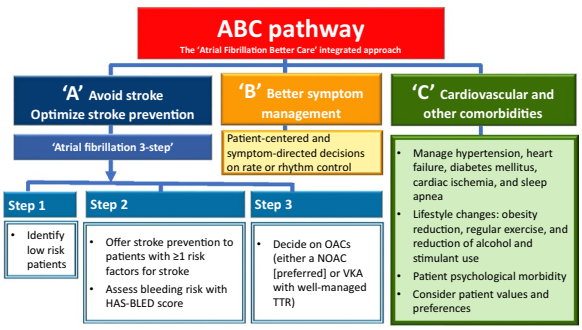

Fig. 2 The Atrial fibrillation Better Care (ABC) pathway

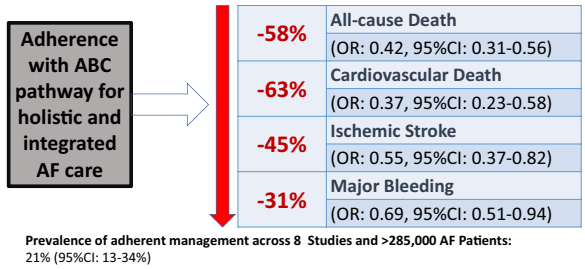

Fig. 3 Impact of ABC pathway adherence on clinical outcomes

In the mAFA trial multimorbidity subgroup [22], the findings were consistent, again, showing a clear reduction in the primary composite outcome with the ABC pathway compared to usual care (HR 0.37, 95% CI 0.26–0.53).

Lifestyle changes

Many modifiable risk factors, such as obesity, physical inactivity, hypertension, sleep apnea, diabetes, hyperlipidemia, alcohol and smoking, are associated with pathophysiological changes that contribute to the pathogenesis and clinical development of AF [23]. Each of these modifiable risk factors can be appropriately evaluated and treated to targets as recommended by various CVD prevention guidelines.

Healthy or unhealthy lifestyle factors tend to cluster together and such clustering of unhealthy lifestyle factors such as poor exercise, smoking and drinking results in an increased risk of new onset AF [24]. A cluster of three unhealthy lifestyle components was associated with a 22% higher risk of AF. Conversely, increasing adoption of healthy lifestyle behaviours leads to a reduction in AF-related outcomes, such as major adverse cardiovascular events, ischaemic stroke, hospitalisation for heart failure, and all-cause mortality [25]. Thus, lifestyle management is an essential part of the overall integrated care or holistic management of patients with AF.

Impact of oral anticoagulation in high-risk groups

It is clear from numerous randomised trials that when compared to placebo or control, oral anticoagulation with vitamin K antagonists (VKA, e.g. warfarin) reduces the risk of stroke/systemic embolism (SSE) by 64%, as well as all-cause mortality by 26%. The target INR range is 2.0–3.0 with attention to maintaining a high time in therapeutic range, to confer the best outcomes [26].

With today's contemporary OAC using the NOACs, there is a clear superiority and terms of efficacy and safety with NOAC use compared to warfarin in the reduction of stroke as well as major bleeding, particularly intracranial bleeding [27]. Furthermore, there is a 10% further reduction all-cause mortality with NOACs compared to VKAs. In the AVERROES trial, apixaban was superior to aspirin, with no difference in major bleeding in AF patients unsuitable or declined warfarin [28].

These clinical trial data with NOACs are supplemented by numerous real-world evidence data from all parts of the world [29]. In AF patients with multimorbidity, there is clear evidence from the ARISTOPHANES study for the improved effectiveness and safety of NOACs among patients with AF and multimorbidity [30]. Compared to warfarin, apixaban and rivaroxaban were associated with a lower risk of stroke/SE (HR 0.63, 95% CI 0.54–0.74; HR 0.70, 95% CI 0.64–0.77, respectively). Apixaban and dabigatran were associated with a *lower risk* of MB (HR 0.61, 95% CI 0.56–0.67; HR 0.75, 95% CI 0.66–0.86, respectively), and rivaroxaban was associated with a *higher risk* of MB (HR 1.06, 95% CI 1.01–1.12) compared to warfarin.

Other evidence from Asia from the Asia Pacific region also clearly shows and confirms the effectiveness and safety of the NOACs compared to warfarin [31]. When NOACs were compared against another NOAC, there were broadly similar rates of major bleeding between dabigatran, apixaban and edoxaban, and all three had lower rates of major bleeding when compared to rivaroxaban [31].

The elderly

In the elderly patients aged ≥ 75 years from the randomised trials, there was clear evidence that the NOACs did not cause excess bleeding and were associated with equal or greater efficacy than conventional treatment [32].

However, the 'extreme elderly' (e.g. age > 80 or > 90) are less well represented in clinical trials, and such patients often have associated comorbidities. In terms of prescribing in AF patients aged ≥ 80 between 2011 and 2019, the proportion prescribed warfarin is declining, whereas the proportion prescribed NOACs is increasing [33]. Nonetheless, there was still a concerning proportion of patients who are not on anticoagulation in this elderly group of patients; for example, in 2019, this was 60%.

This is despite the use of NOACs being associated with improved outcomes compared to warfarin, or no oral anticoagulation. Indeed, when NOACs were compared to no OAC use, there was a reduction in dementia, all-cause mortality and stroke [33]. When NOACs were compared versus warfarin, dementia, mortality, ischaemic stroke and major bleeding were all reduced.

In the extreme elderly, i.e. age 90 and above, with AF, in association with high-risk features such as chronic kidney disease, previous intracranial bleeding or gastrointestinal bleeding, untreated patients had very poor outcomes—and using this as the reference group, warfarin did not

confer an advantage and if anything, was associated with an increase in the composite clinical outcome, whereas the NOACs showed a clear reduction in the composite clinical outcome in favour of NOACs [34].

Extremes of body weight

Patients with extremes of body weight are underrepresented in the clinical trials of NOACs, although some reassuring data are available [35].

One American study [36] subdivided > 36,000 patients into 4 body mass index (BMI) groups: Group one were underweight with a BMI less than 18.5; Group two were normal or overweight, with a BMI 18.5 to 30; Group 3 with grade one two obesity with a BMI of 30 to 40; and Group 4 being grade three obesity with a BMI above 40. When NOACs were compared to warfarin, better safety and effectiveness were evident across all the BMI categories, including underweight and morbidly obese patients. Similar data were available from the Korean nationwide registries showing no significant interaction between BMI strata and effectiveness or safety with NOACs compared to warfarin [37].

Patients at high bleeding risk

Asian patients are at particular risk of bleeding when on antithrombotic therapy [38], and much interested has been directed towards its appropriate assessment and risk stratification [39].

Some high-dose NOACs such as dabigatran 150, rivaroxaban 20 mg and edoxaban 60 mg were associated with an excess of gastrointestinal bleeding compared to warfarin [27]. In real-world data, AF patients at high risk of gastrointestinal bleeding in the ARISTOPHANES study showed lower risk of stroke as well as major bleeding when compared to warfarin [40]. In patients with AF and prior bleeding events, the NOACs were associated with similar or lower risk of stroke or major bleeding versus warfarin and the variable risk of stroke/systemic embolism and major bleeding against each other [41].

Another group of AF patients underrepresented in the prospective randomised trials were AF patients with active cancer. In an analysis from the ARISTOPHANES data set, NOACs were associated with a lower risk of stroke/systemic embolism and major bleeding when compared to warfarin [42]. Dabigatran and rivaroxaban were associated with similar risks for stroke/SE and major bleeding compared with warfarin. Reassuring conclusions are evident from a recent systematic review and metaanalysis [43].

From the Taiwan registries, patients with AF with a history of cancer treated with NOACs, there was significant reduction in major adverse cardiac events, bleeding events, major adverse limb events and venous thromboembolism in favour of the NOACs [44].

Patients who with AF and chronic kidney disease (CKD) are at high risk of thromboembolism as well as major bleeding. A recent systematic review and meta-analysis showed that NOACs, particularly apixaban and edoxaban, presented superior efficacy and safety than warfarin in AF patients with CKD [45]. In AF patients with advanced CKD, apixaban was associated with the lowest risk of major bleeding among the OACs.

Patients with AF may have associated vascular disease and may present with an acute coronary syndrome or undergo percutaneous cardiovascular interventions (PCI) [46]. In this situation, the anticoagulated AF patient may require concomitant antiplatelet therapy, which increases the risk of bleeding, including ICH. Current guidelines [7] recommend the use of a short period of triple therapy (OAC, aspirin, clopidogrel) for up to 2–4 weeks [in patients at particularly high bleeding risk, the aspirin may be dropped even earlier], followed by OAC plus a P2Y12 inhibitor (usually clopidogrel) for up to month 6–12. Beyond 12 months, OAC monotherapy is recommended. The preferred OAC strategy is with a NOAC, rather than warfarin, given the lower potential for serious bleeding when used in combination with antiplatelet drugs.

Off label underdosing

In the ORBIT-AF registry [47], the practice of prescribing underdosing off label does is not associated with a reduction in major bleeding, but this translates to more strokes hospitalisations and all-cause mortality. Similar data were available from the Taiwan registries where off-label underdosing compared to on-label dosing was associated with more strokes, whereas for major bleeding there was no difference when off-label overdosing was compared to on-label correct dosing [48]. There was a clear increase in major bleeding in overdosed patients.

When NOACs were compared to warfarin, on-label dosing was associated with a similar risk of stroke, but markedly better safety in terms of major bleeding when compared to warfarin, whereas with off-label underdosing of NOACs, stroke was actually increased in the underdose NOAC group when compared to warfarin although major bleeding was reduced.

Conclusion

AF patients are often high risk being elderly and having multiple comorbidities. Many risk factors are established to be associated with new onset incident AF, as well as AF-related complications such as stroke and hospitalisations. Multimorbidity AF patients are high risk and require a holistic approach to care, which should be

proactively managing with an integrated care or holistic approach as per the ABC pathway.

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Declarations

Ethics approval and consent to participate
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Consent for publication
I consent.

Competing interests
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