Introduction

The 2016 European Society of Cardiology guidelines introduced the concept of integrated management of atrial fibrillation (AF). This involves four major pillars with patient involvement, multidisciplinary teams, technology tools, and access to all treatment options for AF [1]. Compared to usual care, such integrated management reduces the composite cardiovascular (CV) outcome of CV hospitalizations and CV deaths [2]. Additionally, AF related hospitalizations and strokes may also be reduced with integrated care [3,4]. Therefore, such model of integrated management can be extended to all clinical situations necessitating anticoagulation therapy is feasible. Venous thromboembolism (VTE) necessitates long-term anticoagulation. As India has substantial burden of VTE, incorporating integrated management model in VTE management in hospital and community setting can optimize the outcomes. Developing such model can be complex but effective and is therefore the need of the hour in patients with VTE in India.

Abstract

Atrial fibrillation (AF) is a prevalent dysrhythmic disorder. Use of wearable digital devices helps in screening AF and assist in optimized care. Integrated management of AF reduces the occurrence of adverse cardiovascular (CV) outcome. It is adequately established in the setting of AF with acute coronary syndrome. Extending the integrated management clinical situations necessitating anticoagulation therapy is feasible. Venous thromboembolism (VTE) necessitates long-term anticoagulation. As India has substantial burden of VTE, incorporating integrated management model in VTE management in hospital and community setting can optimize the outcomes. Developing such model can be complex but effective and is therefore the need of the hour in patients with VTE in India.

Keywords: Atrial Fibrillation; Venous Thromboembolism; Anticoagulation; Cardiovascular Outcome; India

The 2016 European Society of Cardiology guidelines introduced the concept of integrated management of atrial fibrillation (AF). This involves four major pillars with patient involvement, multidisciplinary teams, technology tools, and access to all treatment options for AF [1]. Compared to usual care, such integrated management reduces the composite cardiovascular (CV) outcome of CV hospitalizations and CV deaths [2]. Additionally, AF related hospitalizations and strokes may also be reduced with integrated care [3,4]. Therefore, such model of integrated management can be extended to all clinical situations necessitating anticoagulation therapy. Being a long-term process, anticoagulation therapy needs adequate supervision for its optimization. The integrated anticoagulation management is established in AF with coronary artery disease [1,5]. However, there is lack of integrated approach in patients with venous thromboembolism (VTE). Therefore, developing VTE specific integrated anticoagulation management is the need of the hour.

India has significant disease burden of VTE. The ARRIVE registry demonstrated that 23% patients of acute deep vein thrombosis (DVT) developed pulmonary embolism (PE) whereas 13% had only PE. The mortality rate was 7% among patients with VTE diagnosed during the hospital stay [6]. The ENDORSE study observed that among 53.6% of patients at-risk of VTE, only 58.5% and 39.5% of at-risk surgical and at-risk medical patients respectively received VTE prophylaxis [7]. As most VTE referrals are from family or general physicians and surgeons, majority of the VTE patients remain in follow-up with their local physicians. Optimizing educational and collaborative efforts among clinicians, patients, and their families/caregivers can ensure optimal outcomes for VTE patients. Here, we review the current evidence and guidelines recommendations of integrated anticoagulation management in AF with ACS and provide expert opinions for such integrated model for VTE in Indian context.
Diagnosis of AF: Current role of digital screening tools

Diagnosis of AF is typically based on ECG findings of irregular RR interval and no-discernible P-waves. An episode lasting for at least 30-seconds is considered as diagnostic of AF [1]. Asymptomatic, undiagnosed AF is common especially in elderly and in patients with heart failure. Paroxysmal AF is difficult to diagnose which necessitates repeated ECG monitoring. Using ECG screening, AF can be diagnosed in high-risk population such as elderly [8]. Therefore, use of ambulatory ECG monitoring can help in screening such individuals. With technological advances in newer digital tools, it is possible to diagnose AF. Majority of the wearable devices work on principle of single lead analogous to lead I and capture electrical signals from the fingers, thumb, wrist, or palms. The AliveCor devise has high sensitivity and specificity and is approved by the U.S. Food and Drugs Administration (FDA). The Omron HeartScan provides advantage that one of the electrodes on the device can also be placed on the chest. Being a stand-alone device, there is no need of a smart phone. Multiple AF screening devices are available or currently under development (e.g. MyDiagnostick, the Rekae100, MiniscopeM3, InstantCheck, AfibAlert, and Zenicore EKG) A smartphone app, the Cardiio Rhythm, detects the heart rate using phone’s camera has shown sensitivity and specificity similar to AliveCor [9]. The Apple Watch 4, can also perform single lead ECG. Apple Heart study identified irregular pulse in 0.52% (2162/419297) participants without diagnosed AF over median 117 days of follow-up. Among these participants, 34% had AF on subsequent ECG patch readings. The positive predictive value was 0.84 for identifying AF on the ECG simultaneously with a subsequent irregular pulse notification [10]. These data indicate feasibility of using wearable digital screening tools in diagnosis of AF. However, the accessibility and affordability may be a limiting factor in Indian setting.

Expert opinion: Digital tools are feasible in screening AF in undiagnosed patients. Affordability and availability are limiting factors in Indian setting.

Optimal antithrombotic management: AF with ACS

In patients with AF, antithrombotic management remains one of the most important therapeutic strategy to reduce the adverse CV outcomes. It is complicated by the presence of coexisting conditions such as renal or hepatic dysfunction, ACS, and recent stroke; which makes the anticoagulation management more challenging. In particular, AF with ACS poses significant challenge. Nearly, 10% of ACS patients may develop AF and the post-ACS mortality is 2.5 times greater than those who do not develop AF [11]. Requirement of anticoagulation for AF and antithrombotic therapy for ACS increases the bleeding risk substantially. Therefore, understanding the current evidence is necessary to make informed decisions on anticoagulation management in AF with ACS.

Anticoagulation in AF with ACS: Guidelines recommendations

European society of cardiology guidelines, 2016

The 2016 ESC guidelines recommend the following anticoagulation regimes in different coronary disease population:

- **AF patients with stable CAD undergoing elective coronary stenting:** triple anticoagulation with aspirin (75 - 100 mg/d), clopidogrel (75 mg/d) and oral anticoagulant (OAC) for 1 month balancing the risk of bleeding.

- **AF patients with ACS with stenting:** triple anticoagulation with aspirin, clopidogrel and oral anticoagulant for 1 - 6 months followed by dual anticoagulation (Aspirin/clopidogrel + OAC) for 6 to 12 months balancing the risk of bleeding.

- **AF patients with ACS without stenting:** Dual anticoagulation with aspirin or clopidogrel and oral anticoagulant for up to 12 months balancing the risk of bleeding [1].

OAC monotherapy is recommended after 12 months of initial anticoagulation therapy in all the above situations [1].

CHEST guideline and expert panel report, 2018

Based on the HAS-BLED score, the duration of anticoagulation therapy can tailored [5]. The recommendations from CHEST Guideline and Expert Panel Report are as below:

A. Balanced thrombotic and bleeding risk: Triple therapy with OAC, aspirin and clopidogrel for 1 month and continued to 3 months if possible followed by dual therapy (OAC plus clopidogrel) continued till 12 months and OAC alone thereafter.

B. Low thrombotic but high bleeding risk: Dual therapy (OAC plus clopidogrel) for 12 months followed by OAC alone.

C. High thrombotic but low bleeding risk: Triple therapy with OAC, aspirin and clopidogrel for 1 month and continued to 6 months if possible followed by dual therapy (OAC plus clopidogrel) continued till 12 months and OAC alone thereafter.

AHA/ACC/HRS focused update, 2019

Triple anticoagulation using OAC, aspirin and P2Y12 inhibitor can be considered. Clopidogrel preference over prasugrel has been suggested. After 4 to 6 weeks of therapy, transition to double anticoagulation is advised [12].

Compared to triple anticoagulation, reasonable alternatives to reduces the risk of bleeding included the following:

- Clopidogrel/ticagrelor + dose-adjusted Vitamin K antagonist
- Clopidogrel + low-dose Rivaroxaban (15 mg/d)
- Clopidogrel + low-dose Dabigatran (150 mg twice daily).

Expert opinion: From these guideline recommendations, individualization of therapy is necessary in AF patients with ACS or those undergoing stenting. In doing so, one should consider triple or dual therapy based on the risk of bleeding and risk of thrombotic events. Dose of novel oral anticoagulant and duration of P2Y12 inhibitor therapy also require consideration based on risk of bleeding. Determining CHA2DS2-VASC score and HASBLED score to assess cardioembolic and bleeding risk respectively is necessary in individualization of therapy.

Risk of bleeding: Dual Vs triple anticoagulation

In patients of AF with ACS undergoing PCI, standard anticoagulation consisting of triple therapy (OAC plus aspirin plus clopidogrel) reduces the thromboembolic risk effectively but the risk of bleeding is increased substantially. In assessing such bleeding outcomes, PIONEER AF-PCI trial was conducted in 2124 participants with nonvalvular AF who had undergone PCI. Patients were randomized to low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus dual-antiplatelet therapy (DAPT) for 1, 6, or 12 months (group 2), or standard therapy with a dose-adjusted VKA plus DAPT for 1, 6, or 12 months (group 3). Compared to group 3 (26.7%), rates of clinically significant bleeding were lower in group 1 and group 2 (16.8% and 18%). At the same time, cardiovascular death, MI, or stroke were nearly similar in three groups (6.5%, 5.6%, and 6.0% respectively). The results indicate low-dose of rivaroxaban is associated with lower risk of bleeding when considered as part of anticoagulation regimen in AF patient undergoing PCI [13]. In another randomized trial, RE-DUAL PCI trial, AF patients undergoing PCI were randomized to triple therapy (warfarin plus clopidogrel or ticagrelor plus aspirin) for 1 to 3 months or dual therapy (dabigatran 110 mg or 150 mg twice daily plus clopidogrel or ticagrelor). After a mean follow-up of 14 months, the incidence of major or clinically relevant nonmajor bleeding event was 15.4% in the 110-mg dabigatran dual-therapy group than 26.9% in the triple-therapy group. Composite efficacy endpoint of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization was equal in the groups (13.7% in two dual therapy groups vs 13.4% in the triple-therapy group) [14]. The AUGUSTUS trial was two-by-two factorial design study also involved
patients of AF with ACS or who had undergone PCI. In addition to a P2Y$_12$ inhibitor, these patients received apixaban or a VKA and aspirin or matching placebo for 6 months. Major or clinically relevant nonmajor bleeding was significantly lower in patients receiving apixaban than those receiving a VKA (10.5% vs 14.7%; hazard ratio, 0.69; 95% confidence interval [CI], 0.58 to 0.81; P < 0.001) and in patients receiving aspirin than those receiving placebo (16.1% vs 9.0%, hazard ratio, 1.89; 95% CI, 1.59 to 2.24; P < 0.001). The incidence of ischemic events was similar between apixaban and VKA groups. However, the incidence of death or hospitalization was significantly lower with apixaban (23.5% vs. 27.4%; hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P = 0.002). No significant difference were reported for the incidence of death or hospitalization between aspirin and placebo [15]. The evidence from these trials are further substantiated by Gargiulo., et al who performed a meta-analysis to determine the safety and efficacy of double versus triple antithrombotic therapy (DAT vs. TAT) in patients with AF and ACS or who had undergone PCI. Compared to TAT, major or clinically relevant non-major bleeding was significantly lower with DAT [risk ratio (RR) 0.66, 95% CI 0.56 - 0.78; P < 0.0001]. However, the risk of stent thrombosis was increased in DAT (RR 1.59, 95% CI 1.01-2.50; p = 0.04). The outcomes of all-cause and CV death, stroke and MACE did not differ significantly between the groups. NOAC-based DAT was associated with significantly lower risk of intracranial bleeding than VKA-based TAT [16].

**Expert opinion:** Double antithrombotic therapy especially using NOAC with P2Y12 inhibitor is associated with lesser risk of bleeding than triple anti-thrombotic therapy involving VKA and aspirin treatment.

**Integrated management of anticoagulation in venous thromboembolism: Way ahead for India**

Venous thromboembolism (VTE) is associated with adverse outcomes. In the hospital setting, ARRIVE registry data from India showed that 64% develop acute VTE without PE, whereas 23% had PE. The mortality rate was 7% in patients developing VTE during hospitalization and 1% among those who were diagnosed with diagnosed VTE [6]. In acute care setting, almost half of the patients were identified at risk of VTE in the ENDORSE study. Among such patients, VTE prophylaxis was given to 58.5% and 39.5% at risk surgical and medical patients respectively [7]. In India, majority of patients with VTE are primarily referrals from the general physicians, internists, and surgeons. Only 21% of patients visit the hospital directly and post-discharge, they remain in the follow-up with local physician only [6]. Therefore, there is an unmet need of developing integrated care model for anticoagulation management in VTE especially in India to improve the patient outcomes. This integrated care model is necessary to optimize the patients transition from hospital to community care.

The benefits of such integrated care can be multifold. A greater reach to the patients with adequate use of anticoagulants is the first advantage which in turn can reduce the rate of thromboembolic complications. Also, decentralized approach can help in better selection of patients suitable for anticoagulation. At the same, it may help in strategizing the bleeding risk more efficiently and help improve the anticoagulant compliance [17]. The 2019 ESC Guidelines for the diagnosis and management of acute PE developed in collaboration with the European Respiratory Society (ERS) proposed an integrated model for patient care after PE. The objective of this model is to ensure optimal transition from hospital to community care [18]. The requisites identified for effective model included the following:

- Qualified nurses
- Interdisciplinary working with physicians for care of in-hospital as well as ambulatory patients
- Standard treatment protocols (adapted to the capacities of each hospital)
- Bidirectional referral pathways between general practice and the hospital.

**Expert opinion:** Considering the extensive burden of VTE in India, developing an integrated anticoagulation management model is the need of the hour. In our opinion, developing such model can be complex but effective. We urge scientific bodies in India to take a lead in developing such integrated care model to further optimize the outcomes of patients with VTE.

Integrated Management of Patients on Anti-coagulation Therapy (IMPACT): A Review and Expert Opinion

Conclusion

Recently, integrated model with patient involvement, multidisciplinary teams, technology tools, and access to all treatment options in management of AF was introduced in ESC guidelines. Integrated management of patients on anticoagulation therapy is well established for patients AF with ACS and who had PCI. As VTE is one of the major disorders managed with anticoagulation, extending such integrated care model to VTE patients would benefit in long-term. As India has substantial burden of the VTE, developing such integrated model is of critical importance to optimize outcomes in care delivered at hospital and in community.

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Disclosure

The expert meetings were done in association with Abbott Healthcare Pvt. Ltd. The views expressed and discussed in the meetings and stated in this consensus article are the views of the authors and not of Abbott Healthcare Pvt. Ltd.

Bibliography


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