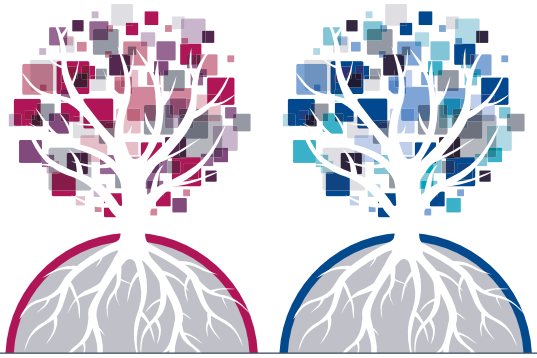
# GARFIELD in Focus



EDITION 3

Welcome to the third edition of the *GARFIELD in Focus* newsletter, a bimonthly communication from the Thrombosis Research Institute (TRI), bringing you data and insights from our Global Anticoagulant Registry in the Field (GARFIELD) registries, GARFIELD-AF and GARFIELD-VTE. With thanks to Professor John Camm, Professor Sylvia Haas and Dr Clifford Smith for their contributions.

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# OUR FOCUS

## What GARFIELD tells us about 10 years of NOAC use

For over 50 years, vitamin K antagonists (VKAs) were the only available oral anticoagulants (ACs). In 2008, the non-vitamin K antagonist oral anticoagulants (NOACs) were introduced, offering fewer drug interactions and a faster onset of action. NOACs either directly target the coagulation enzyme thrombin (e.g. dabigatran) or inhibit Factor Xa (e.g. rivaroxaban, edoxaban, apixaban).

The approval and use of NOACs has evolved rapidly over the last decade, following the outcome of several large clinical studies. These drugs were initially licensed for the prophylaxis of venous thromboembolism (VTE) in orthopedic surgery. Several subsequent studies proved their effectiveness and safety, which led to the expansion of their marketing approval for multiple indications, including prophylaxis of systemic embolism and stroke in patients with non-valvular atrial fibrillation (AF), as well as for the treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT).

The evaluation of data from the GARFIELD registries has provided a valuable perspective on the clinical role of the NOACs in everyday clinical practice. Real-world evidence has also shown that despite the advantages of the NOACs, their adoption into clinical practice was slower than originally anticipated, possibly due to concerns regarding medication adherence without laboratory monitoring and the lack of a reversal agent.

Additionally, the cost impact of moving a large proportion of the anticoagulated population from VKA to NOAC therapy was prohibitive, despite the long-term cost-effectiveness of these therapies.

In the later years of the study, it is evident that as practitioners and healthcare systems in some parts of the world have gained familiarity with NOACs and their effectiveness in everyday practice, their use has increased substantially over time. The GARFIELD-AF registry has shown a positive trend in newly diagnosed patients with AF receiving guideline-recommended AC therapy over a 6-year time period [from 42.1% in cohort 1 to 57.7% in cohort 5]. This change in prescribing practice has been predominantly driven by the increased use of NOACs [up to 43% in 2016] and a decline in the prescribing of VKAs or antiplatelet (AP) therapy alone [from 36% to 17%] or in combination with anticoagulants. For example, the Japanese guidelines no longer recommend AP for stroke prevention in patients with AF, and European Society of Cardiology and National Institute for Health and Care Excellence (NICE) guidelines also restrict the use of aspirin and other AP therapies for patients who refuse anticoagulation.

What has also become increasingly clear from the GARFIELD registries is that treatment patterns can vary substantially from country to country [range: 31% to 93%] and even for countries within the same region.

As we continue to analyse the data from GARFIELD-AF, it will be interesting to see the impact of these variations in clinical practice on patient outcomes.

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# INSIGHT: AF

## Exploring the evolution of AF guidelines and their clinical significance

Recent years have seen the western guidelines for the management of patients with atrial fibrillation (AF) reviewed and refined with the inclusion of non-vitamin K antagonist oral anticoagulants (NOACs) and exclusion of antiplatelet therapy (AP) for stroke prevention. At the same time, they have become sharper and more appropriate in defining the threshold for recommended anticoagulant (AC) therapy.

The GARFIELD-AF registry showed that the majority of patients enrolled with newly diagnosed AF and at least one investigator defined risk factor for stroke met the recommended threshold for AC therapy (83.2% according to the 2012 ESC and 2014 AHA/ACC/HRS Guidelines, and 77.8% of patients according to the 2016 ESC Guidelines).

However, of those who met the criteria for AC recommended treatment, AC ± AP was prescribed approximately two-thirds of the time. We have shown underuse of AC therapy is still common. Bleeding events, both severe and nuisance bleeds, and a perceived 'high risk of bleeding' on anticoagulation among the elderly (the principal reason), are the most common reasons for withholding AC after a diagnosis of AF.

The GARFIELD-AF data confirmed that appropriate treatment of high-risk patients (patients with atrial fibrillation and a $CHADS_2$ score of ≥2 are defined as at a "high-risk" of stroke (1.9% to 7.6% annually)) who meet the Guideline criteria for AC therapy was associated with a net clinical benefit due to the considerable reduction in rates of stroke/SE and all-cause mortality that exceeded the risk of major bleed with AC therapy.

The evidence from several clinical trials show that bleeding risk on aspirin is not much different to the bleeding risk on AC therapy, while VKA and NOACs, but not aspirin, effectively prevent strokes in AF patients. Encouragingly, GARFIELD-AF has shown that there has been a gradual decrease in inappropriate prescribing of antiplatelet (AP) therapy over time – reflecting the change in guideline recommendations of AP therapy.

In conclusion, GARFIELD-AF offers a unique opportunity to obtain a comprehensive, contemporary description of the AF patient spectrum which ultimately allows a bridging of the gap between research and clinical practice.

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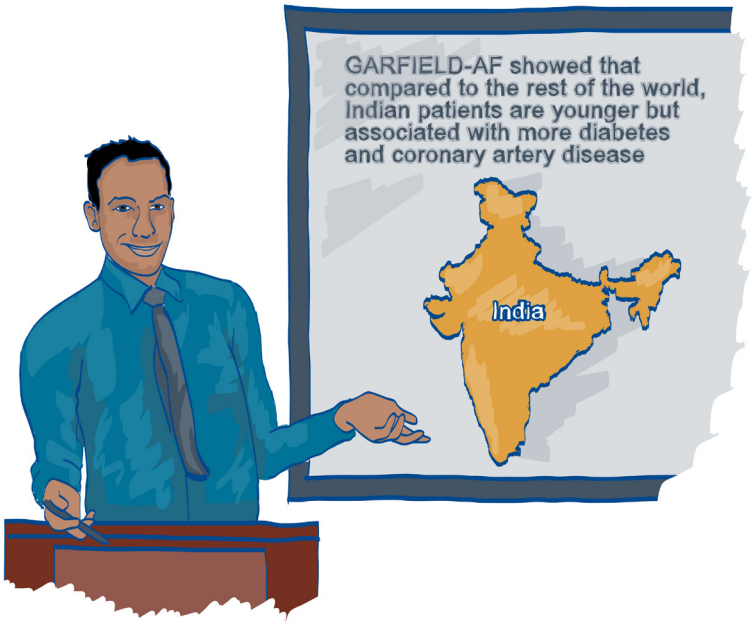
# HIGHLIGHT: AF
## Shedding light on NVAF in India

The GARFIELD-AF registry is the first study (to our knowledge) to describe the trends in stroke prevention treatment and record the burden of disease associated with non-valvular AF in India. The patients in GARFIELD-AF represent a different aetiology for AF that has not been previously studied in India since none of the patients in GARFIELD-AF have rheumatic valvular heart disease (RVHD) compared with up to 60% of patients from other registries in India.

Data presented at the 69th Annual Conference of the Cardiological Society of India (CSICON 2017) in Kolkata, India in late 2017 showed that the mean age at diagnosis of non-valvular AF was 65.8 years with hypertension being the most prevalent risk factor for AF. Despite documenting a lower average body mass index (BMI) in patients from India compared with the average BMI globally, diabetes was prevalent in over a third of Indian patients and cardiovascular comorbidities, such as coronary artery disease, were higher than globally at the time of diagnosis of AF. Interestingly, compared to the rest of the world, Indian patients are younger but associated with more diabetes and coronary artery disease.




The study also revealed antiplatelet therapy to be the most common antithrombotic treatment for prevention of AF-related stroke in India (despite AP no longer being recommended by Asian guidelines). In contrast, NOACs were seldom prescribed, apart from a slight increase in prescribing among patients with the highest risk of stroke, possibly due to the later approvals of NOACs in India.

Although the use of antithrombotic therapy and its monitoring are major challenges for the Indian healthcare system, patients at a high risk of stroke are as likely to receive anticoagulation therapy when compared with the global average, but tend to be underdosed as suggested by the INR.

The global GARFIELD-AF registry continues to shed light on the homogeneity and heterogeneity of baseline characteristics and treatment patterns in patients with newly diagnosed AF.

# INSIGHT: Exploring the clinical value of NOACs in patients with CAT

Patients with cancer, particularly those undergoing chemotherapy and other aggressive cancer treatments, are at an increased risk of VTE. Those patients who face the dual challenge of cancer and VTE have a lower survival rate than those without VTE.

The current guidance calls for low-molecular-weight heparin (LMWH) for treatment and secondary prevention of cancer-associated thrombosis (CAT). However, initial data from two trials late last year suggested that there was good reason for optimism around the use of NOACs for VTE treatment in patients with cancer. This followed an analysis which found that people with cancer treated with rivaroxaban for blood clots had significantly fewer emergency room visits and lower healthcare costs at the end of therapy than those given standard treatment.

The two trials – HOKUSAI-VTE CANCER and the Select-D pilot trial – directly compared treatment with LMWH and NOACs in patients with cancer and VTE and are the first head-to-head comparisons of these drug classes in patients with CAT.

The findings of both are encouraging. HOKUSAI-VTE CANCER found that oral edoxaban was non-inferior to subcutaneous dalteparin with respect to the composite outcome of recurrent VTE or major bleeding. The rate of recurrent VTE was lower but the rate of major bleeding was higher with edoxaban than with dalteparin. The SELECT-D pilot trial researchers found that treating with rivaroxaban resulted in a very low VTE recurrence rate at six months (4%) compared to dalteparin (11%). A similar number of major bleeds was reported across both trial arms, although there was more clinically relevant non-major bleeding with rivaroxaban than with dalteparin.

Both trials suggest the possibility that in the near future, NOACs may also be recommended as one of the standards of care for VTE treatment of patients with CAT; although more data are needed to determine the bleeding risk in these patients.

Bringing a real-world perspective to the field of VTE, preliminary data from the GARFIELD-VTE registry were presented at ISTH in July 2017. A subgroup analysis highlighted the differences in the treatment patterns of VTE in patients with active cancer compared to those with a history of cancer or no cancer. Patients with active cancer (56.1%) were more likely to receive LMHW as initial therapy than those with a history of cancer (15.9%) or no cancer (9.2%). GARFIELD-VTE confirmed that LMWH remains the standard of care for the treatment of CAT in the majority of cases.

As further insights from GARFIELD-VTE emerge, these will help to provide a clearer picture and potentially influence potential changes to treatment guidance in the future.

# HIGHLIGHT: VTE

## VTE in South Africa, and why this is an important subject for future research

One of the core goals of the GARFIELD-VTE registry is to describe the clinical and economic outcomes for patients with treated acute venous thromboembolism (VTE) in real-world settings, using unprecedented insights from unmatched real-world data to truly understand PE/DVT and its treatment.

South Africa is an important and perhaps unique case when it comes to assessing uncommon risk factors in VTE. The clinical characteristics of the South African patient population reveal significant differences to the rest of the world, making this analysis an important and instructive case study for understanding the value of studies such as GARFIELD-VTE.

Firstly, the age of the average patient is under 40 - markedly younger than the global average. Secondly, female preponderance is at 72-74%, which aligns with the higher published incidence of VTE in young women observed in other studies from Sub-Saharan Africa. And finally, the patient population also suffers more acute diseases and has more comorbidities compared to statistics worldwide - in South Africa an estimated 35-50% of patients with acute disease suffer from HIV and 21-35% from tuberculosis (TB).

This high prevalence of HIV/TB in the population is suspected to be behind the increase in VTE incidence in South Africa. It is thought that there are more than 200,000 cases of the VTE in South Africa each year leading to approximately 20,000 deaths, though the precise figures are currently unknown. This provides an excellent reason for continuing to analyse the GARFIELD data in this regard.

GARFIELD-VTE aims to provide a contemporary picture of VTE patient characteristics in South Africa, as well as offer insights into the management of VTE in the country - allowing a comparison with the global clinical picture.

Commenting on the importance of these data, Dr Clifford Smith, a GARFIELD-VTE national coordinating investigator said: “This information is vital in fostering new research in VTE in a unique clinical setting, which may provide important insights of global significance.”

# SPOTLIGHT:
# New TRI website with quick links to GARFIELD sites

You can now access the GARFIELD-AF and GARFIELD-VTE websites directly from the new look TRI website, launched in April. Links are available in the 'Quick Links' and 'Current Projects' sections, allowing you to take advantage of the publications, presentations and key findings from our GARFIELD registries.

In addition to a brighter look and enhanced features, the website contains information about TRI and about thrombosis, as well as information on all of our current clinical and laboratory research programmes. Under the 'Clinical Research' section you can access the TRI project websites, including the GARFIELD studies, reinforcing the breadth and depth of TRI's expertise in thrombosis.

The expanded website also includes:

- A 'Thrombosis News' aggregator that features recent stories on thrombosis from around the world
- A 'Latest Press Releases' feature that includes links to the most recent press releases from the various TRI registries and study websites
- A 'Quick Links' feature that allows for easy access to our video content, infographics and other resources

We've also added new sections to the site, including a Media section to ensure journalists wanting to write about anything thrombosis-related have access to accurate and up-to-date information.

Do log on (http://www.tri-london.ac.uk/) and let us know what you think!

AF Garfield global anticoagulant registry in the field VTE Garfield global anticoagulant registry in the field

To view the full newsletter on either of the GARFIELD websites, please select one of the above logos

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