Welcome to the April 2019 edition of GARFIELD in Focus, published by 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.

In this issue we consider the past, present and future of global clinical research in thrombosis and anticoagulation. We share our big picture thinking as well as some detailed insights into specific areas of current analysis to demonstrate the value that has been derived, and will continue to be derived, from the GARFIELD registries. The ultimate aim always is the practical application of these insights to benefit our patients.

Our guest editors for this edition are: Professor Harold Darius, Professor and Director of the Department of Cardiology, Angiology, Nephrology and Intensive Care Medicine at the Vivantes Neukoelln Medical Center in Berlin, Germany, and Professor Henri Bounameaux, Professor of Medicine and Dean of the Faculty of Medicine of the University of Geneva, Switzerland.

**OUR FOCUS: AF & VTE**

The past, present and future of our global thrombosis registries

Once a year, we take the time to reflect on how we got here, where we are now and where we go next.

**The past**

When we started the GARFIELD-AF registry in 2009, our mission was to enhance the understanding of the burden of thromboembolic stroke and identify opportunities to incorporate innovations designed to improve outcomes, safety and utilisation of healthcare resources. We devised a unique design and methodology that would elicit real-world insights to clarify atrial fibrillation (AF) treatments and outcomes for patients, clinicians and healthcare providers as they evolve over time.

A key resolution was that the registry would be governed by the highest academic and ethical standards in generating, disseminating and communicating the research findings.

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**OUR FOCUS**
The past, present and future of our global thrombosis registries

**INSIGHT: AF**
The value of AF registries

**HIGHLIGHT: AF**
AF in the Middle East and Asia – the same, but different

**INSIGHT: VTE**
Anticoagulation in VTE: How long is long enough?

**HIGHLIGHT: VTE**
What GARFIELD-VTE tells us about upper extremity vs. lower extremity DVT

**SPOTLIGHT**
How we’re using machine learning and artificial intelligence in GARFIELD
Being meticulous in addressing the methodological challenges of real-world data was critical to ensure credibility. To capture a comprehensive picture on the burden of disease, the registry design needed to include prospective patients with long-term follow-up; so we recruited over 57,000 newly-diagnosed AF patients and followed them up for 2-8 years. Our audit and quality control standards were based on 20% source data verification under supervision of an independent Audit Committee, to ensure high data quality. Effectively describing everyday clinical practice involved an appropriate site selection procedure, with randomised selection of sites across a range of national care settings. Unrestrictive inclusion criteria, without exclusions for comorbidities or treatment, allowed for enrolment of representative patient populations. A few years later with GARFIELD-VTE, we applied the same rigorous methodological approach, and similarly with RIVER, our first drug registry.

**The present**

Fast-forward to today, and we now have a substantial dataset. Recruitment across all three registries is complete and we have data on 73,193 patients. Follow-up is ongoing, and we already have 159,742 follow-up years recorded. Our tally of peer-reviewed publications stands at 28, with 75 abstracts presented at congresses and meetings across the globe.

Most importantly GARFIELD is providing critical lessons for clinical management that are being applied across the globe to benefit patients.

Significantly, the real-world evidence we are generating is being applied to answer crucial clinical questions. The branches of inquiry that we have identified across both registries cover burden of disease, treatment practices and patterns both in the acute and long-term, clinical outcomes, geographical differences, risk stratification and health economics.

We have established definitively that prospective studies with newly-diagnosed patients are required to capture a comprehensive understanding of the burden of disease. Prospective incident cohorts are especially important in cases where the burden is greatest early in the natural history of the disease.

We have set the standard for data quality in large-scale prospective registries. Importantly, we are also changing the understanding of the landscape in AF. Our GARFIELD-AF online risk tool, while still in its infancy, has been designed to facilitate decisions on prescribing or withholding anticoagulation.

Regarding patterns of practice, we have demonstrated an increase in the rate of prescribing of anticoagulants and shown how this varies across the globe, alongside an attendant global variation in clinical outcomes. The data we have published on improved clinical outcomes and comparative effectiveness of three oral anticoagulant treatment classes provides greater certainty on the performance of innovation.

Undoubtedly GARFIELD has established TRI as a global leader in the field with a role in shaping the future of real-world evidence. But most importantly, GARFIELD is providing critical lessons for clinical management that are being applied across the globe to benefit patients.

As clinicians, we all have a role in ensuring that these lessons continue to be shared and implemented as rapidly as possible.
The value of AF registries

The gold standard test of a novel intervention is the randomised controlled trial (RCT).

However, patients carefully selected for inclusion in RCTs may not reflect the population that actually will receive the intervention following regulatory approval for its use in the real world. Thus, real-world evidence (RWE) gleaned from routine clinical practice is an important complement to RCT-derived safety and efficacy findings. Indeed, RWE holds a number of advantages over RCTs such as virtually unlimited patient sample size and lack of a study protocol to influence adherence to treatment and guide clinical decision making.

The purpose of registries

Registries are a type of RWE study with a prospective, observational, cohort design. Registry studies are conducted to evaluate outcomes in a patient population exposed to treatment over the duration of follow-up and analysis. Several registries for patients with AF at risk of stroke exist, including the international GARFIELD-AF and GLORIA-AF registries, ORBIT-AF and ORBIT-AF II in USA, the European PREFER in AF, and Dresden NOAC undertaken in Germany. Of these, GARFIELD-AF and GLORIA-AF alone each enrolled well over 50,000 patients, providing a great wealth of RWE data. GARFIELD-AF comprises over 1,000 study centres in 50 countries and has yielded 28 peer-reviewed publications to date, including reports on long-term risk of death, stroke, and bleeding and treatment outcomes spread over two years.

Valuable clinical data

Many important insights have been confirmed in registry studies. The REVISIT-US study looked at a combined endpoint of ischaemic stroke and intracranial haemorrhage (ICH) in AF patients registered on a large US-based medical insurance claims database. They observed marked reductions of these adverse events in patients taking non-vitamin K antagonist oral anticoagulants (NOACs) (apixaban, rivaroxaban, or dabigatran) versus warfarin therapy.

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Another registry study investigated the incidence of major bleeding in nonvalvular AF patients and saw significant reductions of this unwanted effect in patients receiving apixaban and dabigatran as well as numerical reductions on rivaroxaban compared with warfarin. Moreover, the large, RWE XANTUS Study demonstrated a low rate of stroke and major bleeding in AF patients taking rivaroxaban prophylaxis. These examples underscore the importance of RWE from registry studies in providing valuable clinical data in support of RCTs.

Taking GARFIELD-AF as a specific example...

Long-term observations suggest that many patients with AF are at risk of death from several causes other than stroke, indicating the need for better overall management of the condition. Moreover, the data revealed a high rate of anticoagulant overuse in low-risk patients as well as inconsistent use in those deemed at higher risk, calling for better awareness among clinicians. A large proportion of GARFIELD-AF patients were shown to be receiving substandard vitamin K antagonist (VKA) therapy and this treatment should be improved. Temporal trends in GARFIELD-AF data suggest that, over time, increasingly more patients are receiving better care, largely due to the development of NOAC therapy.
The vast majority of epidemiological studies and RCTs investigating the management of AF have been conducted within Europe and North America.

GARFIELD-AF aims to bridge the gap in our understanding of the real-world management of AF outside of these regions in order to improve the global management and outcomes of patients.

GARFIELD-AF recently investigated regional differences in the baseline characteristics, anticoagulation treatment patterns and clinical outcomes in patients enrolled from the Middle East, India and Japan, compared with the rest of the world.

Patients enrolled across the Middle East and Asia were significantly more likely to have been diagnosed in a cardiology setting compared to the rest of the world (82-91% vs. ≈63%). Patients from the Middle East were younger than patients in other countries (63 vs. 70 years), and had almost double the incidence of diabetes (35% vs. 22%). There was also a high incidence of diabetes in Indian patients (36%), although the incidence in Japanese patients (18%) was comparable to the rest of the world.

Anticoagulant use in India was significantly lower (35% vs. 70%) than the rest of the world, with only 7% of patients receiving a NOAC and antiplatelet therapy (45%) being the most common treatment choice.

In contrast, in Japan, 68% of patients received NOACs (with or without antiplatelet therapy) compared to approximately 43% in the rest of the world. Patients from the Middle East were more likely to receive a NOAC (39% vs. 28%) and less likely to receive a VKA (31% vs. 39%) compared to the rest of the world, but the treatment profile was otherwise comparable.

Outcomes

Twelve-month outcomes highlighted that mortality was higher in India (7.68 vs. 4.34 per 100 person years), although the incidence of major bleeding was lower than the rest of the world (0.31 vs. 0.84 per 100 person-years). By comparison, Japan had a lower rate of mortality.

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Patient outcomes are likely reflective of the care settings and the use of anticoagulation in these patients.

GARFIELD-AF continues to provide important information on the heterogeneity of patients with newly diagnosed AF across the globe. It is now incumbent on physicians and healthcare services to apply these national learnings so as to benefit more patients sooner.

Anticoagulation in VTE: How long is long enough?

Anticoagulation is the mainstay of therapy for patients with venous thromboembolism.

Current American College of Chest Physician (ACCP) guidelines suggest treatment for three months as opposed to a longer time-limited period. Typically, three months is sufficient to complete the “active treatment” of VTE, after which further treatment serves to prevent a recurrence. The decision to stop anticoagulants at three months or to treat indefinitely is based upon balancing the long-term risk of recurrence vs. the risk of bleeding. Three months of anticoagulation treatment is adequate for treating a provoked VTE event, triggered by a major transient risk factor, such as hospitalisation or surgery.
Recently, the GARFIELD-VTE database was accessed to obtain data on clinical characteristics, treatment patterns, and six-month outcomes in patients with upper extremity deep vein thrombosis (UEDVT) compared with those with lower extremity DVT (LEDVT).

Among 11,842 patients assessed for eligibility, 8,040 were enrolled; 438 had an objectively confirmed diagnosis of UEDVT and 7,602 LEDVT.

Baseline assessment for risk factors revealed that in comparison with LEDVT patients, UEDVT patients were likelier to have a central venous catheter insertion (11.5% vs 0.5%), recent hospitalisation (19.4% vs 11.2%), and active cancer or history of cancer (16.2% vs 8.7%, 18.0% vs 12.0%) and were less likely to have had a prior episode of VTE (7.5% vs 16.0%).

Treatment strategies over the first six months post-diagnosis were similar in the two groups; both UEDVT and LEDVT were managed primarily with either parenteral therapy plus VKA or NOAC alone for up to 30 days then either VKA or NOAC alone thereafter. Approximately two thirds patients remained on anticoagulant therapy at six months.

No major difference was observed in the rates of adverse outcomes in UEDVT and LEDVT groups (see table below).

<table>
<thead>
<tr>
<th>Adverse outcomes</th>
<th>UEDVT per 100 person-years</th>
<th>95% CI</th>
<th>LEDVT per 100 person-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>14.2</td>
<td>9.9 to 20.4</td>
<td>9.3</td>
<td>8.3 to 10.3</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>5.0</td>
<td>2.7 to 9.2</td>
<td>7.2</td>
<td>6.4 to 8.1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>12.2</td>
<td>8.2 to 18.2</td>
<td>15.4</td>
<td>14.2 to 16.8</td>
</tr>
<tr>
<td>Incident cancer</td>
<td>4.9</td>
<td>2.7 to 9.2</td>
<td>2.9</td>
<td>2.1 to 3.5</td>
</tr>
</tbody>
</table>

Hazard ratios (HRs) for adverse events in UEDVT versus LEDVT group (reference) were death, HR = 1.53 (95% CI, 1.05 to 2.24; p = 0.0280); recurrent VTE, HR = 0.69 (95% CI, 0.37 to 1.30; p = 0.2483); bleeding, HR = 0.79 (95% CI, 0.53 to 1.19; p = 0.2593); and cancer, HR = 1.69 (95% CI, 0.88 to 3.23; p = 0.1127).

There is some discussion regarding the patient populations that fall under this category. Most experts agree that patients with any unprovoked proximal DVT, unprovoked symptomatic PE, or unprovoked recurrent VTE should be included. Some also promote the use of indefinite anticoagulation in patients with recurrent provoked VTE, provoked VTE with persistent major risk factors (e.g. active cancer), or unprovoked isolated distal DVT. The decision to anticoagulate indefinitely should be based on a careful evaluation assessing the risk-benefit balance in each individual patient.

In the case of prolongation, various options are available for extended treatment, including anticoagulant and antiplatelet therapy.

Numerous randomised clinical trials have investigated low-intensity warfarin (PREVENT), rivaroxaban (EINSTEIN), apixaban (AMPLIFY), dabigatran (RE-SONATE), and aspirin (WARFASA/ASPIRE) for the secondary prevention of VTE. Some studies have even shown statin use is associated with a modest reduction in VTE recurrence.

The available treatment regimens can be broadly split into two groups; those with a high antithrombotic efficacy, but with an important incremental risk of bleeding, and those with reduced thrombotic protection but a better bleeding safety profile. This clinical dilemma highlights the importance of risk stratification tools for both recurrence and bleeding within VTE, and underlines the requirement for further research on the secondary prevention of VTE.

Lower-dose NOAC regimens might represent an important step in the solution of this dilemma.
As we contemplate the future of the GARFIELD registries now the active phases are completed, we are well placed to continue to derive insights from these substantial datasets.

In addition to traditional statistical methodologies, our talented team of statisticians are utilising machine learning and artificial intelligence (AI) to achieve disruptive analyses and unearth deeper insights and innovations that could revolutionise patient care and improve outcomes.

What is AI and machine learning?

AI is a vague and broad concept, that in simple terms is considered a means of making computers function in ways that previously we thought only humans could. Machine learning is a subset of AI. It involves looking at large collections of data to find patterns; it is also good for classification. Different types of machine learning can be defined based on the algorithms applied. Deep learning is a subset of machine learning using algorithms that more closely match the network of the human brain.

Machine learning and traditional statistics share some common underlying machinery. Both have their foundations in mathematical theories and utilise techniques like linear and logistic regression. Their differences centre around the use of prediction in machine learning versus estimation in statistics, big data versus small data and many variables versus few variables.

Machine learning and the GARFIELD registries

So how do these apply to the GARFIELD registries and why are they important?

Machine learning and statistics are moving closer together, and we use both in our registries. When the number of variables is small, conventional statistical methodologies are likely to be equivalent or even superior. However, with large quantities of data – like those we have collected from GARFIELD – machine learning and AI are uniquely positioned to incorporate and classify these.

The GARFIELD-AF risk score is an important innovation, and as we look to further leverage our collaborations with ‘big data’ firms, we will continue to tease out clinical lessons using advanced analytics to benefit patients.