Turning Data Into Clinical Insights

ESC Congress 2021: E-posters  p.4
A Look Ahead to World Thrombosis Day  p.9
TRI in the Labs  p.11
# Contents

**COO Welcome**  
3

**ESC Congress 2021**  
4
- Comparing Rivaroxaban and Apixaban in GARFIELD-AF According to ROCKET AF and ARISTOTLE Trial Selection Criteria  
  Dr Jelle Himmelreich’s e-poster  
- Comparative Effectiveness of NOAC vs VKA in AF Patients  
  Saverio Virdone’s e-poster  
- Safety and Efficacy of Apixaban and Rivaroxaban Versus Warfarin  
  Dr Jelle Himmelreich’s e-poster  

**Staff Profile**  
8
- Featuring our Research Fellow, Dr Jelle Himmelreich  

**Feature**  
9
- Eyes Wide Open to Thrombosis  
  Looking ahead to World Thrombosis Day  

**Feature**  
11
- Exploring Mucin-1 and its Effect on Hypercoagulation in Cancer Cells  
  Yunliang Chen shares some of our lab results  

**Publications**  
12
- GARFIELD-AF Publications: Important Insights From Our Registry  
  Prof Jean-Pierre Bassand provides a synopsis of recent papers
Welcome to this edition of TRI in Focus! The last few months have seen the large-scale vaccination programmes allow for a degree of normality to return to our lives. It is my hope that in the coming weeks TRI employees will be able to work in the office again part of the time.

We will keep providing meaningful, exciting and relevant inputs to the thrombosis field.

Whatever the options ahead, we will keep providing meaningful, exciting and relevant inputs to the thrombosis field. Over the last few months TRI has been active in combating a complication of COVID-19 through the ETHIC study. Despite the many challenges faced in patient recruitment, the Clinical Operations Team have continued to push for engagement. I am pleased to say we have now recruited over 200 patients and target more.

Our long-standing studies GARFIELD-VTE and RIVER were officially closed back in February. Even though the research phase of these studies has concluded, the data retrieved from them will help inform clinical practice, and we will keep you informed as the data become available. They will provide the basis for many future publications. Keep your eyes on our social media channels and websites to stay up to date!

The ESC Congress 2021 was organised and executed virtually again this year and TRI was as present as ever, with our statistician and TRI’s first clinical fellow presenting posters focusing on data generated from the GARFIELD-AF Registry. More detailed synopses can be found in this edition.

While most of us have been at home, our lab research has continued. In the last few months our scientists have been investigating anti-cancer immunotherapy and how to reduce the hypercoagulation properties of human cancer cells. The lab work will always play an integral role in TRI and I am excited for the innovative research we will see in the next year.

In conclusion, there is a lot of work to be proud of here at TRI and a lot of reasons to be optimistic for our future.

I hope you enjoy and find this edition of TRI in Focus useful, and please reach out if you wish to be featured next time!

All the best,

Gloria Kayani

P.S. We are no longer including news about our sister company CYTE, a CRO with a global network for clinical research, in TRI in Focus. Look out for CYTE’s own newsletter… coming soon.
TRI had four GARFIELD-AF and two RIVER e-posters at this year’s ESC 2021 Congress, as we continue to derive important insights from our real-world evidence data.

Read about the e-posters two members of TRI’s team presented during the congress, and access the others on our website: www.af.garfieldregistry.org/publications
The landmark trials comparing rivaroxaban to VKA (ROCKET AF) and apixaban to VKA (ARISTOTLE) in AF patients had substantially different inclusion and exclusion criteria. The extent to which differences in entry criteria influences the estimated effects on NOACs efficacy is debated. The aim of this study was to assess the influence of the two trials’ different inclusion and exclusion criteria on safety and efficacy of apixaban and rivaroxaban versus VKA.

We replicated the entry criteria for ROCKET AF and ARISTOTLE in non-valvular atrial fibrillation (AF) were substantially different for patients recruited into the original ARISTOTLE and ROCKET AF trials. Inclusion and exclusion criteria on results for safety and efficacy of apixaban and rivaroxaban versus VKA using uniform endpoints in the world’s largest prospective registry of newly diagnosed AF patients: GARFIELD-AF.

Our results underline the problems faced in comparing treatments across rather than within clinical trials. The current work points to the need for high-quality observational data for assessment of relative drug performance in the absence of direct drug comparisons through randomised trials. While observational data like these do not allow us to conclusively state differences in treatment outcomes, this study does bring us closer to understanding the differences reported in the original landmark NOAC trials.
Comparative Effectiveness of NOAC vs VKA in Patients Representing Common Clinical Challenges: Results from the GARFIELD-AF Registry

Saverio Virdone

large trials of AF patients have shown that NOACs are beneficial compared to VKAs for reducing the risk of stroke and systemic embolism. Although the results of these trials are directly applicable to many AF patients, important subsets of patients were under-represented. Thus, there remains uncertainty about the safety and effectiveness of NOAC therapy in common challenging clinical scenarios. In this study, we have exploited one of the major advantages of the GARFIELD-AF data: the registry has no strict inclusion criteria, enrolling newly diagnosed AF patients independently of their comorbidities. We were thus able to show the impact of NOACs in settings where clinical uncertainty still exists as drugs’ use in these patients is so far limited. We evaluated the effectiveness and safety of NOACs compared to VKAs in four groups of patients:

1) elderly (age ≥75),
2) with increased bleeding risk (HAS-BLED ≥3 or a prior bleeding),
3) with renal impairment (CKD stages II to IV), and
4) with extreme obesity (weight >120 kg or BMI >40 kg/m²).

We found significant all-cause mortality reductions in favour of NOACs in the first three of these groups, while in patients with extreme obesity the all-cause mortality risk reduction was not statistically significant.

Our observations indicate that NOACs are safe and effective in patients who are elderly, at increased bleeding risk, or renally impaired. These results will help to better guide treatment decisions in these vulnerable populations.
Safety and Efficacy of Apixaban and Rivaroxaban Versus Warfarin in Real-world Atrial Fibrillation Patients are Similar to Their Randomised Trials: Insights From the GARFIELD-AF Registry

Dr Jelle Himmelreich

Landmark trials on NOAC efficacy in AF patients frequently have stringent inclusion and exclusion criteria. In this study, we aimed to assess the reproducibility of the ARISTOTLE (comparing apixaban to VKA) and ROCKET AF (comparing rivaroxaban to VKA) trials in a real-world population. To do so, we replicated the two trials’ entry criteria in the GARFIELD-AF registry, assessed eligibility rates and baseline risk factors among NOAC and VKA patients eligible for the respective trials, and compared the effect of each specific NOAC compared to VKA.

We found that the representativeness of the trials’ populations for real-world AF patients was limited, as 71% of GARFIELD-AF patients would have been eligible for ARISTOTLE and only 41% for ROCKET AF. Patients eligible for ROCKET AF had higher prevalence of cardiovascular comorbidities than ARISTOTLE-eligible patients. In comparing NOAC and VKA on all-cause mortality, stroke and major bleeding, all results from GARFIELD-AF data were compatible with those reported in the original trial publications.

In conclusion, despite limited representativeness of both trials for real-world AF patients, with ROCKET AF entry criteria being more restrictive, results from ARISTOTLE and ROCKET AF appear robust and reproducible in real-world data.

When deciding on which anticoagulant to use in a newly diagnosed AF patient, clinicians can point to our data to say that in patients eligible for either of the investigated trials the originally reported safety and efficacy profiles are to be expected in real-world AF patients.
the Garfield-AF data. The freedom to explore the data myself with regular feedback from the TRI stats team was invaluable in this.

My continuing involvement with ETHIC also allows me to gain further experience with a multinational randomised controlled trial. Most importantly, though, I have met so many wonderful people and colleagues with whom I hope to keep working in the future! Despite my inability to join TRI in London due to COVID-19, it has been a great year, and I look back fondly on the fellowship.

TRI’s clinical research fellowship will continue in 2022.
Here at TRI, our focus is on thrombosis every day of the year – but once a year on 13 October we have an opportunity to join with others to draw the world’s attention to thrombosis, its diagnosis, potential adverse impact and clinical management thanks to World Thrombosis Day (WTD).

The date for WTD commemorates the birthday of the German physician, pathologist, biologist and anthropologist Rudolph Virchow who developed the concept of thrombosis. His ‘discovery’ shed light on this often overlooked and misunderstood condition.

**WTD 2021**

The theme for WTD 2021 is ‘Open your Eyes’ and as in previous years there will be thousands of educational events around the world run by WTD and its partners to place a global spotlight on thrombosis as an urgent and growing health problem. Sadly, 1 in 4 people worldwide die from conditions caused by thrombosis, so the need for more insight, illumination and clinical intervention continues. TRI has been actively helping to further elucidate and educate audiences on thrombosis every day for the past 32 years as TRI and before that through the
work of our late founder, Professor Vijay Kakkar OBE. His pioneering programme of research was established in 1965. It delivered breakthrough solutions in thrombosis which have saved millions of lives and this innovation continues today, across medical disciplines and around the world.

**TRI’s contribution**

Our multidisciplinary programme of laboratory and clinical research has contributed to major advances in venous and arterial thromboembolism that have changed clinical practice.

From a real-world perspective, three of our registries GARFIELD-AF, GARFIELD-VTE and RIVER, though now closed, continue to help provide fresh insights and recommendations, as our presentations at the International Society on Thrombosis and Haemostasis (ISTH) and European Society of Cardiology (ESC) congresses this year demonstrate.

We’re focused on thrombosis for the long term and will be supporting WTD again this year through our communications and social media activities, so keep your eyes wide open for these. For more information on what’s planned for this year’s WTD, visit [https://www.worldthrombosisday.org/](https://www.worldthrombosisday.org/).
Researchers in our laboratories have been studying the effect of mucin-1 (MUC1) based anti-cancer immunotherapy to reduce the hypercoagulation properties of human cancer cells, an effect that may ultimately benefit patients clinically.

Hypercoagulability thrombosis are established features of the malignant progression of cancer. The development of hypercoagulability in cancer patients is often associated with mucinous adenocarcinomas.

Our previous work

Tumour-associated MUC1 has been considered as the most likely target for cancer immunotherapy with numerous antibodies and vaccines projects (Gao 2020, M Bose 2020, Taylor-Papadimitriou 2018). Our previous works have also shown that the level of MUC1 exerts a significant effect on the procoagulant and proinflammatory properties of tumour cells. Since such effects are also inducible via the uptake of tumour exosome by normal recipient cells, it indicated that MUC1 has a potential to contribute to the pathogenetic mechanisms of thromboinflammatory associated cancer.

We assume that immunotherapy target to tumour-associated MUC1, like its effect on mediating immune effector functions, may also reduce the pro-coagulate characters and improve the hypercoagulation condition of cancer patients. Such influence could be a consideration with regards to a MUC1-based anti-cancer immunotherapy effect.

Currently numerous anti-MUC1 therapy antibodies are commercially available, but most of them are used as combination approaches with complementary drugs. One of them, gatipotuzumab, has been used in several clinical trials addressing different types of cancers.

**Our recent results**

Our recent work found that therapeutically the anti-MUC1 antibody gatipotuzumab reduced the activities of the p-Akt and p-ERK pathways, the levels of tissue factor (TF), factor Va (F-Va) and thrombin in human breast cancer MCF-7 cell and human breast cancer stem cell (CSC). The clotting assay also showed that clotting activity is reduced by gatipotuzumab treatment in these breast cancer cells.

These results suggest that therapeutically anti-MUC1 antibody may be able to reduce the hypercoagulation properties of human cancer cells. Therefore, it could be considered that immunotherapeutic targeting of tumor-associated MUC1, aside from having an effect in mediating immune effector functions and tumor-targeted drug delivery, may also reduce the pro-coagulant characteristics of the tumours. This, in turn, would reduce thrombotic tendencies and reduce the contribution that thrombin generation makes to cancer biology. This effect could be a novel consideration for a MUC1 based anti-cancer immunotherapy.

Our work continues and we will provide further updates in due course.
A summary of the seven journal publications emanating from GARFIELD-AF data so far in 2021 is presented. The full papers can also be accessed via our website: www.af.garfieldregistry.org/publications

Discontinuation for ≥7 consecutive days of oral anticoagulation (OAC) involved only 13.0% of patients but was associated with significantly higher risk of death and stroke/systemic embolism (SE). This means that OAC discontinuation should be discouraged, even for periods as short as 7 days.¹

The predictive accuracy of the GARFIELD-AF risk tool (available at: www.af.garfieldregistry.org/garfield-af-risk-calculator) was reassessed with 2-year follow-up data. It outperformed both CHA₂DS₂-VASc at predicting death and stroke/SE and HAS-BLED at predicting bleeding in all, including low to very low, risk groups (CHA₂DS₂-VASc 0-1).² In these risk groups age and gender are the only risk factors for stroke/SE, but stroke risk increases from a low 0.7 at age 66 to a high 1.7 per/hundred patient/year at age 74.³ GARFIELD-AF risk tool may help to characterise patients in need of OAC in these risk groups.

Patients from Nordic countries had similar outcomes at 2-year follow-up as non-Nordic-European patients but had a significantly higher risk of bleeding likely due to higher rates of combination therapy OAC+antiplatelet agents⁴. A previous report challenged the practice of combination therapy unless there is a clear indication for adding AP to OAC therapy in newly diagnosed atrial fibrillation⁵.

In practical terms, should at-risk populations be screened for early detection of asymptomatic AF, and with which tools?

Asymptomatic and symptomatic AF patients share the same outcomes and benefits from anticoagulation⁶. In practical terms, should at-risk populations be screened for early detection of asymptomatic AF, and with which tools? Major bleeding is associated with higher risk of death, half of which occurring within the first month, mostly from intracranial haemorrhage. Clinically relevant non-major and minor bleedings are associated with a higher risk of death than no-bleeding patients⁷.
Bleeding avoidance strategies should always be implemented as even non-major bleedings cannot be considered as benign events.

The comparative effectiveness analysis revealed important benefits in terms of mortality and major bleeding with NOAC over VKA, with no significant difference among NOAC subtypes. These results confirm data from meta-analyses of RCTs and that NOAC should be preferred over VKA.

Patients with AF and heart failure have a higher risk of all-cause death and stroke/SE than AF patients devoid of heart failure. Whether pulmonary veins ablation improves outcome in these patients remains debated.

REFERENCES: