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**The Thrombosis Research Institute: past, present and future of global clinical research into thrombosis and anticoagulation**

**Introduction**

Thrombosis of venous or arterial origin is a global killer responsible for 85% of fatal strokes and 95% of fatal heart attacks.1 These diseases cause one quarter of all deaths,1 affecting one in two men and one in three women. Thrombosis is associated with a number of acquired or inherited risk factors. The majority of arterial thrombotic complications are caused by atherosclerotic plaque rupture or erosion. Venous thrombosis may be associated with heritable coagulation disorders, trauma or malignancy and a range of other underlying risk factors.

The prevention and treatment of thrombosis represent a major challenge and will be a critical component of healthcare systems in the 21st century. In 2012, the World Health Assembly (WHA) set a global target to reduce premature deaths from non-infectious disease – including cardiovascular disease – by 25% by 2025.2 Within this goal, prevention mechanisms and treatments for thrombosis are a global priority.

The Thrombosis Research Institute (TRI) is dedicated to obtaining new insights into the detection, prevention and treatment of thrombosis. With a programme of work spanning some 50 years, it remains one of the few academic research institutes solely devoted to working in thrombosis.

**Key milestones**

The programme of research that ultimately led to the foundation of TRI was established by Professor Vijay V. Kakkar in the 1960s. His first milestone contribution arose from the findings of an international, multicentre, randomised trial, published in *The Lancet* in 1975.3 Involving 4,121 patients in 28 centres, it resulted in a major breakthrough with the use of fixed low doses of heparin to prevent thrombosis arising during surgery. Since then, it has been estimated that the widespread adoption of this approach has saved the lives and mitigated complications in tens of thousands of patients worldwide every year. Other breakthrough contributions include demonstrating how commonly fatal blood clots occur post-surgery, leading to the development of novel treatments; pioneering work on the risk of thrombosis in cancer; and the position of antithrombotic medications in the care of cancer patients.

TRI was officially opened in Chelsea, London, UK by Prime Minister Margaret Thatcher in 1989. Professor Vijay Kakkar was the institute's founder and president. It was established as a multi-disciplinary, independent organisation, uniquely positioned to enable scientists from many different disciplines (biochemists, haematologists, enzymologists, cell biologists and molecular geneticists) to work together as a coherent team thereby increasing the opportunity for cross-fertilisation of ideas and the development of new research strategies.

Now in its 30th year, TRI’s laboratory research continues, and today focuses on identifying individuals who are at risk of thrombosis, long before symptoms develop. TRI is also working on understanding the pathology that links cancer with VTE and developing population-level strategies, including the possibility of "vaccines," with the potential to prevent atherosclerosis, the main underlying cause of arterial thromboembolism.

TRI’s research programmes aim to understand the pathogenesis of thrombosis and thereby develop novel and affordable therapies to prevent long-term disability and early death. To this end, TRI's laboratory research projects have focused on fundamental mechanisms involved in blood coagulation, inflammation and atherogenesis, as well as how these processes may be manipulated for therapeutic purposes. An exciting ongoing project at TRI is the development of an affordable vaccine that may prevent atherosclerosis. In future, it may be possible potentially to save countless lives by eliminating the development of one of the world's biggest killer diseases with a simple inoculation.

**A global leader in real-world evidence**

TRI has become a world leader in the field of real-world outcomes research, developing and executing innovative global programmes. The institute’s success comes through partnership with a network of more than 2,500 research centres in 40 countries. Bringing the quality of data and the rigour of clinical trials to real-world studies, TRI’s operation models have extended cutting-edge research to under-represented countries, care settings and patients. The institute runs several thrombosis registries (see Box) that advance the science of real-world data to strengthen the chain of evidence beyond clinical trials and create new data to improve healthcare delivery and patient outcomes.

When TRI launched the Global Anticoagulant Registry in the Field – Atrial Fibrillation (GARFIELD-AF) registry in 2009, its mission was to enhance understanding of the burden of ischaemic stroke in AF and identify opportunities to incorporate innovations designed to improve outcomes, safety and use of healthcare resources4. Led by a distinguished Steering Committee of global leaders in thrombosis research, GARFIELD-AF was designed to elicit real-world insights to clarify 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, interpreting and communicating the research findings.

To capture a comprehensive picture on the burden of thrombosis in AF, the registry included prospectively enrolled patients, extensive quality-control measures and regular audit5; in total, over 57,000 newly diagnosed AF patients were recruited and followed for 2–8 years.

GARFIELD-AF’s audit and quality control standards included 20% source data verification under the supervision of an independent Audit Committee.5 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 modality, allowed for enrolment of representative patient populations. The database, analysis of data and preparation of manuscripts are remits of the Steering Committee, independent of external sponsors.

Following the successful inception of GARFIELD-AF, TRI opened two further large registries. Global Anticoagulant Registry in the Field – Venous Thromboembolism (GARFIELD-VTE)6 enrolled and followed patients with a first VTE or pulmonary embolism (PE) whereas Rivaroxaban Evaluation in Real Life Setting (RIVER) became TRI’s first registry monitoring AF patients prescribed the non-vitamin K antagonist oral anticoagulant (NOAC) drug rivaroxaban.

TRI's registries aim to be the best. For example, while 10% source data verification is considered excellent practice, TRI’s registries apply 20%. The registries are independently reviewed. GARFIELD-AF and GARFIELD-VTE focus on the two disease conditions, AF and VTE, irrespective of severity and treatment; they are not drug registries. Hence these registries are able to assess effectiveness and safety of a range of available treatment options.

**What we have learned from GARFIELD**

TRI now has a substantial dataset. Recruitment across all three registries is complete and data exist on 73,193 patients. Follow-up is ongoing, with 159,742 patient-years of results. To date, TRI has published 28 independent peer-reviewed reports related to GARFIELD registries, with more in progress, and has presented 75 abstracts at congresses and meetings across the globe.

Significantly, TRI's real-world evidence is shedding light on crucial clinical questions on burden of disease, short- and long-term treatment patterns, clinical outcomes, geographical differences, risk stratification and health economics.

TRI has established definitively that prospective studies with newly diagnosed patients are required to capture a comprehensive understanding of AF and VTE.7 TRI set the standard for data quality in large-scale prospective registries. Importantly, it is also changing the understanding of the landscape in AF and VTE.

TRI has developed the GARFIELD-AF risk calculator, an integrated web-based tool that assesses the risk of mortality, ischaemic stroke and major bleeding in a single calculation following demographics data entry.8 The tool aims to help clinicians judge whether the risks of anticoagulation outweigh the benefits in AF patients with a high risk as well as those with a very low risk of stroke. The GARFIELD-AF online risk tool, while still in early application, has been designed to facilitate guideline-based decisions on prescribing or withholding anticoagulation. The risk tool also promises to address current treatment gaps.

Regarding patterns of practice, TRI has demonstrated an increase in the rate of prescribing anticoagulants and shown how this varies across the globe, alongside an attendant global variation in clinical outcomes.9 The data TRI has published on comparative effectiveness of three classes of oral anticoagulants provide important insights to inform clinicians' decision making.

The GARFIELD registries programme has established TRI as a global leader in the field of thrombosis observational research. More importantly, GARFIELD is providing critical lessons for clinical management that are being applied across the globe to benefit patients. On the other hand, despite current guidelines, substantial treatment gaps exist and the ongoing programme is designed to address these. TRI has achieved much via its collaborations to date, and will continue to leverage these partnerships to unlock novel clinical insights that ultimately help to improve patient care.

**A future focused on health technology**

To date, TRI has consistently produced world-leading research and many innovations. And the future of TRI is equally as exciting. TRI is investigating emerging health technologies, including artificial intelligence and machine learning, which are providing data-driven insights on clinical care. TRI envisions a future using intelligent modelling and computer-based "big data” to develop cutting-edge models for optimal care. TRI's ambition is to go beyond traditional methodologies and data sources to explore the potential of clinical, genetic and phenotypic data in the era of digital technology and personalised medicine.

**About the authors**

Prof. the Lord Ajay K. Kakkar is Director of TRI since 2008. Prof. A. John Camm is Chair of the Publications Committee at TRI. Prof. Keith A. A. Fox is Chair of the Audit Committee at TRI.

**Box: Thrombosis Research Institute registries and other observational studies**

* **GARFIELD-AF**: the largest prospective atrial fibrillation (AF) registry with 57,262 patients recruited from 35 countries worldwide, providing insights on stroke prevention in AF and helping to develop strategies for improving patient outcomes.
* **GARFIELD-VTE**: prospective registry describing acute and long-term management and outcomes in 10,874 adult patients with venous thromboembolism (VTE) representative of everyday clinical practice in 28 countries.
* **RIVER**: prospective registry describing outcomes in over 5,000 adult patients with newly diagnosed AF who are treated with rivaroxaban.
* **PERCEIVE**: prospective registry of VTE in over 5,000 adults with newly diagnosed cancer of the breast, ovary, colon and rectum, pancreas, lung, or prostate, with up to 11 years of follow-up.
* **BREACH**: prospective study of biomarkers for thromboembolism in 100 patients with advanced breast cancer treated with chemotherapy.
* **FRONTLINE**: the first comprehensive global survey of thrombosis and cancer, with responses from 3,891 clinicians involved in cancer care from 74 countries.
* **FRONTLINE 2**: international survey of cancer-associated thrombosis, with responses from over 5,000 oncologists, haematologists, surgeons, thrombosis specialists, members of the palliative care team and specialist nurses from 54 countries.

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