# GARFIELD IN FOCUS

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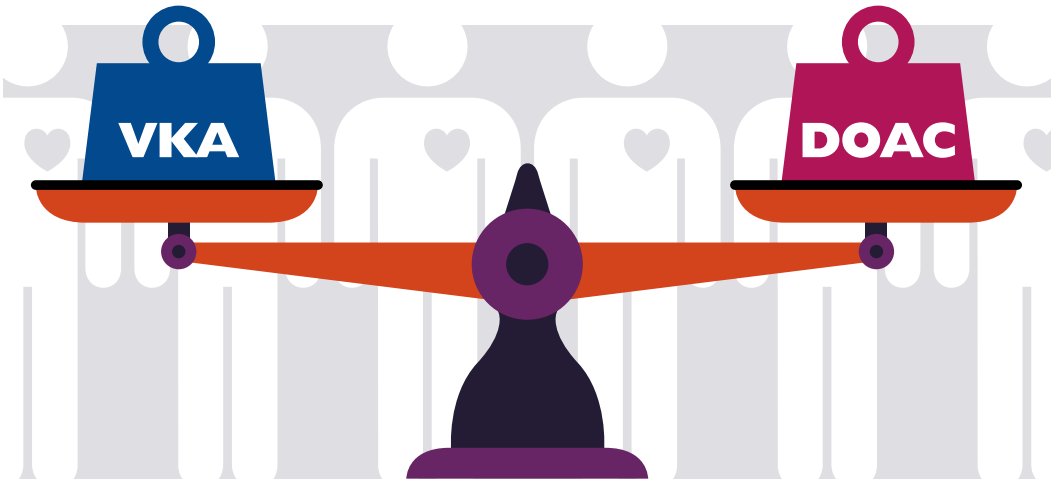
**Welcome to the August 2019 edition of GARFIELD in Focus, published by the Thrombosis Research Institute (TRI), bringing you data and insights from our Global Anticoagulant Registry in the Field (GARFIELD) studies, GARFIELD-AF and GARFIELD-VTE.**

This issue explores the most recent analysis from our GARFIELD registries presented at the International Society of Thrombosis and Haemostasis (ISTH) congress in Melbourne, Australia, 6th-10th July. Additionally, we examine the topic of acute coronary syndromes in atrial fibrillation patients, which has recently been published in the *American Journal of Medicine* (ncbi.nlm.nih.gov/pubmed/31306621).

*Our guest editor for this edition is **Professor Jean-Pierre Bassand** (Department of Cardiology, University of Besançon, Besançon, France).*

## OUR FOCUS: AF & VTE




# Improving patient outcomes through comparative effectiveness research

**Within the field of outcomes research, comparative effectiveness has gained widespread attention over the past decade.**

The aim of comparative effectiveness is to improve health outcomes research by providing evidence for policy makers, clinicians and other healthcare professionals regarding the benefits and risks of treatment options delivered to the diversity of patients in everyday clinical practice. However, when comparing treatments using observational data, differences in baseline characteristics between groups (such as age, gender, ethnicity and medical history) can act as potential confounders and produce biased results. In order to circumvent this in our GARFIELD registries, differences in the characteristics of patients in each treatment group are accounted for using a statistical methodology known as overlap propensity score weighting. This allows us to achieve a balance between the treatment groups by appropriately weighting patients that are similar across treatments based on their observed characteristics. ▶

## IN THIS ISSUE



AF Garfield global anticoagulant registry in the field

VTE Garfield global anticoagulant registry in the field

TRI Thrombosis Research Institute

Large-scale non-interventional registries, such as GARFIELD-AF and GARFIELD-VTE, are uniquely positioned to be able to conduct such analyses, with considerable amounts of data from patients across the globe. In both atrial fibrillation and venous thromboembolism, the introduction of direct oral anticoagulants (DOACs) has altered the therapeutic landscape and offered new treatment choices for clinicians and patients. Analyses from both of our GARFIELD registries were recently presented at the International Society of Thrombosis and Haemostasis (ISTH) congress in Melbourne, Australia (July 6th – 10th, 2019), assessing the comparative effectiveness of DOACs vs vitamin-K antagonists (VKAs).


### Results

Our results showed that even after adjustment for baseline characteristics, AF patients receiving DOACs were at a reduced risk of mortality up to 2 years after AF diagnosis compared to those receiving a VKA (HR 0.83 [95% CI: 0.75-0.93]), with no significant difference in the rate of stroke/systemic embolism. Similarly, in GARFIELD-VTE, patients receiving DOACs had a significantly reduced risk of all-cause mortality 1 year after VTE diagnosis (HR 0.70 [95% CI: 0.53-0.92]), with no significant difference in recurrent VTE. The risk of major bleeding in both studies did not differ between patients receiving DOACs and VKAs.

Our data add to the growing body of evidence supporting the use of DOACs over VKA therapy, in both the VTE and AF setting. However, it is important to emphasise that a 'one size fits all' approach may not be suitable in all situations, and factors such as polypharmacy, comorbidities and patient preferences need to be taken into consideration.

HR = hazard ratio
CI = confidence interval

# INSIGHT: AF

## Atrial fibrillation and acute coronary syndromes

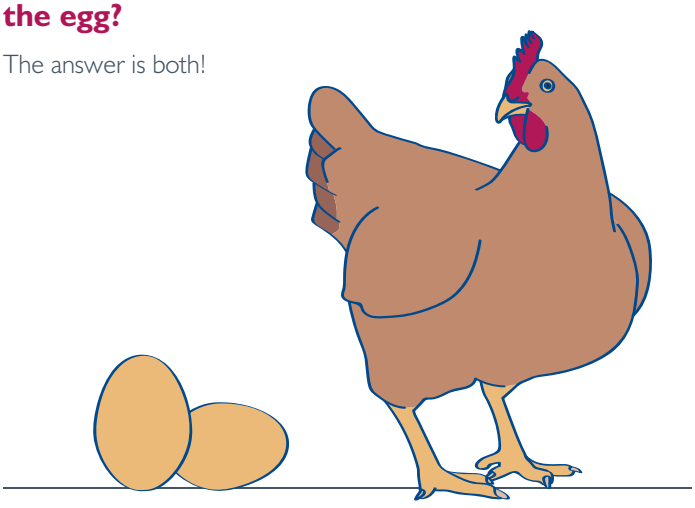
**Approximately 10% of the patients in GARFIELD-AF with newly diagnosed atrial fibrillation have a prior history of acute coronary syndrome (ACS).**

Such patients are at higher risk of death, stroke and bleeding than patients without prior ACS. However, acute coronary syndromes are also frequent outcomes in those with newly diagnosed AF, including myocardial infarction and cardiovascular death.

Why is there this connection between ACS and AF? Firstly they share common risk factors including hypertension, heart failure, diabetes and advancing age. The underlying key mechanisms are atherothrombotic and pro-coagulant. These systemic features are compounded by key local precipitating factors. For example, myocardial infarction can result in left ventricular dysfunction, raised left atrial pressure and atrial dilatation, all of which predispose to AF. AF is also associated with thrombin-induced platelet activation, and hence plaque disruption events are more likely to be complicated by local thrombosis and coronary vessel obstruction. More basic biological and genetic risk mechanisms are also shared.

### AF and ACS – which is the chicken and which is the egg?

The answer is both!



*Article contributed by:*
***Professor Keith Fox** (Professor of Cardiology, University of Edinburgh, UK)*

# HIGHLIGHT: AF

## Antithrombotic therapy and outcomes in patients with atrial fibrillation and acute coronary syndrome

**The risk factors for the development of atrial fibrillation (AF) are very similar to those for developing coronary artery disease (CAD), thus AF is often associated with acute coronary syndrome (ACS).**

anticoagulants alone. The outcomes at 2-year follow-up of patients included in GARFIELD-AF with newly diagnosed AF at moderate or high risk of stroke who had a history of ACS versus those without such a history were recently published. This study also investigated the influence of antithrombotic regimens on differences in outcomes.

**In patients on dual antiplatelet therapy and oral anticoagulation, the risk of bleeding increases two- to three-fold compared with anticoagulants alone.**

In AF, oral anticoagulation is advised for prevention of stroke or systemic embolism (SE), whilst patients with ACS typically receive dual antiplatelet therapy: aspirin and an ADP-receptor antagonist such as clopidogrel, prasugrel or ticagrelor.

### Outcomes at 2-year follow-up

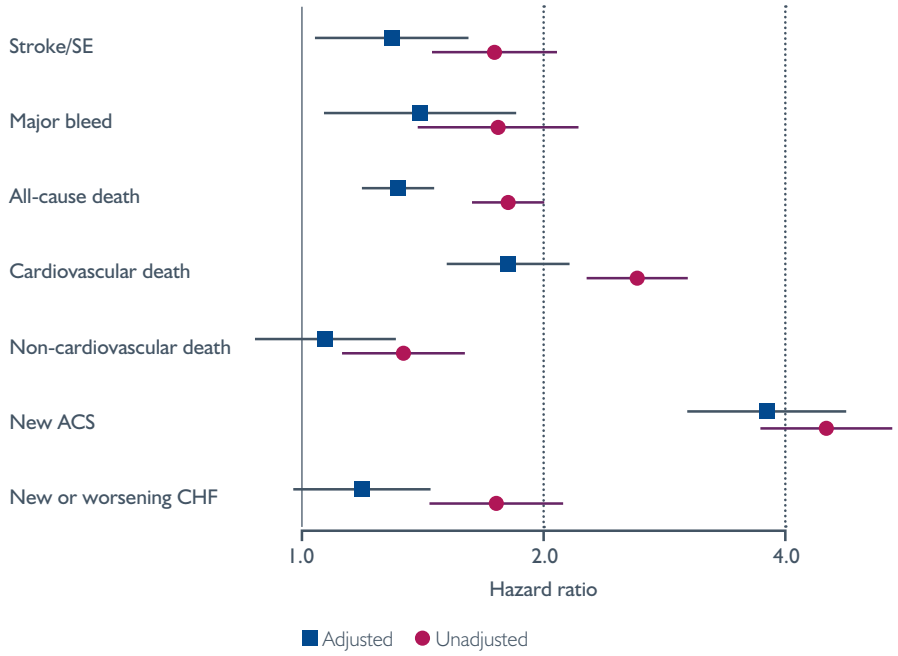
In patients on dual antiplatelet therapy and oral anticoagulation, the risk of bleeding increases two- to three-fold compared with

In total 4,152 (10.5%) of the 39,679 GARFIELD-AF patients studied had a history of ACS. At 2-year follow-up, ACS patients had a higher adjusted risk of stroke/SE (HR: 1.39, 95% CI: 1.08-1.78), major bleeding (1.30, 0.95 - 1.79), all-cause mortality (1.34, 1.21 - 1.49), cardiovascular mortality (1.85, 1.51 -2.26) and new ACS (3.42, 2.62 - 4.45) than the patients without such a history.

Comparing antithrombotic therapy in both groups, most patients with or without ACS received oral anticoagulants ± antiplatelet agents: 60.8% vs 66.1%, respectively. Patients with ACS were more likely to receive antiplatelet therapy compared to those without (68.1% vs. 32.9%), either alone (34.9% vs. 20.8%), or in combination with anticoagulants (33.2% vs. 12.1%). Dual antiplatelet therapy was prescribed in 22.2% of patients in the ACS group, 7.5% with and 14.7% without an oral anticoagulant.

Among patients with moderate/high risk for stroke/systemic embolism, fewer patients in the ACS group received anticoagulation with or without AP; 52.1% vs 64.7% in patients with $CHA_2DS_2$-VASc =2; 62.0% vs 70.8% in patients with $CHA_2DS_2$-VASc ≥3. The majority of patients with a HAS-BLED score ≥3 were on AP therapy (83.8% vs 65.6%).

### Adjusted hazard ratios ACS vs no ACS




Adjusted for age, sex, race, smoking, diabetes, hypertension, history of stroke or TIA, history of bleeding, congestive heart failure, severe CKD, type of AF, heavy alcohol use, AC use and acute coronary syndrome

### Results of the GARFIELD-AF sub study

The GARFIELD-AF sub study showed that a history of ACS in patients with AF was associated with worse 2-year outcomes and a greater likelihood of under-treatment with oral anticoagulation, with two-thirds of patients receiving antiplatelet therapy.

As expected, major bleeding was more common in the patients with a history of ACS, even after adjusting for all risk factors.

Results from this study highlight the importance of considering the increased risk of bleeding in patients receiving both antiplatelet and anticoagulant therapy.

HR = hazard ratio
CI = confidence interval

*Article contributed by:*
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# INSIGHT: VTE

## Anticoagulation in patients with chronic kidney disease

**One of many highlights from the ISTH congress in Melbourne was the oral presentation given by Professor Shinya Goto (Department of Medicine (Cardiology), Tokai University School of Medicine), who discussed the complex issue of renal impairment in VTE patients.**

Renal impairment due to chronic kidney disease (CKD) is increasingly common, especially in our aging society.

Professor Goto compared patients with moderate-to-severe (stages 3-5) CKD and patients with normal-to-mild (stages 1-2) CKD, enrolled in the GARFIELD-VTE registry. CKD status was determined using creatinine measurement, in addition to age, sex, and ethnicity, to calculate the estimated glomerular filtration rate (eGFR). The equation used to calculate this is shown below:

**eGFR = 175 x (Serum creatinine)-1.154 x (age)-0.203 x 0.742 [if female] x 1.212 [if Black]**

Following calculation of the eGFR, patients were grouped into the following categories:

| Stage | CKD stage | GFR (mL/min/ 1.73 m2) |
|---|---|---|
| I | Normal | ≥ 90 |
| II | Mild | 60 - 89 |
| III | Moderate | 30 - 59 |
| IV | Severe | 15 - 29 |
| V | Failure | < 15 |

The impaired renal excretion pathway poses a problem when treating VTE; the resultant high concentrations of anticoagulant drugs mean that bleeding complications are more often severe/fatal in CKD patients. Impaired platelet function may also contribute to higher risk and greater severity of bleeding in these patients.

The introduction of DOACs has led to an increase in the anticoagulant treatment options available. Indeed, DOACs have recently been approved for the treatment of VTE in patients with moderate-to-severe renal impairment in many countries, despite limited clinical evidence[1]. Each of the DOACs are cleared via the renal system, albeit to different extents (e.g apixaban 27%, rivaroxaban 33%)[2], therefore, as renal function decreases, the plasma concentration increases. In AF, each of the DOACs have dosing regimens that require renal function to be taken into account for selection of the correct dosage.

Surprisingly, there is a lack of clinical evidence regarding DOAC dose reductions in renally impaired patients with VTE. For both rivaroxaban and dabigatran, the manufacturers recommend considering a dose reduction in patients with moderate-to-severe renal impairment if the risk of bleeding outweighs the risk of recurrent VTE. However, this is based on pharmacokinetic modelling and has not yet been studied in a clinical setting[3,4]. Thus, results from the VERDICT study, comparing reduced doses of apixaban and rivaroxaban to the standard-of-care in VTE patients with moderate-to-severe renal impairment, are eagerly anticipated[5].

Currently, in clinical practice, VKAs are often preferred in patients with a creatinine clearance <30ml/min, likely due to their familiarity with physicians, the availability of a reversal agent and the ability to adjust the dose based on INR measurements.

In GARFIELD-VTE, the anticoagulation treatment profile 30 days after diagnosis was comparable between patients with normal-to-mild CKD and patients with moderate-to-severe CKD, with a similar proportion receiving parenteral therapy (≈15%), a VKA (≈35%), or a DOAC (≈40%).

Future work within GARFIELD-VTE will assess the impact of both the dose and duration of anticoagulant treatment, and how this influences the risk of both VTE recurrence and bleeding, up to three years after VTE diagnosis.

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3. Harder S. Pharmacokinetic and pharmacodynamic evaluation of rivaroxaban: considerations for the treatment of venous thromboembolism. *Thrombosis Journal.* 2014; 12(1): 22.
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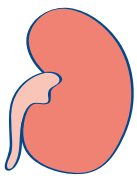
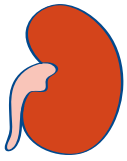
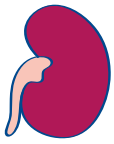
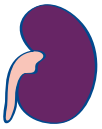
### 5 Stages of Kidney Disease

| Stage I | Stage II | Stage III | Stage IV | Stage V |
|---|---|---|---|---|
| GFR≧90 | GFR 60-89 | GFR 30-59 | GFR 15-29 | GFR<15 |
|  |  |  |  |  |
| Normal or high function | Mildly decreased function | Moderately decreased function | Severely decreased function | Kidney failure |

# HIGHLIGHT: VTE

## What GARFIELD-VTE tells us about provoked versus unprovoked VTE

**As part of TRI's support symposium at the International Society of Thrombosis and Haemostasis (ISTH) in Melbourne, Australia on 6th July, 2019, Professor Walter Ageno (University of Insubria, Varese, Italy) presented the clinical characteristics, anticoagulant treatment patterns and twelve-month outcomes in patients with transient provoking risk factors, persistent provoking risk factors (active cancer), or unprovoked VTE.**

Patients were defined as having transient or provoking risk factors according to the latest guidance from the Scientific and Standardization Committee (SSC) of ISTH[1]. Transient provoking risk factors included surgery, lower limb trauma, hospitalisation, acute medical illness, pregnancy, hormone replacement or oral contraception, within the three months preceding VTE diagnosis.

Patients with transient provoking risk factors were more likely to be younger (52 years vs. 62 years), and female (61.2% vs. 43.1%), than those with unprovoked VTE, respectively. 30 days after VTE diagnosis, a similar proportion of each patient group received anticoagulation therapy (97.5-98.1%). At 6 months, more than two thirds of patients (67.6%) with transient provoking risk factors remained on anticoagulation treatment, compared with 80% of patients with unprovoked VTE. At twelve months, this had decreased to 46.8% and 62.5%, respectively. This observation is of major clinical importance, given that three months of anticoagulation is generally considered adequate for treating a VTE event provoked by a transient factor, with further anticoagulation serving to prevent a recurrence[2].

**At 6 months, more than two thirds of patients (67.6%) with transient provoking risk factors remained on anticoagulation treatment...**

After adjustment for baseline characteristics, patients with a persistent provoking risk factor (active cancer) were at an increased risk of all-cause mortality (HR 9.94 [7.92-12.48]), recurrent VTE (HR 1.35 [0.97-1.89]) and major bleeding HR 2.45 [1.56-3.83), compared to patients with unprovoked VTE. Event rates were comparable between patients with transient provoking factors and unprovoked VTE (all-cause mortality: 0.97 [0.77-1.23], recurrent VTE 0.87 [0.70-1.08], major bleeding: 1.19 [0.79-1.79].


### Results from GARFIELD-VTE

Results from GARFIELD-VTE add to the growing body of evidence suggesting clinicians frequently continue anticoagulation beyond three months.

This decision is based largely on whether the risk of recurrence outweighs the risk of bleeding.

Future research within the GARFIELD-VTE registry will examine the influence of the duration of anticoagulation therapy on clinical outcomes and assess if some patients may be exposed to an unnecessary risk of bleeding.

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# SPOTLIGHT

## From Melbourne to Paris: Looking back, looking forward

**The International Society of Thrombosis and Haemostasis (ISTH) congress took place in Melbourne, Australia, 6th - 10th July, 2019.**

TRI had a major presence at ISTH, with oral presentations, posters, a supported symposium as well as an exhibition stand showcasing the latest findings from GARFIELD-VTE.

The supported symposium, entitled *Understanding the Outcomes of Anticoagulation: Insights from the GARFIELD Registries* received a large amount of interest, including an insightful Panel Discussion, as Steering Committee Members and National Coordinators presented data on a range of topics, including provoked versus unprovoked VTE, cancer-associated thrombosis, and comparative effectiveness of VKAs and DOACs.

You can view all our presentations at ISTH on the GARFIELD-VTE website **vte.garfieldregistry.org/presentations**.

**GARFIELD-AF has a busy programme of presentations planned for this year's European Society of Cardiology (ESC) Congress 2019, in Paris, France, 31st August - 4th September.**

TRI will host a satellite symposium on day 1 of the Congress, from 15:30-17:00 in the Athens Room (Village 3), entitled *What is the Long term Impact of Atrial Fibrillation? Insights from GARFIELD-AF*.

This symposium will review important new data from a broad range of clinical topics, including a three-way comparative effectiveness analysis among oral anticoagulants, the impact of following Guidelines for AF treatment, and showcasing the new online GARFIELD-AF risk tool for stroke, death, and bleeding.

### KEEP UP TO DATE WITH OUR PROGRAMME AT THIS YEAR'S ESC CONGRESS 2019

You can view all our scheduled sessions at ESC on the GARFIELD-AF website **af.garfieldregistry.org/news-events**

The TRI Team will be on hand at **Stand K800** in **Exhibition 2** throughout the Congress, so please come and say hello!

You can also follow us at **@GARFIELD_reg** on Twitter to keep up to date with our work.

TRI Thrombosis Research Institute

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