GARFIELD IN FOCUS

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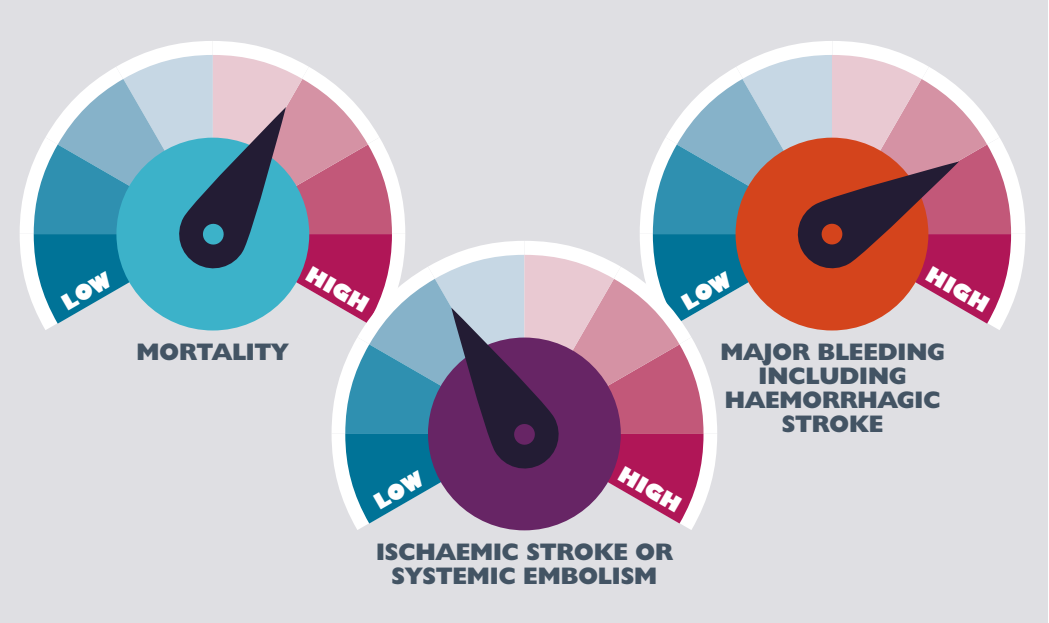
Welcome to the November 2019 edition of GARFIELD in Focus, published by the Thrombosis Research Institute (TRI), bringing you data and insights from our Global Anticoagulant Registry in the FIELD (GARFIELD) studies, GARFIELD-AF and GARFIELD-VTE.

This issue, our last of 2019, explores risk tools in atrial fibrillation as we mark the launch of the GARFIELD-AF Risk Calculator. We also highlight the opportunity for further study in this area in venous thromboembolism, and recount our successful satellite symposium and data presentations at the ESC in Paris.

OUR FOCUS: AF & VTE



Risk scores in thromboembolic disease: Understanding their clinical importance

A risk score, also known as a clinical scoring system or prediction model, is a tool used to aid clinical decision making by improving assessment accuracy.

It utilises individual patient factors that contribute towards prognosis or diagnosis, providing an easily interpretable score.

Some models convert measures such as age, blood pressure, or BMI into categories. When this is done, simple integer weights are usually applied to each. An example in thromboembolism is the CHA_2DS_2-VASc score. Age is categorised into three groups and each factor has a weight of 0, 1 or 2. ▶

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VTE Garfield global anticoagulant registry in the field

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Factor	Score					
Age	< 65	0	65-74	+1	> 75	+2
Sex	Female	+1	Male	0		
Heart failure	No	0	Yes	+1		
History of hypertension	No	0	Yes	+1		
Stroke / TIA / thromboembolism history	No	0	Yes	+2		
Vascular disease history	No	0	Yes	+1		
Diabetes	No	0	Yes	+1		

When a measure is converted into categories, the score implies that everyone in that category has the same level of risk. In other words, an age of 40 has the same risk as an age of 64 and an age of 75 has the same risk as an age of 90. We know this not true. The above model is very simple for a clinician to use but in predicted outcomes does not provide an estimate of actual risk.

We have developed a risk calculator in GARFIELD-AF that provides a simple method of determining risk for mortality, stroke, and major bleeding, while maintaining the actual values of age, weight, pulse rate and blood pressure. The score shows differences in outcomes with treatment selection across 2 years of follow-up.

INSIGHT: AF

Risk Scores: Rationale, development and applications

Why do clinicians need risk scores?

In situations where clinicians have to balance risks and benefits of a therapeutic strategy, or where treatment benefits are dependent on a series of baseline risk characteristics, risk scoring tools help them make informed decisions.

Examples may include the decision to treat a risk factor such as hyperlipidemia in primary prevention, or to use an invasive strategy after non-STEMI, or to anticoagulate a patient with AF.

Challenges

The challenge for clinicians is that simplified risk scores often use binary decisions (heart failure, advanced age, renal dysfunction) but the underlying risk factors have a continuous relationship with hazard, and this may be non-linear (heart rate, blood pressure).

The most accurate risk predictors require smart devices for processing complex algorithms and require simplified versions to minimize the number of inputs. Such scores run on electronic devices, including smart phones.

In the field of anticoagulation for stroke risk the CHA_2DS_2-VASc score is most widely used. Further developments have introduced other risk factors such as renal dysfunction and some scores include biomarkers, although these may not be routinely available. Scores for bleeding have generally low predictive accuracy and may incorporate the same risk predictors as used for stroke prediction (e.g. HAS-BLED). Because of these limitations HAS-BLED has been dropped from the ESC Guidelines.

How does GARFIELD-AF fit in?

A key challenge in patients with AF is that up to one third of the highest-risk patients are not anticoagulated, whereas many patients with a very low stroke risk are prescribed anticoagulation.

To allow clinicians a rapid, simultaneous calculation of the risks of stroke, mortality and bleeding an integrated electronic risk tool is required. GARFIELD-AF risk score was prospectively and externally validated and tested against currently available risk predictors. Risk scores do not replace the need for clinical decisions, but they allow clinicians a more comprehensive context, balancing risks and benefits, to make evidence-based decisions on clinical management.

HIGHLIGHT: AF

The new GARFIELD-AF risk tool wins prize for best Moderated Poster at ESC

The GARFIELD-AF risk tool was originally developed as a web-based tool to facilitate decisions regarding whether to administer or withhold anticoagulation in patients with AF based on their future risk of death, stroke, and bleeding.

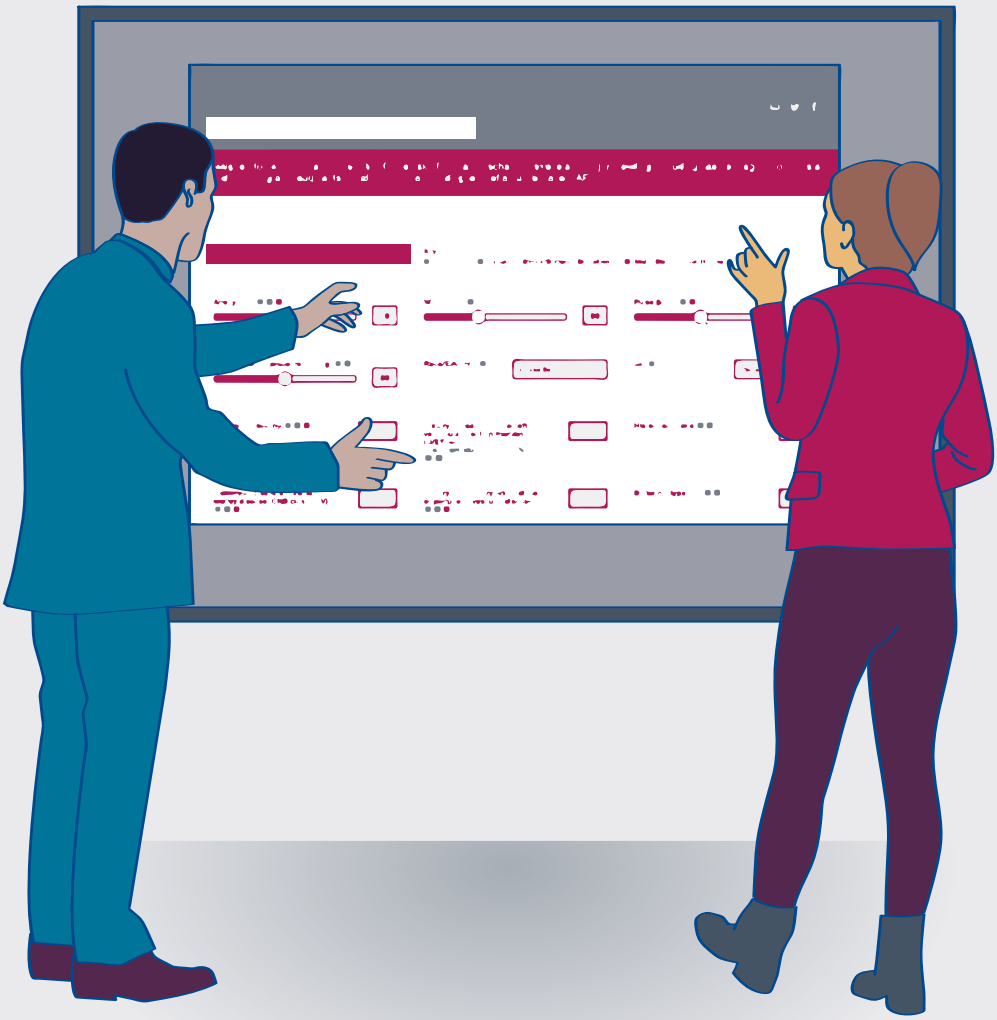
Now, the GARFIELD-AF risk calculator has been updated to include data garnered from more than 52,000 patients, predicting risk over a longer period of up to 2 years. The improved version performed well in comparison with CHA_2DS_2-VASc and HAS-BLED at predicting 2-year mortality,

Prof Fox showed how the tool's simple user interface will allow clinicians to input their patients data, clinical characteristics and medical history to calculate risk of death, stroke and major bleeding.

The original tool was validated in nearly 40,000 GARFIELD-AF participants and externally validated in 10,000 patients enrolled in the US-based ORBIT-AF registry, predicting risk over 1 year.

and provides estimates for rates of death, stroke, and major bleeding according to different treatment options as a novel feature.

Prof Keith Fox (University of Edinburgh) presented the updated GARFIELD-AF risk tool at the European Society of Cardiology (ESC) Congress in Paris in August, and was awarded best Moderated Poster.



Prof Fox showed how the tool's simple user interface will allow clinicians to input their patients' demographic data (sex, race, age, weight) and clinical characteristics (blood pressure, pulse rate) along with medical history items, which are then used to calculate their risk of death, stroke/systemic embolism (SE), and major bleeding based on intended treatment (NOAC, VKA, or no OAC).

For instance, in a male patient with AF aged 65 years with normal body weight, blood pressure, and resting heart rate and no history of cardiovascular disease, the tool estimates his 2-year risk of death, stroke/SE, and major bleeding with no OAC at 2.5%, 1.2%, and 0.5%, respectively, whereas if he is treated with VKA they are 2.3%, 0.9%, and 1.0%, respectively, and NOAC 1.8%, 0.7%, and 0.7%, respectively.

Hence the risk calculator provides a useful means to predict future outcomes of three different treatment options and thereby guide decision making. The risk tool is hosted on the GARFIELD-AF website, with a mobile app also planned.

Article contributed by:
***Prof Keith A. A. Fox** (University of Edinburgh)*

INSIGHT: VTE

Risk prediction models in VTE: A green field space for further research

In contrast to anticoagulation for stroke prevention in atrial fibrillation (AF), which is generally of long-term duration, anticoagulation following a VTE is frequently discontinued after 3-6 months.

This reflects, in comparison to AF-related stroke, the overall lower risk of mortality and long-term morbidity associated with recurrent VTE after discontinuing anticoagulants versus the outcomes if anticoagulation continues.

National and international guidelines recommend that the decision to continue or stop anticoagulation should be reviewed in each patient after 3 months of treatment following a VTE. This presupposes that it is possible to distinguish patients in whom the risk of recurrent VTE is sufficiently high and the risk of bleeding sufficiently low. These guidelines broadly categorise patients' risk of VTE recurrence according to whether the index event was unprovoked (high risk) or associated with a transient provoking factor (low risk). The former patients are advised to continue anticoagulation long-term and the latter to stop after 3 months. However, this approach is not without its problems. Studies that have developed risk prediction models following a first VTE episode (e.g. HERDOO2, Vienna and DASH) have varied in their definitions of unprovoked events, as well as in their inclusion and exclusion criteria. These models appear to be of moderate utility as long as the model-specific definition of unprovoked VTE is used.

... it is surprising how little predictive models of bleeding in this setting have been studied. Current data suggest that active cancer, prior bleeding, anaemia, age, renal dysfunction and uncontrolled hypertension are important factors, but there is a clear need for further work in this area.

Recent clinical trial data suggest that the binary classification of VTE in provoked and unprovoked may be too simplistic. Those with provoked episodes (whether caused by transient risk factors such as immobility or persisting risk factors such as obesity) may be at a similar risk of recurrence in patients with unprovoked VTE. In contrast. there is a low recurrence risk for those with a major transient risk factor such as surgery.

Given the importance of major bleeding risk to the decision on duration of anticoagulation, it is surprising how little predictive models of bleeding in this setting have been studied. Current data suggest that active cancer, prior bleeding, anaemia, age, renal dysfunction and uncontrolled hypertension are important factors, but there is a clear need for further work in this area.

Given its size and real-world global perspective in the DOAC era, GARFIELD-VTE is ideally placed to derive and validate new and existing predictive risk models for both recurrent VTE and major bleeding, and thereby inform decisions on the optimal duration of anticoagulant therapy after an episode of VTE.

Article contributed by:
***Peter McCallum** (TRI)*

HIGHLIGHT: VTE

Risk prediction models in cancer-associated thrombosis

Despite guideline recommendations for the prevention and treatment of cancer-associated thrombosis (CAT), patients with cancer remain at an increased risk of both VTE, and those patients with cancer and VTE are at an increased risk of mortality.

In 2008, Khorana and colleagues derived a VTE risk model for patients undergoing chemotherapy, comprising six predictive variables:

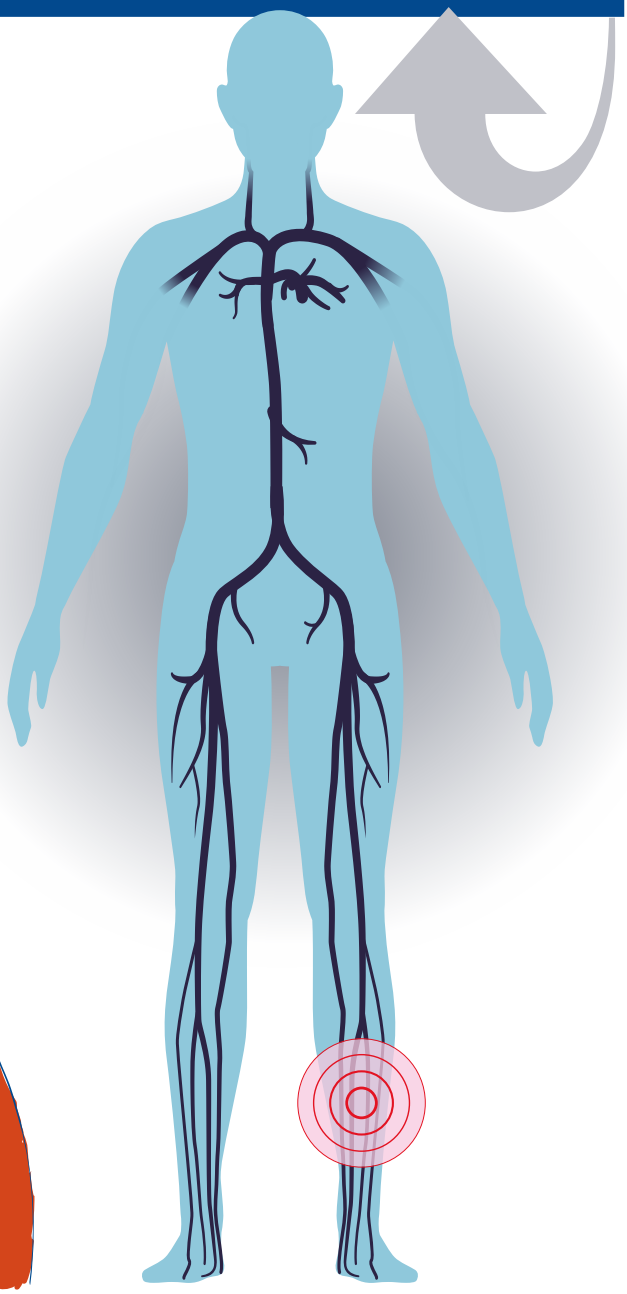
Variable	Score
Very high-risk cancer type (stomach, pancreas)	2
High-risk cancer type (lung, lymphoma, gynaecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350 x 10^9/L	1
Haemoglobin <100g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 x 10^9/L	1
Body mass index ≥35kg/m^2	1

The model divided patients into low (0), intermediate (1-2), and high 3) risk. The patients in the study had a median follow up of 73 days. In a recent validation meta-analysis the Khorana score was found able to select ambulatory patients with cancer at high risk of VTE, showing good sensitivity, but low specificity, as most events were found to occur outside the high-risk group. A recent study has shown that the Khorana score, as well as other available scores (PROTECHT, CONKO, ONKOTEV) are not sufficiently accurate when used at a conventional threshold of three points, and show a decline in predictive value with time.

Article contributed by:
***Gloria Petralia** (TRI)*

The Prospective Registry of Cancer and Events Involving Venous Thromboembolism (PERCEIVE) enrolled 5,000 patients from nine centres in six countries. All patients were followed for 12 months, and in four sites patients continued extended follow-up for up to 10 years. Results from the first 12 months were presented at this year's ISTH conference in Melbourne, exploring a new predictive model for CAT. This model is not limited to patients receiving chemotherapy and covers the 12-month period post-cancer diagnosis.

Being the largest prospective registry of cancer patients designed to investigate thromboembolic and cardiovascular events, PERCEIVE is ideally placed to derive and validate a new predictive risk model for CAT.



SPOTLIGHT

ESC Paris 2019

GARFIELD's perennial presence at the European Society of Cardiology (ESC) Congress continued in Paris, France (31 August to 4 September). We organised a clinically important and exciting satellite symposium and a number of late-breaking oral and poster presentations.

Prof Ajay Kakkar opened the symposium titled *What is the long-term impact of atrial fibrillation? Insights from GARFIELD-AF*. There were five presentations:

- Prof Dan Atar (Norway) gave a talk on *Long-term outcomes in AF*
- Prof Keith Fox (UK) presented a first glimpse of the GARFIELD risk calculator
- Dr Frank Cools (Belgium) spoke about *Changes in antithrombotic therapy after atrial fibrillation diagnosis*
- Prof A. John Camm (UK) discussed *Impact of following guidelines for treatment of AF and co-morbid conditions*
- Prof Shinya Goto (Japan) delivered *Three-way comparison of effectiveness among different classes of anticoagulants*
- Profs Jean-Pierre Bassand (France) and Bernard J. Gersh (USA) closed by summarizing highlights of the day's presentations and added some future perspectives on AF

At the ESC Congress, GARFIELD-AF Investigators contributed two late-breaking scientific presentations, one poster and a Moderated ePoster.

Prof JP Bassand presented a late-breaking oral session titled *Different short- and long-term prognostic implications of bleeding in patients with newly diagnosed atrial fibrillation*. This analysis showed that in GARFIELD-AF, patients with major bleeds were more likely female, older, and diabetic than those with less severe bleeds. Patients receiving VKA versus NOAC therapy were also at significantly higher risk of major bleeds.

Prof Toon Wei Lim (Singapore) delivered a presentation titled *Predictors of intracranial haemorrhage in patients with atrial fibrillation: insights from the GARFIELD-AF and ORBIT-AF registries*. In this analysis of pooled data from two registries, final predictors of ICH included older age, prior stroke, moderate–severe CKD, vascular disease, and use of VKA versus NOAC.

Dr Stefan Verstraete (Belgium) presented a poster titled *Haematuria is not elevated in AF patients treated with NOACs versus VKAs*, which showed that haematuria is a relatively rare event and usually non-serious among anticoagulated patients.

Prof Fox presented a Moderated ePoster titled *Balancing risk and benefit in patients with atrial fibrillation: the GARFIELD-AF risk score*. This prize-winning session confirmed that the new risk calculator performed well in comparison with CHA_2DS_2-VASc and HAS-BLED at predicting 2-year mortality, and provides clinically relevant estimates for rates of death, stroke, and major bleeding according to different treatment options.

TRI Thrombosis Research Institute

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