Refining Thromboembolic Risk in the General Population

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Letters

Refining Thromboembolic Risk in the General Population

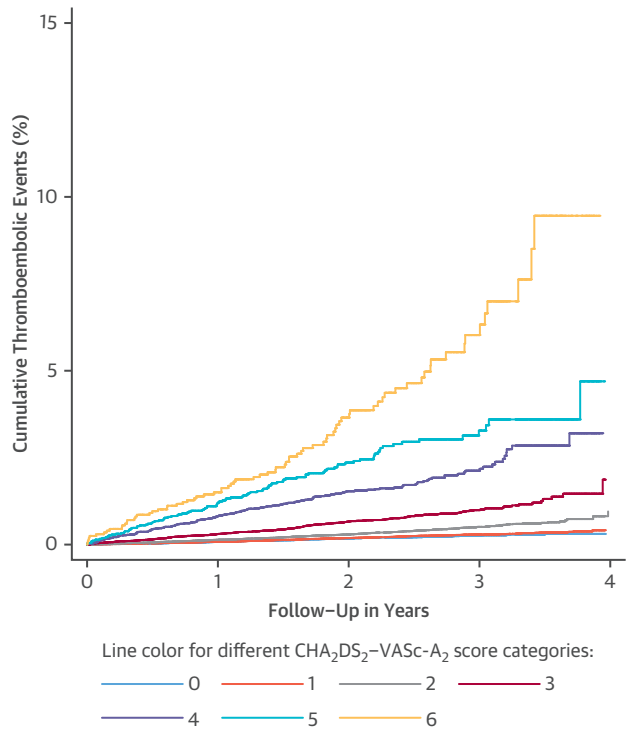
The most widely adapted algorithm to estimate stroke risk is the easily applicable congestive heart failure, hypertension, age >75, diabetes mellitus, prior stroke, vascular disease, age 65 to 74, and sex (CHA_2DS_2-VASc) score. This score has been developed in patients with atrial fibrillation (AF), and anticoagulant therapy is recommended when the score ≥2 (1). Patients with AF are at increased risk for a thromboembolic event, but it is not clear whether AF is a causal risk factor or if AF, as with other risk factors, is rather a manifestation of advanced atherosclerotic state associated with stroke. The notion that AF is the dominant cause of stroke in AF patients has been challenged (2). In addition, the majority (up to 80% to 90%) of stroke patients have no documented history of AF at all.

We hypothesized that AF should not always be considered the cause but rather 1 of the risk factors of thromboembolic events. Therefore, we aimed to accommodate AF as a separate component to the commonly used and recommended CHA_2DS_2-VASc score, thereby extending its applicability to the general population.

We studied 502,353 participants of the U.K. Biobank cohort (3), a large community-based cohort of participants, aged 40 to 69 years, registered via the U.K. National Health Service by a general medical practitioner between 2006 and 2010. Data on cardiovascular phenotypes and events were derived from patient data collected during the Assessment Centre visits and inpatient Hospital Episode Statistics records. Cox proportional hazard regression was used to estimate hazard ratios and Harrell's C-statistic to determine the predictive accuracy.

The average age was 57 ± 8 years, of which 81% were <65 years and 19% between 65 and 74 years; 46% were female. The prevalence of hypertension was 29%, previous stroke/transient ischemic attack 2%, previous thromboembolism 3%, congestive heart failure 1%, vascular disease 3%, and diabetes 5%. The median duration of follow-up for thromboembolic events was 2.2 years (interquartile range: 1.5 to 2.9 years). The thromboembolic event rate in participants with AF was 0.86 (95% confidence interval [CI]: 0.74 to 1.01) per 100 person-years. In participants without AF, the thromboembolic event rate was 0.14 (95% CI: 0.13 to 0.15) per 100 person-years. The CHA_2DS_2-VASc score predicted the incidence of thromboembolic events in participants with AF (N = 9,947; $p < 0.001$; C-statistic: 0.64) but also in those without AF (N = 492,406; $p < 0.001$; C-statistic: 0.64). The thromboembolic event rate of participants with AF and a CHA_2DS_2-VASc score <2 was 0.48 (95% CI: 0.35 to 0.67). The thromboembolic event rate of participants without AF and a CHA_2DS_2-VASc

FIGURE 1 Thromboembolic Event Rates for Each CHA_2DS_2-VASc-A_2 Score Category



Kaplan-Meier failure curve showing the incidence of thromboembolic events in % for congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke, vascular disease, age 65 to 74, and sex with AF as a separate component (CHA_2DS_2-VASc-A_2) score categories in all participants over time (N = 502,353, C-statistic: 0.67).

score <4 was 0.12 (95% CI: 0.11 to 0.13). AF patients with a CHA_2DS_2-VASc score of 2 had a thromboembolic event rate per 100 person-years of 0.80 (95% CI: 0.59 to 1.08). In participants without AF, a similar event rate was observed with a CHA_2DS_2-VASc score of 4 (event rate: 0.76; 95% CI: 0.64 to 0.91). Therefore, we calibrated the CHA_2DS_2-VASc score for the general population by adding 2 points for the presence of AF and 0 for the absence of AF. Accommodation of AF in this refined CHA_2DS_2-VASc-A_2 score significantly predicted thromboembolic events in the overall population of the U.K. Biobank (N = 502,353; C-statistic: 0.67) (Figure 1). We performed sensitivity analyses by excluding participants on antiplatelet therapy, which did not affect our findings.

We have demonstrated that the CHA_2DS_2-VASc score is helpful in predicting thromboembolic events in individuals without AF. We are the first to further refine this score for the general population by accommodating AF as a separate component (A_2), thereby extending its applicability to the general population. Whether anticoagulant therapy should be prescribed to individuals in the general population who have a CHA_2DS_2-VASc-A_2 score ≥4 cannot be concluded from our observational data. We propose to use this refined score in future clinical studies to broaden the inclusion to individuals without AF and determine whether the expected benefits indeed outweigh the potential harmful side effects.

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Bioprosthetic Total Artificial Heart Induces a Profile of Acquired Hemocompatibility With Membranes Recellularization

The Carmat total artificial heart (C-TAH) (Vélizy-Villacoublay, France) is an implantable electrohydraulically actuated biventricular pump that has been developed to minimize mechanical assist device-related morbidities (1). Its blood-contacting surfaces consist of expanded polytetrafluoroethylene and bovine pericardial tissue processed in glutaraldehyde as used in cardiac bioprosthetic valves.

In the 3 first implanted patients, we investigated biological parameters of hemocompatibility (hemolysis and appearance of acquired von Willebrand syndrome) and histological characteristics of explanted devices. The 3 patients were 76, 68, and 74 years of age with severe end-stage biventricular heart failure. Patient 1 made a rapid recovery after implantation but remained in intensive care because of respiratory and renal dysfunction. Patient 2 was successfully rehabilitated and could be discharged from the hospital after 5 months. Both patients experienced a device failure and died after 74 and 270 days, respectively. Patient 3 was discharged home at 5 months. Repeated rehospitalizations for asthenia, cachexia, and renal insufficiency led to the patient's death at 254 days.

Hemolysis, measured by plasma-free hemoglobin level, was below the clinically relevant threshold of 400 mg/l in all patients during the entire follow-up (data not shown). The levels of high-molecular-weight multimers of von Willebrand factor were measured perioperatively and during follow-up in the 3 patients. No significant time-dependent loss was observed after initiating the support (Figure 1A), with the average drop in high-molecular-weight multimer ratio (relative to baseline) reaching 0.97 ± 0.34, 0.88 ± 0.15, and 0.98 ± 0.01 at 5, 30, 60, and 180 min for all