Arterial cardiovascular events and mortality following venous thromboembolism

Kasper Adelborg, Jens Sundbøll, Henrik Toft Sørensen

Department of Clinical Epidemiology, Aarhus University Hospital, Skejby, Aarhus, Denmark

Correspondence to: Kasper Adelborg, MD. Department of Clinical Epidemiology, Aarhus University Hospital, Skejby, Olof Palmes Allé 43-45, DK-8200, Aarhus N, Denmark. Email: kade@clin.au.dk.

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Venous thromboembolism (VTE) is the third most common cardiovascular condition, with an annual incidence of 10-20 cases per 10,000 inhabitants (1,2). It is a major health problem associated with increased mortality (3) and substantial evidence suggests that patients with VTE are at higher risk of arterial cardiovascular events than the general population (4).

In this issue of *Annals of Translational Medicine*, Katz *et al*. report on a cohort study of patients with impaired glucose tolerance with and without previous VTE (5). When they compared VTE patients with non-VTE patients, they observed an increased 5-year risk of the composite endpoint of death, myocardial infarction, and stroke (10.7% *vs.* 5.9%), with a corresponding hazard ratio of 2.12 [95% confidence interval (CI), 1.36-3.31]. Moreover, the authors reported a higher 5-year expanded composite cardiovascular endpoint of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, hospitalization for unstable angina, and arterial revascularization (21.9% *vs.* 12.9%; corresponding hazard ratio =1.49; 95% CI, 1.04-2.13) among VTE patients compared with non-VTE patients (5).

Katz *et al*. provide new information concerning patients with impaired glucose tolerance, highlighting VTE as an important prognostic factor for death and arterial cardiovascular events. However, as discussed by the authors, their results should be considered in the light of certain limitations. Importantly, the time of diagnosis was unknown. Because only a minority of the VTE patients received anticoagulation therapy, most VTE diagnoses likely occurred at least 3-12 months before inclusion in the study. As a result, follow-up time was lost, yielding imprecise effect measures. In addition, the authors did not adjust for VTE risk factors such as surgery, fracture/trauma, and cancer, which might have been confounding factors (6). Particularly important is cancer, which is found more frequently in patients with VTE than in non-VTE patients (7) and which has been shown to lower survival (8). The study may also be hampered by recall bias and inaccurate VTE diagnoses, affecting the validity of the absolute risk estimates. Finally, due to the small sample size, the authors chose a composite endpoint that prevented separate examination of the associations between VTE and mortality and VTE and arterial cardiovascular events.

Katz *et al*.'s study confirms previous research that VTE is associated with myocardial infarction and stroke (4). A meta-analysis showed that the incidence of these conditions in VTE patients is approximately 0.32% per patient-year (4). In that analysis, the risk of arterial cardiovascular events was higher in unprovoked VTE patients (VTE occurring in the absence of malignancy or other provoking factors) when compared with both the general population and patients with provoked VTE (4).

Causes of death in VTE patients require further investigation. A recent study comparing VTE patients with the general population found that the most important causes of death in VTE patients were VTE-related complications, cancer, pneumonia, chronic obstructive pulmonary disease, and cardiovascular diseases (3). The association between VTE and stroke/ischemic heart disease may have several pathophysiological explanations. Risk factors such as smoking, sedentary life style, obesity, hypercholesterolemia, hypertension, diabetes, and metabolic syndrome are common among VTE patients, and thus likely contribute to their increased risk of arterial events (9-12). Also, VTE is strongly linked to inflammation and increased levels of

C-reactive protein, fibrinogen and factor VII, interleukin 1, and to reduced levels of interleukin 10, which may further increase the risk of arterial events and death (13). VTE-related hypercoagulability (14) and endothelial injury (15) have been proposed as additional mediators of arterial events. It has previously been questioned, whether VTE and arterial events are two aspects of the same disease, but further studies on this area are needed (16).

To conclude, Katz *et al.*'s findings are consistent with existing evidence showing that VTE is associated with arterial cardiovascular events and death. Identification of VTE patients at particularly high risk of arterial cardiovascular events remains an important target for future research. As well, further studies are needed to examine the potential benefit of providing extended antithrombotic treatment to VTE patients, in order to reduce the risk of arterial cardiovascular events and death.

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