



## Editorial

## Sex may matter when it comes to the presenting location of deep vein thrombosis



The incidence, risk factors, clinical presentation, and prognosis of cardiovascular diseases differ among men and women [1,2]. Defining, measuring, understanding and responding to these differences is important in an era of individualized and precision medicine. Sex specific differences in the incidence of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), have long been recognized. Women are at higher risk during fertile years, mainly due to the effects of pregnancy and oral contraceptive use [3], and men are at higher risk at older ages [4]. However, it was not until 2004 [5] when it was first shown and later confirmed [6–8] that men had an unexplained 3.6-fold higher risk of recurrence of VTE than women that investigation into the effects of sex on VTE occurrence intensified. This line of research has had an impact on patient management. It is now recommended that patient sex among other factors be considered when determining duration of anticoagulation for unprovoked venous thrombosis [9,10].

There has been a growing interest in understanding the presentation of DVT in men and women. This is relevant as the clinical impact of distal DVT differs from that of proximal DVT [11]. Distal DVT has been less studied than proximal DVT. Nonetheless, the natural history and prognosis of isolated distal DVT is generally considered more benign. The rate of extension into the proximal veins is thought to be low and vary anywhere between 1 and 6% based largely on indirect evidence from serial compression ultrasound management studies [12,13]. This is an important point as the embolic potential of distal DVT is generally considered to be much lower than that of proximal DVT [14]. In the CALTHRO study, where patients and physicians were blinded to the presence of isolated distal DVT, only one patient (of 64 with untreated isolated distal DVT, 1.6%) had a PE complication during follow-up [13]. Finally the risk of recurrence also is considered to be low for patients with isolated distal DVT. In a recent patient-level meta-analysis, patients with proximal DVT had a 4.8-fold higher cumulative recurrence rate than patients with isolated distal DVT [15]. Specifically, the 3-year cumulative recurrence rate of any venous thrombosis event was 0.9% (95% CI (Confidence Interval): 0.1%, 6.3%) and 1.2% (95% CI: 0.2%, 8.2%) for PE recurrence. While proximal and distal DVT are manifestations of the same disease, their phenotypic expression may be mediated by patient sex and its interaction with other factors such as age.

In this issue of *Thrombosis Research*, Trincherro and colleagues explore the effect of sex on the presenting location (distal vs. proximal) of acute isolated DVT [16] and Barco and colleagues on behalf of the RIETE investigators [17] examine the influence of sex among other patient characteristics on the presentation of first isolated symptomatic acute DVT. Trincherro et al. addressed whether the proportion of isolated distal versus proximal acute DVT differs among women and men by means of a meta-analysis of seven studies and a post-hoc analysis of

data from a previously reported [11] single center cohort study of 831 consecutive patients (50.5% women) diagnosed with first symptomatic acute DVT among whom 202 (24%) had isolated distal DVT and 629 (76%) had proximal vein thrombosis between 2000 and 2012. The meta-analysis reported a weighted pool risk difference in the proportion of distal DVT between women and men diagnosed with DVT of 5.4% (95% CI: 0.7%, 9.5%). The difference was up to 6.5% when only looking at first ever DVT events and 5.3% when looking at either recurrent or first DVT presentations. Study limitations included significant statistical heterogeneity, wide variability in the estimates of isolated distal DVT among included studies, and lack of information on absolute risk of isolated distal DVT in men and women. Nonetheless, the cohort study did confirm the findings. Among the 831 DVT events, a larger proportion of isolated distal DVT was diagnosed in women compared to men (5.7% difference; 95% CI: -0.1%, 11.5%) and the largest difference was seen among patients aged 51–70 years (9.5% difference; 95% CI: 2.9%, 16.1%) and possibly in those with unprovoked events (8.5% difference; 95% CI: -0.9%, 17.9%).

Similar findings were previously reported [18] in a registry of 4976 ambulatory patients with clinically suspect DVT. Although women were more likely to be referred for clinically suspect DVT, men had a higher prevalence of confirmed DVT (37.0% vs. 24.3%) with proximal DVT being more common in men (59.6%) vs. 44.5% in women and isolated distal DVT more common in women (41.1%) vs. 29.6% in men. It is possible that sex-specific differences in the perception and awareness of leg symptoms may influence diagnostic workup. It has been suggested [18] that women more often present with nonspecific leg symptoms suggestive of venous thrombosis while symptoms in men are in keeping with more advanced venous disease (e.g. whole leg swelling). This may have consequences to the diagnostic work-up for DVT and ultimately lead to under- or over-diagnosis of isolated distal DVT in patient subgroups. Men may be delaying presentation for diagnostic work-up or alternatively the referral threshold for performing imaging tests in women may be lower because of the higher incidence of nonspecific leg symptoms.

Barco and colleagues [17] explore the interaction of patient sex with common VTE risk factors on the presenting location of DVT to gain insight on possible pathophysiologic mechanisms. Using the RIETE registry [19], a post hoc analysis was conducted of 24,911 patients with first objectively diagnosed acute DVT without symptomatic PE, among whom 4266 (17.1%) had isolated DVT and 20,645 (82.9%) had proximal DVT. Overall, the proportion of patients with first isolated DVT was similar among all women and men (difference 0.3%; 95% CI: -0.6%, 1.2%). However, more isolated distal DVT was diagnosed in women aged 40–69 years with the biggest difference in the proportion of distal DVT between women and men being observed for the group aged 40–49 years (difference 6.7%; 95% CI: 3.7%, 9.9%). This is in

agreement with the findings of Trinchero and colleagues [16]. Moreover, this difference was seen among unprovoked events and possibly among non-cancer-mediated provoked events. The authors noted that age and sex showed significant interactions with VTE risk factors in provoked events. Again older age was associated with provoked distal DVT in women whereas older age was associated with provoked proximal DVT in men. Recent surgery was associated with distal DVT in men and women, whereas active cancer was associated with proximal DVT in both men and women. Pregnancy was associated with proximal DVT (OR (odds ratio) 0.63; 95%CI: 0.20, 0.60) whereas hormonal therapy (75% oral contraception) was associated with distal DVT (OR 1.51; 95%CI: 1.16, 1.96). These findings raise the possibility that VTE risk factors may impact the presenting location of DVT in men and women. However, inferences and firm conclusions are difficult because of study limitations including multiple testing [20], non-uniform diagnostic standards or strategies for the diagnosis of distal DVT across RIETE study sites, lack of information on population level absolute risk of distal DVT, and detection bias possibly due to women undergoing more frequent leg ultrasound examinations than men for non-VTE conditions such as varicosities which are more prevalent in women [21].

It is difficult to postulate possible mechanisms for sex differences in the presenting location of acute DVT in older women and men. As the authors suggest [16], hormonal changes following menopause may be important as they are for other cardiovascular diseases [22,23]. A population level study is needed to address absolute risk of isolated distal DVT and proximal DVT for women and men, by age and by exposure to female-specific risk factors. Unlike proximal DVT and PE, which have been extensively studied and for which management is well standardized and widely endorsed, less is known of the optimal management of isolated distal DVT especially in high risk patients such as cancer or hospitalized patients [24]. Confirming sex-differences in risk of isolated distal and proximal DVT and elucidating the underlying pathophysiology for these differences will be important to optimizing the current management of distal DVT in men and women.

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