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*Original Article*

# CARDIOVASCULAR RISK FACTORS ARE LINKED TO VENOUS THROMBOEBOLISM:

(A systematic review and meta-analysis of case-control studies)

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## ABSTRACT

**Background**

Cardiovascular risk factors are associated with venous thromboembolism (VTE) has received increased attention in the past few years. At present, it is not clear whether the each cardiovascular risk factor is risk factor for venous thromboembolism. Features of cardiovascular risk factor have shown to be been individually associated with VTE. However, whether each of the factors additively increases the risk of VTE is uncertain. We performed a meta-analysis to assess the association between some major cardiovascular risk components and VTE.

**Methods**

Online Pub Med and Embase database were searched for case-control studies evaluating cardiovascular risk factors and incident Venous Thromboembolism in adults. Independent observers extracted data regarding annualized VTE incidence from studies meeting predetermined criteria, (Blood pressure: $\geq$ 140/90 mmHg. Dyslipidemia: triglycerides (TG): $\geq$ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) $\leq$ 0.9 mmol/L in male, $\leq$ 1.0 mmol/L in female, waist circumference $\geq$ 90cm for men, $\geq$ 80cm for women or body mass index > 30 kg/m$^2$. Data were analyzed weighted, random-effects meta-analysis.

**Results**

Thirty two case-control studies with a total of 30929 patients met the inclusion criteria. Odds ratios or weighted means and 95% confidence intervals (CIs) were then calculated and pooled using a random-effects model. Statistical heterogeneity was evaluated through the use of $X^2$ and $I^2$ statistics. Compared with controls, the OR for VTE was 2.24 for obesity (95% CI, 1.83 to 2.75), 1.56 for hypertension (95% CI, 1.26 to 1.92) and 1.55 for diabetes mellitus (95% CI, 1.25 to 1.92). Weighted mean high-density lipoprotein cholesterol (HDL) levels were significantly lower in VTE patients with cardiovascular risk factor compared to controls with inverse correlation with risk of VTE, whereas no difference was observed for total cholesterol levels.

**Conclusion**

Cardiovascular risk factors are significantly associated with higher risk of VTE, which may imply that it may contribute to the multi factorial pathogenesis of VTE. Nevertheless, this report could not determine whether the combination of all three components is associated with a higher risk than each of the components in isolation.

**Keywords:** Cardiovascular, Risk factors, Thromboembolism



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## INTRODUCTION

Cardiovascular risk factors are well-recognized impact on atherosclerotic cardiovascular and cerebrovascular disease is potentially a risk factor for VTE and might be one of the contributors of the multifactorial pathogenesis of VTE.[1] It is a cluster of cardio metabolic risk factors related to. It represents a public health problem as it affects nearly 20–30% of the general population in many countries. It consists of a constellation ofinterrelated cardiovascular abnormalities that includes glucose intolerance, insulin resistance, abdominal obesity, atherogenic dyslipidemia, and hypertension[2,3]. It may play a role in the development of idiopathic VTE and share common risk factors with VTE.[4,15] To date, among cardiovascular disease (CVD) risk factors, only obesity was shown to be consistently associated with VTE risk[5,7,10], whereas the role of diabetes, hypertension, total cholesterol, high density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, and physical inactivity are less clear[7-9]. The impact of diabetes is unclear. Three studies reported that diabetes did not increase VTE risk[10-13] or that the association was confounded by other VTE risk factors such as major surgery, medical illness, or residence in a nursing home[14]. Few studies specifically examined the association of lipid levels and VTE. Some reports have been published on the risk incurred by CVD risk or elements of its cluster, with inconclusive results. We therefore performed a systematic review of the literature and a meta-analysis to evaluate the risk of VTE associated with cardiovascular major components.

## METHODS

We performed a systematic review and meta-analysis of studies to evaluate the impact of cardiovascular risk on the occurrence of VTE. We conducted a literature search of journal articles published on or before 31 December 2012 using Pub Med, Embase, and the Cochrane Database of Systematic Reviews. The index fields were queried for the key words "cardiovascular risk factors, "deep vein thrombosis," "pulmonary embolism," and "venous thromboembolism" and excluded "infant," "newborn," and "fetus." The results of this search were combined with the results of a subsequent search. Terms used in the last search were "arterial hypertension," "blood pressure," "dyslipidemia," "cholesterol," "triglyceride," "diabetes," "hyperglycemia," "impaired glucose tolerance," "obesity," "overweight. We considered only English language publications.

### Data Extraction

Study selection was performed independently by 2 reviewers with disagreements resolved through discussion and by opinion of a third reviewer, whenever needed. Only studies reporting on objectively confirmed diagnosis of VTE (i.e., ultrasonography or computed tomography for deep vein thrombosis and computed tomography, magnetic resonance imaging, or ventilation /perfusion scan for pulmonary embolism) and that had a control group were included in the final data set. We excluded all studies in which the entire population of patients with VTE had a concomitant, known, major risk factor (eg, studies carried out in patients undergoing major surgery or trauma and studies involving pregnant women only). The study selection was assessed by the k statistic[15,16].

The following baseline characteristics for cases and control groups were collected: number of subjects studied, mean age, variation in age, sex, and race. One or more of the following elements were collected in each study: (1) number and proportion of patients and controls with blood pressure: $\geq$ 140/90 mmHg, (2) Dyslipidemia, triglycerides (TG) $\geq$ 1.695 mmol/L and high-density lipoprotein cholesterol (HDL-C) $\leq$ 0.9 mmol/L (male), $\leq$ 1.0 mmol/L (female), (3) waist circumference (**≥**90cm for men, $\geq$ 80cm for women) or body mass index > 30 kg/m$^2$ (4) raised fasting plasma glucose (FPG) >100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If information on the proportion of patients with and without a given risk factor was not available, mean levels and standard deviations were extracted for both cases and controls. If the required data could not be located in the published report, we contacted the corresponding author by mail, with a reminder e-mail sent every 15 days.

### Study validity assessment

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Two unmasked investigators independently completed the assessment of study validity (Umesh, pritam). The internal validity of each study was evaluated considering 2 potential sources of bias of case-control studies[17]. Studies were considered of low quality when subjects were arbitrarily excluded from both the case or control groups, and when baseline characteristics of the control group (age, sex) were not matched with characteristics of the patient group. Otherwise studies were considered of higher quality. Case control studies that were specifically designed to assess the influence of risk factors on the occurrence of VTE were considered to be of higher quality than studies that used a nested case-control design either by identifying cases with VTE by hospital discharge registers or by using existing patient registries. Studies that adequately reported methodology of measurement of risk factors were considered to be of higher quality than studies that just reported result. We subsequently excluded articles in which risk factors were reported instead of actually measured; we then excluded all retrospective cohort studies and case-

control studies that were derived from registers or discharge files. For each step, we assessed statistical heterogeneity.

### Statistical analysis

We pooled results from the studies using Review Manager (RevMan), version 4.3 for Windows (The Cochrane Collaboration 2003, Oxford, England). We calculated odds ratios (ORs) and 95% confidence intervals (CI) to pool data for each risk factor by using the a random-effects model (DerSimonianand Laird[18] method). Statistical heterogeneity was evaluated with the $X^2$ and the $I^2$ statistics, which assess the appropriateness of pooling the individual study results[19]. The $I^2$ value provides an estimate of the amount of variance across studies resulting from heterogeneity rather than chance. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each study, and results were compared through the use of a random-effects model.

## RESULTS

### Study identification and selection

We identified 4662 studies using our search strategy of which 4605 were excluded after scanning titles and abstracts, leaving 57 reports for more detailed evaluation. In 11 studies no comparable data were provided[20-30]. Two studies did not have control group[31-32]. Three studies were from autopsies and postpartum examination[33-35]. In six studies BMI was not calculated or inappropriately evaluated[36-41]. In two studies[42, 75] SD were not provided so email was sent to corresponding author. Studies were removed if no reply were obtained in two week time. Thus 31 studies were eventually included in this meta-analysis[1, 4, 13, 14, 43-69, 75] with a total of 30929 patients. Study populations included were well-characterized case-control study. The mean patient age varied widely. Eight studies investigated patients[23,44,47,48,50,55,63,75] <55years of age. Eleven studies[12, 19, 40, 54-59, 63, 65, 66] investigated for patients >45 years of age. The mean age of the other studies ranged between 42 and 70 years[45,46,49,51-54,56,59,64,65,67]. One study included men only[75]. All the case-control studies evaluated risk factors for VTE.

**Table 1: Case-control studies included in the metanalysis,**

| Source | Participants, n | No. of Case | No. of control | Age, Y | Women% |
|---|---|---|---|---|---|
| Poulter et al, 19995 | 4141 | 1143 | 2998 | 20-44 | 100 |
| Kawaskai, 1997 | 218 | 109 | 109 | 49 | 51 |
| Hoibraaten et al, 1998 | 528 | 176 | 352 | 59 | 100 |
| Nightingale et al, 2000 | 1728 | 394 | 1364 | 15-49 | 100 |
| Lidegard et al, 2002 | 5041 | 987 | 4054 | 15-44 | 100 |
| Quere et al, 2002 | 486 | 86 | 44 | 55 | 55 |
| Vaya et al, 2002b | 337 | 109 | 121 | 42 | 62 |
| Abdollahi et al, 2003 | 908 | 454 | 454 | 45 | 57.5 |
| Gonzalez et al , 2003 | 251 | 126 | 125 | 62 | 51 |
| Paganin et al, 2003 | 138 | 46 | 92 | 51 | 51 |
| Prandon et al, 2003 | 449 | 299 | 150 | 66 | 54 |
| Sydneyet al, 2004 | 942 | 746 | 196 | 15-44 | 100 |
| Deguchi et al, 2005 | 198 | 49 | 49 | <55 | 0 |
| Segui et al, 2000 | 283 | 190 | 93 | 42 | 40 |
| Zamini et al, 2003 | 86 | 43 | 43 | 46 | 56 |
| Doggen et al,2004 | 2463 | 477 | 1986 | 70 | 100 |
| Mc Coll et al, 2000 | 160 | 62 | 98 | <50 | 100 |
| Jang ju et al, 2009 | 508 | 208 | 300 | >50 | 10 |
| Ageno et al, 2006 | 200 | 93 | 107 | 63-65 | 51 |
| Ay et al, 2007 | 245 | 116 | 129 | 53-56 | 59.5 |
| Ambrosetti et al, 2007 | 185 | 86 | 95 | >65 | 28 |
| Minno Di et al, 2010 | 1191 | 323 | 868 | <50 | 63 |
| Vaya et al, 2011 | 296 | 146 | 150 | >50 | 49 |
| Canonico et al, 2006 | 850 | 253 | 597 | 45-70 | 100 |
| Heit et al, 2009 | 4037 | 1922 | 2115 | >60 | 54 |
| Larsen et al, 2007 | 301 | 91 | 210 | 25-35 | 100 |
| Yang et al, 2007 | 719 | 173 | 546 | 36-80 | 28 |
| Maccallum et al, 2011 | 2521 | 550 | 1971 | >18 | 55 |
| Straczek et al, 2005 | 789 | 235 | 554 | 61 | 55 |
| Hong cheng et al, 2005 | 179 | 89 | 89 | 38-79 | 48 |
| Delluce et al, 2011 | 464 | 732 | 732 | 16-99 | 56 |
| Wang et al, 2010 | 90 | 57 | 53 | 25-80 | 34 |

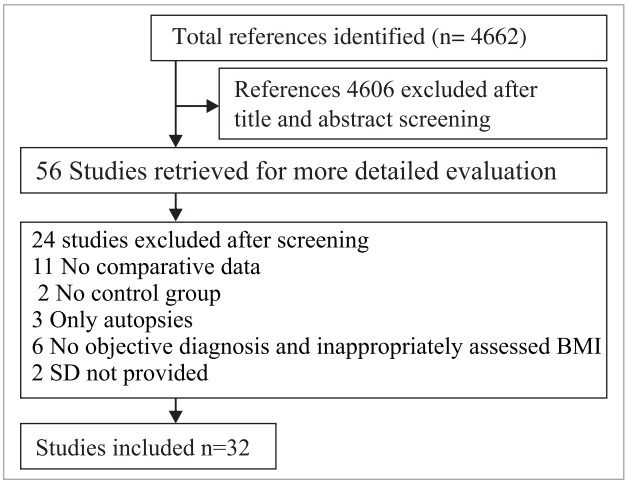


**Figure 1: Study selection**

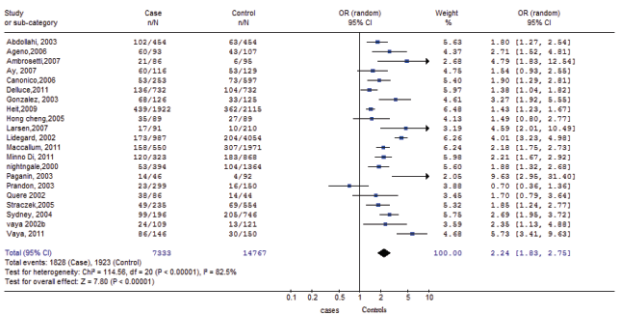

**Figure 2a: The risk of VTE associated with of obesity.**

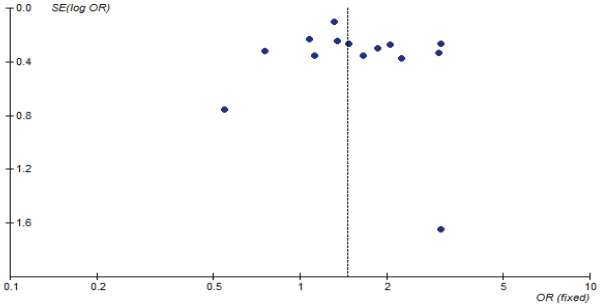


**Figure 2b: Funnel plot of published studies comparing the prevalence of obesity in VTE patient against controls. OR indicates odds ratio.**

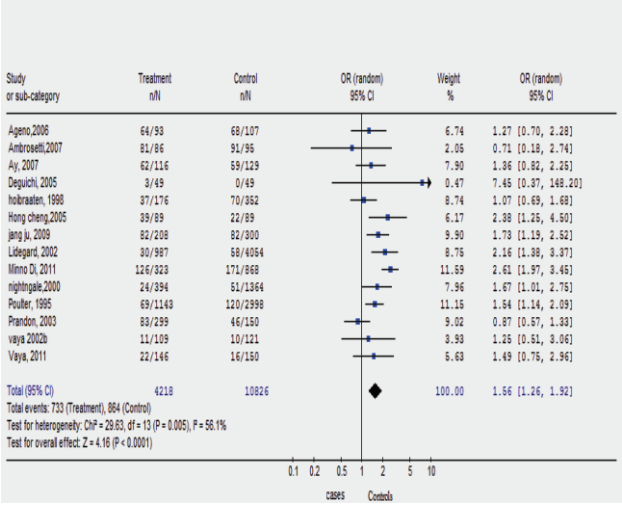


**Figure 3a: The risk of VTE associated with hypertension**

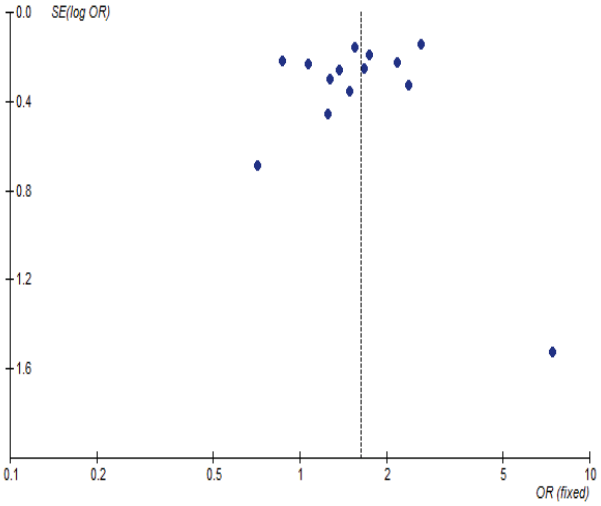


**Figure 3b: Funnel plot of published studies comparing the prevalence of hypertension in VTE.**

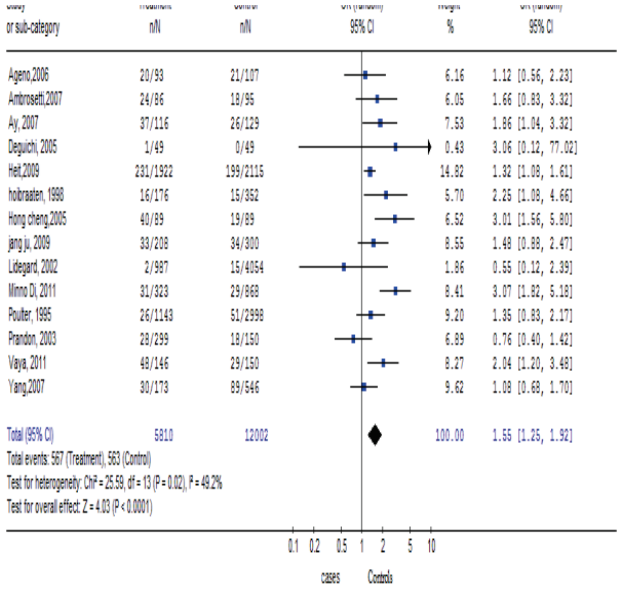


**Figure 4a: The risk of VTE associated with of diabetes.**

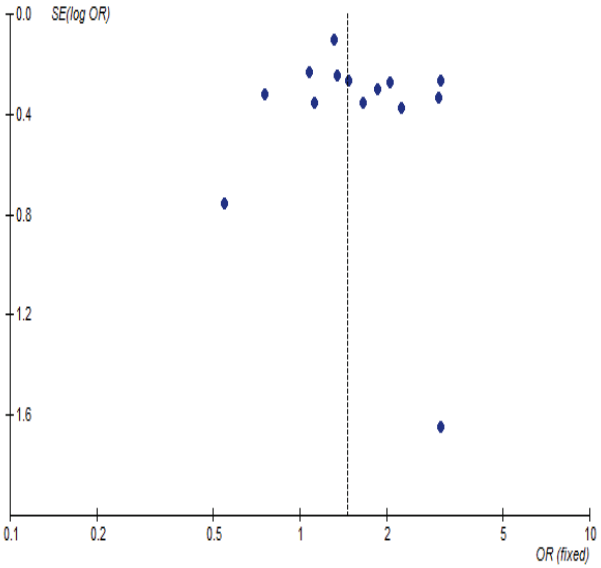


**Figure 4b: Funnel plot of published studies compare the prevalence of diabetes in VTE.**

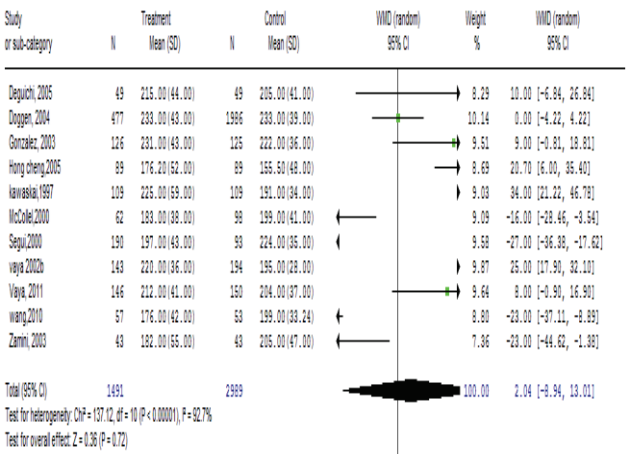


**Figure 5a: The risk of VTE associated with of total cholesterol**

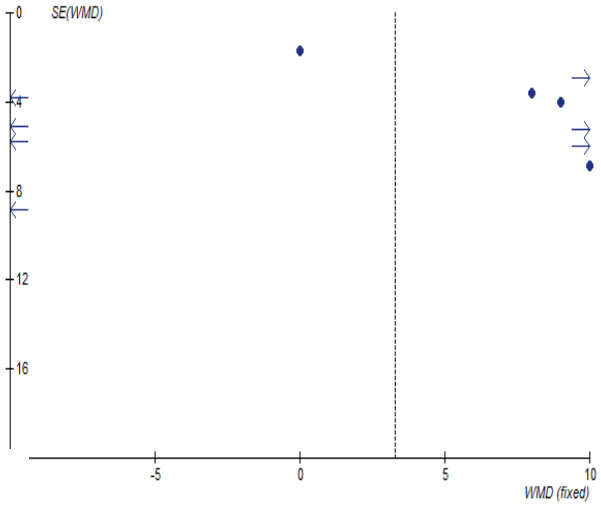


**Figure 5b: Funnel plot of published studies compare the prevalence of hypertension in VTE.**

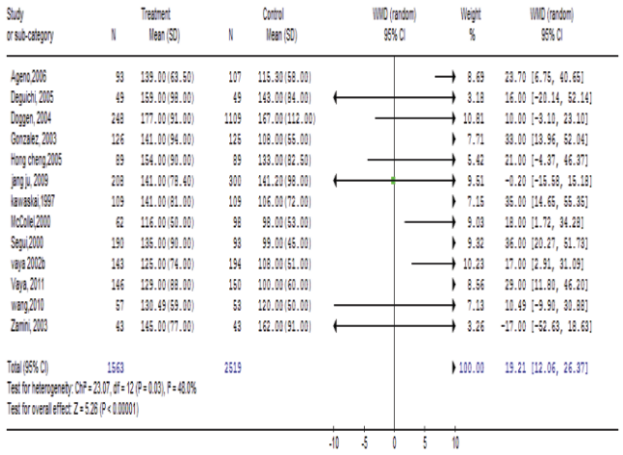


**Figure 6a: The risk of VTE associated with of triglycerides levels.**

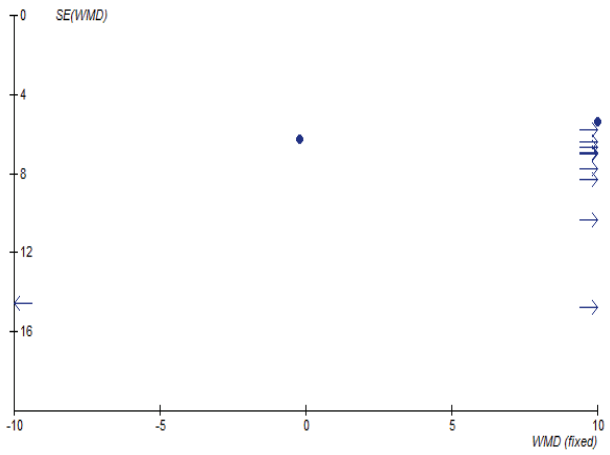


**Figure 6b: Funnel plot of published studies compare the prevalence of triglyceride in VTE**

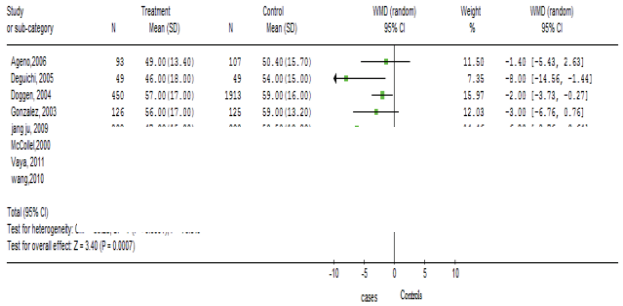


**Figure 7a: The risk of HDL (mg/dl) on the occurrence of VTE.**

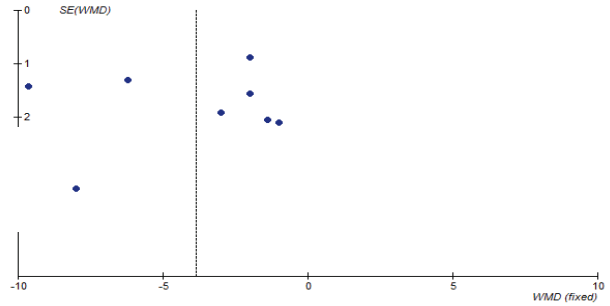


**Figure 7b: Funnel plot of published studies compare the prevalence of triglyceride in VTE**

### *Obesity*

All studies that evaluated the effect of obesity on VTE, waist circumference?90cm for men,?80cm for women or body mass index > 30 kg/m2) were grouped together. Six studies in which BMI was not or inappropriately calculated were removed[36-41], leaving in total 21 studies.[1,4,13,22,43,48,50-53,55-57,59-65,67]. The total of number patients was 7333 VTE cases and 14767 controls (figure 2). VTE cases had higher BMI than controls. Patients with obesity were at higher risk to develop VTE (OR 2.24; 95% CI 1.83 to 2.75) with statistically significant heterogeneity among the studies (I2=82.5%; p<0.00001).

### Hypertension

Fourteen studies examined the association between hypertension and VTE[1, 4, 13, 43, 44, 46, 48, 50, 56, 57, 59, 60, 69, 75] which included 4218 of VTE cases and 10826 controls (figure 3). Patients with hypertension were at higner risk of developing VTE (OR, 1.56; 95% CI, 1.26 to 1.92) with statistical heterogeneity among the studies (I2=56.1%, P=0.0005).

### Diabetes

Fourteen studies investigated to examine the relation between diabetes mellitus and VTE[1,4,13,22,43,44,46,50,56,57,60,66,69,75] with 5910 VTE cases and 12002 controls (figure 4). Patient with diabetes were at higher risk of VTE (OR, 1.55; 95% CI, 1.26 to 1.92 with statistical heterogeneity among the studies (I2 =49.2%; P=0.02).

### Total cholesterol

Eleven studies assessed total cholesterol levels in VTE cases versus controls[45,47,49,52,54,58,59,60,62,68,72]. Four studies that did not report on SD were removed1, 4, 43, 62.The study include total 1491 VTE cases with increased cholesterol level and 2999 controls. Mean levels of total cholesterol were not significantly related to occurrence of VTE, OR=1.26(figure 5).

### Triglycerides

Thirteen studies evaluated elevated the relation between triglyceride levels and risk of VTE including a total of 1563 cases and 2519 controls (figure 6)[13,45,47,49,52,54,57-60,68,69,75]. The mean level of triglyceride was (WMD19.21 mg/dl; 95% CI, 12.06 to 26. 37). The level of measured triglyceride level was higher in patients with VTE than in controls with no higher risk of VTE with TGL. (I2=48.0%, P=0.003).

### High density lipoprotein

Eight studies evaluated HDL cholesterol levels and occurrence of VTE[13,47,52,55,58,60,68,69]. Studies not reporting SD were removed [1, 4, 43,62]. The total number of patients was 1191 VTE cases and 2795 controls (figure 7). The mean level of HDL cholesterol was lower in VTE cases than in controls and significant statistical heter-

ogeneity (I2=76.9%; P=<0.0001). HDL- cholesterol levels were inversely and consistently correlated with the risk of VTE (WMD 4.05 mg/dl 95% CI 6.39-1.72)

## DISCUSSION

The main findings of this metanalysis are that some components of the CVD, namely obesity (OR, 2.24), diabetes (OR, 1.55), hypertension (OR, 1.56) and low HDL cholesterol are significantly associated with the risk of VTE. Weighted mean high-density lipoprotein cholesterol levels were significantly lower in VTE patients, whereas no difference was observed for total and low-density lipoprotein cholesterol levels. HDL-cholesterol levels were inversely and consistently correlated with risk of VTE.

However, our analysis does not make it possible to determine whether all cardiovascular risk factro is a stronger risk factor than each of these 4 components in isolation. Nevertheless, these findings may indicate that some cardiovascular risk factor may be one element of the multifactorial pathogenesis of VTE. However, even though a relation exists between cardiovascular and some of its components with the risk of VTE, a direct causality link is hard to establish. Indeed, physical inactivity may be a common denominator between these 3 components, particularly obesity and diabetes type 2, and to a lesser extent high blood pressure and the risk of VTE. On the other hand, the presence of a pro-inflammatory state, as shown by increase phase reactants[71,72] and also a prothrom-botic state due to elevated levels of fibrinogen, PAI-1, and clotting factors, common features of the metabolic syndrome and cardiovascular disease [49,73], may account for the higher risk of atherothrombosis incurred by MS, but may also play a role in the pathogenesis of VTE. An association between VTE and atherothrombosis as shown by a higher prevalence of asymptomatic atherosclerosis lesions in patients with idiopathic deep vein thrombosis was reported in one study[56].

In previous reports, the risk of VTE incurred by CVD or some of its elements brought in conflicting and/or inconclusive results. In 2 reports it was shown to be associated with a two-fold increased risk of VTE. Metabolic syndrome and CVD had more impact than any of the components taken in isolation[1,46]. However, these 2 studies had too limited sample sizes, and too low statistical power to draw definitive conclusions on this issue. Abdominal obesity was shown to be a predictor for both coronary artery disease and VTE in some studies[1,13]. Hypertriglyceridemia was shown to be associated with VTE, but high blood glucose were inconstantly shown to be associated with VTE in these 2 studies. In the LITE study, HDL cholesterol, sub fractions of HDL cholesterol (HDL-2 and HDL3), and apolipoprotein A-I were not associated with VTE[74]. The Copenhagen Heart Study also failed to find an association between dyslipidaemia and VTE[10]. In contrast, a small case-control study suggested that men < 55 years with VTE had low levels of HDL and elevated levels of LDL compared to match controls[75]. Lipoprotein subclass analyses showed that these differences reflected lower levels of large HDL particles and higher levels of small LDL particles[75].

All in all, from the many reports published so far, there is uncertainty about the risk of VTE incurred by cardiovascular risk, and about the causality of the association. Conflicting results were reported about the purely metabolic and cardiovascular features, namely glycemic balance and dyslipidemia, and the risk of VTE. In this regard, our study brings more insight about this issue as it confirms that important features of the cardiovascular components are associated with a higher risk of VTE. Uncertainty persists in our

Some metanalysis as regards impact of some metabolic features, particularly triglycerides, and risk of VTE.

The strengths of our study are that we carefully searched the literature to identify all the case control studies that examined the risk of VTE incurred by cardiovascular risk or its components. Because of the potential for underreporting of negative studies, we examined publication bias by means of funnel plots. There are several potential limitations in our study. First, although we established predefined criteria for study selection, the quality of metanalysis remains dependent on the quality of the included studies. We found that there is a significant heterogeneity between various studies, which could indicate differences in population demographics, sample size, patient characteristics, and misclassification due to variation in the accuracy of monitoring which may attenuate the scientific validity of this metanalysis and of its conclusions. Second, the studies included were conducted over different time periods (1984s to 2012), and it is unclear how changing clinical practices and the introduction and uptake of new diagnostic and therapeutic approaches might have influenced referral and treatment and diagnostic patterns. Third, we could not obtain missing data from all of the studies despite contacting the authors. Finally, VTE is a multifactorial disorder, caused in part by gene-gene and gene-environment interactions, many of which are still poorly defined and understood. These data showing more frequent elevated triglycerides in DVT patients may also confirm a role of dyslipoproteinemia as a factor venous thrombosis occurence[17]. The effect of age on the strength of the association could not be determined. Despite these limitations, we believe that our study could provide sufficient evidence to consider cardiovascular risk component as an additional independent risk factor for VTE, thus suggesting the use of appropriate preventive strategies.

## CONCLUSIONS

Some components of cardiovascular risk factors are associated with an increased risk of VTE that may suggest that, beside its well-recognized impact on atherosclerotic cardiovascular and cerebrovascular disease has also considerable impact on the risk of VTE and might contribute to the multifactorial pathogenesis of VTE. Further insight could be obtained from prospective studies carefully evaluating this hypothesis. Consequently, early identification, treatment and prevention of the cardiovascular risk include lifestyle changes and management for controlling the components of the cardiovascular, may have a favourable impact on the risk of VTE.

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**Conflict of interest:** None
**Ethical approval:** Yes

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