Heart failure and risk of venous thromboembolism: a systematic review and meta-analysis

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Summary

Background Venous thromboembolism is a major global health problem that is often secondary to other clinical situations. Many studies have investigated the association between venous thromboembolism and heart failure, but have yielded inconsistent findings. We aimed to quantify the absolute and relative risks (RR) for venous thromboembolism in patients with heart failure after hospital admission. We also assessed rates of venous thromboembolism in patients in different settings.

Methods In this systematic review and meta-analysis, we searched for studies investigating the risk of venous thromboembolism in patients in hospital with heart failure. We searched for studies published between Jan 1, 1955, and March 31, 2015, in PubMed, Embase, Evidence-Based Medicine Reviews, Allied and Complementary Medicine Database, Ovid HealthSTAR, Global Health, Ovid Nursing Database, Web of Science, CINAHL Plus, ProQuest Central, Conference Papers Index, BIOSIS Previews, and ClinicalTrials.gov. All cohort studies and subgroup analyses of randomised controlled trials (RCTs) were eligible for inclusion if they reported venous thromboembolism rates (number of events per follow-up period) or RR estimates. We extracted data from published reports and contacted the corresponding authors of records with insufficient quantitative data. RRs and 95% CIs were pooled using a random-effects model. This study is registered with PROSPERO, number CRD42014015504.

Findings Of 8673 records identified, we included 71 studies with data from 88 cohorts in our analysis, with 59 cohorts included in the assessment of venous thromboembolism rates and 46 cohorts included in the meta-analysis of heart failure and risk of venous thromboembolism. Venous thromboembolism rates varied widely in patients in hospital with heart failure from different settings. The overall median symptomatic venous thromboembolism rate was 2·48% (IQR 0·84–5·61); rates was were 3·73% (1·05–7·31) for patients who did not receive thromboprophylaxis and 1·47% (0·64–3·54) for those who did. Overall, patients with heart failure in hospital had an RR of 1·51 (1·36–1·68) for venous thromboembolism. The overall I^2 statistic was 96·1% and there was no evidence of publication bias (Egger's test, p=0·46).

Interpretation Heart failure is a common independent risk factor for venous thromboembolism. Thromboprophylaxis should be considered in clinical practice for high-risk patients.

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Introduction

Venous thromboembolism, which consists of deep vein thrombosis and pulmonary embolism, is a major, increasingly common, costly, and potentially preventable medical problem.[1,2] Each year, about 500 000 venous thromboembolism-related deaths occur in Europe, $1·5 billion are spent on treating venous thromboembolism in the USA, and there are 10 million venous thromboembolism events worldwide.[3–5] Therefore, the International Society on Thrombosis and Haemostasis has held World Thrombosis Day on Oct 13 every year since 2014 to improve awareness and education of thrombosis.[6]

Venous thromboembolism is a multifactorial disease that often occurs in relation to clinical comorbidities.[7] Early epidemiological studies have noted an association between venous thromboembolism and heart failure in elderly patients; and that venous thromboembolism could confer a high risk (up to 15·3%) for heart failure mortality.[8,9] Since 2001, the American College of Chest Physicians Guidelines have recommended thromboprophylaxis for patients with heart failure who have been admitted to hospital.[10] Many studies have investigated the risk of venous thromboembolism in patients with heart failure or the beneficial effects of thromboprophylaxis.[11–16] Nevertheless, large differences exist in the reported frequency of venous thromboembolism in individuals with heart failure, and whether heart failure is an independent risk factor for venous thromboembolism remains controversial. The frequency of objectively proven venous thromboembolism in patients with heart failure ranges from less than 1% to as high as 26%,[17,18] whereas the relative risk (RR) for venous thromboembolism in patients with heart failure varies from high risk (9·6–32·4)[11,12] to mild risk (1·7–2·6),[13,14] and even no increase in risk (0·7–0·8) in studies that use multivariate analysis to control for confounding factors such as advancing age.[15,16] Although some beneficial effects have been reported for thromboprophylaxis, the frequency of venous thromboembolism in patients with heart failure remains high.[18] Additionally, incidence of

venous thromboembolism in patients with heart failure might be attenuated because of high mortality. In this context, we did a systematic review and meta-analysis to quantify the rates of venous thromboembolism and RRs for venous thromboembolism in patients in hospital with heart failure.

Methods

Search strategy and selection criteria

We did this systematic review and meta-analysis in accordance with the PRISMA guidelines.[19] We searched for records published between Jan 1, 1955, and March 31, 2015, in PubMed, Embase, Evidence-Based Medicine Reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database), Allied and Complementary Medicine Database, Ovid HealthSTAR, Global Health, Ovid Nursing Database, Web of Science, CINAHL Plus (via EBSCO), ProQuest Central, Conference Papers Index (via ProQuest), BIOSIS Previews, and ClinicalTrials.gov. We searched with terms related to heart failure and venous thromboembolism (appendix pp 2–4). We identified additional published and unpublished records by cross checking the reference lists of eligible studies and relevant reviews.

See Online for appendix

All cohort studies and secondary or subgroup analyses of randomised controlled trials (RCTs) that included cohorts of patients with heart failure admitted to hospital were eligible, without restrictions on publication type (full-length article or meeting abstract), language, or ethnic origin of patients. We included records if they presented original data on venous thromboembolism rates (number of events per follow-up period) or RR estimates such as risk ratios, incidence rate ratios, and hazard ratios. We excluded animal studies, cross-sectional studies, case-control studies, case reports, studies investigating only deep vein thrombosis or only pulmonary embolism, studies investigating the rate of venous thromboembolism prophylaxis use in ACCP-defined high-risk patients but not reporting outcomes, or studies providing neither venous thromboembolism rates nor adjusted RRs. If the RR was not reported, we did not calculate it because the result would only be a crude RR without any adjustment. In our meta-analysis, we did not exclude patients with cancer or patients undergoing orthopaedic surgery, who are already at high risk for venous thromboembolism. Therefore, we were able to investigate the risk of venous thromboembolism and the efficacy of prophylaxis in these populations with multiple risk factors. We contacted the corresponding authors of records with insufficient quantitative data; if no answer was obtained or these data were not available, the record was excluded.

Two investigators (LT and YY-W) screened all records for eligible studies and extracted summary data for each report independently. Disagreements were adjudicated by a third investigator (YH).

Data analysis

For each record, data were extracted and double entered by two investigators (LT and Y-YW). Duplicate information was removed. From each record, we extracted first author's surname, publication year, country or region, study design, study period, patient population, data source, type of heart failure, type of venous thromboembolism, days of follow-up, use of thromboprophylaxis, number of participants with heart failure, number of venous thromboembolism events, adjusted RRs with 95% CIs, diagnostic criteria for heart failure and venous thromboembolism, and adjustment for confounding factors. We defined prophylaxis for venous thromboembolism as use of drugs (ie, unfractionated heparin, low molecular weight heparins, warfarin, fondaparinux, direct factor Xa inhibitors, or direct thrombin inhibitor).[20,21] We deemed prophylaxis to be present if all patients with heart failure received prophylaxis in studies that enrolled only patients with heart failure; if more than 40% of patients received prophylaxis in studies that enrolled a mixed patient population (since the median prophylaxis rate in these studies was 42·8%); or if studies reported that venous thromboembolism prophylaxis was done in accordance with guidelines at the time of publication. Otherwise, we judged the study to be assessing patients without prophylaxis.

We reported overall venous thromboembolism rates in patients with heart failure following hospital admission as median and interquartile range (IQR) because of the high heterogeneity. We pooled log-transformed RR estimates with a relative risk meta-analysis method that has been validated in previous studies.[22,23] We explored rates of symptomatic venous thromboembolism and asymptomatic plus symptomatic venous thromboembolism separately, but assessed the overall RR only for symptomatic venous thromboembolism. We investigated statistical heterogeneity across studies with the I^2 statistic. To test the robustness of the findings, we did sensitivity analyses by omitting one cohort at a time. We assessed publication bias with Egger's test, which has been reported to have better power than do other methods and is the most common approach for large-scale meta-analyses.[24,25] p values were two-sided. We did all meta-analyses with a random-effects model using Stata SE 12.0.

We did subgroup analyses on the basis of study characteristics: study design (prospective and retrospective cohort studies, and subgroup analyses of RCTs), region (non-Asian and Asian countries), study period (before 1994, 1995–2004, and 2005–15), patient population (unselected patients, heart failure patients in medical

settings, patients with heart failure undergoing non-orthopaedic surgery, patients with heart failure undergoing orthopaedic surgery, and patients with both cancer and heart failure), type of heart failure (acute, chronic, and not reported), days of follow-up (<60 days, 60–119 days, ≥120 days, and not reported), venous thromboembolism prophylaxis (no prophylaxis, prophylaxis in clinical practice, prophylaxis in RCTs, and not reported), and study quality (all studies and high-quality studies).

To judge study quality, we adapted a modified Newcastle-Ottawa Scale for observational studies, as recommended by the Cochrane Collaboration.[26] We assessed six items and one point was scored for each item. Studies that received one point in all six items were judged to be of high quality.

First, we assessed venous thromboembolism diagnosis. We deemed the diagnosis to be validated and gave a point if it was based on objective investigations (colour Doppler ultrasonography or vein angiography for deep vein thrombosis;[27] CT angiography, ventilation/perfusion lung scan, pulmonary angiography, or autopsies for pulmonary embolism);[1] coded according to the International Classification of Diseases (ICD-9 for venous thromboembolism: 453.8 and 415.1; ICD-10 for venous thromboembolism: I26, I80, and I82); or reported in previously validated databases, registries, or study populations. Second, we assessed the diagnosis of heart failure. We judged the diagnosis to be validated and gave a point if it was based on the ESC 2012 guidelines for the diagnosis and treatment of acute and chronic heart failure;[28] based on ACCF/AHA 2013 guidelines for the management of heart failure;[29] coded according to the International Classification of Diseases (ICD-9 for heart failure: 428; ICD-10 for heart failure: I50.0–I50.9); or reported in previous validated databases, registries, or study populations. Third, we assessed the study population. We judged the population to be of good quality and gave a point if it was not restricted to patients after orthopaedic surgery or those who had cancer, because these patients were already at a high risk for venous thromboembolism even if they did not have heart failure. Fourth, we assessed adjustment for age and sex, with a point scored if an adjustment had been made for age and sex. Fifth, we assessed adjustment for major venous thromboembolism risk factors, with a point scored if an adjustment has been made for recent major surgery and active malignancy. Finally, we assessed adjustment for other risk factors for venous thromboembolism. We gave a point if an adjustment had been made for at least one additional risk factor for venous thromboembolism, such as oral contraceptive use or hormone replacement therapy, smoking, pregnancy or postpartum, bed rest or bed confinement, history or family history of venous thromboembolism, or body-mass index more than 25 kg/m².

This study is registered with PROSPERO, number of CRD42014015504.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our initial search yielded 8673 potential records after duplicates were removed. After screening titles and abstracts, we judged 277 records to be potentially eligible and did an in-depth review of each full-text article. Of these studies, we excluded 206 citations (figure 1), resulting in 71 records with data from 88 cohorts.[30–100] Of these records, 68 were full-length articles published in peer-reviewed journals and three were meeting abstracts. 43 cohorts were from

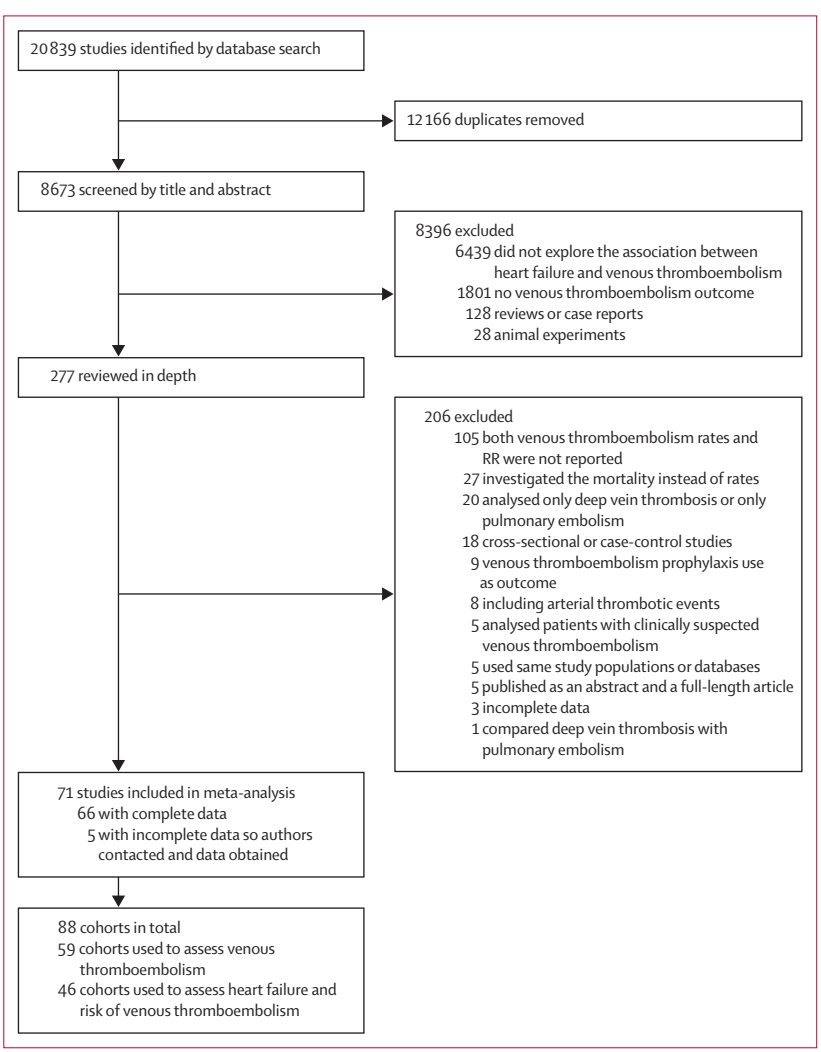

Figure 1: **Study selection**
RR=relative risk.

	Region	Period	Study design	Patient population	Type of heart failure	Prophylaxis	Follow-up (days)	Venous thrombo-embolism (number of patients)	Heart failure (number of patients)	Adjustment	RR estimate (95% CI)
Lim 2015[30]	China (Taiwan)	2000–11	Prospective cohort study	Unselected patients	NR	NR	2409 (mean)	32	2323	Age, sex, hypertension, diabetes, cerebral vascular disease, atrial fibrillation, all cancer types, fracture, surgery	Hazard ratio: deep vein thrombosis 0·99 (0·53–1·84), pulmonary embolism 0·75 (0·30–1·92)
Day 2015[31]	USA	2004–09	Retrospective cohort study	Patients ≥65 years and after total shoulder arthroplasty	Chronic heart failure	No	90	260	5936	Age, sex, fracture, prior venous thromboembolism, cardiac arrhythmia, metastatic tumour, coagulopathy, alcohol abuse, obesity	Rate ratio 0·92 (0·61–1·37)
Day 2015[31]	USA	2004–09	Retrospective cohort study	Patients ≥65 years and after shoulder hemiarthroplasty	Chronic heart failure	No	90	504	6379	Age, sex, fracture, prior venous thromboembolism, cardiac arrhythmia, metastatic tumour, coagulopathy, alcohol abuse, obesity	Rate ratio 1·48 (1·11–1·99)
Wu 2014[32]	China (Taiwan)	2002–06	Retrospective cohort study	Patients after hip arthroplasty	Chronic heart failure	No	28	16	3787	NR	Rate ratio 1·66 (0·99–2·79)
Wu 2014[32]	China (Taiwan)	2002–06	Retrospective cohort study	Patients after knee arthroplasty	Chronic heart failure	No	28	37	3244	Age, sex, history of venous thromboembolism, stroke, cancer, surgery, diabetes mellitus, hypertension	Rate ratio 1·61 (1·12–2·31)
Tyson 2014[33]	USA	2005–11	Retrospective cohort study	Patients after urological surgery	Chronic heart failure	NR	30	17	364	Age, sex, BMI, functional status, cancer, COPD, surgery, hypertension, steroid use, anaesthesia time	Hazard ratio 2·97 (1·77–4·98)
Stecker 2014[34]	USA	2008–12	Retrospective cohort study	Patients with stroke	Chronic heart failure	Unfractionated heparin, low molecular weight heparin, warfarin	14	5	160	Age, sex, coronary artery disease, diabetes, BMI, hypertension, peripheral vascular disease, smoking, carotid stenosis, hyperlipidaemia, prior stroke, cancer, surgery	Rate ratio 2·65 (1·01–7·00)
Peng 2014[35]	China (Taiwan)	2000–11	Retrospective cohort study	Unselected patients	NR	Unfractionated heparin, low molecular weight heparin	4380	7	488	Age, sex, hypertension, diabetes, hyperlipidaemia, surgery, malignancy, atrial fibrillation, cerebral vascular disease	Hazard ratio 1·96 (0·82–4·65)
Nendaz 2014[36]	Switzerland	2010–11	Prospective cohort study	Medical patients	NR	Unfractionated heparin, low molecular weight heparin	90	7	177	NR	NR
Mueller 2014[37]	USA	2006–12	Retrospective cohort study	Women after reconstructive pelvic surgery	Chronic heart failure	NR	30	1	25	NR	NR
Mejer 2014[38]	Denmark	1995–2008	Prospective cohort study	Patients with *Staphylococcus aureus* bacteraemia	NR	NR	365	12	2008	Age, sex, cocaine use, HIVB, alcoholism, obesity, surgery, haematological malignancy, diabetes, solid malignancy, acute myocardial infarction, diabetes	Hazard ratio 0·90 (0·50–1·60)
Mejer 2014[38]	Denmark	1995–2008	Prospective cohort study	Unselected patients	NR	NR	365	57	6754	NR	NR

(Table 1 continues on next page)

	Region	Period	Study design	Patient population	Type of heart failure	Prophylaxis	Follow-up (days)	Venous thrombo-embolism (number of patients)	Heart failure (number of patients)	Adjustment	RR estimate (95% CI)
(Continued from previous page)											
Kshettry 2014[39]	USA	2002–10	Retrospective cohort study	Patients with aneurysmal subarachnoid haemorrhage	Chronic heart failure	No	16·9 (mean)	57	765	Age, sex, ethnic origin, neurological disorder, surgery, coagulopathy, weight loss, cancer	Rate ratio 1·40 (1·10–1·90)
Khera 2014[40]	USA	2002–11	Retrospective cohort study	Unselected inpatient population	NR	NR	NR	1064343	42573726	NR	NR
Kester 2014[41]	USA	2008–10	Retrospective cohort study	Patients after hip arthroplasty or knee arthroplasty	Chronic heart failure	Unfractionated heparin, low molecular weight heparin	30	3	55	Age, ethnic origin, sex, dyspnoea, sepsis or septic shock, BMI, wound class, COPD, pneumonia, ascites, coronary artery disease, peripheral vascular disease, neurological disease, diabetes, cancer, corticosteroid use	Rate ratio 3·19 (0·87–11·69)
Haskins 2014[42]	USA	2005–12	Retrospective cohort study	Patients after laparoscopic bariatric surgery	Chronic heart failure	NR	30	NR	NR	Age, sex, ethnic origin, BMI, COPD, surgery, hypertension, diabetes mellitus	Odds ratio: deep vein thrombosis 4·64 (1·13–19·11), pulmonary embolism 6·03 (1·45–25·10)
Haskins 2014[42]	USA	2005–12	Retrospective cohort study	Patients after open bariatric surgery	Chronic heart failure	NR	30	NR	NR	Age, sex, ethnic origin, BMI, COPD, surgery, hypertension, diabetes mellitus	Odds ratio: deep vein thrombosis 7·72 (0·97–61·49), pulmonary embolism 10·32 (1·29–82·65)
Guijarro 2014[43]	Spain	2005–06	Retrospective cohort study	Medical patients	Acute heart failure	NR	90	851	13751	Gender, age, BMI, lung disease, ischaemic heart disease, ischaemic stroke, infection, cancer, inflammatory bowel disease, gastrointestinal disease, liver disease, coagulation disorders, renal failure, diabetes, hypertension	Odds ratio 0·97 (0·90–1·04)
Guijarro 2014[43]	Spain	2005–06	Retrospective cohort study	Medical patients	Chronic heart failure	NR	90	1597	124354	Gender, age, BMI, lung disease, ischaemic heart disease, ischaemic stroke, infection, cancer, inflammatory bowel disease, gastrointestinal disease, liver disease, coagulation disorders, renal failure, diabetes, hypertension	Odds ratio 1·13 (1·07–1·19)
Fontaine 2014[44]	USA	2007–13	Retrospective cohort study	Medical patients	NR	Unfractionated heparin, low molecular weight heparin	90	NR	NR	Age, sex, Charlson Comorbidity Index, prior venous thromboembolism, cancer, surgery	Rate ratio 1·33 (1·05–1·68)
Tran 2013[45]	USA	2005–09	Prospective cohort study	Patients after mastectomy	Chronic heart failure	NR	30	1	96	NR	NR
Pendergraft 2013[46]	USA	2003–08	Retrospective cohort study	Medical patients ≥40 years	NR	No	180	NR	NR	Age, sex, prior venous thromboembolism, venous catheter, sepsis, venous insufficiency, cancer, BMI, oral contraceptive, COPD, thrombophilia	Rate ratio 1·44 (1·18–1·76)

(Table 1 continues on next page)

	Region	Period	Study design	Patient population	Type of heart failure	Prophylaxis	Follow-up (days)	Venous thrombo-embolism (number of patients)	Heart failure (number of patients)	Adjustment	RR estimate (95% CI)
(Continued from previous page)											
Oh 2013[47]	Korea	2004–08	Retrospective cohort study	Unselected patients	NR	NR	NR	20737	2424206	NR	NR
Kapoor 2013[48]	USA	2002–09	Retrospective cohort study	Male veterans ≥65 years and after hip arthroplasty or knee arthroplasty	Chronic heart failure	Unfractionated heparin, low molecular weight heparin	90	NR	NR	Age, sex, ethnic origin, surgery type, chronic kidney disease, BMI, malignancy, COPD, hypertension, cerebrovascular disease, coronary artery disease, diabetes mellitus, prophylaxis regimen, anaesthesia type, income	Rate ratio 1·30 (0·52–3·27)
Isma 2013[49]	Sweden	1991–2003	Prospective cohort study	Unselected female patients	NR	NR	4745	164	3487	Age, income level, education, COPD, diabetes mellitus, trauma, cancer, inflammatory bowel disease, surgery, sepsis, pneumonia	Hazard ratio 1·25 (1·06–1·47)
Isma 2013[49]	Sweden	1991–2003	Prospective cohort study	Unselected male patients	NR	NR	4745	169	3252	Age, income level, education, COPD, diabetes mellitus, trauma, cancer, inflammatory bowel disease, surgery, sepsis, pneumonia	Hazard ratio 1·57 (1·33–1·85)
Iannuzzi 2013[50]	USA	2005–09	Retrospective cohort study	Patients after non-orthopaedic surgery	Chronic heart failure	NR	30	43	5091	NR	NR
Müller-Bühl 2012[51]	Germany	2008–11	Retrospective cohort study	Unselected inpatient population	NR	NR	180	NR	NR	Age, sex, previous venous thromboembolism, surgery, malignancy, pregnancy, puerperium, respiratory infection	Rate ratio 1·02 (0·82–1·25)
Mitchell 2012[52]	USA	2008–10	Retrospective cohort study	Unselected inpatient population	Chronic heart failure	Unfractionated heparin, low molecular weight heparin	90	1	271	NR	Rate ratio 0·44 (0·06–3·18)
Markovic-Denic 2012[53]	Serbia	2008–10	Prospective cohort study	Patients after hip arthroplasty or knee arthroplasty	Chronic heart failure	Unfractionated heparin, low molecular weight heparin, warfarin	26·5 (mean)	5	90	NR	Rate ratio 2·95 (0·94–9·23)
Lee 2012[54]	China (Taiwan)	1998–2007	Retrospective cohort study	Patients after knee arthroplasty	Chronic heart failure	No	90	81	10588	Age, sex, hypertension, coronary heart disease, COPD, stroke, diabetes mellitus, varicose veins, thrombophilia, previous venous thromboembolism, malignant neoplasm, serious neurological diseases, renal insufficiency	Hazard ratio 1·39 (1·19–1·86)
Kato 2012[55]	USA	2007–09	Retrospective cohort study	Medical patients	NR	Unfractionated heparin, low molecular weight heparin	In-hospital (<60 days)	11	1461	NR	Rate ratio 1·40 (0·70–2·70)
Gephart 2012[56]	USA	2002–08	Retrospective cohort study	Patients after thoracic/ thoracolumbar spinal fusion	Chronic heart failure	NR	In-hospital (<60 days)	11	179	Age, ethnic origin, sex, insurance provider, surgical approach, anaemia, diabetes, renal failure, weight loss	Rate ratio 2·29 (1·03–3·59)

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	Region	Period	Study design	Patient population	Type of heart failure	Prophylaxis	Follow-up (days)	Venous thrombo-embolism (number of patients)	Heart failure (number of patients)	Adjustment	RR estimate (95% CI)
(Continued from previous page)											
Connolly 2012[57]	USA	2005–08	Retrospective cohort study	Lung cancer patients	NR	NR	365 (mean)	NR	NR	Age, sex, cancer therapy type, diabetes, stroke, hypertension, BMI, surgery, atrial fibrillation	Rate ratio 1·29 (1·01–1·66)
Amin 2012[58]	USA	2005–08	Prospective cohort study	Medical patients	NR	Unfractionated heparin, low molecular weight heparin, warfarin, fondaparinux	180	53	1705	NR	NR
Aispuru 2012[59]	Argentina	2009–11	Prospective cohort study	Patients with acute heart failure	Acute heart failure	Low molecular weight heparin	11 (mean)	13	140	NR	NR
Woller 2011[60]	USA	2000–09	Retrospective cohort study	Medical patients	NR	NR	90	2373	41 983	NR	NR
Spyropoulos 2011[61]	52 centres (France, Italy, Australia, USA, Spain, Germany, Brazil, Canada, Japan, UK, Columbia, and Venezuela)	2002–06	Prospective cohort study	Medical patients	NR	Unfractionated heparin, low molecular weight heparin	90	23	1560	NR	NR
Rothberg 2011[62]	USA	2004–05	Retrospective cohort study	Medical patients with primary diagnosis of heart failure	NR	Unfractionated heparin, low molecular weight heparin	30	167	46 503	Age, sex, cancer, prior venous thromboembolism, use of oestrogens, inflammatory bowel disease, nephrotic syndrome, myeloproliferative disorders, BMI, smoking, venous catheter, thrombophilia, diabetes, varicose veins	Rate ratio 0·86 (0·70–1·06)
Rothberg 2011[62]	USA	2004–05	Retrospective cohort study	Medical patients with heart failure diagnosed as a comorbidity	NR	Unfractionated heparin, low molecular weight heparin	30	107	18 900	NR	NR
Rojnuckarin 2011[63]	Thailand	2009	Retrospective cohort study	Medical patients	NR	No	42	0	155	NR	NR
Merkow 2011[64]	USA	2006–08	Retrospective cohort study	Patients after cancer surgery	Chronic heart failure	NR	30	15	239	Age, sex, cancer type, metastatic disease, BMI, ascites, thrombocytosis, surgery duration	Odds ratio 2·88 (1·66–5·00)
Masoomi 2011[65]	USA	2006–08	Retrospective cohort study	Patients after bariatric surgery	Chronic heart failure	NR	In-hospital (<60 days)	NR	NR	Age, sex, ethnic origin, hypertension, smoking, diabetes, renal failure, alcohol abuse	Rate ratio 2·00 (1·20–3·40)
Hippisley-Cox 2011[66]	UK	2004–10	Prospective cohort study	Unselected inpatient population	NR	NR	1825	374	15 081	Age, sex, varicose veins, hormone replacement therapy, family history of cardiovascular disease, smoking status, educational attainment, chronic renal disease, cancer, hip surgery, atrial fibrillation, COPD	Hazard ratio: women 1·40 (1·20–1·62), men 1·33 (1·13–1·57)

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	Region	Period	Study design	Patient population	Type of heart failure	Prophylaxis	Follow-up (days)	Venous thrombo-embolism (number of patients)	Heart failure (number of patients)	Adjustment	RR estimate (95% CI)
(Continued from previous page)											
Nisio 2011[67]	Italy	2001–06	Prospective cohort study	Unselected patients aged ≥65 years	Chronic heart failure	No	2190	25	388	NR	NR
Buchberg 2011[68]	USA	2002–06	Retrospective cohort study	Patients after laparoscopic colorectal surgery	Chronic heart failure	NR	In-hospital (<60 days)	NR	NR	Age, sex, BMI, malignancy, chronic pulmonary disease, inflammatory bowel disease	Odds ratio 2·00 (1·30–3·20)
Buchberg 2011[68]	USA	2002–06	Retrospective cohort study	Patients after open colorectal surgery	Chronic heart failure	NR	In-hospital (<60 days)	NR	NR	Age, sex, BMI, malignancy, chronic pulmonary disease, inflammatory bowel disease	Odds ratio 1·10 (1·10–1·20)
Amin 2011[69]	USA	2005–07	Retrospective cohort study	Medical patients	NR	No	30	41	1333	NR	NR
Kapoor 2010[70]	USA	2003–06	Retrospective cohort study	Patients ≥65 years and after hip arthroplasty	Chronic heart failure	Unfractionated heparin, low molecular weight heparin	In-hospital (<60 days)	25	1097	Age, sex, ethnic origin, insurance status, hospital surgical volume, BMI, cerebrovascular disease, COPD, coronary artery disease, thrombophilia	Rate ratio 3·08 (2·05–4·65)
Kapoor 2010[70]	USA	2003–06	Retrospective cohort study	Patients ≥65 years and after knee arthroplasty	Chronic heart failure	Unfractionated heparin, low molecular weight heparin	In-hospital (<60 days)	73	2746	Age, sex, ethnic origin, insurance status, hospital surgical volume, BMI, cerebrovascular disease, COPD, coronary artery disease, thrombophilia	Rate ratio 2·47 (1·95–3·14)
Barba 2010[71]	Spain	2005–07	Retrospective cohort study	Medical patients	Acute heart failure	NR	11·2 (mean)	1071	150 311	Age, sex	Odds ratio 0·69 (0·65–0·74)
Bahl 2010[72]	USA	2001–08	Retrospective cohort study	Surgical patients	Chronic heart failure	Unfractionated heparin, low molecular weight heparin	30	2	323	Age, sex, pregnancy or post partum, sepsis, malignancy, history of venous thromboembolism, central venous access, varicose veins, major surgery, BMI, thrombophilia, pneumonia, COPD, inflammatory bowel disease	Rate ratio 0·70 (0·27–1·78)
Spyropoulos 2009[73]	USA	2001–05	Retrospective cohort study	Medical patients	NR	Unfractionated heparin, low molecular weight heparin	360	914	16 357	NR	NR
Gulley 2008[74]	USA	1995–2005	Retrospective cohort study	Unselected inpatient population	NR	NR	NR	348	4489	NR	NR
Keenan 2007[75]	USA	1995–2000	Prospective cohort study	Medical patients	NR	NR	91	1393	136 665	Age, ethnic origin, sex, depression, diabetes, renal failure, myocardial infarction, sepsis, connective tissue disease, inflammatory bowel disease, COPD	Hazard ratio 9·10 (6·40–12·90)
Khorana 2006[76]	USA	1995–2002	Retrospective cohort study	Adult neutropenic cancer patients	NR	NR	8 (mean)	191	2722	Age, sex, ethnic origin, hypertension, diabetes mellitus, hepatic disease, cancer type, arterial thromboembolism, infection, pulmonary disease, renal disease	Rate ratio 1·05 (0·89–1·22)

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	Region	Period	Study design	Patient population	Type of heart failure	Prophylaxis	Follow-up (days)	Venous thrombo-embolism (number of patients)	Heart failure (number of patients)	Adjustment	RR estimate (95% CI)
(Continued from previous page)											
Edelsberg 2006[77]	USA	1998–2002	Retrospective cohort study	Medical patients ≥40 years	NR	NR	90	471	17 885	Age, sex, acute coronary syndromes, stroke, peripheral artery disease, neurological disease, post-thrombotic syndrome, prior venous thromboembolism, cancer	Hazard ratio 1·72 (1·52–1·95)
Beemath 2006[78]	USA	1979–2003	Retrospective cohort study	Unselected inpatient population	NR	NR	NR	960 000	58 873 000	NR	Rate ratio 1·47 (1·47–1·48)
Cokkinos 2006[79]	8 centres (Greece, Cyprus, Yugoslavia, Romania, Bulgaria, Poland, and USA)	1998–99	Secondary or subgroup analyses of randomised controlled trials	Patients with chronic heart failure	Chronic heart failure	Aspirin, warfarin	730	0	197	NR	NR
Schiff 2005[80]	Canada	1999–2000	Retrospective cohort study	Patients after orthopaedic surgery	Chronic heart failure	No	60	3	19	Previous venous thromboembolism, age, sex, thrombophilia, BMI, malignancy, myocardial infarction, stasis, acuity of surgery, hormone replacement therapy, type of operation	Rate ratio 1·12 (0·38–3·29)
Leizorovicz 2005[81]	39 centres in Asia	2001–02	Prospective cohort study	Patients after orthopaedic surgery	Chronic heart failure	No	30	3	53	Age, sex, history of venous thromboembolism, cancer, varicose veins	Rate ratio 5·10 (1·50–17·80)
Grady 2000[82]	USA	1993–94	Prospective cohort study	Postmenopausal women with coronary artery disease	NR	NR	1451	16	658	NR	NR
Dries 1997[83]	USA	1984–86	Retrospective cohort study	Patients with heart failure	NR	No	1095	114	6378	NR	NR
Pahor 1996[84]	USA	1985–92	Prospective cohort study	Unselected patients aged ≥65 years	NR	No	2190	NR	NR	Age, sex, alcohol abuse, cancer, surgery, social characteristics, BMI, blood pressure, health status, medications	Hazard ratio 2·30 (1·60–3·40)
Dunkman 1993[85]	USA	1980–91	Retrospective cohort study	Men with chronic heart failure	Chronic heart failure	No	832	105	1446	NR	NR
Ciaccheri 1989[86]	Italy	1980–87	Prospective cohort study	Patients with dilated cardiomyopathy	Chronic heart failure	No	1236	3	126	NR	NR

RR=adjusted relative risk. COPD=chronic obstructive pulmonary disease. NR=not reported. BMI=body-mass index.

Table 1: **Characteristics of studies investigating symptomatic venous thromboembolism**

North America, 18 from Europe, 12 from Asia, two from Latin America, and 13 from multicentre studies with most centres in Europe and the USA. The largest study[78] was a retrospective survey that used the National Hospital Discharge Database in the USA up to 2003. However, this study included no data on adjustments, thromboprophylaxis, and days of follow-up. The smallest study[80] that we identified was done to identify which patients who underwent orthopaedic surgery were at high risk for venous thromboembolism. Overall, we extracted study level data for 104 538 076 patients with heart failure with at 2 056 991 venous thromboembolism events recorded (table 1; appendix p 5). The median quality of the included studies was 3 (range 1–6) points (appendix pp 6–9).

	No prophylaxis		Prophylaxis		Not reported		Total	
	Rate	Number of cohorts	Rate	Number of cohorts	Rate	Number of cohorts	Rate (events per follow-up period)	Number of cohorts
Region								
Non-Asia	6·44% (2·91–7·68)	9	1·78% (0·60–3·74)	20	2·57% (1·22–5·78)	22	2·66% (0·89–5·65)	51
Asia	0·77% (0·51–3·80)	5	1·43% (1·43–1·43)	1	1·12% (0·86–1·38)	2	1·00% (0·64–1·42)	8
Period								
2005–15	4·38% (1·84–7·68)	5	2·19% (0·61–3·74)	16	2·49% (1·18–5·78)	14	2·50% (0·84–5·61)	35
1995–2004	3·79% (0·68–9·20)	6	0·89% (0·59–3·53)	5	3·67% (0·89–6·56)	8	1·47% (0·76–6·44)	19
Before 1995	2·74% (1·79–7·26)	3	..	0	2·03% (1·63–2·43)	2	2·43% (1·71–5·00)	5
Population								
Unselected	6·44% (6·44–6·44)	1	0·99% (0·54–1·43)	2	2·06% (0·85–4·83)	10	1·63% (0·85–4·95)	13
Medical	2·91% (1·49–7·31)	6	1·47% (0·52–3·54)	13	2·43% (1·02–5·65)	7	2·26% (0·71–4·36)	26
Surgical	..	0	0·76% (0·76–0·76)	1	3·09% (1·00–5·38)	4	1·50% (0·80–5·14)	5
Orthopaedic	4·38% (0·77–7·90)	7	2·66% (1·59–5·89)	5	6·15% (6·15–6·15)	1	4·38% (1·02–6·34)	13
Cancer	..	0	..	0	6·65% (6·28–7·02)	2	6·65% (6·28–7·02)	2
Heart failure								
Acute heart failure	..	0	1·40% (0·52–7·49)	4	3·45% (0·71–6·19)	2	1·40% (0·64–6·96)	6
Chronic heart failure	6·44% (1·14–7·45)	11	2·28% (0·65–4·34)	9	4·67% (1·28–6·15)	7	3·12% (0·89–6·28)	27
NR	1·79% (0·59–3·08)	3	1·45% (0·61–3·74)	8	2·48% (1·02–5·20)	15	2·11% (0·85–4·14)	26
Follow-up (days)								
<60	2·11% (0·55–6·70)	6	2·28% (0·57–5·56)	11	5·14% (1·00–6·24)	8	2·66% (0·73–6·18)	25
60–119	6·14% (1·67–15·05)	4	1·47% (0·62–3·02)	5	2·63% (1·15–5·92)	5	2·36% (0·96–5·79)	14
≥120	4·59% (2·03–7·06)	4	1·43% (0·68–4·35)	5	2·43% (0·84–4·70)	7	2·46% (1·02–5·07)	16
NR	..	0	..	0	2·07% (1·05–6·44)	4	2·07% (1·05–6·44)	4
Design								
Prospective cohort	6·44% (2·74–6·45)	3	3·95% (2·29–7·42)	5	1·50% (1·02–2·48)	7	2·74% (1·47–5·56)	15
Retrospective cohort	3·08% (0·76–7·45)	11	1·16% (0·61–3·01)	12	4·67% (1·07–6·17)	17	2·57% (0·84–6·02)	40
Secondary or subgroup analyses of randomised controlled trials	..	0	0·59% (0·46–1·75)	4	..	0	0·59% (0·46–1·75)	4
Overall	3·73% (1·05–7·31)	14	1·47% (0·64–3·54)	21	2·49% (1·09–5·64)	24	2·48% (0·84–5·61)	59

Data are median (IQR) or n. NR=not reported.

Table 2: **Subgroup rates of symptomatic venous thromboembolism**

Rates of symptomatic venous thromboembolism were investigated in 59 cohorts.[30-41,43,45,47,49,50,52-56,58-64,66,67,69-83,85,86] We stratified these cohorts based on thromboprophylaxis. Pooled symptomatic venous thromboembolism rates were 3·73% (IQR 1·05–7·31) for patients who did not receive thromboprophylaxis and 1·47% (0·64–3·54) for those who did (table 2).

We did additional analyses by cohort characteristics (table 2). In our subgroup analysis based on the study region, we noted that, without prophylaxis, rate of thromboembolism was much higher in non-Asian cohorts than that in Asian cohorts. In our analysis of types of patients, we noted that the rate of venous thromboembolism was highest in patients with cancer and heart failure. The rate of venous thromboembolism was also high in patients with heart failure who underwent orthopaedic surgery and did not receive prophylaxis. Although the rate was lower in those patients who received prophylaxis, it remained high. In our subgroup analysis based on follow-up duration, patients who did not receive prophylaxis had notably lower rates of venous thromboembolism in studies with follow-up less than 60 days than in studies with longer follow-up. We also did subgroup analyses based on the study design. Because all four subgroup analyses of RCTs reported that thromboprophylaxis had been given, the pooled venous thromboembolism rate was lower in these studies than in other study designs.

Rates of all venous thromboembolism (symptomatic plus asymptomatic) events were investigated in 21 cohorts, among which 14 were subgroup analyses of cohorts with heart failure from RCTs. The overall venous thromboembolism rate was 11·69% (IQR 6·64–17·34) in 10 cohorts who did not receive prophylaxis and 5·61% (3·32–12·35) in 11 cohorts who received prophylaxis prophylaxis (appendix p 10).

The association between heart failure and venous thromboembolism was investigated in 46 cohorts (appendix p 11). Overall, the pooled RR for venous thromboembolism was 1·51 (95% CI 1·36–1·68, I^2 96·1%). There was no evidence of publication bias

(Egger's test, p=0·46). Our sensitivity analysis of these cohorts suggested that the conclusion remained robust (appendix p 12). Additionally, 24 of these cohorts were deemed to be of high quality, as judged by the risk of bias scale. The pooled RR in high-quality studies only was 1·50 (95% CI 1·32–1·71, I^2=92·3%), which was similar to the overall RR estimated for all cohorts (appendix p 13). Likewise, sensitivity analysis using high-quality studies consistently supported these findings (appendix p 14). We did six more types of subgroup analyses by the cohorts' characteristics (figure 2). We noted an association between symptomatic venous thromboembolism and heart failure in various subgroups. The highest RR was for patients undergoing surgery, who had up to doubled risk. In patients with acute heart failure the RR was attenuated. When we examined risk in relation to thromboprophylaxis, it seemed that thromboprophylaxis was effective for reducing risk for venous thrombosis (appendix p 15).

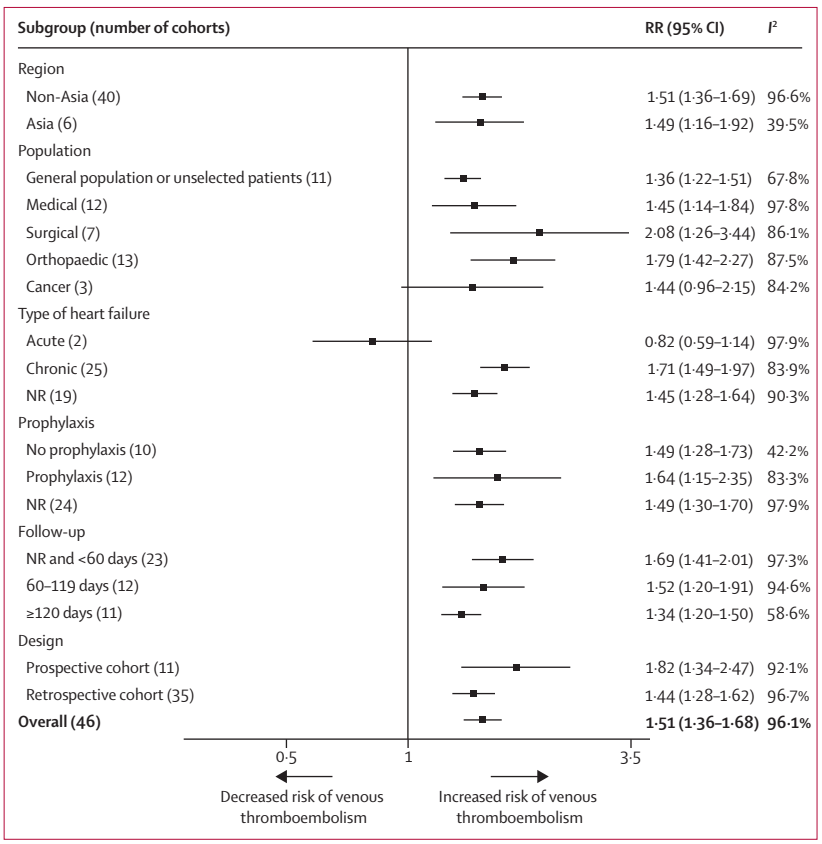

Figure 2: **Risk of symptomatic venous thromboembolism**
The x-axis is on a log scale and effect estimates were calculated with a log scale ($\log_e$). RR=adjusted relative risk. NR=not reported.

Discussion

In this systematic review and meta-analysis of patients with heart failure who were admitted to hospital, we noted that heart failure seemed to be an independent risk factor for venous thromboembolism after adjustment for confounders, with an RR of about 1·5; and that rates of venous thromboembolism varied widely with patient characteristics (eg, reason for hospital admission). Use of thromboprophylaxis seemed to be effective for reducing risk of thromboembolism in terms of both absolute risk and RR; and finally, a regional difference (ie, Asian cohorts *vs* non-Asian cohorts) existed in terms of absolute risk for venous thromboembolism, possibly because of differences in treatment approaches and variations in lifestyle factors and the underlying genetics of thrombosis between people of different ethnic origins.[101–103]

Our findings have several clinical implications. First, we identified populations of patients who were at high risk for thrombosis, which might help to improve risk stratification. Cancer confers a high risk for venous thromboembolism. However, clinicians are often reluctant to prescribe thromboprophylaxis to patients in hospital with cancer because of concerns about bleeding complications and the fact that more than 97% of patients would not have a venous thromboembolism event.[104–106] In our study, the overall venous thromboembolism rate was as high as 6·65% in patients with cancer and heart failure. Therefore, patients with cancer and heart failure could be regarded as a high-risk patient subset.

Furthermore, venous thromboembolism remains a challenging complication in some clinical settings, even when prophylaxis is used. Previous studies have suggested that, with use of prophylaxis for venous thromboembolism, less than 1% of patients undergoing major orthopaedic surgery will develop symptomatic venous thromboembolism.[107–111] However, we noted that 2·66% of patients with heart failure who received thromboprophylaxis developed venous thromboembolism after orthopaedic surgery (table 2). Therefore, based on our findings and previous evidence, it seems that patients undergoing orthopaedic surgery who had heart failure were at higher risk for thrombosis than were other patients undergoing orthopaedic surgery. More effective strategies for prophylaxis of venous thromboembolism are warranted,[112,113] and more attention should be paid to such patients with multiple risk factors.

Notably, in clinical trials, the rate of symptomatic venous thromboembolism could still be high despite use of best available prophylaxis. Of the four RCTs included in our study, the most recent study compared enoxaparin with rivaroxaban, showing the highest venous thromboembolism rate of these RCTs, at 2·09%. Additionally, if asymptomatic events are included in our meta-analysis, the rate of all venous thromboembolism was as high as 5·61% in patients with heart failure who received prophylaxis (appendix p 10). Results from previous studies have suggested objective confirmed asymptomatic venous thromboembolism (especially for asymptomatic proximal deep vein thrombosis) to be associated with an increased risk of late development of post-thrombotic syndrome and a high mortality rate.[114,115] Therefore, the high rate of asymptomatic thrombo-embolism in patients in RCTs shows that identification

and treatment of asymptomatic VTE is an important challenge in clinical settings. Personalised management of venous thromboembolism should be developed in the future to take account of patient characteristics.

The overall venous thromboembolism rate was substantially higher in studies with follow-up between 60 and 120 days than in those with follow-up less than 60 days. This discrepancy suggests that many venous thromboembolism events occur at 2–4 months after initial admissions. In a previous study[73] of median times to venous thromboembolism events in various patient groups, 55·5% of venous thromboembolisms occurred after 90 days from admission in the groups of patients with heart failure. Therefore, patients with heart failure should be made aware of the long-term risk of venous thromboembolism even after discharge from hospital. In our meta-analysis, the overall rate of venous thromboembolism in studies with more than 120 days of follow-up seemed to be lower than that in studies with 60–120 days of follow-up. This result might be because the studies with more than 120 days of follow-up had a lower proportion of cohorts of patients at high-risk of venous thromboembolism (eg, patients with heart failure undergoing orthopaedic surgery) than did studies with shorter follow-up (appendix p 16).

The main strengths of this study included its large size; the absence of restrictions on the type of publication, language, and study populations for included data; our subgroup analyses; the absence of evidence of publication bias; the consistency in study findings; and the fact that clinical practice data were distinguished from those from RCTs. To our knowledge, this study represents the most comprehensive review so far and the first meta-analysis of venous thromboembolism risk in patients with heart failure.

However, our study has several limitations. First, we were unable to do subgroup analyses by the severity level of heart failure because data subsets divided by the New York Heart Association (NYHA) functional classification and cardiac biomarkers were not available in most of the included studies. Evidence suggests that risk of venous thromboembolism might be associated with the NYHA classification and ejection fraction.[13,59] However, results from another study[116] suggested that risk of venous thromboembolism was higher in patients with more severe heart failure than in those with less severe heart failure, as defined by the plasma concentration of N-terminal probrain natriuretic peptide rather than the NYHA classification.[87,116] Therefore, our analysis represents an estimate for the overall population of patients with heart failure, and additional studies are needed to further investigate the effects of heart failure severity on the venous thromboembolism risk. Second, only six studies focused on acute heart failure and, as a result, we were unable to make a precise estimate for this subset. Nevertheless, the findings from 26 studies that did not distinguish acute heart failure from chronic heart failure and the findings from cohorts with chronic heart failure suggested that whether heart failure was acute or chronic would not have a noticeable effect on the venous thromboembolism risk. Only two studies were available for the acute heart failure estimate, and one of them was deemed to be not of high-quality study because the RR was only adjusted for age and sex. Additionally, the acute heart failure subgroup had no non-prophylaxis cohort. These reasons might explain the low RR in the acute heart failure subgroup. Third, we identified substantial heterogeneity in most analyses. Although we assessed subgroup data, substantial residual heterogeneity remained. In the 18 subgroups, I^2 values exceeded 90% in nine of them, showing clear heterogeneity. The high heterogeneity might have been caused by a combination of large cohort sizes and large differences with respect to study populations, patient characteristics, protocols, reported outcome measures, proportions of prophylaxis use, and prophylaxis strategies. Therefore, we noted large uncertainty in the overall venous thromboembolism rates in various subgroups. Variation in heart failure severity might be one of the most important sources of heterogeneity because a dose–response association seems to exist, with the absolute risk and RR for venous thromboembolism being higher in patients with severe heart failure than in those with mild heart failure.[116] Fourth, thorough assessment or stratification for all potential confounders is not possible, which is an inherent limitation of observational studies. Adjustments differed across studies and other unknown risk factors for venous thromboembolism might exist and not be included in adjustments. Additionally, both heart failure and venous thromboembolism have common risk factors. For example, advancing age, an important risk factor for heart failure, is also associated with venous thromboembolism. Without randomisation, colinear associations are difficult to rule out. However, because of the large number of cohorts and robust findings in various sensitivity and subgroup analyses, our study was able to provide a representative overall estimate of the relative risk of venous thromboembolism. Fifth, in studies that enrolled mixed patient populations, use of prophylaxis was deemed to be present if more than 40% of patients received prophylaxis. Therefore, the overall venous thromboembolism rates might be underestimated in the no-prophylaxis subgroups and overestimated in the prophylaxis subgroups. Sixth, in studies based on administrative databases, errors of commission and omission during data entry might affect the recording of venous thromboembolism, heart failure, and other medical conditions that were identified via ICD codes, which could bias the results obtained.

With an ageing population, a greater proportion of venous thromboembolism events are occurring in patients with heart failure who have been admitted to hospital. In the absence of active bleeding or high bleeding risk, adequate and rigorous prophylaxis for venous thromboembolism as done in clinical trials

should be applied to patients with heart failure in clinical practice, although treating patients in a general setting can be very different to a clinical trial. Making physicians more aware of the association between heart failure and venous thromboembolism could help to reduce the incidence of this potentially avoidable and costly disease.

Contributors

LT, GYHL, and YH conceived and designed the study. LT, Y-YW, PY, and YH contributed to the literature searches, study selection, data extraction, and quality assessment. LT, GYHL, PY, and YH did the meta-analyses. LT, PY, and GHYL analysed and interpreted the data. LT and Y-YW drafted the initial manuscript and GHYL, PY, and YH made critical revisions to the intellectual content. All authors approved the final version of the study.

Declaration of interests

GYHL declares consultant fees from Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb and Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; and speaker fees from Bayer, Bristol-Myers Squibb and Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. Other authors declare no conflicts of interest.

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