

## Venous Thromboembolism in Hospitalized Patients With Heart Failure Incidence, Prognosis, and Prevention

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**H**ear failure (HF) is a common cardiovascular cause of hospitalizations in the United States and the most frequent reason among patients aged 65 years and older.<sup>1</sup> A recent report by the National Hospital Discharge Survey showed an increase in the number of hospital admissions with a diagnosis of HF from  $\approx$ 1.3 million in 1979 to 3.9 million in 2004, with 30% to 35% of these carrying a primary diagnosis of HF.<sup>2</sup> Recent data from several large registries of HF hospitalizations have demonstrated in-hospital mortality as high as 4% to 7%.<sup>3,4</sup> Contributing to this is a significant incidence of VTE among hospitalized patients with HF.<sup>5</sup> In addition, VTE is associated with thromboembolic complications, which are associated with long-term sequelae including postthrombotic syndromes, venous stasis, venous ulcers, chronic thromboembolic pulmonary hypertension, and pulmonary embolism (PE).<sup>6–8</sup> These conditions are often associated with edema and chronic pain, which can have a significant impact on mobility and quality of life. Recurrent VTE and PE are also common complications reported in as many as 30% of patients.<sup>9</sup>

Published information suggests that despite availability of effective therapy and existence of practice guidelines,<sup>10,11</sup> there is a significant underutilization of VTE prophylaxis in hospitalized patients with HF.<sup>12–15</sup> Analysis of the Acute Decompensated Heart Failure National Registry revealed that of 71 376 patients eligible for VTE prophylaxis only 21 847 (31%) received prophylactic regimen.<sup>16</sup> An analysis of the PREMIER database showed that although 79% of 34 286 patients admitted with HF received an order for VTE prophylaxis, only 15.8% received recommended appropriate prophylactic regimen in terms of the type of medications, dose, and duration of therapy.<sup>17</sup> These data clearly demonstrate the need for increased awareness of prevention of VTE in hospitalized patients with HF. Therefore, the purpose of this article is to review the incidence, clinical significance, and preventive treatment of VTE in hospitalized patients with HF.

### Rationale for VTE Prophylaxis in Hospitalized Patients With HF

#### Risk Factors for VTE in HF

In general, hospitalized patients can exhibit many of the traditional risk factors for the development of VTE including

surgery, trauma, immobility, malignancy, venous compression, previous VTE, advanced age, pregnancy, medications (especially estrogen and erythropoiesis stimulating agents), obesity, myeloproliferative disorders, and acute medical illness.<sup>18–22</sup> Many of these are also apparent in the hospitalized patients with HF. Characteristics of patients from the Acute Decompensated Heart Failure National Registry, which includes >160 000 patient visits, reported a median age of >75 years, active malignancy in 5%, and history of stroke or transient ischemic attack in 17%.<sup>23</sup> Renal insufficiency and dialysis are also associated with an increased risk for deep venous thrombosis (DVT) and PE,<sup>24–27</sup> and may be present in up to one third of hospitalized patients with HF.<sup>23</sup> Ischemic cardiomyopathy is arguably the most common cause of HF in the United States. Atherosclerotic disease and risk factors for development of obstructive coronary artery disease have also been linked to risk for VTE. In a study of 299 patients with DVT and no symptomatic atherosclerosis and 150 controls, spontaneous thrombosis was associated with a 2.3-fold increased odds of having at least 1 carotid plaque.<sup>28</sup> Similarly, in a study comparing 136 patients with peripheral vascular disease and 40 controls, the incidence of ultrasound-defined VTE was higher in the patients with peripheral vascular disease (20%) than the controls (4%).<sup>29</sup> Additional evidence comes from a meta-analysis of 63 552 patients in 21 case-control or cohort studies that compared traditional cardiovascular risk factors and risk for VTE. This study concluded that presence of obesity (odds ratio, 2.33), hypertension (1.51), diabetes (1.42), smoking (1.18), and dyslipidemia (1.16) were all associated with an increased risk for VTE.<sup>29a</sup> These cardiovascular risk factors were also common in Acute Decompensated Heart Failure National Registry.<sup>23</sup> These traditional risk factors and comorbid conditions have been shown to be predictive of PE in patients with HF.<sup>30</sup>

Patients with HF are also at risk for upper extremity VTE. Risk factors such as pacemakers/implantable cardioverter defibrillators and central venous catheters are commonplace in patients with HF.<sup>23</sup> In an analysis of the US Multicenter Registry of 5451 patients with ultrasound-confirmed DVT,

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presence of an indwelling central venous catheter was the strongest independent predictor of DVT (odds 7.3).<sup>31</sup>

Finally, there is also evidence to suggest the risk for thromboembolism, including VTE, in HF may be graded and correlate to the degree of left ventricular dysfunction. In an analysis of 103 patients who experienced a stroke in the Survival and Ventricular Enlargement trial, each 5% decrease in ejection fraction was associated with an 18% increase in the relative risk (RR) of fatal or nonfatal stroke.<sup>32</sup> Strikingly, the same relationship was seen in a post hoc analysis of 2114 patients with no history of atrial fibrillation in the Sudden Cardiac Death in Heart Failure Trial.<sup>33</sup> For each 5% increase in left ventricular ejection fraction, there was an associated 18% reduction in risk for thromboembolism. In addition, in a case-control study of DVT in a veterans affairs hospital, HF was associated with an overall 2.6-fold increased risk, which jumped to 38.3-fold higher in patients with an ejection fraction <20%.<sup>21</sup>

### Procoagulant State in HF

Hospitalized patients with HF are at increased risk for VTE, most commonly presenting as DVT and PE, which are associated with significant morbidity and mortality. Thromboembolic risk is due to a variety of mechanisms including stasis of blood because of dilatation of cardiac chambers, reduced myocardial contractility, decreased mobility, and increased intracardiac and central venous pressures.<sup>34,35</sup> In addition, increase in plasma viscosity,<sup>36,37</sup> altered coagulability,<sup>35,36,38</sup> inflammation,<sup>39</sup> neurohormonal activation,<sup>37</sup> and endothelial dysfunction<sup>40</sup> also contribute to the hypercoagulable state.<sup>35,36,38,41</sup>

### Incidence and Risk for VTE in Hospitalized Patients With HF

The incidence of VTE in hospitalized patients with HF has been described in a retrospective registry and prospective studies of VTE prophylaxis, which have included a substantial number of patients with HF on placebo (Table 1).<sup>42–46</sup> In a retrospective analysis of data from the National Hospital Discharge Survey, DVT and PE were diagnosed in 1.03% and 0.73% of patients with HF, respectively.<sup>42</sup> Although these figures may seem small, the RRs compared with patients without HF were 2.15 for PE and 1.21 for DVT. In addition, these data most likely represent an underestimation of the true prevalence of thromboembolic events in patients with HF because of the retrospective study design and the clinically silent nature of thromboembolic complications. This is supported by a higher incidence of complications reported in prospective clinical studies of VTE prophylaxis that included patients with HF. In these studies, the placebo rates of DVT ranged from 4.0% to 14.6% in the HF subgroups.<sup>43–45</sup> The assumption of underestimation by the retrospective registry is also supported by the studies that demonstrate that HF is a common comorbid condition in patients with VTE. The International Cooperative Pulmonary Embolism Registry of 2454 patients with acute PE reported concomitant HF in 10.5% of these patients.<sup>47</sup> A similar registry of 5451 DVT patients identified congestive HF in 13% of the study population.<sup>15,48</sup> In a population-based, case-control study of 625

**Table 1. Incidence of VTE in Hospitalized Patients With HF**

Study	Patient Population	Incidence of VTE, %
Beemath et al <sup>42</sup>	58 873 000 hospitalized patients with HF	0.73 PE; 1.03 DVT
Alikhan et al <sup>43</sup>	290 hospitalized patients with HF aged 40 years or older	14.6
Leizorovicz et al <sup>44</sup>	3706 hospitalized medical patients aged 40 years or older (51% HF)	4.96
Cohen et al <sup>45</sup>	849 medical patients aged 60 years or older (25% HF)	10.5

patients who experienced either a DVT or a PE, HF was found to contribute 9.5% of the attributable risk after adjustment for other risk factors.<sup>6</sup> In addition, symptoms of PE in patients with HF may be largely underestimated and attributed to HF manifestations. A postmortem interrogation of implantable defibrillators in 83 patients with HF found that the prime mode of death was not an arrhythmia in 69% of the patients, with 16.9% dying of thromboembolic events including PE, stroke, and other forms of peripheral embolization.<sup>49</sup> An autopsy study in 152 patients with dilated cardiomyopathy revealed either pulmonary or systemic emboli or both in more than half of the patients.<sup>50</sup>

### Prognosis

Importantly, available data suggest that the occurrence of VTE in hospitalized patients with HF is associated with poor clinical outcomes. In a pooled analysis of trials evaluating the role of angiotensin-converting enzyme inhibitors in >7000 patients with HF, PE was identified as the fifth most common cause of death.<sup>51</sup> In a prospective cohort study of 198 severe decompensated patients with HF, PE was associated with longer length of hospital stay ( $37.5 \pm 71.6$  days versus  $15.4 \pm 15.0$  days,  $P=0.001$ ) and greater death or rehospitalization at 3 months (72.2% versus 43.9%,  $P=0.02$ ) compared with those without PE.<sup>52</sup>

In summary, there seems to be a large discrepancy between retrospective observations suggesting a low incidence of thromboembolic events and prospective or autopsy studies that show a relatively high incidence of clinically occult VTE, which is likely to contribute to the short- and long-term morbidity and mortality of patients with HF.

### Current Recommendations for Prevention of VTE in Patients With HF

For acutely ill medical patients admitted to hospital with HF, the eighth American College of Chest Physicians Guidelines for the Prevention of Thromboembolism recommend thromboprophylaxis with either low dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH), or fondaparinux (all grade 1A), except for patients with contraindications to anticoagulant thromboprophylaxis for whom an optimal use of mechanical thromboprophylaxis is recommended (grade 1A).<sup>11</sup>

### Evidence for Efficacy of Drug Therapy in HF LDUH

No randomized clinical trials have evaluated the efficacy and safety of LDUH for VTE prophylaxis specifically in HF,

although several small studies have included patients with HF (Table 2).<sup>53–58</sup> Specifically, 2 randomized trials have demonstrated a reduction in incidence of VTE in a subset of patients with HF (26 and 63 patients, respectively) with a regimen of heparin 5000 U given subcutaneously every 8 hours compared with placebo or control.<sup>53,54</sup> Overall, early randomized studies in medical patients support the effectiveness of heparin given as 5000 U every 8 or 12 hours for reducing the incidence of VTE (mainly DVT and PE) without an increased risk for bleeding.<sup>11,69</sup>

### LMWH

Only 2 randomized studies that evaluated LMWH for prophylaxis of VTE in medical patients also reported findings in a subgroup of patients with HF (Table 2).<sup>43,44,46,59–61</sup> The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial randomized 1102 hospitalized patients, immobilized for >3 days, to enoxaparin 20 mg or 40 mg once-daily for up to 14 days or placebo.<sup>46</sup> The primary end point was DVT detected by bilateral venography, duplex ultrasonography, or documented PE between days 6 and 14, with a follow-up of 110 days. Of the 1102 patients, 34% were hospitalized for New York Heart Association class III or IV HF. In these patients, the incidence of VTE was 14.6% (12.3% class III and 21.7% class IV). Enoxaparin 40 mg was associated with a significant reduction in incidence of VTE at 2 weeks compared with placebo (4.0% versus 14.6%,  $P=0.02$ ), with the greatest effect seen in class IV (0.0% versus 21.7%,  $P=0.05$ ).<sup>43</sup> The incidence of adverse events was not specified for the subgroup of patients with HF; but in the total MEDENOX study population, there was no significant difference between all 3 study groups in death (placebo 13.9% versus enoxaparin 20 mg 14.7% versus enoxaparin 40 mg 11.4%,  $P=NS$ ), major bleeding (2.0% versus 1.2% versus 3.4%,  $P=NS$ ), or thrombocytopenia (4.8% versus 3.2% versus 2.8%,  $P=NS$ ) at 110 days.

The value of dalteparin for VTE prophylaxis was evaluated in the PREVENT (Prevention of Venous Thromboembolism in Acutely Ill Medical Patients) trial, a randomized, double-blind, placebo-controlled multicenter study of 3706 patients, aged 40 years and older, hospitalized for an acute medical condition.<sup>44</sup> The patients were randomized to dalteparin 5000 IU or placebo for 14 days and followed up for 90 days. The primary end point was a combination of symptomatic or asymptomatic DVT detected by ultrasound, symptomatic PE at day 21, and sudden death by day 21. The number of patients with acute congestive HF, New York Heart Association class III or IV, was 52% in the dalteparin group and 51% in the placebo group. In the entire study cohort, the primary end point was lower with dalteparin compared with placebo; however, there were no significant differences at day 14, 21, or 90 in the incidence of mortality, major bleeding, or thrombocytopenia. In a retrospective analysis of PREVENT, the RR of the primary end point in patients with acute congestive HF was 3.07% in the dalteparin group versus 4.23% in the placebo group (RR 0.73; 95% CI 0.44 to 1.21).<sup>59</sup>

### Studies Comparing LDUH and LMWH

Four randomized clinical trials and 1 retrospective study have compared LDUH and LMWH with 4 of the studies reporting

HF specific data.<sup>58,61–68</sup> A randomized, double-blind controlled trial in a high-risk group of 959 hospitalized medical patients compared enoxaparin 40 mg once daily with LDUH 5000 U three times daily. Enoxaparin was found to be at least as efficacious as LDUH with fewer adverse events. A randomized, double-blind controlled trial in 442 hospitalized elderly patients bedridden for acute illness demonstrated similar efficacy of enoxaparin 20 mg once daily compared with LDUH 5000 U twice daily.<sup>64</sup> A large randomized, double-blind controlled trial of 1590 hospitalized bedridden patients, aged 50 to 80 years, including 293 patients with HF compared enoxaparin 36 mg once daily with LDUH 5000 U three times daily for 8 to 11 days<sup>65</sup> and found enoxaparin and LDUH to be equivalent in incidence of VTE. More recently, the Thromboembolism-Prevention in Cardiac or Respiratory Disease with Enoxaparin trial, a randomized, open-label controlled study, randomized 451 patients with HF or severe respiratory illness who were confined to bed for >two thirds of each day, to enoxaparin 40 mg once daily or LDUH 5000 U three times daily.<sup>66</sup> Although the results including all patients demonstrated equivalence between the 2 therapies in incidence of venographically detected VTE, in the subset of 206 patients with HF, enoxaparin was associated with a numerically lower incidence of VTE (9.7% versus 16.1%,  $P=0.0139$  for equivalence). No patients with HF developed PE during enoxaparin therapy, whereas 1 patient in the LDUH group was found to have PE on autopsy. In the entire study population, there were no differences between enoxaparin and LDUH in minor and major bleeding; however, injection hematoma was more frequent in those who received LDUH. Adverse events related to the drug used occurred less often with enoxaparin than with LDUH.

### Fondaparinux

Fondaparinux, a synthetic indirect factor Xa inhibitor, has also been shown to be effective for VTE prevention in medical patients. The Arixtra for Thromboembolism Prevention in a Medical Indications Study, a double-blind trial of patients aged 60 years and older, randomized 429 patients to fondaparinux 2.5 mg subcutaneously once daily and 420 patients to placebo for 6 to 14 days.<sup>45</sup> Overall, fondaparinux was associated with a lower incidence of VTE (RR 0.53, 95% CI 0.31 to 0.92,  $P=0.029$ ) with no difference in major bleeding (0.2% with each study treatment). In the subset of patients admitted with only HF (New York Heart Association functional class III or IV), fondaparinux (9.0%, 7 of 78 patients) was associated with a reduced incidence of symptomatic or venographically detected VTE compared with placebo (12.2%, 10 of 82 patients). It should be noted that fondaparinux exhibits a long half-life, which can be prolonged in renal insufficiency. Thus, the dose may require adjustment. Because worsening of renal function often occurs during hospitalization, it is important to continually reassess the appropriate dosing of fondaparinux or the choice of heparin for prophylaxis.

### Considerations in Patients With HF and Renal Insufficiency

The guidelines recommend that renal function be considered when making decisions about the use and dose of LMWH,

**Table 2. Studies of VTE Prophylaxis in Medically Ill Patients, Which Included Patients With HF**

Study	Study Population	Study Design	VTE Prophylaxis Regimens	VTE Results	
				Overall Study Population	HF Subgroup
<b>UFH</b>					
Gallus <sup>53</sup>	272 high-risk surgical and 78 medical patients	R, C	UFH 5000 U TID vs P	Medical patients only: DVT: UFH 2.6% vs P 22.5%, $P=0.05$	UFH (1/11) 0.91% vs P (7/15) 46.7% ( $P$ value not available)
Belch et al <sup>54</sup>	63 patients with HF or 37 with chest infection	R	UFH 5000 U TID vs control	DVT: UFH 4% vs control 26%, $P<0.01$	
Halkin et al <sup>55</sup>	1358 patients admitted to medical wards of acute care hospital	Consecutive, alternating treatment assignment	UFH 5000 U BID vs control	Mortality: UFH 7.8% vs control 10.9%, $P=0.025$	Cardiopulmonary disorder (N=267): UFH 3.1% vs control 4.9% ( $P$ value not available)
Cade <sup>56</sup>	119 critically ill ICU patients and 131 medical patients	R, DB, C	UFH 5000 U BID vs P	Critically ill patients: DVT: UFH 13% vs P 29%, $P<0.05$ Medical patients: DVT: UFH 2% vs P 10%, $P=NS$	
Gardlund <sup>57</sup>	11 693 infectious disease department admissions	R, C	UFH 5000 U BID vs control	Necropsy-verified PE: UFH 15 vs Control 16, $P=NS$ ; median time to fatal PE: UFH 28 vs control 12.5 days, $P=0.007$ nonfatal VTE: UFH 70 vs control 116, $P=0.0012$	HF was a finding on necropsy in 141 of 383 (37%) patient deaths
Mismetti et al <sup>58</sup>	845	Meta-analysis	UFH vs control	DVT: RR 0.44 (0.29 to 0.64, $P<0.001$ ) PE: RR 0.48 (0.34 to 0.68, $P=0.52$ )	
<b>LMWH</b>					
Samama et al <sup>46</sup>	866 medical patients older than 40 years	R, DB, C	E 40 mg daily vs E 20 mg daily vs P	DVT or PE: E 40 mg 5.5% vs E 20 mg 15.0% vs P 14.9%, E 40 mg vs P, $P<0.001$ E 20 mg vs P, $P=NS$ . Death from any cause: E 40 mg 3.3% vs E 20 mg 4.3% vs P 4.4%	34% of patients were hospitalized for NYHA FC III or IV HF
Alikhan et al <sup>43</sup>	290 patients with HF older than 40 years	Post hoc analysis of Samama et al	E 40 mg daily vs E 20 mg daily vs P		E 40 mg 4.0% vs P 14.6%, $P=0.02$ NYHA FC III: E 40 mg 5.1% vs P 12.3%, $P=0.2$ NYHA FC IV: E 40 mg 0% vs P 21.7%, $P=0.05$ Chronic HF: E 40 mg 2.2% vs P 12.1%, $P=0.04$
Leizorovicz et al <sup>44</sup>	3706 medical patients aged 40 years and older	R, DB, C	D 5000 IU once daily vs P	DVT or PE: D 2.77% vs P 4.96%, $P=0.0015$	Acute HF (N=1905), trend favoring D: D 3.07% vs P 4.23%, $P=NS$
Cohen et al <sup>59</sup>				All-cause mortality: D 2.35% vs P 2.32%, $P=NS$	
McGarry and Thompson <sup>60</sup>	3719 medical patients aged 40 years and older	Retrospective, database	E 30 to 60 mg once daily (N=162) vs Control	DVT: E 1.9% vs control 6.2%, $P=0.023$ PE: E 0.0% vs control 1.0%, $P=NS$ Death: E 8.0% vs control 7.3%, $P=NS$	
Kanaan et al <sup>61</sup>	7639	Meta-analysis	LMWH vs P	DVT: OR 0.92 (0.56 to 1.52, $P=0.75$ ) PE: OR 0.80 (0.22 to 2.89, $P=0.73$ ) VTE: OR 0.89 (0.54 to 1.46, $P=0.64$ )	29.4% patients with HF in entire study population

(Continued)

Table 2. Continued

Study	Study Population	Study Design	VTE Prophylaxis Regimens	VTE Results	
				Overall Study Population	HF Subgroup
Comparative studies of UFH vs LMWH					
Harenberg et al <sup>62</sup>	166 medical patients	R, DB, C	UFH 5000 U TID vs LMWH 1.5 aPTT units once daily	DVT: UFH 4.8% vs LWMH 3.4%	23 (13.8%) patients with HF
Lechler et al <sup>63</sup>	959 medical patients	R, DB, C	UFH 5000 U TID vs E 40 mg once daily	DVT: UFH 1.4% vs E 0.2%, $P=0.12$ , $P<0.05$ for equivalence	
Bergmann and Neuhart <sup>64</sup>	442 elderly patients bedridden for acute medical illness	R, DB, C	UFH 5000 U TID vs E 20 mg once daily	DVT or PE: UFH 4.6% vs E 4.8%, $P=0.0005$ for equivalence	Incidence of cardiac failure was similar between patients with VTE vs patients without VTE (35% vs 29%, $P=NS$ )
Harenberg et al <sup>65</sup>	1590 bedridden patients aged 50 to 80 years	R, DB, C	UFH 5000 U TID vs E 36 mg once daily	DVT or PE: UFH 0.51% vs E 0.74%, $P=0.012$ for equivalence	293 (18.5%) patients with HF
Kleber et al <sup>66</sup>	206 HF and 245 severe respiratory disease patients	R, O, C	UFH 5000 U TID vs E 40 mg once daily	DVT or PE: UFH 10.4% vs E 8.4%, $P=0.015$ for equivalence	206 patients with HF: UFH 16.1% vs E 9.7%, $P=0.0139$ for equivalence  Incidence of VTE was higher in patients with HF (HF 12.6% vs respiratory disease 6.8%)
McGarry et al <sup>67</sup>	3316 medical patients aged 40 years and older	Retrospective, database	UFH 5000 to 15 000 U/day vs E 30 to 60 mg/day	DVT or PE: UFH 6.3% vs E 1.7%, $P<0.001$	1004 patients with HF (UFH 810, E 194)
Mismetti et al <sup>58</sup>	4669	Meta-analysis	LMWH vs UFH	DVT: RR 0.83 (0.56 to 1.24, $P=0.37$ ) PE: RR 0.74 (0.29 to 1.88, $P=0.52$ )	
Kanaan et al <sup>61</sup>	3581	Meta-analysis	LMWH vs UFH	DVT: OR 0.92 (0.56 to 1.52, $P=0.75$ ) PE: OR 0.80 (0.22 to 2.89, $P=0.73$ ) VTE: OR 0.89 (0.54 to 1.46, $P=0.64$ )	29.4% patients with HF in entire study population
Any prophylaxis vs no treatment					
Dentali et al <sup>68</sup>	19 958	Meta-analysis	UFH or LMWH or F vs P or No Treatment	Symptomatic DVT: RR 0.47 (0.22 to 1.00) Any PE: RR 0.43 (0.26 to 0.71) Fatal PE: RR 0.38 (0.21 to 0.69) All-cause mortality: RR 0.97 (0.79 to 1.19)	
Factor Xa inhibitors					
Cohen et al <sup>45</sup>	849 medical patients aged 60 years and older	R, DB, C	F 2.5 mg once daily vs P	DVT or PE: F 5.6% vs P 10.5%, $P=0.029$ Symptomatic VTE: F 0.9% vs P 2.6%, $P=0.029$ Death: F 3.3% vs P 6.0%, $P=0.06$	160 patients with HF: F 9.0% vs P 12.2% ( $P$ value not provided)

NYHA FC indicates New York Heart Association functional classification; C controlled; D, dalteparin; DB, double-blind; E, enoxaparin; F, fondaparinux; ICU, intensive care unit; O, open-label; P, placebo; R, randomized; UFH, unfractionated heparin.

fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients, patients with diabetes mellitus, and those with a high risk for bleeding (grade 1A). Depending on the circumstances, it may be necessary to avoid the use of an anticoagulant that bioaccumulates in the presence of renal impairment, use a lower dose of the agent, or monitor the drug level or its anticoagulant effect (grade 1B).

### Nonpharmacologic Approaches to VTE Prevention

In patients with contraindications to pharmacological prophylaxis, mechanical approaches to VTE prevention may be an appropriate alternative. Despite very limited data in the medically ill population, intermittent pneumatic compression and elastic compression stockings are commonly used in the United States.<sup>70</sup> The only randomized study in medical patients compared graduated compression stockings with no prophylaxis in 80 acute myocardial infarction patients.<sup>70a</sup> DVT, detected by fibrinogen uptake test, was found in 8 control patients compared with no patients with stockings. Otherwise, the efficacy is extrapolated mainly from surgical studies, specifically general and orthopedic surgery<sup>71–73</sup> where these approaches, when applied the day before or the day of surgery, was associated with a reduced incidence of VTE. Mechanical approaches when combined with pharmacological prophylaxis is also associated with greater efficacy than either approach alone.<sup>71,72,74</sup> Unfortunately, these surgical studies did not stratify patients for DVT risk, thus making comparisons with the medically ill, such as patients with HF, difficult.

### Duration of therapy

Duration of prophylactic therapy of VTE in studies with hospitalized patients with HF has ranged from 6 to 14 days. Discharged patients, however, may still remain relatively immobile and are still at risk of developing VTE because of venous stasis, altered coagulation, and endothelial dysfunction. The PREVENT and MEDENOX trials showed VTE still occurring at 90 and 110 days of follow-up, respectively, raising the question of whether extended-duration therapy is needed.<sup>44,46</sup> The EXtended Clinical prophylaxis in Acutely Ill Medical patients (EXCLAIM) study, randomized 5101 hospitalized patients (4114 included in final analysis) with varying degrees of immobility starting at least 3 days before randomization for reasons that included cancer, ischemic stroke, HF, respiratory failure, and infections to either subcutaneous enoxaparin 40 mg once daily for an average of 10 days on an open-label basis.<sup>75,76</sup> The majority of the patients were then randomized, double blindly, to receive either placebo or continued prophylaxis for a mean of 28 additional days. Continued prophylaxis resulted in a reduction of VTE from 4.9% to 2.8% ( $P=0.0011$ ). The significant reduction in VTE persisted out to 90 days (5.3% versus 3.1%,  $P=0.0015$ ). However, there was no effect on all-cause mortality at 6 months (8.9% versus 10.1%,  $P=0.18$ ). Extended prophylaxis was associated with an increased incidence of total bleeding events (5.7% versus 3.8%,  $P=0.007$ ) and major bleeding events (0.6% and 0.15%,  $P=0.019$ ) in the enoxaparin group.

Although no information has been published on the subgroup of patients with HF in the EXCLAIM study, the results of the study suggest that continuation of VTE prophylaxis may be beneficial in patients with HF who continue to be immobile after discharge, but this needs to be supported by further investigations.

### Improving VTE Prophylaxis in HF

Despite established guidelines recommending prophylaxis against VTE in the majority of hospitalized patients, multiple studies and registries continue to demonstrate underutilization.<sup>14,77</sup> Postulated reasons include lack of awareness, complexity of the guidelines, lack of standardization or institutional protocols, and perceived bleeding risk. In a cross-sectional study of medical patients older than 40 years, the most common documented reasons for avoiding pharmacological prophylaxis were bleeding on admission and hepatic impairment.<sup>14</sup> In the observational Canadian study of VTE prophylaxis in acutely ill medical patients, cancer was associated with lower use.<sup>77</sup> Data also suggest that rates of prophylaxis may be greater at academic institutions than community-based hospitals.<sup>77</sup>

Numerous studies have demonstrated the value of 3 main interventions related to improving adherence to VTE guidelines. (1) Computerized programs and physician alerts; (2) personal alert systems, and (3) educational programs. Computerized programs that estimate VTE risk and provide electronic reminders to the caring physician have been universally shown to improve the proportion of eligible patients who receive pharmacological and mechanical prophylaxis.<sup>78–84</sup> Although rates of pharmacological prophylaxis generally doubled in most studies, the largest improvement was in use of mechanical prophylaxis. Importantly, in the randomized and longitudinal observational studies, the electronic alert system was associated with a significant decrease in the incidence of VTE.<sup>79,80</sup> In the absence of a computerized system, preprinted risk stratification scoring systems to identify VTE prophylaxis eligible hospitalized patients and personal or written physician alerts have also been shown to improve VTE prophylaxis rates<sup>85,86</sup> and reduce the incidence of symptomatic VTE.<sup>85</sup> In addition, institution or health-system wide education programs using methods such as in-services, institution guideline development, verbal reminders, weekly audits with reporting, and clinical pharmacy led education and monitoring have demonstrated efficacy at improving prophylaxis prescribing.<sup>87–90</sup> Ultimately, a combination of these methods may be the best approach. In a systematic review of 30 studies that evaluated various strategies for improving VTE prophylaxis in hospitalized patients, it was concluded that the most effective programs were those that incorporated multiple methods, and the poorest effect was seen in response to interventions that only passively disseminated the guidelines.<sup>91</sup>

The current ACCP guidelines reflect the earlier findings. The guidelines recommend that each institution implement a formal strategy to improve adherence to VTE prophylaxis and that an institution-wide policy be adopted.<sup>11</sup> They also recommend use of interventions to increase adherence such as computer support systems, preprinted order forms, and

periodic audits with feedback. Using only passive methods such as distribution of educational materials is discouraged.

### Conclusions

There is a significant increase in the rate of thromboembolic events in hospitalized patients with HF, which seems to be underrecognized and contributes importantly to the morbidity and mortality in this patient population. Guidelines recommend that all hospitalized patients with HF who are not at high risk for bleeding be treated prophylactically with LDUH, LMWH, or fondaparinux.<sup>11</sup> Recent evidence shows a large gap between these guidelines and clinical practice. An effort should be made to increase the awareness of both the risk for VTE in hospitalized patients with HF and the importance of appropriate VTE prophylaxis in the majority of these patients.

### Disclosures

Dr Elkayam reports having been a consultant/speaker for Sanofi-Aventis.

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KEY WORDS: thrombosis ■ heart failure ■ anticoagulants ■ prevention