Physician Alerts to Prevent Symptomatic Venous Thromboembolism in Hospitalized Patients

Gregory Piazza, MD; Erin J. Rosenbaum, BA; William Pendergast, MD; Joseph O. Jacobson, MD; Robert C. Pendleton, MD; Gordon D. McLaren, MD; C. Gregory Elliott, MD; Scott M. Stevens, MD; William F. Patton, MD; Ousama Dabbagh, MD; Marilyn D. Paterno, MBI; Elaine Catapano, MEd, MT; Zhongzhen Li, MD; Samuel Z. Goldhaber, MD

Background—Venous thromboembolism (VTE) prophylaxis remains underused among hospitalized patients. We designed and carried out a large, multicenter, randomized controlled trial to test the hypothesis that an alert from a hospital staff member to the attending physician will reduce the rate of symptomatic VTE among high-risk patients not receiving prophylaxis.

Methods and Results—We enrolled patients using a validated point score system to detect hospitalized patients at high risk for symptomatic VTE who were not receiving prophylaxis. We randomized 2493 patients (82% on Medical Services) from 25 study sites to the intervention group (n=1238), in which the responsible physician was alerted by another hospital staff member, or the control group (n=1255), in which no alert was issued. The primary end point was symptomatic, objectively confirmed VTE within 90 days. Patients whose physicians were alerted were more than twice as likely to receive VTE prophylaxis as control subjects (46.0% versus 20.6%; P<0.0001). The symptomatic VTE rate was lower in the intervention group (2.7% versus 3.4%; hazard ratio, 0.79; 95% CI, 0.50 to 1.25), but the difference did not achieve statistical significance. The rate of major bleeding at 30 days in the alert group was similar to that in the control group (2.1% versus 2.3%; P=0.68).

Conclusions—A strategy of direct notification of the physician by a staff member increases prophylaxis use and leads to a reduction in the rate of symptomatic VTE in hospitalized patients. However, VTE prophylaxis continues to be underused even after physician notification, especially among Medical Service patients. (Circulation. 2009;119:2196-2201.)

Key Words: prevention ■ prevention and control ■ pulmonary embolism ■ venous thromboembolism ■ venous thrombosis

In 2005, we described a new system using electronic alerts to prevent symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) in hospitalized patients.1 First, we devised a point score system to detect hospitalized patients at high risk for developing DVT or PE. Next, we created a computer program linked to the patient database to identify consecutive hospitalized patients at high risk for venous thromboembolism (VTE) who were not receiving prophylaxis. Finally, we programmed the hospital computer system as a quality improvement initiative to randomize the notification (versus no notification) of physicians caring for 2506 high-risk patients not receiving any VTE prophylaxis. The physicians in the intervention group received electronic alerts, which resulted in a 41% reduction in symptomatic VTE at 90 days compared with the control group.1

Clinical Perspective p 2201

We designed the current multicenter randomized trial with an eye toward applying the alert strategy to a broad array of hospitals across the United States. As we organized partici-
Methods

Study Design
From July 2006 to November 2007, we identified 2493 consecutive patients admitted to Medical or Surgical Services who were at least 18 years of age, were at high risk of VTE on the basis of our score point system, and were not receiving any VTE prophylaxis (Figure 1). Patients on the Neurology Service, Newborn Service, Neonatal Intensive Care Unit, and Rehabilitation Units and those receiving mechanical or pharmacological prophylaxis were excluded. Patients who were not at increased risk for developing VTE also were excluded. Patients were enrolled from 25 medical centers throughout the United States, including urban, nonurban, teaching, and non-teaching hospitals. Institutional Review Board approval was obtained from all 25 study sites.

Identification of Patients at Risk for VTE

Patients who were admitted overnight were screened for VTE risk by research nurses, pharmacists, physicians, or other professional staff. Our previously established scoring system was used to identify patients at increased risk for VTE. Each risk factor was weighted according to a point scale. Major risk factors of cancer, prior VTE, and hypercoagulable states were identified on the basis of available laboratory test results (not all patients were tested), including the presence of factor V Leiden mutation, prothrombin gene mutation, lupus anticoagulant, antiphospholipid antibodies, and deficiencies of protein C, protein S, and antithrombin III. Major surgery was defined as any surgical procedure lasting >60 minutes. Bedrest was defined as an active order for bedrest not related to surgery. Advanced age was defined as an age >70 years. If data on weight and height were available, body mass index (weight in kilograms divided by the square of height in meters) was calculated. Obesity was defined as a body mass index >29 kg/m². If weight and height were unavailable, inpatient and outpatient records were screened for a diagnosis of obesity and for the ICD-9 code for obesity (278.0). Ongoing use of hormone replacement therapy or oral contraceptives was identified by reviewing patients’ active medications.

Screening for VTE Prophylaxis
If the cumulative VTE risk score was at least 4 points, the patient was defined as being at high risk for developing VTE, and the screener reviewed orders to identify the ongoing use of any pharmacological or mechanical prophylaxis. Active medication orders were screened for pharmacological prophylaxis, including unfractionated heparin, enoxaparin, dalteparin, tinzaparin, fondaparinux, and warfarin. Orders also were searched for mechanical prophylactic measures, including the use of graduated compression stockings or intermittent pneumatic compression devices. Patients with orders for VTE prophylaxis were excluded. However, control patients could receive VTE prophylaxis in the 2 days between randomization and our in-hospital follow-up.

Randomization and Physician Alerts
Randomization envelopes containing the statement “alert” (intervention group) or “no alert” (control group) were provided by the Harvard Clinical Research Institute to randomize eligible patients. Among 2493 eligible patients, 1238 were assigned to the intervention group, and 1255 were assigned to the control group. For patients randomized to the intervention group, the attending physician was paged and informed that his or her patient was at high risk for VTE, that the patient was not currently receiving VTE prophylaxis, and that VTE prophylaxis was recommended. A sample script was provided that read as follows: “Hello, this is [name of hospital staff member, title, and department]. I am calling to alert you that your patient, [patient’s name], is at high risk for DVT. This is based on a point scale of DVT risk factors and the absence of current prophylaxis orders.” One study center that enrolled 178 patients violated the study protocol and paged house officers rather than the attending physicians. For patients in the control group, VTE prevention guidelines were available, but no specific communication regarding VTE risk or prophylaxis was issued.

Follow-Up
We conducted 90-day follow-up of all study patients by reviewing their medical records. Clinical events were identified through the use of data from the index hospitalization, subsequent hospitalizations, and office visits, including discharge summaries, healthcare provider’s notes, laboratory test results, vascular laboratory reports, nuclear medicine reports, and radiology reports. If patient outcomes could not be determined by medical record review alone, study representatives contacted the responsible primary care provider for necessary information. Investigational Review Board approval was obtained at each site before any contact with primary care providers. In addition, the Social Security Death Index was used to identify patients who died during the 90-day follow-up period. Overall, 2493 (100%) had follow-up data beyond the index hospitalization.

Data Collection
The primary end point was clinically diagnosed DVT or PE within 90 days of hospital discharge. For patients with >1 clinical event,
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Alert (n=1238)</th>
<th>Control (n=1255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>69.3±15.46</td>
<td>68.28±14.99</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>73 (20 to 100)</td>
<td>72 (19 to 103)</td>
</tr>
<tr>
<td>Age ≥75 y, n (%)</td>
<td>508 (42.5)</td>
<td>454 (37.8)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>672 (54.5)</td>
<td>666 (53.4)</td>
</tr>
<tr>
<td>BMI, mean±SD, kg/m²</td>
<td>29.15±7.41</td>
<td>29.98±8.18</td>
</tr>
<tr>
<td>Obesity (BMI &gt;29 kg/m²), n (%)</td>
<td>512 (41.4)</td>
<td>554 (44.1)</td>
</tr>
<tr>
<td>Bedrest/immobilization, n (%)</td>
<td>370 (29.9)</td>
<td>402 (32.0)</td>
</tr>
<tr>
<td>Hormone replacement therapy/oral contraceptive pills, n (%)</td>
<td>112 (9.0)</td>
<td>114 (9.1)</td>
</tr>
<tr>
<td>Major surgery, n (%)</td>
<td>215 (17.4)</td>
<td>238 (19.0)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td>923 (74.6)</td>
<td>922 (73.5)</td>
</tr>
<tr>
<td>History of VTE, n (%)</td>
<td>358 (28.9)</td>
<td>379 (30.2)</td>
</tr>
<tr>
<td>Hypercoagulable state, n (%)</td>
<td>75 (6.1)</td>
<td>93 (7.4)</td>
</tr>
</tbody>
</table>

Risk score for VTE, n (%)‡

<table>
<thead>
<tr>
<th>Risk score for VTE, n (%)‡</th>
<th>Alert</th>
<th>Control</th>
<th>Difference (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>808 (65.3)</td>
<td>801 (63.8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>286 (23.1)</td>
<td>310 (24.7)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>90 (7.3)</td>
<td>95 (7.6)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>42 (3.4)</td>
<td>36 (2.9)</td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>12 (1.0)</td>
<td>13 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

| BMI indicates body mass index. *P<0.05 unless otherwise noted. |
| Higher scores indicate greater risk. |

only the first event was counted. Safety end points included total mortality and major bleeding events at 90 and 30 days, respectively. We defined major bleeding as intracranial, intraocular, retroperitoneal, or pericardial bleeding; bleeding that required surgical intervention; or clinically overt bleeding that resulted in a hemoglobin decrease of ≥3 g/dL.² DVT was diagnosed if there was loss of compressibility on venous ultrasonography³ or evidence of a filling defect on conventional contrast venography. PE was diagnosed on the basis of findings on contrast-enhanced chest computed tomography,⁴ ventilation-perfusion lung scanning, or invasive pulmonary angiography. Events suspected clinically to be VTE related were not counted unless objective diagnostic imaging evidence was obtained. All end points were adjudicated by investigators who were unaware of the patients’ group assignments.

Statistical Analysis

We estimated a 4.1% rate for the primary end point in the intervention group and a 7% rate for the primary end point in the control group, with an odds ratio of 0.59. We estimated a sample size of ~2150 patients for the study to have 80% power to detect a difference between the intervention and control group (2-sided α=5%). We aimed for a trial enrollment of ~2500 patients to provide a “cushion” of about 350 patients for potential administrative problems such as improper randomization or withdrawal from the study.

We used Wilcoxon rank-sum tests to compare the distributions of continuous variables between groups and χ² tests or Fisher’s exact tests to compare categorical variables. Freedom from DVT or PE at day 90 for the intervention and control groups was estimated with the Kaplan–Meier method. SEs were estimated with Greenwood’s formula. The comparison between the intervention and control groups was assessed by the log-rank test. We used the proportional-hazards model to estimate the relative hazard of clinical end points associated with the physician alert and obtained 95% CIs from this model. All reported probability values are 2 sided.

Table 2. VTE Prophylaxis

<table>
<thead>
<tr>
<th>Prophylactic Measures</th>
<th>Alert, n (%)</th>
<th>Control, n (%)</th>
<th>Difference (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prophylaxis</td>
<td>569 (46.0)</td>
<td>259 (20.6)</td>
<td>25.3 (21.8 to 28.9)</td>
</tr>
<tr>
<td>Mechanical prophylaxis</td>
<td>258 (20.8)</td>
<td>95 (7.6)</td>
<td>13.3 (10.6 to 16.0)</td>
</tr>
<tr>
<td>Pneumatic compression device</td>
<td>188 (15.3)</td>
<td>69 (5.5)</td>
<td>9.7 (7.4 to 12.1)</td>
</tr>
<tr>
<td>Graduated compression stockings</td>
<td>79 (6.4)</td>
<td>25 (2.0)</td>
<td>4.4 (2.8 to 6.0)</td>
</tr>
<tr>
<td>Pharmacological prophylaxis</td>
<td>343 (27.7)</td>
<td>177 (14.1)</td>
<td>13.6 (10.5 to 16.8)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>140 (11.3)</td>
<td>79 (6.3)</td>
<td>5.0 (2.8 to 7.3)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>167 (13.5)</td>
<td>61 (4.9)</td>
<td>8.7 (6.4 to 10.9)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>35 (2.8)</td>
<td>40 (3.2)</td>
<td>−0.4 (−1.7 to 1.0)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>3 (0.2)</td>
<td>2 (0.2)</td>
<td>0.1 (−0.3 to 0.4)</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>0.1 (−0.1 to 0.2)</td>
</tr>
</tbody>
</table>

*Patients could receive ≥1 type of prophylaxis.

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

Results

Baseline Demographic and Clinical Characteristics

The intervention and control groups were similar with regard to baseline characteristics, except that patients randomized to a physician alert were more likely to be >75 years (42.5% versus 37.8%; P=0.02; Table 1). The overall study population (intervention and control groups) comprised 46.1% women and 53.9% men. Nearly two thirds of the study population had a VTE risk score of 4. The remaining 35.5% had a VTE risk score of ≥5. Overall, 18% of patients had undergone major surgery, and 82% were hospitalized for nonsurgical indications. Almost 30% of patients had suffered prior VTE, and nearly 75% had a history of cancer.

VTE Prophylaxis

Patients in the intervention group were more than twice as likely to receive VTE prophylaxis as those in the control group (46.0% versus 20.6%, respectively; 95% CI, 21.8 to 28.9; Table 2). The intervention group had a 3-times-higher rate of mechanical prophylaxis (20.8% versus 7.6%; 95% CI, 10.6 to 16.0) and a 2-times-higher rate of pharmacological prophylaxis (27.7% versus 14.1%; 95% CI, 10.5 to 16.8) than the control group. Urban sites were less likely to prescribe VTE prophylaxis after a physician alert between academic and nonacademic sites.

Study End Points

The primary end point of symptomatic DVT or PE at 90 days occurred in 32 patients in the intervention group (2.7%) compared with 41 patients in the control group (3.4%).
There was a nonsignificant trend toward a reduction in symptomatic proximal lower-extremity DVT among patients in the intervention group (0.3% versus 1.0%; hazard ratio, 0.34; 95% CI, 0.11 to 1.04). Kaplan–Meier estimates of the absence of symptomatic DVT or PE at 90 days were 97.1% (95% CI, 96.1 to 98.1) in the intervention group and 96.3% (95% CI, 95.1 to 97.5) in the control group (Figure 2). There was no significant difference in the rate of VTE at 90 days between the intervention group and control group in clinically important subgroups, including patients with a risk score of ≥4, age ≥70 years, cancer, major surgery or trauma, and prior VTE.

The overall rate of death at 90 days was similar between the intervention group and control group (Table 3). The rate of major bleeding at 30 days in the intervention group was similar to that in the control group (2.1% versus 2.3%; P=0.68).

Table 3. Study End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Alert, n (%)</th>
<th>Control, n (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy end point at 90 d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>32 (2.7)</td>
<td>41 (3.4)</td>
<td>0.79 (0.50 to 1.25)</td>
</tr>
<tr>
<td>DVT only</td>
<td>19 (1.6)</td>
<td>24 (2.0)</td>
<td>0.8 (0.44 to 1.46)</td>
</tr>
<tr>
<td>PE only</td>
<td>5 (0.4)</td>
<td>8 (0.7)</td>
<td>0.63 (0.21 to 1.93)</td>
</tr>
<tr>
<td>DVT and PE</td>
<td>7 (0.6)</td>
<td>9 (0.6)</td>
<td>1.01 (0.35 to 2.87)</td>
</tr>
<tr>
<td><strong>VTE by location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral DVT</td>
<td>11 (0.9)</td>
<td>9 (0.8)</td>
<td>1.23 (0.51 to 2.97)</td>
</tr>
<tr>
<td>Bilateral DVT</td>
<td>2 (0.2)</td>
<td>4 (0.3)</td>
<td>0.5 (0.09 to 2.75)</td>
</tr>
<tr>
<td>Upper-extremity DVT</td>
<td>8 (0.7)</td>
<td>8 (0.7)</td>
<td>1.01 (0.38 to 2.68)</td>
</tr>
<tr>
<td>Proximal lower-extremity DVT</td>
<td>4 (0.3)</td>
<td>12 (1.0)</td>
<td>0.34 (0.11 to 1.04)</td>
</tr>
<tr>
<td>Calf DVT</td>
<td>8 (0.7)</td>
<td>3 (0.3)</td>
<td>2.7 (0.72 to 10.18)</td>
</tr>
<tr>
<td>Smaller than saddle PE</td>
<td>7 (0.6)</td>
<td>7 (0.6)</td>
<td>1.01 (0.35 to 2.88)</td>
</tr>
<tr>
<td>Saddle PE</td>
<td>3 (0.3)</td>
<td>5 (0.4)</td>
<td>0.6 (0.14 to 2.53)</td>
</tr>
<tr>
<td><strong>Safety end point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at 90 d</td>
<td>215 (17.6)</td>
<td>209 (16.9)</td>
<td>1.04 (0.86 to 1.25)</td>
</tr>
<tr>
<td>Hemorrhage at 30 d</td>
<td>25 (2.1)</td>
<td>28 (2.3)</td>
<td>0.89 (0.52 to 1.53)</td>
</tr>
</tbody>
</table>

We observed a 21% reduction in symptomatic VTE with the use of physician alerts. This rate trended toward but did not achieve statistical significance. The overall rate of VTE prophylaxis was low, despite fewer than half of patients in the intervention group receiving any preventive measures. However, patients for whom a physician alert was issued were more than twice as likely to receive VTE prophylaxis.

In our prior trial of electronic alerts, the reduction in symptomatic VTE was 41% compared with 21% in the present study. This was surprising because the median age was 73 years in that study compared with 63 years in the electronic alert study. A history of VTE was present in 30% in this study compared with 20% in the electronic alert trial. The older patient population and higher rate of prior VTE should have provided the substrate for higher baseline VTE rates and for greater reductions in symptomatic DVT and PE than we observed. On the basis of the event rate in this trial, we would have needed to enroll ~9000 patients to detect a significant difference (with 80% power) in symptomatic VTE between the 2 groups.

The most likely explanation for the smaller reduction in symptomatic VTE in this trial is the fundamental difference between the 2 trials: human versus computer alerts. We had thought that the personal touch of direct staff communication with the attending physician might be more effective than an impersonal computer-generated alert in raising awareness of a patient’s VTE risk, encouraging prophylaxis use, and reducing symptomatic VTE events. However, from our data, it is likely that a computer alerting system is inherently more effective. Computer-based systems can provide direct access to a wide range of decision-support tools, including evidence-based practice guidelines, that would not be possible through a human alerting system.5,6 A computer-based alerting system such as the one used in our previous trial may be more difficult to ignore because it forces the clinician to acknowledge the alert before the clinician can continue using the
Our data suggest that a strategy of manually screening patients for VTE risk and alerting healthcare providers about high-risk patients who are not receiving prophylaxis measures increases prophylaxis use and trends toward a reduction of symptomatic VTE. However, a human alerting system does not appear to be as effective as a computer-based decision-support strategy. Increasing resources for computer-based decision-support strategies and medical informatics may enhance effectiveness of VTE prevention measures.

Source of Funding
This investigator-initiated study was funded in part by an unrestricted research grant from sanofi-aventis and Dr Piazza is supported by a Research Career Development Award (K12 HL083786) from the National Heart, Lung, and Blood Institute (NHLBI).

Disclosures
Dr Pendergast has received a research grant from and served on the advisory board for sanofi-aventis and served on the speaker’s bureau for sanofi-aventis, Pfizer, and Novartis. Dr McLaren has received research grants from sanofi-aventis and Bristol-Myers Squibb. Dr Patton has received honoraria from St Joseph Mercy Health System. Dr Dabbagh has received research grant from Bristol-Myers Squibb and Pfizer and honoraria from the Missouri Society of Respiratory Therapists. Dr Goldhaber has received research grants from and served on the advisory boards for sanofi-aventis, Eisai, and Boehr-
ring Engelheim and served on the advisory board for Bristol-Myers Squibb. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Despite published guidelines for venous thromboembolism (VTE) prevention, underuse of prophylaxis in hospitalized patients remains problematic. We previously described a novel system using electronic alerts to prevent symptomatic VTE in hospitalized patients. We created a computer program linked to the patient database to identify hospitalized patients at high risk for VTE who were not receiving prophylaxis and randomize notification (versus no notification) of physicians caring for these patients. The physicians in the intervention group received electronic alerts urging them to order prophylaxis. This resulted in a 41% reduction in symptomatic VTE at 90 days compared with the control group. Because it required an intricate electronic notification system and medical informatics support, this strategy could not be easily implemented by most hospitals. Therefore, we devised a clinical trial that used a human rather than an electronic alerting system. We randomized 2493 patients to the intervention group, in which the attending physician was alerted by another hospital staff member by direct page, or the control group, in which no alert was issued. Patients whose physicians were alerted were more than twice as likely to receive VTE prophylaxis. Although a human alerting system more than doubled VTE prophylaxis use, the ensuing 21% reduction in symptomatic VTE at 90 days did not achieve statistical significance (P=0.31). Increasing resources for computer-based decision-support strategies may enhance the effectiveness of VTE prevention measures.
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SUPPLEMENTAL MATERIAL

APPENDIX (25 participating sites)

1. The Washington Hospital, Washington, PA; N=313; Principal Investigator: William J. Pendergast, MD; Study Coordinators: Pamela S. Cummings, RN, MBA, CCM, Cathy Cordisco, Linda Wade, Kristie Wood, and Eileen Bazzoli.

2. North Shore Medical Center, Salem, MA; N=251; Principal Investigator: Joseph O. Jacobson, MD; Study Coordinator: Karen Conti, RN.

3. University of Utah Health Sciences, Salt Lake City, UT; N=190; Principal Investigator: Robert C. Pendleton, MD; Study Coordinator: Paula Hansen, BS.

4. Veterans Administration Long Beach Healthcare System, Long Beach, CA; N=178; Principal Investigator: Gordon D. McLaren, MD; Study Coordinators: Sakineh Khalaghizadeh, BS and Mahmood Novin, MD.

5. Intermountain Healthcare Urban Central Region Hospitals, Murray, UT; N=176; Principal Investigators: Scott M. Stevens, MD and C. Gregory Elliott, MD; Study Coordinator: Valerie Aston, RRT.
6. St. Joseph Mercy Health System, Ann Arbor, MI; N=163; Principal Investigator: William F. Patton, MD; Study Coordinator: Jennifer Fowler, BSN, RN.

7. University of Missouri Health Center, Columbia, MO; N=161; Principal Investigator: Ousama Dabbagh, MD; Study Coordinators: Catherine L. Munger, BSN, RN, Murtaza M. Kazmi, MD, Craig Karpman, MD, Shadi M. Haddadin, MD, Steven R. Schuster, MD, and Jason A. Goodin, MD.

8. Washington County Hospital, Hagerstown, MD; N=137; Principal Investigators: Catherine Ware, RN and Thomas Pianta, MPT.

9. Henry Ford Hospital, Detroit, MI; N=134; Principal Investigator: Scott Kaatz, DO, MSc; Study Coordinator: Stacy Ellsworth, RN, MSN, CCRC.

10. North Shore University Hospital, Manhasset, NY; N=114; Principal Investigator: David Rosenberg, MD, MPH; Study Coordinator: Sara Merwin, MPH.

11. United Hospital System, Kenosha, WI; N=100; Principal Investigators: Wendell Friedl, MD and Paula Carson, RN, MSN, CCRN.

12. Franklin Square Hospital, Baltimore, MD; N=93; Principal Investigator: James Welker, DO, CPI; Study Coordinator: Andrea Bowling, MS.
13. Presbyterian Hospital of Dallas, Dallas, TX; N=77; Principal Investigator: Tammy Chung, PharmD; Co-Investigators: Gary L. Weinstein, MD and Mark Feldman, MD; Study Coordinator: Susie Hubbard, RN, MSN.

14. Emory Crawford Long Hospital, Atlanta, GA; N= 76; Principal Investigator: Kenneth V. Leeper, Jr., MD; Study Coordinator: Ann Thron, RN, MSN, ACNP and Stacey Sadler Mitchell, RN, BSN.

15. The Denver Veterans Administration Medical Center, Denver, CO; N=62; Principal Investigator: Carolyn Welsh, MD and Melver Anderson, MD; Study Coordinator: Nancy G. Boyd, RN.

16. The University of Oklahoma Health Sciences Center and Veterans Affairs Medical Center, Oklahoma City, OK; N=60; Principal Investigator: Suman W. Rathbun, MD, MS; Study Coordinator: Penny L. Razo-Mosier, LPN, CCRP.

17. Florida Hospital, Orlando, FL; N=59; Principal Investigator: Janet W. Montgomery, PharmD.

18. University of California, Davis Medical Center, Sacramento, CA; N=41; Principal Investigator: Richard H. White, MD; Study Coordinators: Maya Juarez, Tina Tran, Chan Yuan Dong, Steven Lee, and Martina Garcia.
19. The William Backus Hospital, Norwich, CT; N=38; Principal Investigator: Jan Akus, MD; Co-Investigator: Michael Smith, PharmD; Study Coordinator: Paula Provost, EdM.

20. Lahey Clinic, Burlington, MA; N=32; Principal Investigator: Nicholas Tsapatsaris, MD; Study Coordinators: Gail Woodhead, RN, Michelle Ribicki, RN, MSN, Patricia Baum, RN, and Durathan Farha, MD.

21. Washington Hospital Center, Washington, DC; N=14; Principal Investigator: Andrew F. Shorr, MD; Study Coordinator: Nazli Bolouri, MD.

22. Thomas Jefferson Hospital, Philadelphia, PA; N=12; Principal Investigator: James Fink, MD and Geno Merli, MD; Study Coordinator: Lynda Thomson, PharmD.

23. University of California, Irvine Medical Center, Irvine, CA; N=6; Principal Investigator: Alpesh Amin, MD, MBA; Study Coordinator: Parmis Khatibi, PharmD, and Anna Aledia.

24. Spartanburg Regional Medical Center, Spartanburg, SC; N=3; Principal Investigator: Harold Fleming, MD; Study Coordinators: Tamara Cole, RN and Bunny McKown, RN.

25. Scottsdale Healthcare Shea, Scottsdale, AZ; N=3; Principal Investigator: A. Judson Tillinghast, MD; Study Coordinator: Annette Conly, RN, BSN, CCRC.
SUPPLEMENTAL MATERIAL

APPENDIX (25 participating sites)

1. The Washington Hospital, Washington, PA; N=313; Principal Investigator: William J. Pendergast, MD; Study Coordinators: Pamela S. Cummings, RN, MBA, CCM, Cathy Cordisco, Linda Wade, Kristie Wood, and Eileen Bazzoli.

2. North Shore Medical Center, Salem, MA; N=251; Principal Investigator: Joseph O. Jacobson, MD; Study Coordinator: Karen Conti, RN.

3. University of Utah Health Sciences, Salt Lake City, UT; N=190; Principal Investigator: Robert C. Pendleton, MD; Study Coordinator: Paula Hansen, BS.

4. Veterans Administration Long Beach Healthcare System, Long Beach, CA; N=178; Principal Investigator: Gordon D. McLaren, MD; Study Coordinators: Sakineh Khalaghizadeh, BS and Mahmood Novin, MD.

5. Intermountain Healthcare Urban Central Region Hospitals, Murray, UT; N=176; Principal Investigators: Scott M. Stevens, MD and C. Gregory Elliott, MD; Study Coordinator: Valerie Aston, RRT.
6. St. Joseph Mercy Health System, Ann Arbor, MI; N=163; Principal Investigator: William F. Patton, MD; Study Coordinator: Jennifer Fowler, BSN, RN.

7. University of Missouri Health Center, Columbia, MO; N=161; Principal Investigator: Ousama Dabbagh, MD; Study Coordinators: Catherine L. Munger, BSN, RN, Murtaza M. Kazmi, MD, Craig Karpman, MD, Shadi M. Haddadin, MD, Steven R. Schuster, MD, and Jason A. Goodin, MD.

8. Washington County Hospital, Hagerstown, MD; N=137; Principal Investigators: Catherine Ware, RN and Thomas Pianta, MPT.

9. Henry Ford Hospital, Detroit, MI; N=134; Principal Investigator: Scott Kaatz, DO, MSc; Study Coordinator: Stacy Ellsworth, RN, MSN, CCRC.

10. North Shore University Hospital, Manhasset, NY; N=114; Principal Investigator: David Rosenberg, MD, MPH; Study Coordinator: Sara Merwin, MPH.

11. United Hospital System, Kenosha, WI; N=100; Principal Investigators: Wendell Friedl, MD and Paula Carson, RN, MSN, CCRN.

12. Franklin Square Hospital, Baltimore, MD; N=93; Principal Investigator: James Welker, DO, CPI; Study Coordinator: Andrea Bowling, MS.
13. Presbyterian Hospital of Dallas, Dallas, TX; N=77; Principal Investigator: Tammy Chung, PharmD; Co-Investigators: Gary L. Weinstein, MD and Mark Feldman, MD; Study Coordinator: Susie Hubbard, RN, MSN.

14. Emory Crawford Long Hospital, Atlanta, GA; N= 76; Principal Investigator: Kenneth V. Leeper, Jr., MD; Study Coordinator: Ann Thron, RN, MSN, ACNP and Stacey Sadler Mitchell, RN, BSN.

15. The Denver Veterans Administration Medical Center, Denver, CO; N=62; Principal Investigator: Carolyn Welsh, MD and Melver Anderson, MD; Study Coordinator: Nancy G. Boyd, RN.

16. The University of Oklahoma Health Sciences Center and Veterans Affairs Medical Center, Oklahoma City, OK; N=60; Principal Investigator: Suman W. Rathbun, MD, MS; Study Coordinator: Penny L. Razo-Mosier, LPN, CCRP.

17. Florida Hospital, Orlando, FL; N=59; Principal Investigator: Janet W. Montgomery, PharmD.

18. University of California, Davis Medical Center, Sacramento, CA; N=41; Principal Investigator: Richard H. White, MD; Study Coordinators: Maya Juarez, Tina Tran, Chan Yuan Dong, Steven Lee, and Martina Garcia.
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21. Washington Hospital Center, Washington, DC; N=14; Principal Investigator: Andrew F. Shorr, MD; Study Coordinator: Nazli Bolouri, MD.

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25. Scottsdale Healthcare Shea, Scottsdale, AZ; N=3; Principal Investigator: A. Judson Tillinghast, MD; Study Coordinator: Annette Conly, RN, BSN, CCRC.