Implementing a Diagnostic Algorithm for Deep Venous Thrombosis

By Joel Handler, MD
Michael Hedderman, RN, MHP, CPHQ
Diana Davodi, CLS, ASCP, BS
Deborah Chantry, CLS, ASCP, BS
Curt Anderson, RT, CNMT
Jim Moore, RVT, RDMS, BA

Abstract

Context: An alternative to compression ultrasonography (CUS) examination of the lower extremity to diagnose deep venous thrombosis (DVT) is an equally effective and more cost-effective diagnostic algorithm using pretest clinical probability scoring, plasma D-dimer assay, and CUS.

Objective: To implement a DVT diagnostic algorithm in a Kaiser Permanente environment and assess patient outcomes and resource utilization.

Design: Prospective ten-month study in one area of 310,000 members surrounding one hospital.

Methods: A clinical probability score was determined for outpatients with symptoms suggestive of lower extremity DVT. Patients with a high score received immediate CUS. Patients with a low or moderate score had a rapid, quantitative, ELISA D-dimer assay; those with a positive assay result (>500 ng/mL) received CUS.

Main Outcome Measures: Venous thromboembolic events within three months of negative diagnostic evaluation for DVT. Change in utilization of CUS.

Results: Of 520 patients seen for possible DVT, 483 patients received a D-dimer assay; one false-negative D-dimer assay result and two false-negative CUS results (for patients with positive D-dimer assay) occurred. D-dimer negative predictive value was 99.5%. Utilization of CUS was reduced 47.6%.

Conclusion: A diagnostic algorithm using pretest clinical probability assessment, plasma D-dimer assay, and CUS can effectively diagnose lower-extremity DVT and can significantly reduce ultrasonography utilization.

Introduction

Epidemiologic data suggest that 0.48 to 1.6 in 1000 adults in North America and Europe develop venous thromboembolism each year[1,2] and that symptomatic pulmonary embolus occurs in approximately one third to one half of people who have untreated deep venous thrombosis (DVT).[3,4] However, clinical signs of DVT are nonspecific; signs such as calf pain and edema more commonly result from myofascial injury or venous insufficiency. Although compression ultrasonography (CUS) is highly sensitive and specific for diagnosing symptomatic proximal DVT, this test requires about 15 to 20 minutes of trained technician time per leg as well as follow-up interpretation by a radiologist. Less than 10% of these CUS examinations yielded results diagnostic of DVT in the referred outpatient population of the Orange County (California) Kaiser Permanente (KP) Service Area, a rate similar to that of other KP Southern California populations.

D-dimer, a product of cross-linked fibrin that has been degraded by plasmin, is a marker for intravascular thrombosis. In November 2001, we initiated a program using a diagnostic algorithm for DVT evaluation that incorporated pretest clinical probability scoring, plasma D-dimer determination (with rapid, quantitative, ELISA D-dimer assay), and CUS and then assessed patient outcome and resource utilization.

Methods
Patients

We studied prospectively all patients who were seen in the KP Orange County Service Area from November 2000 through September 2001 and for whom CUS was intended to rule out DVT. We excluded inpatients and skilled nursing facility residents for whom the false-positive rate of the sensitive D-dimer assay was believed to be prohibitively high, and patients already receiving warfarin, because sufficient data regarding D-dimer performance were lacking in this population. Patients were referred primarily from pri-

Joel Handler, MD, Department of Internal Medicine, Kaiser Permanente Medical Center, Anaheim, California.
Michael Hedderman, RN, MHP, CPHQ, Quality Management, Kaiser Permanente, Orange County, Anaheim, California.
Diana Davodi, CLS, ASCP, BS, Laboratory Supervisor, Kaiser Permanente Medical Center, Anaheim, California.
Deborah Chantry, CLS, ASCP, BS, Laboratory Department Administrator, Kaiser Permanente Medical Center, Anaheim, California.
Curt Anderson, RT, CNMT, Department of Radiology Administrator, Kaiser Permanente Medical Center, Anaheim, California.
Jim Moore, RVT, RDMS, BA, Department of Radiology/Ultrasonography, Kaiser Permanente Medical Center, Anaheim, California.

mary care clinics and the emergency department, but some patients were referred from subspecialty and surgery clinics and from the obstetrics/gynecology departments.

Setting

The KP Orange County Service Area consists of a central hospital to which all outpatient CUS requests are directed. Although the membership of 310,000 patients is served by 12 satellite clinics and each clinic has laboratory services, the specific D-dimer assay and CUS are performed only at the central hospital.

Pretest Probability Scale and D-dimer Assay

The Pretest Probability Scale for Deep Venous Thrombophlebitis was based on a validated instrument[5] with adaptations to enhance usability (Figure 1). The pretest probability sheet also incorporated key algorithmic instructions. Primary care physicians, registered nurse practitioners, and physician assistants received training via department meetings and e-mails. Probability scales were made available in all outpatient examination rooms and could be transmitted from the hospital laboratory electronically upon request. Key laboratory and ultrasonography personnel helped guide use of the diagnostic algorithm, and requests that did not follow process guidelines received individualized follow-up from a laboratory supervisor and a physician champion. In particular, providers were urged to use the algorithm only for patients who would otherwise receive CUS to diagnose DVT.

VIDAS D-dimer assay is a rapid, quantitative ELISA technique done using a compact automated immunoanalyzer (bioMerieux, Marcy-Etoile, France). A value of >500 ng/mL was considered a positive D-dimer assay result.

Diagnostic Algorithm

Before referring a study-eligible patient to the central hospital for CUS to diagnose DVT, the provider entered patient clinical data on the pretest probability scale (Figure 1). Patients with a high score received CUS im-mediately and were excluded from further analysis. Patients with a low or moderate score were given written instructional information and directed to the hospital laboratory for D-dimer assay; the medical assistant faxed the scoring sheet to the labora-

Figure 1. Scoring sheet used in study protocol to assess clinical probability for deep vein thrombosis (DVT)

Patient Name: _____

Patient MRN: _____

PRETEST PROBABILITY SCALE FOR DEEP VEIN THROMBOPHLEBITIS
(OUTPATIENTS ONLY)

Risk Factors: Score:

1. Active cancer: curative or palliative treatment initiated within 6 months 2

2. Prior history of idiopathic VTE (or known primary thrombophilia) 2

3. Paralysis, paresis, plaster immobilization of lower extremity
    within 12 weeks 1

4. Bedridden ≥ 3 days, or major surgery within 12 weeks 1

Clinical Signs:

5. Entire symptomatic leg swollen (asymptomatic leg is not swollen) 2

6. Calf swelling > 3 cm compared to asymptomatic leg 1

7. Pitting edema, greater in symptomatic leg 1

8. Alternative diagnosis as likely or greater than that of deep
    vein thrombosis (usually muscle pain or venous insufficiency) .... -2

NOTE: Tenderness or Homan's sign is nonspecific and receives <u>NO</u> points.

Total Score   _____

Affected Extremity(s):

_ Left Leg

_ Right Leg

High probability	≥ 3	Order compression ultrasound
Moderate probability	1-2	Order D-dimer
Low probability	≤ 0	Order D-dimer

- **Lab procedure ordering code for D-dimer (low and moderate probability):**
- **Ordering code for compression ultrasound (high probability only):**
- **For low and moderate risk patients, fax this form to Lakeview laboratory:**
- **Give attached instruction sheet (next page) to patient.**

Physician Name: _____

Pager Number: _____

Test results will be given to the patient by the laboratory technician

Figure 2. Algorithm for using probability scoring, D-dimer assay, and compression ultrasonography (CUS) for diagnosing DVT with summary of disposition of patients in study
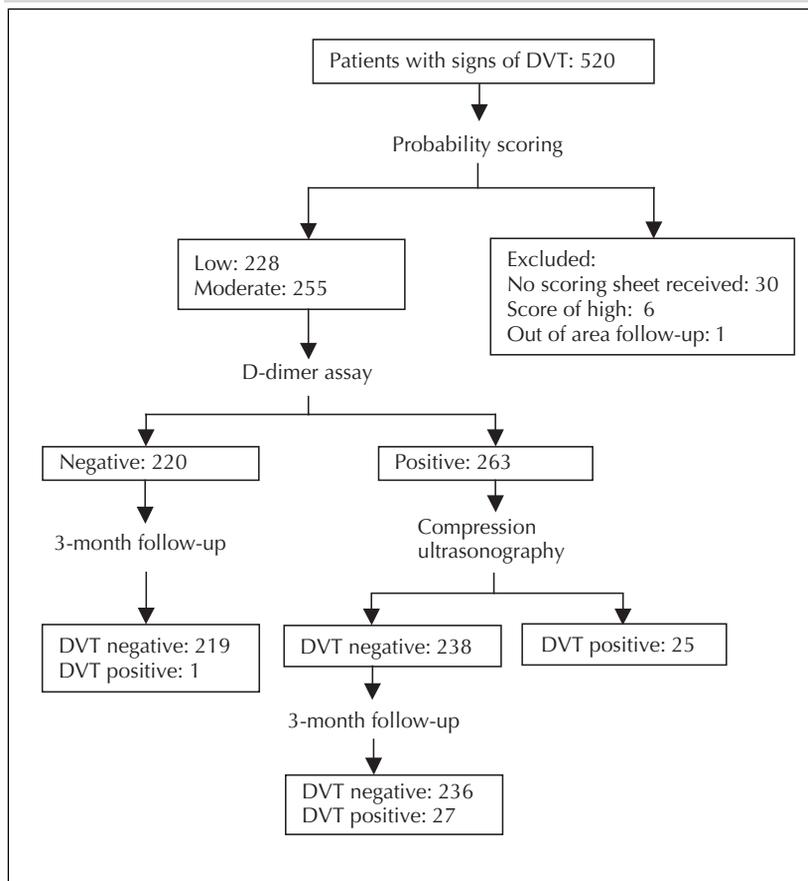
tory. A negative assay result led to the patient going home with directions to call their provider to discuss further diagnostic and treatment options, whereas a positive assay result led to the patient receiving expedited CUS. As with the system that preceded the present diagnostic algorithm, the ultrasound technician sent home patients with negative CUS results but paged the ordering provider (via the number entered onto the scoring sheet and passed on to the ultrasound department) in the event of a positive CUS result. Patients from outlying clinics who arrived late to the laboratory and who then had a positive D-dimer result had CUS done by a previously alerted ultrasonographer who stayed after hours.

Results

The flowchart (Figure 2) shows disposition of patients through use of the diagnostic algorithm. Excluded from analysis were six patients with high probability scores, 30 patients for whom no scoring sheet was received, and one patient whose follow-up occurred out of the study area. During the ten-month study, 483 patients received D-dimer assay, and DVT was diagnosed in 28 of these patients (DVT prevalence, 5.6%). During the three-month follow-up, one of the 220 negative D-dimer assay results proved false, and two patients with positive D-dimer results and negative initial CUS results had DVT diagnosed. D-dimer assay diagnostic performance is sum-

marized in Table 1. Negative predictive value of the D-dimer assay was 99.5%, and the positive predictive value was 9.8% with sensitivity of 96.3% and specificity of 47.9%.

The one false-negative D-dimer assay was for a patient who had received four months of warfarin therapy for a previous episode of idiopathic DVT, diagnosed by CUS before the current diagnostic algorithm was initiated. Two months after completing warfarin therapy and after initiation of the algorithm, the patient was seen again for leg pain. The pretest probability was scored inaccurately as zero despite the history of idiopathic DVT and presence of new leg findings, and D-dimer assay results were negative (415 ng/mL). Five days later, the patient returned and had thigh pain; physical examination showed tightness and tenderness without edema in this area, and CUS revealed thrombosis from the calf to the common femoral vein.

Two patients had positive D-dimer assay results and negative CUS results but had DVT diagnoses during the three-month follow-up period. One patient ought to have received a high probability score because of ongoing chemotherapy for adenocarcinoma from an unknown primary site but instead received a low score. At the initial visit and at a four-month follow-up visit, this patient's D-dimer assay results were positive (>1000 ng/mL) and CUS results were negative. The result of a second follow-up CUS (two months, 22 days after the first follow-up) was positive for DVT. The second patient was also misscored as having zero probability of DVT despite a recent history of idiopathic DVT and presence of new leg swelling. This patient's D-dimer assay result was positive (>1000 ng/mL), and the CUS result was negative for DVT.

Two months later, the result of follow-up CUS was positive for DVT.

Initiation of the diagnostic algorithm decreased utilization of CUS for diagnosing lower-extremity DVT by 47.6% (Figure 3). Significantly higher disease prevalence at moderate probability scores was found, thus validating the scoring format modified from the literature: of 228 patients with low scores, 7 (3.1%) had positive CUS results; of 255 patients with moderate scores, 19 (7.5%) had positive CUS results (p = .03). Ninety-eight patients with moderate pretest probability score had a negative D-dimer assay result.

Discussion
Diagnosing Deep Venous Thrombosis

Venography historically had been the standard procedure to rule out presence of lower-extremity DVT. A 1997 study by Hull[6] found recurrent DVT in two (1.3%) of 160 patients who had previously negative venography results. Because of the inherent difficulty of an invasive approach, and because technically adequate venograms cannot be obtained in 10% to 20% of subjects,[7] an alternative diagnostic strategy for detecting DVT in outpatients using serial CUS[8] became widely accepted. More recently, a trend toward single CUS has become popular.

A meta-analysis pooled results from three prospective studies which assessed serial CUS to diagnose DVT.[8] After receiving an initial negative CUS, anticoagulant therapy was withheld, and patients received one or two follow-up CUS examinations during seven or eight days. During three months of follow-up, venous thromboembolic complications developed in 15 (0.9%) of the 1753 pooled patients,[8] comparable with the percentage reported in the Hull study. In a study

by Cogo et al,[9] a single follow-up CUS at seven days was equally effective and safe compared with strategies using more frequent CUS.

Sluzewski et al found that none of 118 outpatients with a negative initial CUS result had a positive CUS result on day seven.[10] At three-month follow-up, DVT recurrence was 1.3%,[10] identical to recurrence rate of the Hull study group.[6] Although the sample size was small, some justification for a single CUS approach was provided.

Using phlebography as a reference standard, ultrasonography has 97% sensitivity and specificity for diagnosing proximal DVT in a symptomatic leg but is insensitive to calf thrombi, which may later propagate.[7] Variable propagation rates (converting negative CUS results to positive at follow-up examination) have been reported. One large study reported that 5.3% of patients who had negative initial CUS results had positive serial follow-up CUS results.[11] A second large study found that the yield of positive results at follow-up CUS was 3%,[9] and a third study found no positive CUS results at seven-day follow-up and 1.3% of CUS examinations positive at three-month follow-up.[10] These low propagation rates are supportive of a diagnostic process involving a single CUS to rule out DVT. There is also evidence for an alternative sequence after initial negative CUS, targeting a follow-up CUS only for patients with a positive D-dimer assay result.[12] The latter approach is less attractive because of the high rate of false positive assays.

A noninvasive algorithm to rule out DVT described by Perrier uses pretest clinical probability assessment combined with D-dimer assay.[13] Ultrasonography was not required for 27% of study patients when they had both a disease prob-

Table 1. D-dimer assay diagnostic performance in 483 patients with signs of deep venous thrombosis (DVT)[a]

D-dimer assay results	DVT positive[b]	DVT negative
Positive (n = 263)	27	237
Negative (n = 220)	1	219

[a] Patient pretest clinical probability scores were low (228) or moderate (255).

[b] Although clinical signs for all forms of venous thrombolic events were monitored during three-month follow-up, DVT was the only type of thrombolic event diagnosed in these patients.

ability score less than high and a negative D-dimer assay result; follow-up ultrasonography was also not required for patients who had a probability score less than high, a positive D-dimer assay result, and a negative CUS result.[13] Because of varying pretest disease probability, a negative D-dimer assay result alone does not provide sufficient information to withhold initial ultrasonography safely for all patients.[14] Likewise, without initial disease probability assessment, a patient with a positive D-dimer result and an initial negative ultrasound result probably still requires follow-up CUS examination.[15]

In the Perrier study that used VIDAS rapid quantitative ELISA D-dimer assay,[13] the negative predictive value of the assay was 99.3%. Using the same apparatus, made available to most KP Southern California Medical Centers via regional procurement, and replicating the Perrier algorithm, we achieved a negative predictive value of 99.5%. Of patients with signs of possible DVT, 47.6% did not receive CUS, because they each had a pretest clinical probability score less than high (low or moderate) and a negative D-dimer assay result.

In the Perrier study, only two patients with high pretest clinical probability and a positive D-dimer assay result had a negative CUS result, both of whom had positive venography results.[13] However, dis-

> **Venography historically had been the standard procedure to rule out presence of lower-extremity DVT.**

ease prevalence in the high-probability group for that study was 96%[13] compared with disease prevalence of 56%[16] and 75%[5] for high-probability groups in other studies. In our study, patients with high pretest clinical probability received immediate CUS but did not have mandatory follow-up CUS or venography if CUS result was negative. Although we could not precisely determine disease prevalence in our high-probability group because of small sample size, prevalence was estimated at 20%. Therefore, we were able to validate the Perrier algorithm for excluding the diagnosis of DVT with extreme safety by using a system incorporating pretest clinical probability assessment and VIDAS D-dimer assay.

Choosing the D-dimer Assay

For a low-disease-prevalence population, such as ours, the question arises as to whether a more rapid but less sensitive D-dimer assay would be equally safe to use. Our DVT prevalence of 5.8% is much lower than the 20% to 30% prevalence from other studies.[9,11,17] Compared with VIDAS D-dimer assay sensitivity of 96%, specificity of 75%,[17]

> **A more sensitive assay provides an additional safety margin.**

and the one hour required to run the test, the SimpliRED D-dimer assay (AGEN Biomedical Limited, Brisbane, Australia) has sensitivity of 86%, specificity of 57%,[18] and can be performed at the bedside in five minutes. A combination of pretest probability assessment and SimpliRED D-dimer assay has been used, with high sensitivity, to rule out DVT in a low-disease-prevalence population,[18-20] but not in a population with moderate disease prevalence.

We prefer the VIDAS D-dimer to the SimpliRED assay for the following reasons: 1) On the basis of the Perrier study results, we could safely eliminate initial CUS for the 98 patients in the moderate pretest probability group who had a negative D-dimer assay result. 2) Our false-positive assay rate was an acceptable 53.3%; cutting that rate in half by using the SimpliRED assay would not compensate for the increased number of moderate probability patients that would require CUS. 3) A more sensitive assay provides an additional safety margin.

Another family of D-dimer tests, the latex agglutination assay, has sensitivity (83%) and specificity (68%)

values that are closer to ELISA assay than to whole blood agglutination,[21] takes only 30 minutes to do, and has been validated to evaluate patients with intermediate probability of DVT.[16] However, the experience with latex agglutination assay has not been uniformly rewarding.[22]

Study Limitations

Results of this study may not be generalizable to patient populations with higher prevalence of DVT. Although disease prevalence was higher for patients in our moderate-probability group (7.5%) than in the low-probability group (3.1%) using our modified Wells' pretest probability score sheet, our moderate group prevalence was intermediate between Wells' low group (3%) and moderate group (17%).[5]

Our moderate-probability assessment yielded relatively low DVT incidence, but such an outcome might not be generalizable to other KP populations; for example, analysis of identical patient history evaluation forms found disparate prevalence of coronary disease for outpatients at KP Santa Clara compared with Stanford Palo Alto Clinics.[23]

Patient recruitment for this study occurred almost entirely from primary care and the emergency de-

Figure 3. Trend in utilization of CUS tests before and after DVT diagnostic algorithm was initiated
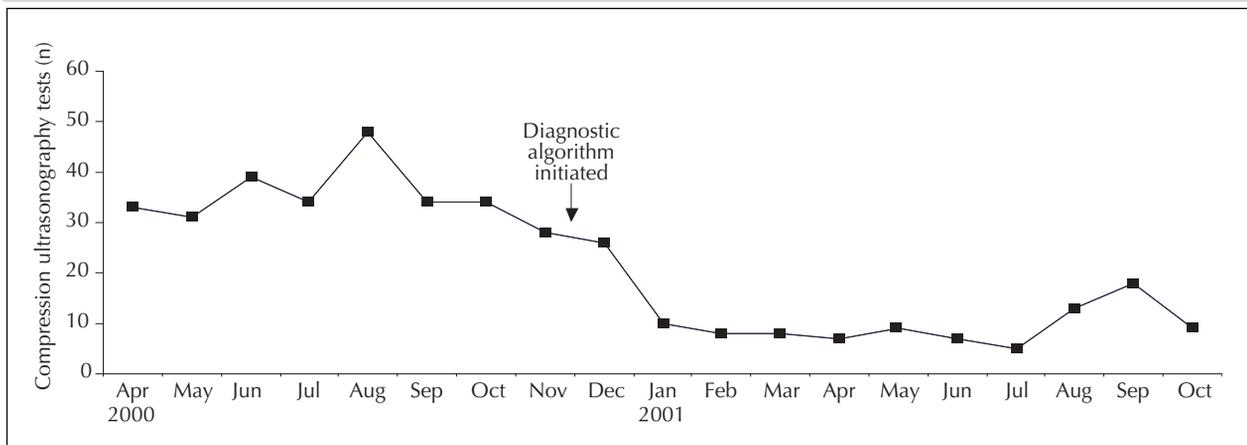
partment, and conclusions are therefore mostly pertinent to these groups of patients. Only two post-operative surgery clinic follow-up patients (one general surgery, one orthopedic) and three pregnant patients were included in this study, thereby preventing any assessment of efficacy for these subgroups.

A few patients were directed to have CUS without probability assessment or D-dimer assay, and their CUS results proved negative; inclusion of these patients in the analysis may have enhanced D-dimer negative predictive value and overall CUS reduction rate.

Recent Changes in the Algorithm

Data from a KP Orange County Service Area project assessing D-dimer levels in normal pregnancy showed that 3 (50%) of 6 women at less than 20 weeks' gestation had negative D-dimer assay (<500 ng/mL), a result consistent with our entire study population, but that only 3 (12%) of 25 women after 20 weeks' gestation had negative assay (JH, unpublished data, May, 2002). Because that observation confirmed data from bioMerieux that described a 3- to 4-fold rise in D-dimer levels during the course of normal pregnancy (which could lead to a high rate of false-positive results), we decided to exclude from our algorithm women who were more than 20 weeks pregnant.

No patients were referred directly from the oncology clinic during this study, although cancer patients referred from other outpatient settings were included. Because patients who are actively being treated for cancer are at high risk for DVT, we have now decided to exclude from the diagnostic algorithm any patients referred directly from the on-

cology clinic; these patients receive immediate CUS examination.

Effective Cost Management

After introduction of this algorithm, utilization of CUS was reduced 47.6%, without excessive D-dimer assay utilization. Our ultrasonographers and radiologists, who had been performing a large number of lower-extremity CUS examinations with negative results, were thankful for the change.

Our experience thus far has been that nearly 50% of eligible patients have been excluded from further evaluation. Given cost estimation of single-leg CUS of $200 and D-dimer assay performance of $70, prorated 12-month savings for our Orange County population was $41,000. Many areas perform bilateral CUS for all requisitions and higher savings would consequently be expected.

Because it would not take a significant increase in orders for D-dimer assay, which has a high false-positive rate, to lead to increased ultrasound requisitions, we instruct our providers to use the algorithm only when they consider ordering lower-extremity CUS to diagnose DVT. We also insist that the pretest probability scoring sheet is faxed to the central hospital laboratory for all such patients. Although studies show that low-probability patients can be identified whether the clinical assessment was empirical or done on the basis of prediction rules,[24] we prefer and have validated a user-friendly scoring sheet. Provider interviewing has shown that many patients who score at low or intermediate level would have otherwise been empirically rated as high probability. Feedback has led us to incorporate the coaching instruction that "tenderness, or Homan's sign, is nonspecific and receives no points."

Conclusion

Introduction of a new diagnostic algorithm for DVT led to 47.6% reduction in lower-extremity ultrasonography with a 99.5% negative predictive value during ten months of ongoing usage. This method incorporates user-friendly assessment of pretest disease probability along with rapid, quantitative D-dimer assay. ❖

References

1. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991 May;151(5):933-8.
2. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med 1992 Aug;232(2):155-60.
3. Barritt DW, Jordon SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. Lancet 1960 Jun 18;1:1309-12.
4. Huisman MV, Buller HR, ten Cate JW, et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. Chest 1989 Mar;95(3):498-502.
5. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997 Dec 20-27;350(9094):1795-8.
6. Hull R, Hirsh J, Sackett DL, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation 1981 Sep;64(3):622-5.
7. Weinmann EE, Salzman EW. Deep-

> **Our ultrasonographers and radiologists, who had been performing a large number of lower-extremity CUS examinations with negative results, were thankful for the change.**

vein thrombosis. N Engl J Med 1994 Dec 15;331(24):1630-41.

8. Kraaijenhagen RA, Lensing AW, Lijmer JG, et al. Diagnostic strategies for the management of patients with clinically suspected deep-vein thrombosis. Curr Opin Pulm Med 1997 Jul;3(4):268-74.

9. Cogo A, Lensing AW, Koopman MM, et al. Compressive ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. BMJ 1998 Jan 3;316(7124):17-20.

10. Sluzewski M, Koopman MM, Schuur KH, van Vroonhoven TJ, Ruijs JH. Influence of negative ultrasound findings on the management of in- and outpatients with suspected deep-vein thrombosis. Eur J Radiol 1991 Nov-Dec;13(3):174-7.

11. Heijboer H, Buller HR, Lensing AW, Turpie AG, Colly LP, ten Cate JW. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. N Engl J Med 1993 Nov 4;329(19):1365-9.

12. Ginsberg JS. Management of venous thromboembolism. N Engl J Med 1996 Dec 12;335(24):1816-28.

13. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999 Jan 16;353(9148):190-5.

14. Farrell S, Hayes T, Shaw M. A negative SimpliRED D-dimer assay result does not exclude the diagnosis of deep vein thrombosis or pulmonary embolus in emergency department patients. Ann Emerg Med 2000 Feb;35(2):121-5.

15. Bernardi E, Prandoni P, Lensing AW, et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multicentre Italian D-dimer Ultrasound Study Investigators Group. BMJ 1998 Oct 17;317(7165):1037-40.

16. Bates SM, Grand'Maison A, Johnston M, Naguit I, Kovacs MJ, Ginsberg JS. A latex D-dimer reliably excludes venous thromboembolism. Arch Intern Med 2001 Feb 12;161(3):447-53.

17. D'Angelo A, D'Alessandro G, Tomassini L, Pittet JL, Dupuy G, Crippa L. Evaluation of a new rapid quantitative D-dimer assay in patients with clinically suspected deep vein thrombosis. Thromb Haemost 1996 Mar;75(3):412-6.

18. Aschwanden M, Labs KH, Jeanneret C, Gehrig A, Jaeger KA. The value of rapid D-dimer testing combined with structured clinical evaluation for the diagnosis of deep vein thrombosis. J Vasc Surg 1999 Nov;30(5):929-35.

19. Lennox AF, Delis KT, Serunkuma S, Zarka ZA, Daskalopoulou SE, Nicolaides AN. Combination of a

clinical risk assessment score and rapid whole blood D-dimer testing in the diagnosis of deep vein thrombosis in symptomatic patients. J Vasc Surg 1999 Nov;30(5):794-803.

20. Kearon C, Gonsberg JS, Douketis J, et al. Management of suspected deep venous thrombosis in outpatients by using clinical assessment and D-dimer testing. Ann Intern Med 2001 Jul 17;135(2):108-11.

21. Bounameaux H, de Moerloose P, Perrier A, Reber G. Plasma measurement of D-dimer as diagnostic aid in suspected venous thromboembolism: an overview. Thromb Haemost 1994 Jan;71(1):1-6.

22. Kutinsky I, Blakley S, Roche V. Normal D-dimer levels in patients with pulmonary embolism. Arch Intern Med 1999 Jul 26;159(14):1569-72.

23. Sox HC Jr, Hickam DH, Marton KI, et al. Using the patient's history to estimate the probability of coronary artery disease: a comparison of primary care and referral practices [published erratum appears in Am J Med 1990 Oct;89(4):550]. Am J Med 1990 Jul;89(1):7-14.

24. Miron MJ, Perrier A, Bounameaux H. Clinical assessment of suspected deep vein thrombosis: comparison between a score and empirical assessment. J Intern Med 2000 Feb;247(2):249-54.

Expense

Poor quality is our most costly expense item.

— Dr Paul Fitzgibbon, one of the founding physicians of The Permanente Medical Group –
quoted in a report to the TPMG Executive Committee – 1964