Thrombophilia: What's a Practitioner to Do?

B. Gail Macik, Jacob H. Rand, and Barbara A. Konkle

Management of thrombophilia is an ever-changing field as new disorders are described and additional clinical experience accrues. This paper addresses three common management issues in the care of patients with thrombophilia. The first two topics are updates for common but perplexing hypercoagulable states and the last topic introduces a new option for optimal management of oral anticoagulant therapy. Dr. Jacob Rand updates and organizes the approach to patients with antiphospholipid syndrome. This syndrome is a common acquired thrombophilic state, but the diagnosis and treatment of patients remains a challenge. Dr. Rand outlines his diagnostic and treatment strategies based on the current understanding of this complicated syndrome. Dr. Barbara Konkle addresses the special concerns of managing women with thrombophilia. Hematologists are often asked to advise on the risks of hormonal therapy or pregnancy in a woman with a personal or family history of thrombosis or with an abnormal laboratory finding. Dr. Konkle reviews the available data on the risks of hormonal therapy and pregnancy in women with and without known underlying thrombophilic risk factors. In Section III, Dr. Gail Macik will discuss a new approach to warfarin management. Several instruments are now available for home prothrombin time (PT) monitoring. Self-testing and self management of warfarin are slowly emerging as reliable alternatives to traditional provider-based care and Dr. Macik reviews the instruments available and the results of studies that support this new management option.

I. Diagnosis and Treatment of the Antiphospholipid Syndrome

*Jacob H. Rand, MD**

The antiphospholipid (aPL) antibody syndrome is an acquired autoimmune thrombophilia in which vascular thrombosis and/or recurrent pregnancy losses occur in patients having laboratory evidence for antibodies against phospholipids or phospholipid-binding protein cofactors in their blood. Occasional patients present with "catastrophic aPL syndrome," marked by disseminated small and large vessel occlusions with end-organ damage. Additional clinical manifestations that have been reported in association with aPL antibodies include thrombocytopenia, livedo reticularis, necrotizing skin vasculitis, coronary and peripheral artery diseases, valvular heart disease, pulmonary hypertension, acute respiratory distress syndrome, hemorrhagic adrenal infarction and sensorineural hearing loss.[1]

The aPL antibody syndrome is classified as "primary" in the absence of another major autoimmune condition—such as systemic lupus erythematosus (SLE)—and "secondary" in the presence of such disorders. The elucidation of the syndrome and the development of diagnostic tests were derived from two laboratory anomalies: the "biological false-positive" serological test for syphilis (BFP-syphilis test),[2] and the "lupus anticoagulant (LA)" phenomenon.[3]

Diagnosis

Although criteria have been proposed to identify patients with "definite" aPL syndrome for research purposes,[4] the diagnosis of the aPL syndrome in clinical practice is frequently difficult because many patients exhibit isolated, transient or borderline laboratory abnormalities. The diagnosis of "equivocal" aPL syndrome presents major difficulties, especially regarding critical decisions on initiation and duration of anticoagulant therapy. [5] The prevalence of positive tests in the asymptomatic general population ranges between ~3-10%. In a prospective study of 2,132 consecutive Spanish patients with venous thromboembolism, 4.1% were found to have elevated anti-cardiolipin (aCL) antibodies (i.e., the same prevalence as the asymptomatic population).[6]

Currently, no single test is sufficient for diagnosis of this disorder. The panel of tests performed should include coagulation tests for LA, syphilis testing, and as-

* Hematology Division, Box 1079, Mount Sinai School of Medicine, 5 East 98th St, 10th Floor, New York NY 10029

says for antibodies against cardiolipin (aCL), phosphatidylserine (aPS) and $\beta_2$glycoprotein I (β2GPI).

Laboratory Tests

Lupus anticoagulant tests

One of the most perplexing features of the aPL syndrome is the frequent presence of the LA phenomenon in vitro.[7,8] LAs act by reducing the quantity of phospholipid available to support coagulation reactions, thereby prolonging the coagulation times. A number of different methods have been devised to detect the LA phenomenon (discussed below); all of these detect the inhibition of the phospholipid-dependent blood coagulation reactions.[3] Remarkably, these in vitro "anticoagulants" are not associated with bleeding problems unless other hemostatic defects are present (e.g. hypoprothrombinemia, thrombocytopenia, platelet function abnormalities, or specific inhibitors of blood coagulation factors).[3]

There is no agreement yet as to which specific test methods should be used for diagnosis of aPL. However, the following consensus criteria for defining the LA phenomenon have been published:[9] 1) the prolongation of a phospholipid-dependent coagulation test, 2) evidence of inhibitor activity in the test plasma determined by mixing tests with pooled normal plasma, and 3) confirmation that the inhibitory effect is due to blocking phospholipid-dependent coagulation (i.e., neutralization of the inhibitory effect by addition of excess phospholipids or by changing the source of phospholipid). LA tests are notoriously fickle, and even specialized laboratories frequently disagree as to the presence or absence of the LA effect in a given plasma.[10]

The LA is better than immunoassays for predicting the risk of thrombosis.[11] A meta-analysis of the risk for aPL-associated venous thromboembolism in individuals with aPL antibodies without underlying autoimmune disease or previous thrombosis followed for a 15 year period showed the mean odds ratios to be 1.6 for aCL antibodies, 3.2 for high titers of aCL, and 11.0 for LA.[12] The dilute Russell viper venom time (dRVVT) is considered to be one of the most sensitive LA tests.[13] The test is performed by adding Russell viper venom (RVV) to a sample containing diluted rabbit brain phospholipid and patient plasma. RVV directly activates coagulation factor X, leading to the formation of fibrin clot. LAs prolong the dRVVT by interfering with assembly of the prothrombinase complex. To ensure that prolongation of the clotting time is not due to a factor deficiency (i.e., liver disease or warfarin effect), a mixture of patient and control plasma is also tested. The presence of heparin may yield a falsely abnormal test unless measures are taken to neutralize the drug.

LAs are a frequent cause of prolonged aPTT tests.[14] The currently available reagents for performing aPTTs vary widely in their sensitivity to LAs. When the aPTT is prolonged and not "correctable" by mixture with normal plasma, the presence of an "anticoagulant" or "inhibitor" should be suspected. The LA is differentiated from inhibitors of specific coagulation factors (most commonly, factor VIII) and from anticoagulants such as heparin by using specific assays to exclude these possibilities. Alternatively, if the aPTT is normalized when an "LA-insensitive" aPTT reagent is used or when frozen washed platelets are added to the aPTT assay—the "platelet neutralization procedure"—then a LA effect is likely present. Incubating a mixture of patient and normal plasma at 37° C may help distinguish factor VIII antibodies (aPTT prolongs further after incubation) from LA (aPTT usually unaffected by incubation). In rare patients, both types of anticoagulants—LA and specific coagulation factor inhibitors—coexist. Specific coagulation factor assays using LA-insensitive phospholipids and specific inhibitor assays usually clarify this issue.

Several other LA tests exist that are used most commonly as secondary confirmatory tests. The kaolin clotting time is similar to the aPTT but uses a different activator (kaolin) and limited phospholipid concentrations to better detect interference from aPL antibodies. The tissue thromboplastin inhibition test is a prothrombin time assay done with diluted tissue factor-phospholipid complex, either rabbit brain or recombinant human.[15] The results are expressed as a ratio of the patient:control clotting times. Hexagonal phase phospholipids absorb the aPL antibodies present in the patient's plasma and thereby reversing the prolongation of clotting times due to LAs. The textarin/ecarin test depends on the different coagulation mechanisms initiated by two snake venoms; textarin activates prothrombin via a phospholipid dependent pathway and ecarin activates prothrombin in the absence of phospholipid.[16]

Immunoassays

Many patients are identified by elevated levels of aCL antibodies. There are data to suggest that high levels of aCL antibodies predict an increased risk of thrombosis. During a 10-year follow-up of asymptomatic patients with raised levels of aCL antibodies, about 50% of patients subsequently developed clinical manifestations of the syndrome.[17] Also, the presence of elevated titers of anticardiolipin antibodies six months after an episode of venous thromboembolism has been found to be predictive for an increased risk of recurrence and of death.[17] Women with IgM antibodies, IgG aCL antibodies lower than 20 IgG binding units and without an LA do not appear to be at risk for aPL-syndrome.[18] In contrast, women with an IgG aCL titer greater than 20 binding units or a positive LA are more likely to develop com-

plications.[18] aPL syndrome has been described primarily with elevated aCL IgG antibodies, but it also occurs with elevated IgM antibodies and infrequently with IgA antibodies.[19] aCL antibody isotype distributions may vary in different ethnic groups.[20] With respect to stroke, elevated anticardiolipin antibodies, IgG or IgM isotype, are a significant risk factor.[21]

Many individuals have aCL antibodies that are elevated in response to microbial infections and are not associated with risk for thrombotic complications. Patients with syphilis, Lyme disease, kala-azar, leptospirosis and other infections who have coincident thrombosis could be misdiagnosed with the aPL syndrome on the basis of elevated aCL antibodies alone. Antibodies induced by infection generally recognize phospholipids directly and not via protein cofactors such as β2GPI.

Theoretically, tests for antibodies against phosphatidylserine (located on the plasma membrane of cells) are more pathophysiologically relevant than antibodies against cardiolipin (located on intracellular membranes not exposed to plasma). Antibodies to phosphatidylserine (aPS) correlate more specifically with aPL syndrome than aCL antibodies.[22-24] The risk of stroke with elevated aPS antibodies is comparable to the risk with aCL antibodies.[21] It has been reported that a proprietary antiphospholipid assay, named the aPhL ELISA, may have improved specificity for the aPL syndrome, as compared to the aCL assay.[25]

β2GPI is believed to be the major protein cofactor for the aPL antibodies.[26] Despite their higher specificity for the aPL syndrome (98%) and high positive predictive value (~90%), β2GPI antibodies cannot be relied upon alone for the diagnosis because of their low sensitivity (40-50%).[27] The usefulness of testing for anti-β2GPI antibodies in patients with SLE has been questioned.[28]

Prothrombin is the second major cofactor for aPL antibodies. Although antiprothrombin antibodies occur in 30% of patients with SLE and were previously reported to be significantly associated with thrombosis,[29] a recent study has questioned their usefulness.[30] The presence of these antibodies correlates with hypoprothrombinemia and with thrombocytopenia.[31]

Treatment

Thrombosis associated with aPL

Physicians' opinions concerning treatments of aPL syndrome vary widely.[32] The available evidence indicates that the *acute* treatment for patients presenting with thrombosis associated with the aPL syndrome should be the same as for patients with other thrombotic etiologies. Patients with a pre-existing LA that interferes with aPTT who are treated with intravenous unfractionated heparin present a problem with anticoagulant monitoring. These patients can have their heparin concentrations estimated with an LA-insensitive aPTT reagents, with a specific heparin assay, or with the activated coagulation time test (ACT). Alternatively, they may be treated with weight-adjusted doses of a low-molecular weight heparin (LMWH).

Patients with spontaneous thromboembolism and the aPL syndrome should be treated with long-term oral anticoagulant therapy. Results of studies vary as to the recommended intensity of anticoagulant therapy. A retrospective study concluded that an international normalized ratio (INR) of $\geq$ 3.0 was necessary to protect patients from recurrence of venous or arterial thrombosis.[33] However, prospective studies on the treatment of venous thromboembolism conclude that an INR in the range of 2.0-3.0[11] or 2.0-2.85[34] is effective. In one retrospective study, 6/16 patients (37%) followed over 6-42 months developed deep venous thrombosis in spite of oral anticoagulation (INR 1.5-3.0).[35] A large prospective trial that includes randomized and observational arms, the Warfarin in Antiphospholipid Syndrome (WAPS) Study[36] is currently in progress to study optimal treatment. Other awaited studies include 1) PAPRE (Patients with Antiphospholipid antibodies; Prevent Recurrent Events) trial in which low intensity warfarin is compared to high intensity warfarin treatment; 2) WARRS-APASS (Warfarin-Aspirin Recurrent Stroke Study-AntiPhospholipid Antibody Stroke Study) in which warfarin is compared to aspirin treatment; and 3) the UK trial in primary prophylaxis in which treatment with low dose aspirin is compared to low dose aspirin plus low intensity warfarin for primary prevention of thrombosis in aPL patients with SLE or an adverse pregnancy history.[37]

Until conclusive data emerge, I recommend that patients with venous thromboembolism be anticoagulated to an INR of 2.0-3.0 and that patients with arterial thrombosis be targeted to an INR of 3.0. Patients who are being anticoagulated do not benefit from concurrent treatment with aspirin.[33] A high titer of aCL (> 30 U/ml) is not sufficient to justify prophylactic anticoagulation therapy in asymptomatic patients.[35] The same conclusion can probably be applied to patients with LAs who have not experienced thrombotic or embolic events. Anticoagulant therapy may be considered for the following groups of asymptomatic patients: patients with convincing family histories for thromboembolic complications of the aPL syndrome who themselves manifest significant laboratory abnormalities, patients with SLE who have significant aPL laboratory abnormalities, and rare patients with extremely marked laboratory abnormalities. The antimalarial drug hydroxychloroquine may be considered for treating patients with SLE who

have aPL antibodies but not thrombosis since there are data that indicate its having an antithrombotic effect in these patients.[38] Further studies are necessary to establish its effectiveness in this setting. Anticoagulant therapy is necessary for SLE patients with thrombosis.

Patients with the catastrophic aPL syndrome may be refractory to therapy with anticoagulation alone. A review of 50 cases showed that 70% of the patients recovered following management with the combination of anticoagulation, steroids, and plasmapheresis or intravenous gammaglobulins.[39]

Pregnancy Loss

Women with a history of three or more spontaneous pregnancy losses and evidence of aPL antibodies should be treated with a combination of low dose aspirin (75-81 mg daily) and unfractionated heparin (5,000 units subcutaneously every 12 hours).[40-42]

Treatment with LMWHs has been studied,[43-45] but these drugs are not approved by the FDA for treating pregnancy losses—i.e. their use would constitute an "off-label" treatment. The potential advantages of LMWH include once daily injections, a decreased rate of heparin-induced thrombocytopenia, and the possibility of decreased bone loss compared to unfractionated heparins.

Treatment should begin as soon as pregnancy is documented. Discontinuance for labor and delivery will vary depending upon whether spontaneous or scheduled delivery is planned. Complications such as thromboembolism, intrauterine growth retardation, oligohydramnios or fetal distress will require that the patient be anticoagulated until delivery. In uncomplicated situations, some clinicians discontinue heparin at 36 weeks gestation but may extend treatment with aspirin until about 1 week before term. In any case, prophylactic doses of heparin (whether unfractionated or LMWH) should be started about 4-6 hours after delivery if significant bleeding has ceased. Anticoagulant treatment should be continued at least until the patient is fully ambulatory; some clinicians continue to treat these patients for the period of the puerperium, i.e. an additional 6 weeks, to reduce the risk of thromboembolism. For patients who have a previous history of thromboembolism, full dose oral anticoagulant therapy is warranted for the puerperium.

Prophylactic anticoagulant treatment of women having low titer aCL antibodies, without a history of prior spontaneous abortion and without a history of thrombosis, is not warranted.[46] Nevertheless, many physicians generally treat these patients with low dose aspirin on empiric grounds since there is low risk to this treatment.

Although prednisone may improve the outcomes of pregnant patients with the aPL syndrome,[46,47] the benefit is questionable[48] and comes with significant toxicity.[46] Corticosteroids should only be considered for patients who are refractory to anticoagulant therapy, who have a severe immune thrombocytopenia, or who have a contraindication to heparin therapy. Treatment with the combination of prednisone and heparin should generally be avoided, since this combination will markedly increase the risk of osteopenia and of vertebral fractures.[49] While there have been several reports of successful treatment of aPL-associated recurrent pregnancy losses with intravenous immunoglobulin, only one small prospective randomized placebo-controlled trial was published, and it did not show any significant benefit.[50]

II. Thrombophilic States in Women—Special Concerns

*Barbara A. Konkle, MD**

In their lifetimes, women are likely to face situations associated with an increased risk of venous thromboembolism (VTE), be it through hormonal therapy or pregnancy. Hormones are used in various forms for contraception, postmenopausal hormone replacement, treatment of hormone-responsive cancers and, recently, breast cancer risk reduction. Additionally, in the past few years, underlying thrombophilic states have been linked to poor pregnancy outcomes. As hematologists we are often asked to advise on the risks of hormonal therapy or pregnancy in a patient with a personal or family history of thrombosis or with a laboratory finding associated with an increased risk. Although we need much more data in this area, we are asked now to answer questions such as: My sister has factor V Leiden and had a DVT on birth control pills; can I take birth control pills? I had a DVT with pregnancy 20 years ago; can I take hormone replacement therapy? I had a DVT with pregnancy 5 years ago, now they say I should take tamoxifen for my breast cancer, what should I do? I have factor V Leiden; will I have problems with pregnancy? To help answer these questions, we will review the currently available data on the risks of hormonal therapy and pregnancy in women with and without known underlying thrombophilic risk factors.

* Department of Hematology/Oncology, University of Pennsylvania, School of Medicine, PMC-MAB, Suite 103, 39th and Market Street, Philadelphia PA 19104

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Oral Contraceptives

Oral contraceptives and risk of VTE

Since their introduction, oral contraceptives (OCPs) have been associated with an increased incidence of thromboembolic events (reviewed in reference 1). First generation OCP included at least 50 mg of ethinyl estradiol or mestranol and a progestin, typically norethindrone. Because estrogen was suspected of increasing the risk for VTE, a hypothesis supported by later clinical studies, second generation OCP that contained less than 50 mg of estrogen and a new progestin, levonorgestrel, were introduced. Compared with non-OCP users, women who take second generation OCP still have an ~4-fold increased risk for venous thrombosis.[2]

More recently, the newest progestins (desogestrel, gestodene, and norgestimate) in combination with no more than 35 mg of ethinyl estradiol are available as a third generation of OCP (**Table 1**). Surprisingly, third generation OCPs appear to impart an approximately 2-fold increased risk of VTE over that seen in users of second generation products. This finding has been extremely controversial, although several studies have confirmed this risk.[3-6] Possible confounding variables include the fact that women at higher risk of thrombosis were given the third generation products, with the premise that these products would carry a lower risk of thrombosis, and that more first time OCP users were in the studies of third generation products and would be more likely to have thrombotic events in the study period than long time users of second generation OCP. However, when these and other variables were examined, the excess risk remained (reviewed in reference 7). Activated protein C (APC) resistance has been a laboratory finding in some women on OCP, although its causality in thrombotic risk is unproven. Interestingly, several studies have found increased APC resistance in women on third generation compared to second generation OCPs.[8-10]

OCP and risk of VTE in patients with thrombophilic risk factors

Other risk factors may interact with OCP to increase the risk of VTE. The increasing identification of common inherited thrombotic risk factors has allowed study of how they interact in the setting of OCP use. This is best illustrated by reports that women who are heterozygotes for the factor V Leiden mutation and use OCP have a considerably increased risk of thrombosis. In these women, the risk for thromboembolic events was found to be increased ~35-fold (95% CI: 7.8-154) in one study,[11] and 20-fold (95% CI: 4.29-4.3) in another.[12] This risk is further increased in users of third generation OCPs to ~50-fold compared with non-users without the mutation.[3] Antithrombin III, protein C and protein S deficiency are rare, and OCP use in these patients has been evaluated only in retrospective case review-type analyses. However, these deficiencies also appear to increase the risk of thrombosis with OCP use,[13-15] particularly ATIII deficiency. Recently, elevated factor VIII levels have been associated with an ~4-fold increased risk of venous thrombosis.[16-19] OCP use appears to be additive to this risk, with one study reporting an ~10-fold risk.[20]

The most recently described inherited thrombophilic risk factor, the prothrombin (factor II) variant (G20210A), is also associated with a further increased risk of VTE in women taking OCP. Martinelli, et al[12] found an ~16-fold increased risk of thrombosis in patients heterozygous for the prothrombin variant who also took OCP, compared to an ~6-fold increased risk for those not taking OCP. The prothrombin G20210A variant may carry a higher risk for cerebral vein thrombosis.[21] The use of OCP is independently associated with this disorder. In one study, for women who were taking OCP and had the prothrombin gene mutation (7 patients with cerebral vein thrombosis but only 1 control), the odds ratio for cerebral vein thrombosis rose to 149.3 (95% CI: 31-711). However, one must view this increased risk in light of the fact that cerebral vein thrombosis is a rare condition. The incidence of cerebral vein thrombosis is not precisely known, but it is much lower than the incidence of approximately 1 per 1000 persons per year reported for deep venous thrombosis (DVT).

Women with thrombophilia are more likely to develop VTE early in their course of OCP use. Among women with thrombophilia, the risk of developing deep vein thrombosis during the first six months of OCP use is increased 19-fold (95% CI: 1.9-175.7), and in the first year of use it is increased 11-fold (95% CI: 2.1-57.3), according to one study.[22] Patients and controls in this study were considered thrombophilic if they had protein C deficiency, protein S deficiency, antithrombin

Table 1. Progestins used in oral contraceptives (OCP), with selected OCP brands.

Second Generation

- Ethynodiol (*Demulin®, Zovia®)*
- Levonorgestrel (*Alesse®, Tri/Levlen®, Nordette®, Triphasil®)*
- Norethindrone (*Brevicon®, Micronor®*, Ortho-Novum®, Modicon®)*
- Norethindrone acetate (*Estrostep®, Loestrin®)*
- Norgestrel (*Lo/Ovral®, Ovrette®*)*

Third Generation

- Desogestrel (*Desogen®, Mircettte®)*
- Gestodene (*Not used in U.S.*)
- Norgestimate (*Ortho Tri-Cyclen®*)

*Progestin only pills

deficiency, or heterozygosity for the factor V Leiden mutation or prothrombin 20210 A mutation.

Postcoital contraception is accomplished using either higher dose combination ethinyl estradiol (100 μg) and levonorgestrel (0.5 mg) taken twice, 12 hours apart, within 72 hours of unprotected intercourse, or levonorgestrel only, 0.75 mg taken in a similar manner. While these products contain higher dosages of the hormones, they are taken for only 24 hours rather than over a long period of time. Using the UK general practice database, Vasilakis et al[23] reported a nested case control analysis of VTE and combination post-coital contraceptive use. This database contains information on 73,302 women < 50 years of age who collectively received 100,615 prescriptions for post-coital contraceptive sometime between 1/1/89 and 10/31/96. No women in this group were diagnosed with VTE during a 45-day interval after using post-coital contraceptive, suggesting that short-term post-coital contraceptive use is not associated with a substantially increased risk for developing VTE.

Progesterone-only contraceptives and VTE risk

In counseling women with underlying thrombophilia, alternatives for birth control that do not carry a risk of thrombosis, yet are highly effective, are needed. For many women, options are needed other than, or in addition to, barrier methods of contraception. Pregnancy carries its own risk of thrombosis in thrombophilic women, which must be considered. Alternatives include progesterone-only containing contraceptives. Do these products carry risks of thrombosis? A World Health Organization (WHO) sponsored study of VTE associated with progesterone only use evaluated 74,086 women in the UK general practice research database. A nested case control study of 59 women with idiopathic VTE found an overall 2.4 increased relative risk.[24] When they separated those who used progestins only for contraception the risk was 1.3 (95% CI: 0.3–6.8) compared to 5.3 (95% CI: 1.5–18.7) for those who used progestins for other reasons. Progestins are used at higher doses for indications other than contraception, raising the question of whether there is a dose-dependent effect. An alternative explanation is that the increased risk of thrombosis was due to the underlying reason for which they received progestin treatment. A WHO international, multicenter, case-control study of progesterone-only contraception found an adjusted odds ratio of 1.74 (95% CI: 0.76–3.99) for oral progestins (norgestrel, ethynodiol diacetate, lynestrenol, norethisterone) and of 2.19 (95% CI: 0.66–7.26) for injectable progestins (medroxyprogesterone acetate, norethisterone oenanthate).[25] There are no data on progesterone-releasing IUDs, although one study found no change in plasma coagulation or lipid parameters.[26] Thus the data we currently have suggests that, when used as contraception, progestins used alone carry a lower risk than estrogen containing compounds. Since progestin-only containing compounds are more likely to produce irregular bleeding, special monitoring for pregnancy may be needed if used in women on warfarin therapy.

Hormone Replacement Therapy

Hormone replacement therapy and risk of VTE

Hormone replacement therapy (HRT) is used in peri- and post-menopausal women for a number of indications including cardiovascular disease prevention, osteoporosis, and menopausal symptoms. Recent studies have questioned the role of estrogen therapy in cardiovascular disease treatment, prompting reconsideration of risk/benefit ratios when considering hormonal therapy. Conjugated equine estrogen is by far the most widely used estrogen in the United States and has the most epidemiological data available regarding its use.

At present it is thought that HRT increases the risk for VTE 2- to 3-fold compared to the that in non-users. Daly et al[27] found an adjusted odds ratio for VTE in current users of HRT compared with non-users (never-users and past users combined) of 3.5 (95% CI: 1.8-7.0). In that study no association was found with past use, and the risk of VTE appeared to be highest among short-term current users. Jick et al[28] reported a case-control study of women aged 50-74 years admitted to hospital for idiopathic VTE from the Group Health Cooperative of Puget Sound. They reported a relative risk of 3.6 (95% CI: 1.6-7.8) for current users of estrogens compared to non-users. Data from the Nurses Health study show that current users of postmenopausal hormones have an increased risk of primary pulmonary embolism of 2.1 (95% CI: 1.2-3.8),[29] but there is no association with past use. All studies, however, note that in this population of women the risk of DVT attributable to HRT remains low, and HRT use accounts for only a modest increase in morbidity.

The 2- to 3-fold increased relative risk for thromboembolic events reported in observational studies have been confirmed by clinical trial data from the Heart and Estrogen/Progestin Replacement Study (HERS).[30] In the HERS trial, confirmed venous thromboembolic events occurred in 34 women in the hormone group (6.3/1000 woman-years) and in 12 women in the placebo group (2.2/1000 woman-years). This translates to a relative hazard ratio of 2.89 for users of the estrogen/progestin combination. More women in the hormone group experienced deep venous thromboses (25 vs 8; $p = 0.004$) and pulmonary emboli (11 vs 4; $p = 0.08$). Two of the pulmonary emboli, both in the hormone group, were fatal. The question of whether the transdermal route of

administration is less thrombogenic is often raised. Studies have shown less change in coagulation parameters in women receiving HRT through the transdermal versus the oral route. However, no clinical study has confirmed a lower risk of thrombosis.

OCP and risk of VTE in patients with thrombophilic risk factors

Few studies are available regarding HRT in thrombophilic patients. One case controlled study of 66 women with HRT-associated VTE found a 13-fold increased risk in women with APC resistance on HRT, compared to unaffected women not on HRT.[31] This needs to be confirmed but suggests a risk similar to that seen with OCP in this setting.

Hormone Therapy for Breast Cancer Prevention and Treatment

Selective estrogen receptor modulators and risk of VTE

Selective estrogen receptor modulators (SERMs) are nonsteroidal antiestrogens. The potential value of SERMs is their combination of estrogenic and antiestrogenic activity, i.e., the ability to obtain antitumor activity in the breast without antiestrogenic side effects such as decreased bone density and increased risk of cardiovascular disease. Two agents (tamoxifen and raloxifene) are discussed further below, but a number of compounds are in development.

The estrogen agonist/antagonist tamoxifen is widely used in the management of breast cancer. Currently this drug is used in the adjuvant setting after local therapy for early stage breast cancer that is hormone receptor positive, in the treatment of metastatic breast cancer, and prophylactically in women deemed high risk for the development of invasive breast cancer. Several case reports and clinical trials have described deep vein thrombosis or pulmonary embolism in women with breast cancer being treated with tamoxifen.

Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) published in 1996 demonstrated a 1.7% VTE rate in tamoxifen treated women as compared to 0.4% in the placebo-treated group.[32] A large UK-based General Practice Research Database study concluded that the relative risk estimate for VTE for current tamoxifen exposure, as compared with never and past use as a reference group, was 7.1 (95% CI: 1.5-33).[33] In the NSABP B24 randomized trial, the use of tamoxifen after lumpectomy and radiation therapy for ductal carcinoma in situ was compared to placebo.[34] There were 891 women in the tamoxifen group with 9 deep venous thromboses (1%) and 2 pulmonary emboli (0.2%) reported. In the placebo arm containing 890 women, only 2 deep venous thromboses (0.2%) and 1 pulmonary embolus (0.1%) occurred.

A 10 year retrospective analysis of 2673 women with breast cancer in multicenter trials conducted by the Eastern Cooperative Oncology Group demonstrated an increase in VTE associated with tamoxifen therapy alone and a substantial increase in VTE in patients allocated to combined treatment with tamoxifen plus chemotherapy when these groups were compared to untreated controls or to patients who received chemotherapy alone.[35] Specifically, the data show that pre-menopausal patients who received chemotherapy and tamoxifen had more venous events than those who received chemotherapy without tamoxifen (2.8% vs 0.8%, $p = 0.03$). Postmenopausal patients who received tamoxifen and chemotherapy had more VTE than those who received tamoxifen alone (8.0% vs 2.3%, $p = 0.03$) or those who were observed (8.0% vs 0.4%, $p < 0.0001$). These findings and those from other studies suggest that chemotherapy contributes to thrombosis in patients with breast cancer.[35,37] Metastatic disease increases this risk further.

The Breast Cancer Prevention Trial[38] NSABP P-1 was a randomized clinical trial of 13,388 women undertaken to evaluate the effectiveness of tamoxifen in the prevention of breast cancer in women considered to be at increased risk for the disease. Again, the use of tamoxifen was associated with an increased risk of VTE. Pulmonary emboli were observed in almost three times as many women in the tamoxifen group as in the placebo group (RR = 3.01; 95% CI: 15-9.27). More women who received tamoxifen developed deep venous thromboses than did women who received placebo. The average annual rate per 1000 women treated was 1.34 versus 0.84 (RR = 1.60; 95% CI: 0.91-2.86).

Raloxifene hydrochloride is a SERM, chemically distinct from tamoxifen and estradiol that has antiestrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism and coagulation. In the Multiple Outcomes of Raloxifene Evaluation (MORE) study, the use of raloxifene increased the risk of VTE (RR = 3.1, 95% CI: 1.5-6.2).[39] By 40 months of follow-up, there was a higher rate of DVT (38 cases) and pulmonary embolus (17 cases) in the combined raloxifene groups (60 mg and 120 mg doses were used) than in the placebo groups (5 and 3 cases, respectively). One case of VTE occurred per 155 women treated with raloxifene for three years.

SERMS and thrombophilic risk factors

There are some data on the SERM-associated increased risk for VTE in the setting of thrombophilia, but at the present time these data are in the form of case reports.[40]

Thrombophilia and Pregnancy

Pregnancy and risk of VTE

Pregnancy is associated with a 5- to 6-fold increased risk of VTE.[23,41] A cohort analysis of the UK general practice database found an ~6-fold relative risk (95% CI: 1.2-33.5) of VTE in pregnancy.[23] In another study that evaluated retrospectively 62 objectively confirmed thrombotic events in 72,000 deliveries (51 DVT, 11 PE), the incidence of DVT was 0.71 and of PE was 0.15 per 1000 deliveries.[42] Most DVT in pregnancy involve the left leg (90%), and there are a greater proportion of ileofemoral DVT that may predispose to pulmonary embolism (reviewed in reference 43).

VTE during pregnancy in patients with thrombophilic risk factors

Thrombophilia appears to further increase the risk of VTE in pregnancy. Gerhardt et al[41] reported a multivariate analysis of a study of 119 women with VTE during pregnancy and the puerperium. They found a 6.9-fold (95% CI: 3.3-15.2) and 9.5-fold (95% CI: 2.1-66.7) relative risk of VTE in carriers of the factor V Leiden and the prothrombin mutations, respectively. Another study estimated the risk of VTE in women with factor V Leiden to be 1 in 400 to 500 pregnancies.[42] Because the number of patients affected by ATIII, protein C and protein S deficiency is small, studies involve fewer women and the results are variable, particularly for protein C and protein S. ATIII deficiency, probably because it carries such a strong risk for thrombosis, is associated with a high risk of thrombosis during the pregnancy (reviewed in reference 44). Studies report conflicting results regarding the time during pregnancy when the risk of thrombosis is highest, and some studies suggest that the post-partum period is the period of highest risk.[44,45]

Women with a prior history of thrombosis are often anticoagulated through subsequent pregnancies because of a presumed increased risk of recurrence. A recent study evaluates antepartum recurrence in 125 pregnant women with a single previous episode of VTE.[46] All women received anticoagulation for 4–6 weeks postpartum; thus, recurrences during that time could not be assessed. There were no antepartum recurrences in 45 women who had neither a laboratory finding of thrombophilia nor a history of idiopathic VTE. This included women with a history of hormonal or pregnancy-induced thrombosis who did not have a laboratory abnormality defined. Of the 51 women with thrombophilia or a history of an idiopathic event, 3 had antepartum recurrences. These findings suggest that anticoagulant therapy may be unnecessary in some circumstances, but further studies are needed to evaluate the best approach for thrombophilic women.

Thrombophilia and poor pregnancy outcomes

Several pregnancy complications, including recurrent miscarriage, intrauterine fetal growth retardation, intrauterine death and possibly abruption and eclampsia, are reported to be more common in women with thrombophilic defects (reviewed in reference 44). The association is strongest with second or third trimester fetal loss. Thrombophilia is not a risk factor for first trimester loss. Women with factor V Leiden or the prothrombin mutation are reported to have a 2- to 3-fold increased risk of late fetal loss.[47-50] This risk may be significantly greater in women with multiple thrombophilic defects. Whether anticoagulation will prevent any or all of these associated risks is unknown. One small study evaluated enoxaparin in 50 women with a history of fetal loss and thrombophilia. Compared to past pregnancies there was a higher success rate (84% vs 20%)[51] in treated women. Larger prospective studies are needed to confirm these findings.

Conclusion

When advising women on the use of hormonal therapy, one needs to keep in mind that the absolute risk of VTE may be low even if studies indicate a high relative risk if the incidence of VTE in the population of interest is low. In a young woman choosing OCP, the risk of VTE at baseline is ~1/10,000 women years. Even if the risk is increased 35- to 50-fold, the attributable risk to OCP is still low. For this reason screening for thrombophilic mutations, and particularly factor V Leiden, is not indicated in women without a personal or family history of thrombosis. While alternatives to products that carry an increased risk of thrombosis should be explored in women with thrombophilia, depending on the individual situation and risk/benefit ratio, patients or providers may still elect their use. Estimated relative risks with different hormonal exposure are shown in **Table 2**. Based on the available data, if a women with thrombophilia elects to use OCP, a second generation product, rather than a third generation product, should be used. In addition, the risk of VTE associated with all therapies is greater in the first few months of treatment, and the presence of an underlying thrombophilia appears to shorten the time to VTE further. Thus, a woman who has been on hormonal therapy for some time should receive different advice regarding her risk of VTE than a woman who is beginning hormonal therapy.

Counseling women regarding the use of HRT is, at present, very difficult. Questions have been raised regarding the benefit of HRT for cardiovascular health. In addition, effective treatment for osteoporosis using bisphosphanates further decreases the need for hormones to treat this complication. Still, women who do not tolerate bisphosphanates and women who have severe es-

Table 2. Estimated risks of venous thromboembolism (VTE) in patients exposed to hormonal therapy or pregnancy.*

	Baseline relative risk	20 year old with thrombophilia; est. events per 10,000 women-yrs**	60 year old with thrombophilia; est. events per 10,000 women-yrs**	***Risk in Factor V Leiden heterozygote	***Risk in Prothrombin 20210 heterozygote
2nd generation OCP	4	4		*20-35*	
3rd generation OCP	6 – 8	5-6		*50*	*16***
Pregnancy	5 - 6				
HRT	2 - 4		20-40	*13*	
Tamoxifen/Raloxifene	3 - 7		30-70		
Tamoxifen with adjuvant chemotherapy	*5 - 15*		*50-150*		

*Estimated from available literature. Numbers shown in italics are based on limited data.
**Calculated based on incidence of VTE in 20 year old of 1/10,000 and in 60 year old of 10/10,000
*** Risk compared to women without the mutation and not receiving hormonal therapy or pregnant
****Estimate based on combined 2nd and 3rd generation OCP data, but 73% of women enrolled in study were on 3rd generation OCP

trogen responsive peri- and post-menopausal symptoms remain candidates for HRT. Women should be educated regarding the known risks and they must be involved in making the treatment decision. Women with a history of a hormonally induced thrombosis are most likely at greatest risk of re-thrombosis if hormones are re-instituted. Laboratory data may be helpful in making the decision to start HRT in these women, particularly factor V Leiden testing, since considerable data exists regarding the additive VTE risk in patients with this disorder. Unfortunately, most data regarding VTE risk and HRT apply only to Caucasian women since other racial groups, such as African-American women, are underrepresented in existing studies. Also, the factor V Leiden and prothrombin mutations are uncommon in non-Caucasian women. If HRT is strongly indicated in a woman with significant risk of thrombosis, one could consider co-incident anticoagulation, taking into account the risks associated with that therapy.

Treatment of breast cancer with tamoxifen is a situation where the risk of thrombosis is usually less than the risk of recurrent of progressive breast cancer. Defining the baseline risk in this population is needed to optimize therapy and should be an area of research investigation. If a group with higher VTE risk can be defined, co-incident anticoagulation should be considered for the group. Whether low dose anticoagulation with warfarin (INR 1.5-2.0) to lower bleeding risk would be effective as prophylaxis is unknown.

In women with defined thrombophilic risk factors with or without a history of thrombosis who become pregnant, recommendations for DVT prophylaxis still need to be individualized considering the underlying risks and history of thrombosis. Most women with a known thrombophilic defect without a history of poor pregnancy outcomes can be reassured that their individual risk of pregnancy complications is low. However, women need to be aware that pregnancy problems are more common in this setting, and if problems do occur, therapeutic interventions may be indicated. In the future, more data in this area should be available to help guide treatment recommendations.

III. New Concepts in Management of Thrombophilia—Home Patient Monitoring

*B. Gail Macik, MD**

Thromboembolism is a major cause of morbidity and mortality. When a patient is stricken with a blood clot, the clinician is faced with two major questions: "Why did the patient clot?" and "How can further thrombosis be prevented?" Diagnosing the cause of thrombophilia is important epidemiologically and can help guide management decisions, but preventing further thrombosis is the key to improving or saving the patient's life. The long-term management of the thrombophilic patient remains a clinical challenge.

For the past 50 years, the oral anticoagulant warfarin has been used successfully to control pathologic thrombosis and decrease the morbid consequences of hypercoagulability. Managing warfarin, however, can be precarious due primarily to the narrow therapeutic window; that is, too much anticoagulation may result in bleeding and too little anticoagulation does not protect from re-thrombosis. Given the many factors that influence a patient's response to warfarin, strict monitoring

* Division of Hematology/Oncology, University of Virginia, HSC Box 800747, Jordan Hall Annex, Rm. 2352, Charlottesville VA 22908-0747

is required to maintain the therapeutic goal. [1] The Prothrombin time (PT) test is a quick, easy and reliable method for monitoring the anticoagulant effect of warfarin.

Despite the ready availability of the PT test in doctors offices and hospital laboratories, connecting the patient, the test, and the clinician together can be a formidable chore. For the thrombophilic patient anticipating a lifetime of anticoagulant treatment, practical and effective monitoring of warfarin is a serious concern. How can warfarin management be further improved? During the last decade, a new wave of portable, automated instruments emerged that produce rapid, easy, and accurate PT results on a drop of fingerstick blood. [2-4] In this paper, the concept of patient self-management using this new technology is explored as a means to improve further the safety and effectiveness of warfarin therapy. Available instruments are described, clinical trials that have addressed the feasibility of patient self-testing and self-management are presented, and the advantages of the process are discussed.

Home Prothrombin Time Monitors

Evaluating the instruments available for point-of-care (POC) and home PT testing can be a daunting experience. The ideal POC test system is rapid, accurate, easy to use, transportable and low cost. Additional desirable features include continuous electronic monitoring of the system, electronic quality control, and a compact design. For home testing, the instrument must be extremely easy to use with a limited number of steps. Fingerstick sampling allows for easy and rapid blood collection.

Knowing the limitations of the PT assay improves the chance of selecting an appropriate test system. When is a second not a second? When it is used to report the result of a coagulation test. Clotting time is determined by assay design not clinical condition. Simply put, clotting times are "man-made" and there is nothing "physiological" about a 12-second clot time. Results differ due to the sample type, reagent, or detection method used by an instrument.[5-8] POC testing must provide clinical information equivalent to that obtained with a standard laboratory method. Equality does not imply identical form or numerical result. The INR improves comparability; however, the INR fails to "normalize" whole blood results reliably, cannot overcome inherent differences in clot detection methods, and cannot completely offset the effect of reagents with markedly different sensitivities (ISI).[5-8] The take-home message, look for correlation between methods, but don't expect identical results when comparing a POC analyzer to the routine laboratory system or, for that matter, when comparing two different POC analyzers or two different laboratory methods.[8]

The instruments in this review are cleared by the Food and Drug Administration (FDA) for home use and are designated a waived test under the Clinical Laboratories Improvement Act (CLIA). To expedite inquiries regarding a product, **Table 3** lists the manufacturer contact information, current list price for the instrument and reagents, and product specifications. No specific endorsement or ranking of systems is implied. One instrument previously available, the AvoSure PT, is no longer being marketed and will not be discussed in this review.

CoaguChek™ S

The CoaguChek™ S PT monitoring system (Roche Diagnostics Corporation, Indianapolis, IN) is an updated version of the original CoaguChek™, which is no longer being marketed. The CoaguChek was cleared for home use, but as of the summer 2001 the company has elected not to market the instrument for this indication in the US. The instrument is used widely in Europe for home PT testing.[9-13] The system has onboard error control and electronic quality control (EQC). Blood (~10 μL) is ap-

Table 3. Home protrombin time (PT) monitors.

Company	Instrument	List Price	Specifications
International Technidyne Corp Edison, NJ 800-631-5945 www.itcmed.com	ProTime™	Instrument Kit* $1500 PT Cuvettes (25) $125	- 2.5 X 4.5 X 9 inches, 3 pounds - 6 minutes for test result - controls on test cartridge - 35 μL whole blood sample
LifeScan, Inc. Milpitas, CA 800-972-2699 www.lifescan.com	HARMONY™ INR Monitoring System	Instrument Kit* $1,200 INR Test Strips (5) $50	- 7.9 x 3.3 x 2.2 inches, 355 grams - 90 seconds - 2 levels of on-board quality controls - ≈20 μL whole blood sample
Roche Diagnostics Corp* Indianapolis, IN 800-329-8566 www.roche.com	CoaguChek™ S	N/A for home testing in the US. Pre-existing users of CoaguChek will still be supported	- 8.8 X 5.5 X 2.2 inches, 1.51 pounds - 1 minute for test result (QC separate) - electronic/wet control available -10 μL whole blood sample

*includes case, manual, etc
Abbreviations: INR, international normalized ratio; N/A, not available

plied to the sample well on the test strip and drawn by capillary action into a reaction chamber containing PT reagent. Paramagnetic iron particles in the reaction chamber move in response to a magnetic field. Changes in movement are detected optically and indicate clot formation. The CoaguChek S provides a test result in about one minute (without concurrent quality control). The CoaguChek S software is available in multiple languages and results are reported as INR, Quick % or ratio. Numerous studies find the imprecision to be between 3-6% and the representative correlation coefficients range from r = 0.9 to r = 0.97. Roche Diagnostics Corporation also markets a different POC technology, the CoaguChek DM (previously used in the Biotrack, Coumatrak, and CoaguChek Plus instruments). This technology is also used for home testing in Europe, but it is not FDA cleared for home use in the US.

ProTime® Microcoagulation System

The ProTime® microcoagulation analyzer (International Technidyne, Edison, New Jersey) is a slightly larger but easily portable POC instrument. Fresh whole blood is dropped into the sample cup on the disposable cuvette. An error message appears if the cup is inappropriately filled. The sample mixes with reagents as it is drawn into 5 parallel reaction channels. When the blood clots, it no longer flows past the optical detector and a clotting time is generated and reported as an INR or Quick %. The two outside channels serve as a high and low control, and the three middle channels test the patient's blood in triplicate and a mean value is reported. It takes approximately 6 minutes to generate a test result with simultaneous quality control tests.

The ProTime has been evaluated at many clinical sites including several comparison studies with laboratory and other POC devices and home testing studies.[2,3,7,14,15] A representative correlation coefficient compared to a laboratory standard is r = 0.93, and imprecision studies reveal coefficients of variation of 3-6%. As for other POC PT monitors, the INR result shows a positive bias (i.e, overestimation on the lower end of the therapeutic range) when compared to standard laboratory methods.[7] The integrated high and low controls are a clear advantage for the Pro Time. The relatively large volume of fresh whole blood required to fill the cuvette may provide some testing difficulty.

HARMONY™ INR Monitoring System

The newest instrument to enter the market for home protime monitoring is the HARMONY™ INR Monitoring System (LifeScan, Inc., Milpitas, CA). On September 5, 2001, the company announced that the FDA cleared the product for use by patients at home and by healthcare professionals in medical offices. The new system is expected to be available for purchase in 2002 by healthcare professionals and by prescription to patients that have completed a training program on the use of the device. The instrument is small (~8 x 2 x 3 inches) and weighs only 355 grams. A 20 μL whole blood sample is added to the test strip, the blood is drawn into the reaction cells and mixed with recombinant human thromboplastin reagent. The clot is detected by a change in light transmission through the blood sample. The result is ready in 90 seconds. There are two levels of quality control material integrated into the test strip, eliminating the need for separate quality control tests. The instrument has been compared to other POC PT monitors and found equivalent. Publications are pending and should be available soon.

Patient Self-Testing and Self-Management

Self-testing and self-management of warfarin are emerging as reliable alternatives to traditional provider-based care. The concept of home testing emerged almost simultaneously with the introduction of reliable, fingerstick, whole blood, PT monitors. As early as 1989, White et al[16] reported that 46 patients were randomized to either anticoagulation clinic care or home monitoring at time of discharge from the hospital. The self-monitoring group called the results into a physician who adjusted the warfarin dose. Patients in the self-monitoring group were in the therapeutic PT range 93% of the time compared to 75% for patients managed by the clinic ($p = 0.003$), and they were less likely to be in a subtherapeutic range during the follow-up period (6.3% vs. 23%; $p < 0.001$). Anderson et al [17] likewise reported on the successful use of a home testing program in a cohort of 40 patients over a period of 6 months to 2 years. The patients were instructed in the use of a whole blood monitor. They performed a PT at least every 2 weeks and, periodically, they had their blood drawn at their usual center within 4 hours of the home test so that matched testing could be performed. Using the criteria of no more than 0.4 INR difference identified by Lassen et al[18] as a meaningful descriptor of system reliability, 96% of the tests done by the patients agreed with the center's routine testing. Patient satisfaction was high, with 97% preferring the home test to routine testing and all study patients preferring to continue to use the home device. Several other studies compared home monitors to one or more laboratory systems and confirmed the feasibility and accuracy of home testing.[9,11-15,19,20]

Based on the success of glucose monitors and diabetic management, the next obvious step after patient self-testing is patient self-management of warfarin dose. Initially, critics argued that patients could never understand the nuances of warfarin management well enough to manage their own medication. Studies are proving oth-

erwise. Ansell et al reported a home management trial in a small cohort of patients in 1989[21] and then reported the follow-up of both the original patients and new enrollees in 1995.[22] Patients instructed in the use of the home monitor and given guidelines for dose adjustment were matched to control patients selected from the same anticoagulation clinic. Twenty of 23 patients enrolled in the study were followed over the course of 7.5 years. Self-management patients measured their PT more frequently. They demonstrated a therapeutic PT INR for 88.6% of the measurements compared to only 68% in the professionally managed group ($p < 0.001$). The control group had significantly more dose changes during the study period than the self-management group (28.2% vs 10.7%, $p < 0.001$). Only 3.1% of dose adjustments made by the home group did not follow guidelines. The study group suffered two major bleeding episodes, a peptic ulcer hemorrhage and a thigh hematoma, and each group had a single thromboembolism, deep venous thrombosis in the study group and myocardial infarction in control group. These small, early studies are very encouraging and helped spur greater interest in patient self-management.

Currently, over 40,000 patients in Europe and North America are using PT monitor at home. In Germany, especially, the concept of home management spread quickly, in part fueled by aggressive early and ongoing studies. Bernardo [23] reports that 83.1% of PT measurements performed by 216 self-management patients followed from 1986-1992 were within target therapeutic range with no serious adverse events reported. Horstkotte et al[24] studied the association between frequency of PT tests and time spent in the therapeutic range. Aggressive monitoring performed every 4 days resulted in 89% of the PT being in the therapeutic range compared to 48% for patients monitored by their private physician. This increased time in the therapeutic range correlated with a reduction in thromboembolic events (0.9% per year for frequent testing and 3.6% per year for routine testing). A prospective, controlled trial reported by Watzke et al[12] compared the quality of anticoagulation based on self-testing versus management by a physician directed anticoagulation clinic in 113 consecutive patients. The self-management group performed 4-fold more tests, made a significantly greater number of dose adjustments, and achieved an 84.5% success rate for keeping the PT in the target range compared to 73.8% for the control group. Complications included a severe gastrointestinal bleed (INR 2.9) and a transient ischemic attack (TIA; INR 2.6), both occurring at therapeutic INR levels in the self-management group. For additional studies, Jacobson[11] reviewed the international experience with patient self-management through 1998. Data from these and other warfarin home-management trials corroborate that patients can test, adjust dosage, and achieve therapeutic goals as well as or better than healthcare providers or an anticoagulation clinic.

Most self-management studies include patients with a variety of indications for warfarin therapy. Studies are now appearing that target particular patient populations. Marzinotto et al[25] report that whole blood PT INR monitoring is safe and accurate for children requiring oral anticoagulation therapy in either the outpatient clinic or home setting. The difficulty in obtaining repeated venous samples from this population of patients makes capillary sampling particularly attractive. Hasenkam et al[26] concluded that the self-testing and treatment quality is comparable or even better than conventional therapy in a selected population of patients with mechanical heart valves requiring strict management of anticoagulant therapy.

Advantages of Self-Management

Clinicians for years have relied on centralized testing and professional management of anticoagulation. The first clinical trials evaluating the feasibility of patient self-management suggest that a powerful new tool for improving anticoagulation care is now available. Are these instruments necessary for optimal patient care? Maybe not, but the list of advantages is growing.

A clear advantage to self-management is the improvement in control of anticoagulation manifested by the significantly higher percentage of PT results in the therapeutic range when compared to patients managed by anticoagulation clinics.[11-17,20-24] Safe and effective long-term anticoagulation requires strict maintenance of the target therapeutic range to avoid hemorrhagic or thrombotic complications.[27] As reviewed by Ansell and Hughes,[28] several studies show that, compared to routine medical care, coordinated care of patients improves clinical outcomes through greater achievement of therapeutic PT goals and a reduction in hemorrhage and thromboembolism. Although more studies are needed, patient self-management is proving to be at least as good if not better than specialized coordinated care, the current gold standard for anticoagulation management.

A second advantage is the ready availability of testing that allows for more frequent and clinically relevant test intervals for self-management patients. Preliminary evidence suggests that maintenance of the therapeutic range is related directly to the frequency of PT testing.[11-13,16,17,22-24] In almost all cases, patients perform self-testing every 1-2 weeks while, often due to inconvenience, patients managed by routine medical care are tested at intervals of 4-8 weeks. In addition, patients have the ability to test and react immediately to changes in medications, diet, concurrent illness or minor bleeding without having to schedule an appointment or travel to a labo-

ratory. Anticoagulant management is simplified for patients who need to stop or decrease anticoagulation for an invasive procedure. Future studies will need to confirm prospectively whether clinical benefit correlates with a decreased testing frequency, but early trials show an overwhelming advantage to more frequent monitoring.

Another advantage is the ability to use the same test system for more consistent PT results. As described by many investigators, the PT INR cannot eliminate differences between test systems.[5-8] Self-testing prevents variation in results that may be due solely to the method by which the test was done. This consistency in testing is particularly important when patients travel or change medical care location.

Patient satisfaction with self-management is uniformly high. Anderson et al[17] report that 97% of patients preferred to self-test at home. Sawicki et al[29] studied patient satisfaction based on quality of life scores performed for 179 patients initially and after 6 months of self-management. Patients showed statistically significant improvement in general treatment satisfaction (mean score 4.21 of a possible 6) compared to patients managed by routine care (mean score 2.96 out of a possible 6). Similarly, Kulinna et al[30] evaluated the changes in quality of life reported by 100 patients using self-testing for 6 months. In particular, patients cite independence in daily routine, ability to travel, decreased pain with sample collection, fewer visits to the doctors office or laboratory and improved sense of involvement and control of their medical condition as the leading advantages of self-management.[17,29,30]

What are the cost implications of instituting self-testing or self-management programs? POC tests usually cost more per test than similar automated, batch testing performed in the central laboratory. Cost effectiveness, however, must take into account the effect on all aspects of care. Does home testing lead to improved outcome and fewer complications? Does the patient spend less time in doctor's offices or hospital? Is patient acceptance high? Is compliance with anticoagulant regimens improved? Clinical trials are addressing the above issues and validating the perceived benefit of patient self-management.

Patient self-management is a promising new concept for improving the care of patients taking warfarin. Additional studies are needed to confirm whether the initial encouraging results can be repeated. For example, patients in the studies of self-management were carefully selected, and improvements in outcome may decrease if patient selection and instruction are less rigorously applied.[28] Patients currently testing at home may become less compliant as the novelty of self-management fades. However, advantages appear great enough to weather the transition from clinical trial to routine care.

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