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ARTICLE

Usefulness of factor V Leiden mutation testing in clinical practice

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We have investigated the clinical usefulness of the activated protein C resistance (APCR)/factor V Leiden mutation (FVL) test by sending out questionnaires to all Norwegian physicians who ordered these tests from our publicly funded service laboratory during a 3-month period, and of whom 70% (267/383) responded. Indications for testing, patient follow-up, the use of APCR *versus* FVL tests and differences in practice between hospital doctors and GPs were examined. We found that 46% of the tests were predictive, ordered for risk assessment in healthy individuals with no previous history of venous thromboembolism (VTE). Among these, 42% of the tests were taken on the initiative of the patient and 24% were screening tests before prescription of oral contraceptives. In total, 54% of the tests were classified as diagnostic, among which 42% were ordered owing to a previous history of VTE and 22% to a history of brain stroke or myocardial infarction. The prevalence of FVL heterozygotes was not significantly different between the predictive and diagnostic test groups, that is, 26 and 20%, respectively. Only the predictive tests influenced patient follow-up. Here, the physician's advice to patients depended on the test result. In general, the clinical usefulness of APCR/FVL testing was low. Many tests were performed on unsubstantiated or vague indications. Furthermore, normal test results led to unwarranted refrain from giving advice about antithrombotic measures, leading to potential harm to the patient.
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INTRODUCTION

The clinical utility of tests for common genetic variants associated with slightly increased risk for multi-factorial disorders such as type II diabetes[1] and atherosclerosis[2] has been questioned.[3] Among such tests, the currently most commonly used test is the activated protein C resistance (APCR) test or factor V Leiden mutation DNA (FVL) test. Clinical utility refers to the likelihood that a test will lead to improved outcome for the patient tested.[3] As the presence of APCR (measured by the second generation APCR assay) is almost always because of the FVL, these tests are equivalent in a population with high FVL mutation prevalence, regardless of the test being performed on the biochemical or DNA level.[4] Both tests identify heterozygotes and homozygotes for the FVL mutation. About 3–8% of subjects in Caucasian populations are heterozygous for the FVL mutation and ~0.2% are FVL homozygous.[4] In our laboratory, FVL heterozygosity was found in 8.5% of anonymous blood samples from 200 healthy blood donors (unpublished data). The heterozygotes have a fivefold and the homozygotes an 18-fold increased relative risk for venous thromboembolism (VTE).[5,6] The risk for VTE is determined by several known genetic factors (for example, the FVL and factor II prothrombin 20210G>A mutations, protein C, protein S and antithrombin deficiency), as well as by age, obesity, immobility, anti-phospholipid antibodies, infections, malignancies and smoking.

The annual incidence of VTE is about 1 per 1000 individuals,[7,8] which corresponds to a lifetime risk of about 8%. FVL was found in only 20% of patients having a first-time VTE occurrence, and the majority of heterozygous individuals identified with FVL will never suffer from VTE.[9–11] Guidelines for investigation and management of patients with thrombophilia in the presence or absence of VTE have been developed.[12–15] These guidelines have been established despite limited knowledge on the clinical utility of APCR/FVL testing.[16–18] The different guidelines make recommendations, but there is no real consensus on the management and follow-up of asymptomatic and healthy FVL heterozygotes or of VTE patients found to be FVL heterozygotes.[12–15] Because of this situation, we wanted to assess the usefulness of such testing in current clinical practice by exploring the physicians' indications for testing, including a distinction between predictive and diagnostic tests, and the practical consequences of the results for patient treatment and follow-up. In our study, we did not examine patient outcomes. We have examined doctor's behaviour when requesting the test and when making use of the test result in decision making. Accordingly, we have used the term *clinical usefulness* of FVL testing instead of the more strictly defined term clinical utility. In a recent study, Hindorff *et al*[18] have modelled the results of such an assessment on hypothetical patients being treated by GPs. As the authors point out, their results may not reflect the actual behaviour. As our study is on the actual behaviour of clinicians requesting APCR/FVL tests, it gives an indication of the validity of their results.

SUBJECTS AND METHODS

During a 3-month period in 2006, all physicians, both hospital doctors and GPs, who ordered APCR, FVL or both tests from the Haukeland University Hospital were mailed a questionnaire. One questionnaire was mailed per patient sample received. Accordingly, one physician could receive several

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questionnaires. The questionnaire was sent out 8 weeks after the result of the test had been forwarded. This was considered a reasonable time for the physician to have decided on the follow-up of the patient subsequent to the test result. In total, 383 questionnaires were mailed to 316 physicians. The majority of physicians (291 or 92%) received one or two questionnaires. No physician received more than six questionnaires.

The questionnaire had nine multiple-choice questions and took 10 min to complete. The physicians were asked to choose between alternatives and to specify some of the answers in open text boxes. Questions 1–4 addressed indications for testing (for example, patient history of VTE, family history of VTE, family member with FVL, screening before oral contraceptives etc.), ordering details (initiated by doctor or patient) and explored the consequences of the test result regarding the patient follow-up. Question 5 asked about the information given to the patient regarding the test, for example, oral or written, the duration of oral information (in minutes) and whether the information was given before the test or after receiving the test result. Question 6 asked the doctor to estimate the patient's risk for VTEs based on the test result and the doctor's general knowledge of the patient. Questions 7, 8 and 9 collected information about the physician and his/her relationship with the patient, for example, hospital doctor or GP, familiar patient or new patient.

The laboratory analyses for APCR and FVL were performed by two different departments at the Haukeland University Hospital that use different request forms. APC resistance was measured at the Laboratory of Clinical Biochemistry, using the COATEST APC Resistance V kit (Chromogenix, Orangeburg, NY, USA) in combination with the STA-R analyzer (Diagnostico Stago, Asnieres sur Seine, France), and the procedure was performed as described by the manufacturer. The test for the FVL was performed at the Center for Medical Genetics and Molecular Medicine by allele discrimination, using real-time PCR with the TaqMan probe assay (Applied Biosystems Inc., Foster City, CA, USA).

Statistical analyses were performed using descriptive statistics in SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). Differences between groups were assessed using a χ^2-test and a *P*-value less than 0.01 indicated statistical significance.

RESULTS

From the 354 doctors who were contacted, 70% (267/383) of the questionnaires were completed and returned. The distribution of responders was representative of the total number of physicians who received questionnaires, in terms of gender, frequency of test ordering and test results. In total, 55% of the responders were GP's, 42% were hospital doctors and 3% were private practice gynaecologists. Of the 267 responders, 78% ordered APCR only, 9% ordered FVL only and 13% ordered both tests (Table 1). In the latter case, the correspondence between the biochemical APCR and the DNA-based FVL test results was 100%. Two-thirds (66%) of the individuals tested were women (mean age, 38 years) and one-third (34%) were men (mean age, 49 years). Overall, 77% of the test results were normal, 23% were found to be FVL heterozygotes and only one was a FVL homozygote (Table 1).

The indication for ordering a test was categorized either as diagnostic test (n=144; 54% of total), that is, the test was used to identify the cause of the patient's disease, or as predictive test (n=123; 46% of total), that is, the test was used to evaluate the risk of thrombosis in an apparently healthy patient (Table 2). The prevalence of FVL heterozygotes was 26% in the predictive test group and 20% in the diagnostic test group (Table 2).

The choice of type of test (APCR or FVL) was significantly different ($P<0.01$) between predictive and diagnostic tests. The APCR tests were usually diagnostic (125/208; 60%), whereas the FVL tests were usually predictive (18/24; 75%). Almost all diagnostic tests (136/144; 94%) were carried out on the initiative of the physician, in contrast to the predictive tests (70/121; 58%), which were more often initiated by the patients.

Among the diagnostic tests (n=144), 'history of VTE' was the most common indication (42%), followed by 'history of myocardial infarction or stroke' (22%) and 'early pregnancy failure and intrauterine foetal death' (14%). The predictive tests (n=123) were mainly requested because of a 'family history of VTE' (58%), followed by 'family member has Leiden mutation' (33%) and 'screening before oral contraceptives' (25%). In the group 'family member has Leiden mutation', half of the cases (19/41; 46%) had no additional indication for taking the test.

Hospital doctors and GP's had significantly different reasons for using the tests ($P<0.01$): hospital doctors ordered more diagnostic (97/114; 85%) than predictive (17/114; 15%) tests, whereas GP's ordered fewer diagnostic (47/153; 30%) than predictive tests (106/153; 70%) (Table 3). Before carrying out the APCR/FVL test, half of the patients (129/259; 50%, 8 cases missing) had been given oral (87%) or written (13%) information. Oral information was brief, usually <10 min (84%). Such information was significantly ($P<0.01$) more likely to have been given if the test was predictive (78/116; 67%) as compared with diagnostic test (51/143; 36%) (data not shown in Tables). Only one patient (an FVL heterozygote) was referred to genetic counselling.

It was of particular interest to register the clinical consequences, if any, of the test results. The majority (142/205; 69%) of normal test results did not have consequences for patient treatment or follow-up, including advice about antithrombotic measures (Table 4). For FVL heterozygotes, the three most frequently reported clinical actions were: special advice (36%), that is, supportive stockings and ample water intake on long flights and observation if protracted bed rest; general advice (33%), that is, stop smoking, reduce weight, healthy nutrition, enough exercise; and no action (30%). General advice was given to FVL heterozygotes regardless of the choice of test (APCR or FVL). In contrast, special advice was only given in 15% of cases with a positive APCR test, whereas 67% of FVL-positive cases, a significantly higher percentage ($P<0.01$), received such advice.

For the predictive tests, the physician's choice of follow-up differed significantly ($P<0.01$) between heterozygotes and patients with a normal test result: general advice was given to 33% of heterozygotes, but only to 12% of patients with a normal test result. Special advice was given to 36% of heterozygotes in contrast to 5% of normal cases. In 13% of positive cases, the physician recommended family investigation of APCR/FVL, whereas only 1% of normal cases were given similar advice. In 23% of positive cases, the physician referred the patient to a specialist or ordered new analyses, whereas this happened in only 6% of normal cases.

Table 1 APCR/FVL test results

	Only APCR (n=*208*)	*Only FVL* (n=*24*)[a]	*Both tests* (n=*35*)	*Total* (n=*267*)[a]
Normal	87% (181)	46% (11)	37% (13)	77% (205)
Heterozygote	13% (27)	59% (12)	63% (22)	23% (61)

[a]One FVL homozygote not listed.

Table 2 Test results of diagnostic *versus* predictive tests

	Diagnostic test (n=*143*)[a]	*Predictive test* (n=*123*)	*Total* (n=*267*)[a]
Normal	80% (114)	74% (91)	77% (205)
FVL heterozygote	20% (29)	26% (32)	23% (61)

[a]One FVL homozygote not listed.

Table 3 Choice of analysis (APCR, FVL or both)

Type of analysis (APCR/FVL/both)	*Respondents* (n=*267*)		
	GPs+gynaecologists[a] (n=*153*)	*Hospital doctors* (n=*114*)	*Combined* (n=*267*)
Diagnostic tests (n=144; 54%)			
Only APCR	22% (34)	80% (91)	47% (125)
Only FVL	3% (4)	2% (2)	2% (6)
Both	6% (9)	4% (4)	5% (13)
Predictive tests (n=123; 46%)			
Only APCR	46% (71)	11 % (12)	31% (83)
Only FVL	11% (17)	1% (1)	7% (18)
Both	12% (18)	4% (4)	8% (22)

[a]GPs and private practice gynaecologists merged.

Table 4 Reported choice of follow-up, sorted by test results (normal and heterozygote)

Patient follow-up	*Test result APCR/FVL* (n=*266*)[a]		
	Normal (n=*205*)	*Heterozygote* (n=*61*)	*Total* (n=*266*)[a]
Drug treatment was initiated, prolonged or stopped	10% (20)	23% (14)	13% (34)
Did not prescribe oral contraceptive	2% (4)	8% (5)	3% (9)
General advice (stop smoking, reduce weight, nutrition and exercise)	12% (25)	33% (20)	17% (45)
Special advice (supportive stockings and ample water intake on long flights and observation if protracted bed rest)	5% (10)	36% (22)	12% (32)
Advised family investigation of APCR/FVL	1% (2)	13% (8)	4% (10)
Referred to specialist or ordered new analyses	6% (12)	23.0% (14)	10% (26)
No action	69% (142)	30% (18)	60% (160)
Others	11% (22)	21% (13)	13% (35)

[a]One homozygote not listed.

Testing on account of VTE in the patient or the family

A total of 60 patients in the survey had been treated for VTE (that is, diagnostic tests), of whom 45 (75%) had normal test results, 14 (23%) were FVL heterozygotes and one was a FVL homozygote (not included) (Table 4). A total of 70 individuals had a 'family history of VTE' (that is, predictive tests), of whom 55 (79%) had a normal test result and 15 (21%) were FVL heterozygotes.

Predictive tests with normal results, when the indication was 'family history of VTE', had in most cases (35/55; 64%) no clinical consequences, that is, the doctor reported 'no action' for follow-up. Only 12 of the 55 subjects (22%) with a family history of VTE, but with a normal test result, were given general advice and/or special advice. If, on the other hand, an individual turned out to be a heterozygous FVL carrier, the doctor reported 'no action' only in 2 of 13 cases. When there was a family history of VTE and the individual tested turned out to be a FVL heterozygote, general and/or special advice was given significantly more often (12/15) ($P<0.01$).

We also decided to examine whether the test result influenced the antithrombotic treatment in the VTE patient group. In 9 of 14 cases in which VTE patients were found to be FVL heterozygous, the physician answered that the drug therapy was either initiated or prolonged after the test result was received. However, more detailed analysis of the data from the open text boxes in the questionnaires showed that the type of drug (low-molecular-weight heparin or warfarin) and the decision to initiate drug treatment was quite unaffected by the test result. The same treatment would have been given if the test result had been normal or if no test had been carried out.

Testing in relation to the use of oral contraceptives

One-fourth of the predictive tests (31/123; 25%) were ordered for risk assessment in women before oral contraceptive use. In only half of these cases (15/31; 48%), there was also a family history of VTE. In this latter group, only a positive test result (found in 2/15) led to advise against oral contraceptives. Almost half of APCR/FVL tests (13/31; 42%) in relation to oral contraceptives had no additional indications, that is, the tests were taken only because of oral contraceptive use. A total of 5 of the 13 individuals tested were FVL heterozygotes, but only one was advised against oral contraceptives.

Testing on account of cerebrovascular disease (stroke) or myocardial infarction

A total of 22% of diagnostic APCR/FVL tests were ordered owing to a history of either stroke or myocardial infarction. The test result did not affect patient treatment or follow-up. A few FVL heterozygotes were given general advice.

DISCUSSION

Almost half of the APCR/FVL tests were carried out on healthy individuals with no family history of VTE. Such susceptibility testing is controversial and without proven clinical utility. Although guidelines for thrombophilia and FVL testing exist, there is no consensus regarding special management and follow-up of asymptomatic and healthy FVL heterozygotes.[12–15] Long-term antithrombotic therapy is not recommended, and the antithrombotic prophylaxis related to surgery is not different from what all patients should receive.

The above-mentioned general advice (stop smoking, reduce weight, healthy nutrition and enough exercise) and special advice (supportive stockings and ample water intake on long flights and observation if protracted bed rest), chosen by the majority of doctors for follow-up, are not mentioned in the guidelines. This advice should undoubtedly be given, regardless of the FVL mutation status. Still, only 22% of individuals with a family history of VTE and a normal test result received such advice, even though a normal test result does not eliminate the risk for VTE. In a recent study, Bezemer *et al*[19] states that in clinical practice, family history may be more useful for risk assessment than thrombophilia testing. Our results suggest that normal test results may give false assurance to doctors as well as patients, refraining doctors from giving health advice that may be warranted.

It is recommended that screening of family members for a FVL mutation should only be carried out if there is a strong family history of VTE at relatively young age (for example, <50 years), such as, a first-degree relative with proven symptomatic thrombophilia.[12,14] A major reason for this advice is that there is only a two- to threefold increased risk for VTE in first-degree relatives of VTE patients and the FVL mutation status is not helpful for further risk stratification.[20] The risk for VTE in relatives of asymptomatic FVL heterozygotes is even lower. None of the genetic markers for VTE (FVL and others) have been associated with highly increased risk of VTE in the absence of a first-degree family history of VTE and/or own history of a previous VTE event.[21]

Factor V Leiden mutation testing is not recommended as a routine test before or during oral contraceptive use or hormone replacement therapy in the absence of additional indications.[13] However, the age and gender bias in our study (2/3 of the individuals tested were women, and the mean age for females were 38 years *versus* 49 years for males) could be explained by many tests in relation to gynaecological problems, including obstetrical complications. In our survey, 42% of APCR/FVL tests in relation to oral contraceptives had no additional indications, that is, the tests were taken only because of oral contraceptive use. Even though 5 of the 13 individuals tested were FVL heterozygotes, only one was advised against oral contraceptives. In 13 other oral contraceptive cases, the FVL test was normal, but a family history of VTE existed. In these cases, the advice against oral contraceptives depended on the FVL mutation status; none of the women with normal APCR/FVL test result were advised against oral contraceptives, even though a family history of VTE is an independent and more important risk factor.

Testing for FVL is recommended in patients with unusual or more severe types of VTE, for example, recurrent VTEs, VTE <50 years or VTEs without provoking factors or at unusual anatomic sites.[12,13] The cost-effectiveness of testing patients after a first VTE episode has been questioned,[9] especially because a positive FVL test after one VTE episode does not change the recommended VTE therapy.[12,20,21]

It is noteworthy that 22% of the diagnostic FVL tests were performed because of arterial thrombosis in the patient (brain stroke or myocardial infarction). FVL is only a known risk factor for VTE, and testing in relation to arterial thrombosis is not recommended. This discrepancy indicates that adequate knowledge about the genetic risk factors for thrombophilia is lacking among many physicians. It is also of interest to note that most of the diagnostic tests were requested by hospital physicians, whereas the predictive tests were mostly ordered by GPs, usually on patient requests. This may reflect a general interest for risk assessment in the population, but it is also likely that relatives may have overestimated their own risk for thrombosis if a family member has VTE or tests positive for the FVL mutation. Such risk overestimation may also be a consequence of suboptimal advice from the physicians. The latter is supported by our study, in which a number of physicians recommended family investigation on finding an FVL mutation only. Furthermore, a positive APCR test was not considered 'as genetic' as a positive FVL result, because family follow-up was rarely recommended in these cases. Another explanation might be that physicians requesting a DNA test for FVL are more concerned about the heritability of thrombophilia than the physicians ordering APCR tests only. If the FVL test is thought to be of larger clinical importance than the APCR test, this may also explain why 'special advice' was given to the heterozygote patients significantly more frequently after FVL than after APCR testing.

For the predictive tests, the great majority of the test results led to either no action or to advices that should have been given independent of the test result. Similarly, the majority of diagnostic tests were followed by no action or only general advice. In the cases in which the test results were reported to 'initiate drug treatment' or 'prolong drug treatment', we found that the follow-up would have been the same without the APCR/FVL result. The numbers in this study are small and should therefore not be overinterpreted. Still, our study clearly indicates that APCR/FVL testing, especially predictive testing of healthy individuals, often lacks a justified indication. The test result has, in general, little consequence for the patient follow-up.

In addition to draining resources from limited health budgets, unjustified FVL testing may also lead to false assurance or unnecessary anxiety and unwarranted denial of oral contraceptives. False assurance may lead to thrombotic episodes that might have been avoided by prophylactic measures taken after proper advice; unnecessary anxiety may negatively influence an individuals' health perception; and oral contraceptive denial may lead to unwanted pregnancies and abortions, representing a much higher risk for thrombosis than the FVL mutation itself. In conclusion, our survey indicates that APCR/FVL testing in current practice might do more harm than good, supporting the recent suggestion that thrombosis susceptibility testing, when warranted, should not include FVL.[22]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The first author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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