

Trombofilijos ir insultas 2013-2018



Vilniaus universiteto ligoninė
SANTAROS KLINIKOS

Kristina Ryliškienė

2013 m. išvada

- Tik atrinkti trombofilijos testai atrinktiems jauniems insultu sergantiems ligoniams bus kliniškai vertingi ir keis gydymo ir prevencijos taktiką



Recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 13–15 November 2016

Niaz Ahmed^{1,2}, Thorsten Steiner^{3,4}, Valeria Caso⁵ and
Nils Wahlgren²; for the ESO-KSU session participants*

Thrombophilia 0
Hypercoagulation 0
Prothrombotic 0

Consensus Paper

**Cerebrovascular
Diseases**

Cerebrovasc Dis 2008;25:457–507

DOI: 10.1159/000131083

**Jei yra hiperkoaguliacija –
reikia tirti**

Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008

The European Stroke Organisation (ESO) Executive Committee and the
ESO Writing Committee

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

(*Stroke*. 2018;49:eXXX–eXXX. DOI: 10.1161/STR.000000000000158.)

6.6. Other Tests for Secondary Prevention (Continued)	COR	LOE	New, Revised, or Unchanged
3. The usefulness of screening for thrombophilic states in patients with ischemic stroke is unknown.			Recommendation reworded for clarity from 2014 Secondary Prevention. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
A recent review article concludes that there is little, if any, contribution of the inherited thrombophilias to the development of arterial thrombotic events and <u>therefore tests for inherited thrombophilia should not be ordered for the evaluation of stroke.</u> ³⁰⁹			

Žr. 2014 m. rekomendacijas

Section	2014 Recommendation	Description of Change From 2011
Hypercoagulation	<ul style="list-style-type: none"> • Tyrimų nauda nėra aiški • Gydymas priklauso nuo rasto sutrikimo ir klinikinės situacijos 	<p>New recommendation</p> <p>Substantial rewording Class changed from IIa to IIb</p>
Hypercoagulation cont'd	<p>Antiplatelet therapy is recommended in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA if anticoagulation therapy is not administered (<i>Class I; Level of Evidence A</i>).</p>	<p>Represents a more firm recommendation for antiplatelet therapy in the circumstance described</p>
Antiphospholipid antibodies	<ul style="list-style-type: none"> • Rutininis tyrimas nerekomenduojamas, jei yra aiški insulto/PSIP etiologija ir nėra kitų AFS požymių • AF ak be klinikos – gydymas antiagregantais • AF ak su klinika (AFS) – jei dar nevartoja antikoagulantų, skirti antiagregantus <p>(<i>Class I; Level of Evidence B</i>).</p> <p>For patients with ischemic stroke or TIA who meet the criteria for the antiphospholipid antibody syndrome but in whom anticoagulation is not begun, antiplatelet therapy is indicated (<i>Class I; Level of Evidence A</i>).</p>	<p>New recommendation</p> <p>Clarifies circumstances in which antiplatelet therapy is recommended over anticoagulation</p> <p>New recommendation</p>
Homocysteinemia	<ul style="list-style-type: none"> • Rutininis tyrimas nerekomenduojamas • Nedidelė/vidutinė hiperhomocisteinemija – folatai, B₆ ir B₁₂ <p>reduces levels of homocysteine but has not been shown to prevent stroke (<i>Class III; Level of Evidence B</i>).</p>	<p>New recommendation</p> <p>Class changed from IIb to III</p>

Metil-folatai



Thrombotic Management of Antiphospholipid Syndrome: Towards Novel Targeted Therapies

Author(s): Md. Asiful Islam*, Fahmida Alam, Kah Keng Wong, Mohammad Amjad Kamal, Siew Hua Gan*.

Journal Name: Current Vascular Pharmacology

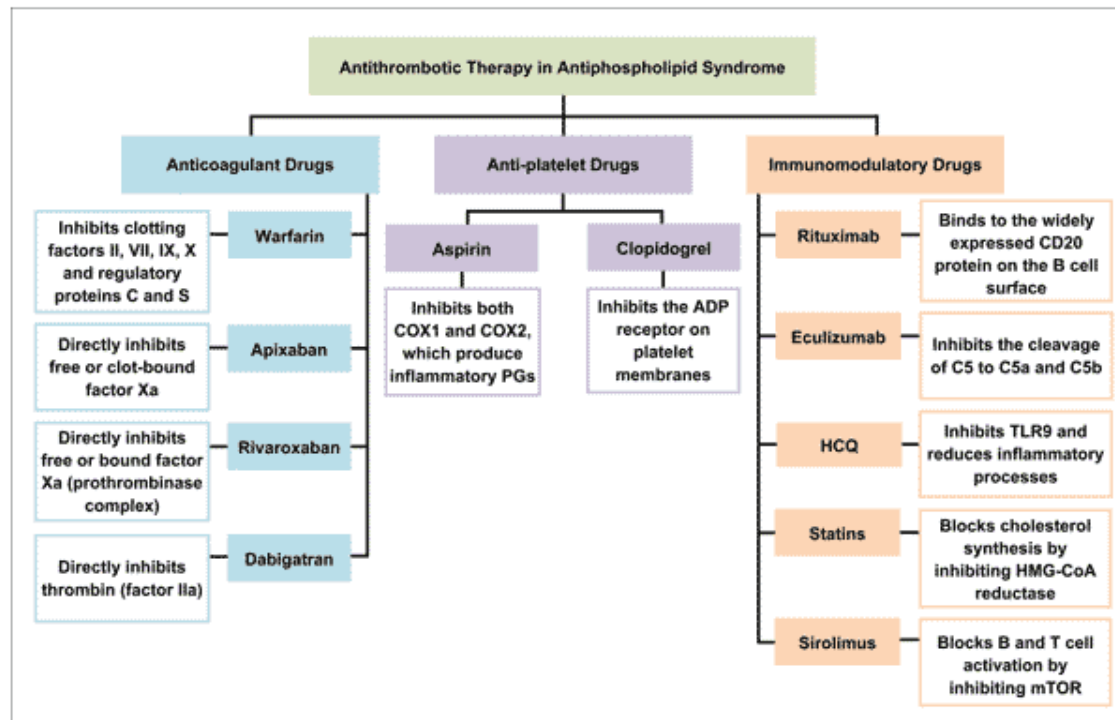
Volume 15 , Issue 4 , 2017

DOI : 10.2174/1570161115666170105120931

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Graphical Abstract:



Thrombophilia Screening: Universal, Selected, or Neither?

Clinical and Applied
Thrombosis/Hemostasis
1-7
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DOI: 10.1177/1076029616683803

Trombofilija – įgimtas ar įgytas homeostazės sutrikimas didinantis trombozių riziką

Age >65 years

BMI >30 kg/m²

Immobilization—flight >6 hours

Trauma

Surgery

Pregnancy—puerperium

Medication

Synthetic estrogens

Chemotherapy

Antiphospholipid antibodies

Lupus anticoagulant

Severe infection

Inflammatory states

Malignancy

Extended varicosis

Post thrombotic syndrome

Myeloproliferative neoplasm

Essential thrombocythemia

Polycythemia vera

Nephrotic syndrome

PNH

Depression

Smoking

Thrombophilia Testing and Venous Thrombosis

Jean M. Connors, M.D.

ORDERING THROMBOPHILIA TESTS IS EASY; DETERMINING WHOM TO test and how to use the results is not. Although inherited and acquired thrombophilias are acknowledged to increase the risk of venous thromboembolism (VTE), the majority of patients with VTE should not be tested for thrombophilia. Data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone. Testing for inherited thrombophilia is controversial, with some arguing that these tests should never be performed. No validated testing guidelines have been published.

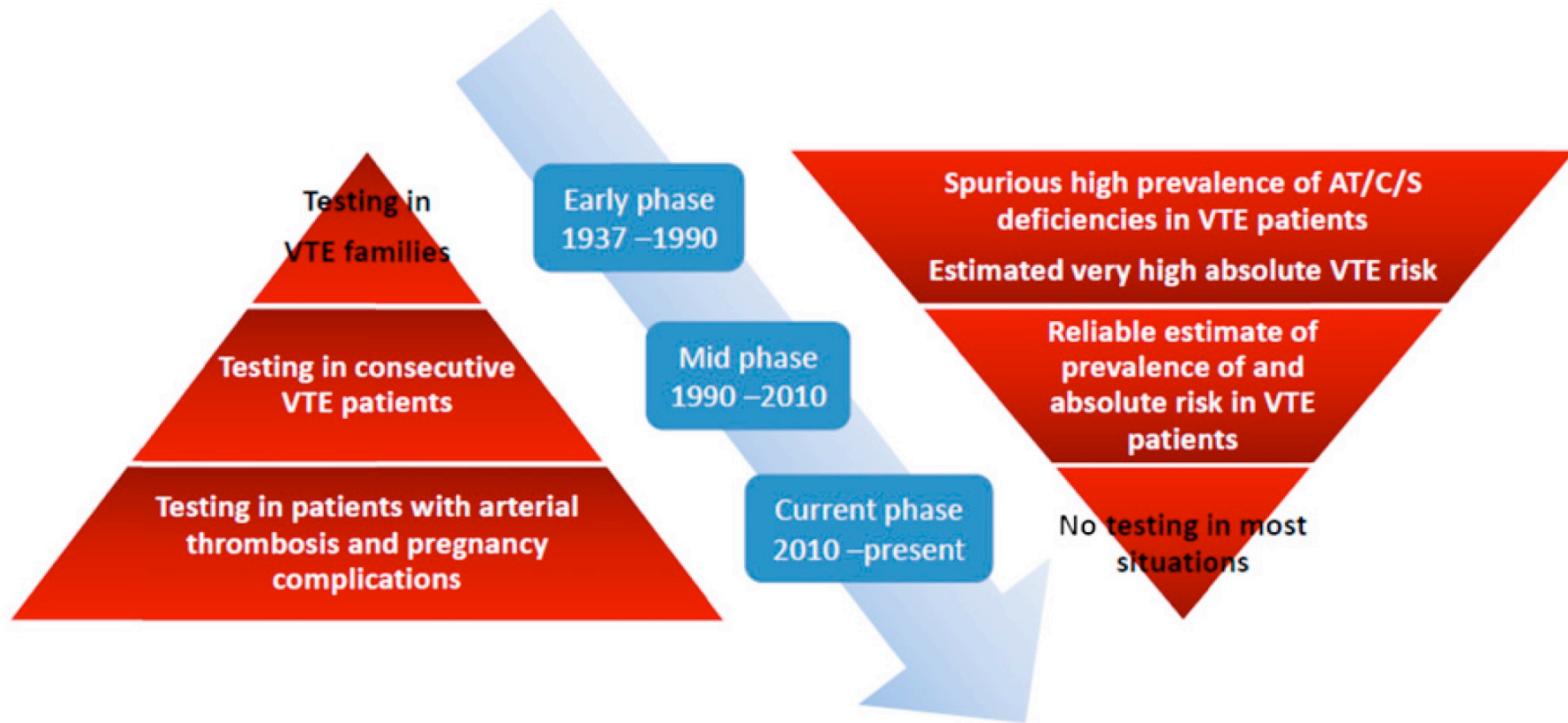


Inherited thrombophilia: a double-edged sword

Saskia Middeldorp

Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Hematology 2016



REVIEW ARTICLE

WILEY



Optimal utilization of thrombophilia testing

R. K. Pruthi

Table 4. Comparison of thrombophilia testing before and after guideline implementation.

	Before guideline implementation	22 months after guideline implementation	% Reduction
Patients having testing ordered per month	87	18	79%
Patients having testing performed per month	87	5	94%
Tests ordered per month ^a	484.5	76	84%
Tests performed per month ^b	484.5	37.5	92%

^aNumber of tests ordered includes LA, aCL, a β_2 GPI, aPS, aPT, APCR, FVL, PGM, AT, PC, PS, FVIII.

^bPrior to guideline implementation, all ordered tests were performed. After guideline implementation, tests were performed only after consultation with the Transfusion Medicine and Hemostasis service.

Optimal utilization of thrombophilia testing

R. K. Pruthi

TABLE 3 Indications for thrombophilia testing

Thrombophilia testing not indicated for patient management

Population screening

VTE occurring in association with temporary risk factor

Patients currently on therapeutic anticoagulation

Patients with arterial thrombosis^a

Patients on whom long-term therapeutic anticoagulation is planned

To tailor VTE prophylaxis in high-risk situations^b

Thrombophilia testing is reasonable

Young individuals with VTE, for example, <50 years^c

VTE in 1st-degree relatives


Recurrent VTE^c

^aLupus anticoagulant testing is indicated; VTE, venous thromboembolism.

^bFor example, duration of prophylactic anticoagulation after hip or knee replacement surgery.

^cFor diagnostic purposes, information may be used to counsel at-risk family members.

Thrombophilia Screening: Universal, Selected, or Neither?

Clinical and Applied
Thrombosis/Hemostasis
1-7
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Giuseppe Colucci, MD^{1,2} and Dimitrios A. Tsakiris, MD²

Table 5. Proposed Indications for Venous Thrombophilia Screening.

Age <50 years

Women with VTE during pregnancy or puerperium

Women with VTE during use of oral contraceptive or hormonal replacement

Women with VTE before prescribing hormonal replacement

Women with multiple inexplicable pregnancy losses

Young women with a positive family history, before prescribing oral contraceptive

VTE in unusual sites

First VTE and a positive family history for VTE

Young patients with arterial ischemia and right-to-left shunt (paradoxical embolism)

The Therapeutic Value of Laboratory Testing for Hypercoagulable States in Secondary Stroke Prevention



Neurol Clin 33 (2015) 501–513
<http://dx.doi.org/10.1016/j.ncl.2015.01.003>

Chandni Kalaria, MD^a, Steven Kittner, MD, MPH^{a,b,*}

Įgimtos trombofilijos:

- V f. Leiden mutacija, PT geno mutacija, PC, PS, ATIII – nenustatyta ryšio arba labai silpnas ryšys su arteriniu išeminiu insultu
 - MTHR geno homozigotinis variantas neturi ryšio su homocisteino koncentracijos dydžiu
 - Labai padidinta homocisteino koncentracija nustatoma labai retai, o vidutiniškai padidintos gydymas neturi kraujagyslinių įvykiu rizikos mažinimo įrodymų
- AFS** didina pirmo ir pakartotinio arterinio išeminio insulto riziką jauniems ligoniams.
- AF ak radimas ≠ AFS
 - Nėra antitrombozinio gydymo rekomendacijų

Po pirmojo epizodo gali būti naudingas tik AF ak tyrimas, net ir esant AOA*

Po antrojo epizodo gali būti naudingas išsamus trombofilijų tyrimas

*esant AOA trombofilijų tyrimas leidžia nuspręsti ką rinktis: AOA uždarymą ar antikoaguliaciją, jei antiagregantų nepakanka

Thrombophilia Testing and Venous Thrombosis

N Engl J Med 2017;377:1177-87.

DOI: 10.1056/NEJMra1700365

Jean M. Connors, M.D.

Table 2. Summary of Recommendations Regarding Testing for Thrombophilia.*

Recommendation	Explanation
Do not test at time of VTE event	Trombozinis įvykis > 3 mėn. for unprovoked VTE, antithrombotic therapy is contemplated and test results might change management strategy
Do not test while patient is receiving anticoagulant therapy	Vaistai nebevertojami*: <ul style="list-style-type: none">• VKA > 2 sav.• NOAK > 2 d.• Heparinas, MMMH > 24 val. been stopped for at least 24 hours and antithrombin levels has

*Colucci 2017 >1 mėn. po antikoaguliacinio gydymo nutraukimo

Table 1. Effect of Direct Oral Anticoagulants and Vitamin K Antagonists on Laboratory Testing or Interpretation.

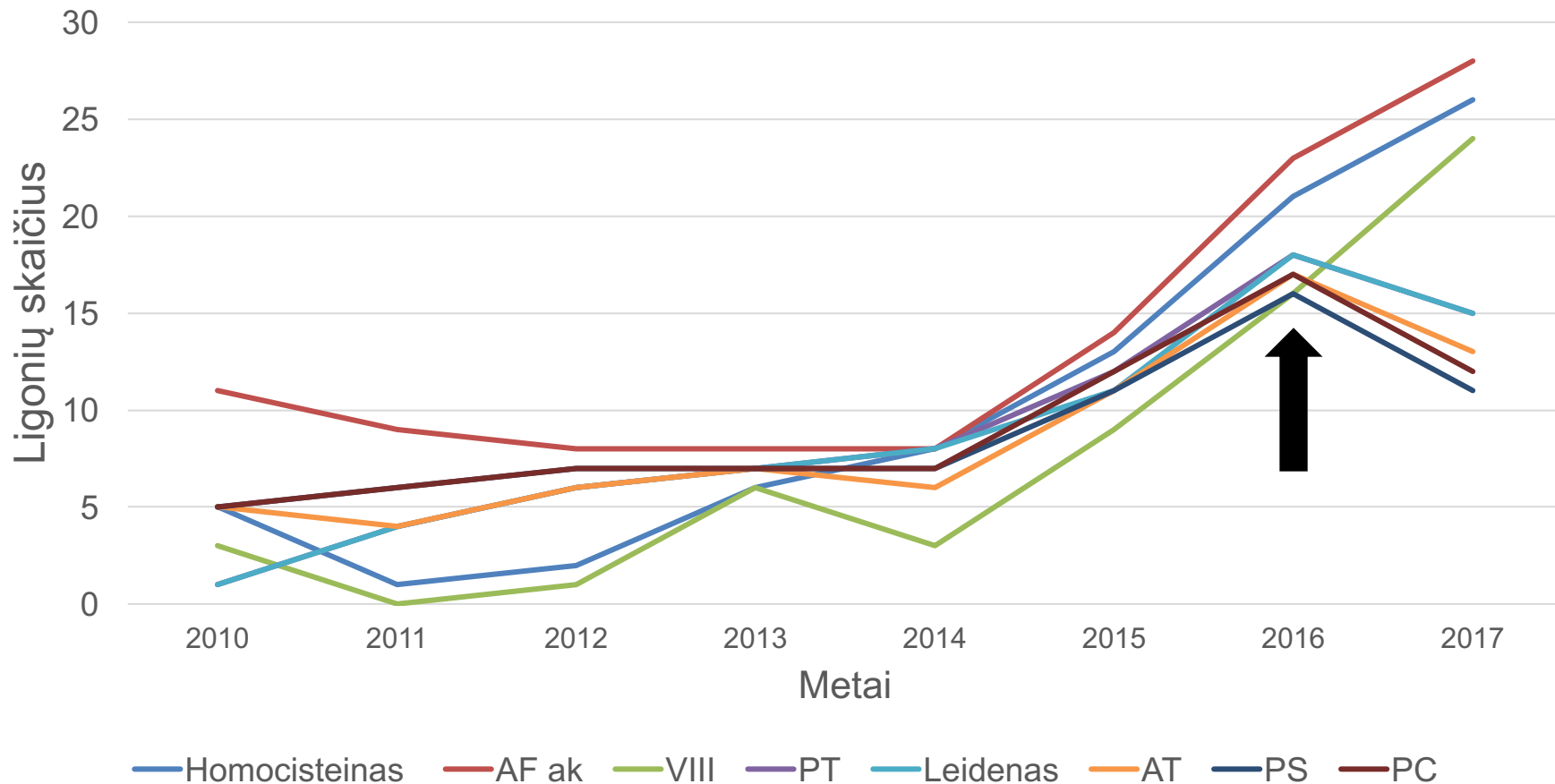
Coagulation Assay	Drug Class*		
	Direct Factor Xa Inhibitor	Direct Thrombin Inhibitor	Vitamin K Antagonist
Fibrinogen Clauss method	No effect	Potentially false underestimation, depending on drug concentration and assay reagent	No effect
Thrombin time	No effect	Prolonged	No effect
Antithrombin activity			
FXa-based	False overestimation		
FIIa-based	No effect		
Protein C activity			
Clot-based	False overestimation		
Chromogenic-based	No effect	No effect	Decreased†
Protein S activity (clot-based)	False overestimation	False overestimation	Decreased†
Free protein S antigen immunoassay	No effect	No effect	Decreased†
Lupus anticoagulant panel (final interpretation)	False positive, depending on assay or reagent	False positive, depending on assay or reagent	False positive, depending on assay or reagent
Cardiolipin and β 2GP1 antibodies (immunoassay)	No effect	No effect	No effect
Activated protein C resistance ratio based on aPTT plus factor V–deficient plasma	False elevation	False elevation	Potential for false elevation
von Willebrand antigen and activity	No effect	No effect	No effect
D-Dimer (quantitative)	No effect	No effect	No effect

**Genetiniai testai
Homocisteinas
antiCL
anti β 2GP1**

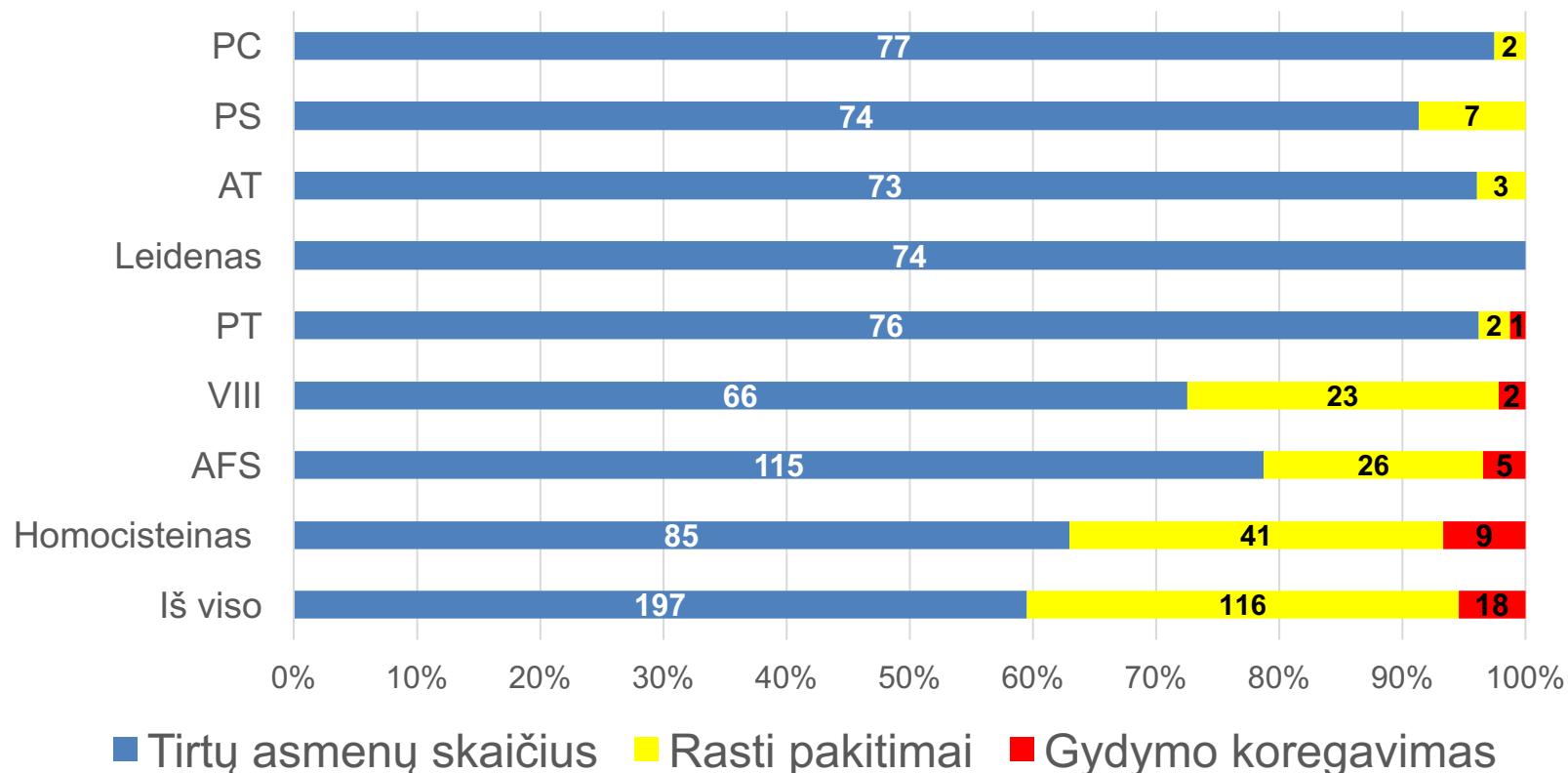
* Direct Xa inhibitors include rivaroxaban, apixaban, edoxaban, and betrixaban. Direct thrombin inhibitors include dabigatran, argatroban, and bivalirudin. Vitamin K antagonists include warfarin. The abbreviation aPTT denotes activated partial thromboplastin time.

† Protein C and protein S synthesis is vitamin K–dependent, so the activity and antigen level of each will decrease in the presence of warfarin, potentially leading to an incorrect diagnosis.

Jaunų asmenų, susirgusių insultu/PSIP, tyrimai dėl trombofilijos 2010-2017 m. VUL Santaros klinikose



Trombofilijų tyrimo rezultatai 2008-2017



Regresinės lygties kintamieji: lytis, amžius, tradicinė rizika, kardiovaskuliniai įvykiai anamnezėje, trombozinė ligonio, **trombozinė šeimos anamnezė**, nėštumo patologija, D-dimerai, AOA.



Inherited thrombophilia: a double-edged sword

Saskia Middeldorp

Hematology 2016

Priežastys, dėl kurių reikėtų ieškoti paveldimos trombofilijos:

- Gali padėti paaiškinti ligos priežastį
- Teigiamas rezultatas gali keisti nuolatinę profilaktiką ar koreguoti gydymą
 - Antikoagulantai vs AOA uždarymas
 - Hormoninės kontracepcijos nutraukimas ar neskyrimas
 - Antikoagulantai pagal poreikį nėštumo metu, po operacijų, po ilgesnių imobilizacijų
- Pacientas jaučiasi gerai ir išsamiai ištirtas
- Gydytojas jaučiasi savo srities ekspertas

Priežastys, dėl kurių nereikėtų ieškoti paveldimos trombofilijos:

- Vienai trombofilijai nustatyti reikia atlikti l. daug tyrimų
- Didelė tyrimų kaina
- Nesant rekomendacijų, net ir teigiami radiniai gali nekeisti gydymo taktikos
- Dėl be griežtų rekomendacijų skirtos profilaktikos kyla šalutiniai reiškiniai (kraujavimai, nepageidautini nėštumai)
- Psichologinis ir socialinis (draudiminis) teigiamų rezultatų poveikis
- Nenustačius, nepagrįstai sumenkinama galimų įvykių pasikartojimo rizika

2013/18 m. išvada

gali būti

- Tik atrinkti trombofilijos testai atrinktiems jauniems insultu sergantiems ligoniams ~~bus~~ kliniškai vertingi ir ~~keis~~ gydymo ir prevencijos taktiką

gali keisti

Insultas <50 m.

- KT/MRT lakuniniai infarktai
- Kaklo ir galvos arterijos stenoze $\geq 50\%$, disekacija, vazospazmas, vaskulitas
- EKG – PV
- TTE – kardioembolijos priežastis
- BKT, CRB, elektrolitai, glc, kreatininas, D-dimerai*, toksikologija

Priežastis nerasta

Holter ≥ 24 val.

Priežastis nerasta

Neurologo k-ja
kTKD

VUL SK III
9:00-11:00
868862809

Šunto
nėra/mažas

Didelis šuntas

Hematologo k-ja
Arterinė trombofilija

Hematologo k-ja
Veninė ir arterinė
trombofilija

Kojų venų
echoskopija*

Neurologo k-ja
RoPE ≥ 7
Didelės rizikos AOA

Kardiologo k-ja
TEE