Diploma Thesis

The impact of MTHFR mutations on the primary patency of PTFE haemodialysis shunt prostheses

by

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Declaration

I, Stefanie Christine Santler, declare that, this thesis has been written by me and, to the best of my knowledge and belief, this thesis is authentic except where acknowledgements are made in the text. It does not include any material for which any other university degree or diploma has been awarded.

Stefanie Christine Santler, BSc, eh Graz, 28th of February, 2017

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1 List of abbreviations

µmol ..... micromol

AA ..... homozygous prothrombin G20210A mutation

APCR ..... activated protein C resistance

aPTT ..... lupus sensitive activated partial thromboplastin time

CC ..... no MTHFR 677 mutation

CRF ..... case report form

CT ..... heterozygous MTHFR 677 mutation

dL ..... deciliter

GA ..... heterozygous prothrombin G20210A mutation

GG..... no prothrombin G20210A mutation

LA..... lupus anticoagulant

M ..... months

MEDOCS..... openMedocs (the electronic data system of the University Hospital of Graz to manage patients records and medical data)

mg ..... milligram

mL ..... milliliter

MTHFR..... methylenetetrahydrofolate reductase

n ..... number of data

PP ..... primary patency (the time between shunt implantation and the first shunt thrombosis)

PTFE ..... polytetrafluoroethylene

QQ..... homozygous Factor V Leiden thrombophilia

RQ ..... heterozygous Factor V Leiden thrombophilia

RR ..... no Factor V Leiden thrombophilia

s ..... seconds

SE ..... standard error = standard deviation

SPSS ..... Statistical Package for the Social Sciences

TT ..... homozygous MTHFR 677 mutation

U ..... Units

Y ..... years

2 List of Tables

3 List of Figures

4 Abstract in German

4.1 Einleitung

Die beste Option zur Durchführung einer Hämodialyse ist die Anlage eines autologen Shunts. Bei Fehlen einer geeigneten Vene ist die Verwendung eines Kunststoffes eine akzeptable Alternative, wenn auch mit höheren Verschlussraten. Der am häufigsten verwendete Kunststoff ist PTFE (Polytetrafluorethylen).

Nach derzeitigem Wissen ist es nicht erforderlich asymptomatische Träger einer heterozygoten MTHFR (Methylentetrahydrofolat Reduktase) Mutation medikamentös vor einer Thromboembolie zu schützen. Es ist nicht untersucht, ob Patientinnen mit PTFE-Shunts und einer MTHFR-Mutation höhere Verschlussraten haben und einen medikamentösen Thromboseschutz benötigen. Ziel dieser Studie ist zu untersuchen, ob der MTHFR Gentypus die primäre Shuntoffenheit (PP) beeinflusst. Diese ist definiert als Zeit zwischen Implantation der Shuntprothese und der ersten Shuntthrombose.

4.2 Material und Methoden

Zwischen 2009 und 2014 wurden 135 PTFE Shunts an der Medizinischen Universität in Graz implantiert. Für diese Studie konnten 43 Patienten mit 59 Shunts gewonnen werden. Eine Blutabnahme zur Bestimmung von zahlreichen Gerinnungsfaktoren wurde durchgeführt und klinische Daten wurden retrospektiv erhoben.

Eine genetische Untersuchung auf MTHFR Mutation, Faktor V Leiden Mutation und Prothrombin G20210A Mutation wurde gemacht. Außerdem wurde ein Thrombophiliescreening mit folgenden Werten durchgeführt: Homozystein, Lipoprotein a, APCR, Protein C Aktivität, Protein S Aktivität, aPTT, Lupus Antikoagulant (LA), Cardiolipin Antikörper und ß2-Glykoprotein Antikörper.

Die PP wurde bezogen auf die Ergebnisse des Thrombophiliescreenings und der genetischen Untersuchungen statistisch ausgewertet. Entsprechende p-Werte wurden bestimmt.

Die statistische Analyse wurde mittels SPSS 23.0.0.0 durchgeführt und die primäre Shuntoffenheit mittels Kaplan Meier berechnet. Unterschiede zwischen Subgruppen wurden mittels Cox Regression analysiert und ein p-Wert unter 0,05 wurde als signifikant angesehen.

4.3 Ergebnisse

Die durchschnittliche primäre Shuntoffenheit der 43 Patienten betrug 18,44 Monate (± 3,16 SE).

Die Studienteilnehmer waren im Mittel zum Zeitpunkt der Shuntimplantation 63,71 (± 1,62 SE, Spannweite 40,03 - 82,10) Jahre alt.

Die primäre Zielgröße, heterozygote MTHFR Mutation, war mit einem p-Wert von 0,370 nicht signifikant. APCR war mit einem p-Wert von 0,005 signifikant. Die Faktor V Leiden Mutation hatte einen p-Wert von 0,141 und war somit nicht signifikant. Homozystein (p = 0,485), Lipoprotein a (p = 0,893), Protein C Aktivität (p = 0,257) und das fraktionierte Protein S Antigen (p = 0,149) waren ebenfalls nicht signifikant. Die Lupus aPTT hatte einen nicht signifikanten p-Wert von 0,226 und auch das Lupus Antikoagulant war mit 0,565 nicht signifikant. Die Anticardiolipin Antikörper (p = 0,075) und die ß2-Glykoprotein Antikörper (p = 0,153) hatten keine signifikanten p-Werte.

32,6 % der 43 Patienten hatten eine MTHFR Mutation und eine primäre Shuntoffenheit von 19,6 Monaten (± 4,7 SE). 55,8 % waren heterozygot mit einer primären Shuntoffenheit von 15,6 Monaten (± 4,0 SE) und 11,6 % hatten eine homozygote MTHFR Mutation mit einer primären Shuntoffenheit von 21,8 Monaten (± 7,2 SE).

Der Hauptteil (90,7 %) der 43 Patienten hatte keine Faktor V Leiden Mutation. 7,0 % waren heterozygot und 2,3 % homozygot für diese Mutation. Das bedeutet, dass 9,3 % der Patienten eine Faktor V Leiden Mutation (heterozygot + homozygot) hatten. Alle von ihnen hatten einen pathologischen APCR-Wert.

Keiner der untersuchten Patienten hatte eine Prothrombin Mutation G20210A.

4.4 Diskussion

Es ist allgemeine Lehrmeinung, dass Patienten mit einer Faktor V Leiden Mutation (heterozygot oder homozygot) pathologische APCR-Werte haben und einen medikamentösen thromboembolischen Schutz benötigen, wenn sie sich in einer Risikosituation (Schwangerschaft, Immobilisation) befinden. Unsere Daten zeigen, dass die Verwendung eines PTFE Shunts die Patienten in eine Risikosituation bringt und diese daher ebenfalls oral antikoaguliert werden sollten.

Um unnötige Thrombektomien zu vermeiden und eine längere Shuntoffenheit zu erreichen, sollten Patienten ein Thrombophiliescreening bekommen bevor ein PTFE Shunt implantiert wird.

Eine Auswirkung auf die primäre Shuntoffenheit der heterozygote MTHFR Mutation konnte in dieser Studie nicht nachgewiesen werden.

5 Abstract

5.1 Objectives

For performing haemodialysis patients often get an arteriovenous shunt. Ideally, this is made of a body's own vein (autologous vein). If there is no such vein available, a plastic shunt may also be implanted, although the rate of thromboses is much higher. The most frequently used plastic is PTFE (Polytetrafluoroethylene).

According to current doctrine people with an asymptomatic heterozygous MTHFR (methylenetetrahydrofolate reductase) mutation need no medical protection against thromboembolic events. Currently it is unknown, whether patients with PTFE grafts and heterozygous MTHFR mutations have a higher thrombosis rate and therefore need medical protection from thrombosis. The aim of this study is to examine whether MTHFR mutation has an impact on the primary patency (PP). PP is defined as the time between graft implantation and the first shunt thrombosis.

5.2 Material and Methods

From 2009 to 2014 135 PTFE grafts were implanted at the Medical University of Graz. For this study 43 patients with 59 shunts could be included. Blood was taken for determination of various thrombophilic factors, clinical data was drawn retrospectively.

Genetic typing, including MTHFR mutation, Factor V Leiden thrombophilia and prothrombin G20210A mutation, was performed. Additionally a thrombophilia screening including homocysteine, lipoprotein a, activated protein C resistance (APCR), protein C activity, fractionated protein S antigen, lupus sensitive activated partial thromboplastin time (aPTT), lupus anticoagulant (LA), anti-cardiolipin antibodies and ß2-glycoprotein antibodies was executed.

The PP was statistically evaluated in relation to the results of the thrombophilia screening and the genetic typing. Corresponding p-values were determined.

Statistical analysis was performed with SPSS 23.0.0.0. Primary patency (PP) was calculated using the Kaplan Meier method whereas differences between subgroups were identified with Cox regression analysis. A p-value below 0.05 was considered significant.

5.3 Results

The overall primary patency for the 43 patients was 18.44 months (± 3.16 SE).

The mean age of the 43 patients at the time of shunt implantation was 63.71 (± 1.62 SE, range 40.03 - 82.10) years.

The primary aim was the heterozygous MTHFR mutation. With a p-value of 0.370, it was not significant. APCR was significant with a p-value of 0.005. The Factor V Leiden mutation had a p-value of 0.141 and was not significant. Homocystein (p = 0.485), lipoprotein a (p = 0.893), protein C activity (p = 0.257) and the fractionated protein S antigen (p = 0.149) were not significant as well. Neither the lupus aPTT had a significant p-value (p = 0.226) nor the lupus anticoagulant was significant (0.565). Also the anti-cardiolipin antibodies (p = 0.075) and the ß2-glycoprotein antibodies (p = 0.153) had no significant p-values.

32.6 % of the 43 patients with a primary patency of 19.6 months (± 4.7 SE) did not have a MTHFR mutation. 55.8 % were heterozygous with a primary patency of 15.6 months (± 4.0 SE) and 11.6 % were homozygous for MTHFR with a primary patency of 21.8 months (± 7.2 SE).

The main part (90.7 %) of the 43 patients had no Factor V Leiden thrombophilia. 7.0 % were heterozygous and 2.3 % were homozygous for this mutation. This means that 9.3 % of the patients with prostheses had a Factor V Leiden mutation (heterozygous or homozygous). All of them had pathologic activated protein C resistance (APCR) values.

There was no prothrombin G20210A mutation found in any of the 43 patients.

5.4 Conclusions

An impact on the primary patency of the heterozygous MTHFR mutation could not be proven in this study.

It is a common doctrine, that patients with Factor V Leiden mutations (heterozygous or homozygous) have pathologic activated protein C resistance (APCR) values and in general only need protection against thromboembolic events in high risk situations (pregnancy, immobilization). Our data revealed that the use of PTFE shunt grafts puts the patients at risk for thromboembolic events. Those particular patients should also be treated with oral anticoagulation.

To reduce the frequency of unnecessary thrombectomies and to prolong primary patency, we advice that patients undergo thrombophilia screening before a PTFE shunt graft is implanted.

An impact of the heterozygous MTHFR mutation on the primary patency could not be proven in this study.

6 Introduction

For performing haemodialysis patients with chronic renal failure often get an arteriovenous shunt. Ideally, this is made of a body's own vein (autologous vein). If there is no such vein available, a plastic shunt (in Graz for years exclusively PTFE) may also be implanted. According to current doctrine people with heterozygous MTHFR mutation need no medical protection against thromboembolic events.

Methylenetetrahydrofolate reductase is an enzyme which converts homocysteine into Methionin. If there is a mutation in the MTHFR gene (heterozygous or homozygous), homocysteine cannot be transformed into Methionin with the same power. Consecutively the blood level of homocysteine rises, which is called homocystinuria. This might trigger a lot of illnesses such as abnormal blood clotting, thrombosis, coronary heart disease, skeletal abnormalities, eye problems and cognitive problems. Researchers have not yet found out, how increased levels of homocysteine lead to the various health problems (1,2,3,4,5,6).

Primary patency is defined as the time between shunt implantation and the first shunt thrombosis. The issue of the proposed study is to determine whether heterozygous MTHFR mutations have an impact on the primary patency of PTFE shunt prostheses or not. This is an important topic, because patients with a heterozygous MTHFR mutation maybe will require a specific anticoagulation regime to prevent shunt thrombosis. Up to now no such correlation has been reported.

This study is a combination of a pro- and retrospective observation study. Blood was taken from patients with PTFE-shunts and analyzed (MTHFR mutation, Factor V Leiden thrombophilia, prothrombin mutation G20210A, homocysteine, lipoprotein a, APCR, protein C activity, fractionated protein S antibodies, lupus anticoagulant, anti-cardiolipin antibodies, ß2-glycoprotein antibodies) and clinical data were drawn retrospectively.

Factor V Leiden thrombophilia is a genetic disorder of blood clotting which results in thrombophilia. Thrombophilia is an increased tendency to form abnormal blood clots that can block blood vessels. A mutation in the F5 gene causes the Factor V Leiden thrombophilia. This gene codes for the coagulation Factor V protein which plays a big role in the formation of blood clots in response to injuries (7).

Prothrombin mutation G20210A is an inherited disorder of blood clotting which causes thrombophilia. It is caused by a genetic mutation in the F2 gene and plays a critical role in the coagulation system. The F2 gen produces the protein prothrombin which is the precursor of thrombin and starts a series of reactions in order to form a blood clot (8).

Lipoprotein a is a lipoprotein which can increase the risk of blood clots, thrombosis, stroke or heart attack if its blood level is too high (9).

Protein C is an anti-inflammatory and anti-coagulant enzyme which requires protein S, a coenzyme, and vitamin K to function. Protein C has a “blood-thinning” effect. It is produced in the liver and circulates in the bloodstream. Protein C is a major impact factor for blood clotting which is very important to keep the blood loss under control, but has to be regulated strictly, because otherwise thrombotic events such as heart attack or strokes can be the consequences. Protein S is produced in the inner lining of the blood vessels and circulates in the bloodstream. A low protein C or protein S level can lead to excessive blood clotting (10).

On the other hand, an activated protein C has an anticoagulatory effect. It removes clotting factors and stimulates plasmin. An activated protein C is not able to recognize the clotting factors in the blood. This leads to oversensitive blood with an increased tendency to clot. This disorder is called activated protein C resistance (APCR). 90 % of the APCR cases are genetically induced by a mutation in the DNA, which codes for Factor V (10).

The immunoglobulin lupus anticoagulant binds to phospholipids and proteins which are located on the cell membrane. It is a prothrombotic agent which means that a high blood level of it causes inappropriate blood clotting (11).

Anti-cardiolipin antibodies are a subgroup of anti-mitochondrial antibodies and often directed against cardiolipin. Patients with a high blood level of anti-cardiolipin

antibodies can suffer from recurrent thrombotic events. The according disease is called antiphospholipid syndrome (12,13).

ß2-glycoprotein antibodies are a subset of anti-cardiolipin antibodies and lupus anticoagulants.

7 Material and Methods

7.1 Design

This work is a combination of a pro- and retrospective observation study.

Blood was taken from patients with PTFE-shunts. The patients' clinical data were acquired by history taking and from medical reports (MEDOCS). The primary patencies of patients were calculated and the impact of genetic factors (MTHFR mutation, Factor V Leiden thrombophilia and prothrombin mutation G20210A) as well as distinct blood levels (homocysteine, lipoprotein a, APCR, protein C activity, fractionated protein S antibodies, lupus anticoagulant, anti-cardiolipin antibodies and ß2-glycoprotein antibodies) were determined statistically.

7.2 Trial procedure

Patients were called and asked for participation. After giving informed consent, blood was taken for analysis (MTHFR mutation, Factor V Leiden thrombophilia, prothrombin mutation G20210A, homocysteine, lipoprotein a, APCR, protein C activity, fractionated protein S antibodies, lupus anticoagulant, anti-cardiolipin antibodies, ß2-glycoprotein antibodies) and clinical data were retrieved from the patient by taking history and from written medical reports (MEDOCS).

7.3 Power calculation

Since there were no pre-existing data of the impact of heterozygous MTHFR status on the primary patency of PTFE shunt prostheses, we were not able to perform a proper power calculation.

7.4 Selection of trial subjects

7.4.1 Inclusion criteria

- dialysis and implanted PTFE shunt prostheses
- informed consent
- age 20 -100

- implantation between 2009 and 2014
- preexisting data in the database (even if not in the time period)

7.4.2 Exclusion criteria

- pregnancy (due to the atypical thromboembolic nature during that period)
- interpositions

7.4.3 Criteria to censor

- kidney transplantation
- death
- address unknown

In case of missing shunt use (criteria to censor), the observation of the graft was cut and the shunt was counted open at this point of time.

7.5 Subject enrolment

Patients selected for the study were called and asked to participate. The patients were informed by the principal investigator, or an authorized team member who is a medical doctor, about the character, objectives, expected benefits, possible risks and duration of the trial. Information was given in oral and written form. After giving informed consent (Appendix, 12.1. Informed consent, page 56) a singular blood collection followed and history (Appendix, 12.2. CRF, page 61) was taken from the patient (Table 1).

Flow Chart

Table 1: Flow Chart valid for each patient

Visit	1
Informed consent	x
blood collection	x
acquisition of clinical data	x

Duration of the study visit: 15 minutes

7.6 Data handling and record keeping

Source data in the sense of the ICH GCP guideline are as follows:

- for clinical data or demographic data: the patient file and actual patients history
  - gender
  - age
  - number and dates of shunt thromboses
  - absence or presence of diabetes and the type
  - hypertonia
  - coronary heart disease
  - strokes
  - cardio vascular events
  - current medication
  - smoking habits and pack years
  - malignant tumors
  - mobility impairments

- the blood analysis of the patients' blood (special blood tube for the homocysteine)
  - MTHFR status
  - current coagulation management
  - presence of other coagulation defects such as Factor V Leiden thrombophilia, prothrombin mutation G20210A, homocysteine, lipoprotein a, APCR, protein C activity, fractionated protein S antibodies, lupus anticoagulant, anti-cardiolipin antibodies and ß2-glycoprotein antibodies

The obtained clinical and demographic findings were documented on case report forms in accordance with the study protocol. The trial team handled individual-related data strictly confidential.

7.7 Used titles

During this study different titles have been used. There is the original and official title and its short version. A German title was used for communicating with

colleagues. For the communication with patients the title was simplified for better understanding (11. Titles, page 55).

7.8 Biometry

The primary patency during follow-up was determined according to the Kaplan-Meier method. The impact of MTHFR-status (primary endpoint) and other factors (secondary endpoints) like Factor V Leiden thrombophilia, prothrombin mutation G20210A, homocysteine, lipoprotein a, APCR, protein C activity, fractionated protein S antibodies, lupus anticoagulant, anti-cardiolipin antibodies and ß2-glycoprotein antibodies were evaluated with Cox-regression.

7.9 Statistical evaluation

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) 23.0.0.0. For every analyzed value all of the following statistical measures were evaluated. A p-value under 0.05 was considered significant. The p-value is the probability of getting the results given that the null hypothesis is true (14).

The mean (Eq.1) is the sum of all elements of a sample divided by the sample size (15).

$$\bar{x} = \frac{x_1 + x_2 + \cdots + x_n}{n} \qquad \text{Eq.1}$$

$\bar{x}$ ...mean, x_1...1st element of sample, x_2...2nd element of sample, x_n...nth element of sample, n...sample size

The 95 % confidence interval for mean has a lower and a upper bound. There is a 95 % certainty that the mean is between these two bounds. The formula for the lower bound (-) and the upper bound (+) is shown in Eq. 2. The confidence level used for our evaluations was always a = 0.95 (16,17).

$$\bar{x} \pm Z\frac{a}{2} \times \frac{\sigma}{\sqrt{(n)}} \quad \text{Eq.2}$$

x̄ ...mean, Z...confidence coefficient (tabulated value), a...confidence level, б...standard error, n...sample size

The 5 % trimmed mean is calculated like an ordinary mean except that the lowest 5 % and the highest 5 % of the data are excluded (18).

The median is the value associated to the element in the center of the sample, if the sample has an odd number of elements. If the sample has an even number of elements, the mean of the two central elements is calculated (19).

The variance is a measure of the spread between the elements in a sample. It gives an estimation of the average distance of each element of the sample to the mean (Eq.3) (20).

$$\sigma^2 = \frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n} \quad \text{Eq.3}$$

$б^2$...variance, x_i...element i of the sample, x̄ ....mean, n...sample size

The standard error (SE) is square root of the variance (Eq.4) (21).

$$\sigma = \sqrt{\sigma^2} \quad \text{Eq.4}$$

б...standard error, $б^2$...variance

The minimum is the lowest of all elements in the sample. The maximum is the highest of all elements in the sample. The range is the subtraction of the minimum from the maximum. It measures the spread of the sample.

The interquartile range is a measure of the position of the sample's bulk. For its calculation the first quartile is subtracted from the third one (Eq.5) (22).

$$IQR = Q_3 - Q_1 \quad \text{Eq.5}$$

IQR...interquartile range, Q_3...3rd quartile of sample, Q_1...1st quartile of sample

The skewness is a measure for the asymmetry of the distribution of a variable about its mean (Eq.6). Because of the cubic function the result can be negative or positive (23).

$$S = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{x_i - \bar{x}}{\sigma}\right)^3 \quad \text{Eq.6}$$

S...skewness, n...sample size, x_i...element i of the sample, $\bar{x}$ ....mean, б...standard error

Kurtosis is a measure of the concentration of a distribution around its mean. It is calculated with the following formula (Eq.7) (24).

$$K = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{x_i - \bar{x}}{\sigma}\right)^4 \quad \text{Eq.7}$$

K..kurtosis, n...sample size, x_i...element i of the sample, $\bar{x}$ ....mean, б...standard error

7.10 Legal and ethical assessment

The study was performed in accordance with ethical principles that have their origins in the Declaration of Helsinki and are consistent with the Conference of Harmonisation (ICH)/ Good Clinical Practice (GCP).

Data handling was performed according to the Austrian laws and ordinances on data protection and privacy law (*Datenschutzgesetz 2000*) in its current version.

The clinical trial was started after the competent ethics committee had issued its statement of approval (Appendix, 12.3. Ethic approval, page 63).

7.11 Storage and data protection

7.11.1 Responsibilities

At all times the principal investigator had the final responsibility for the accuracy and authenticity of all clinical data.

7.11.2 Adverse events - Serious adverse events

All adverse events (is defined as any harmful incident experienced by a study participant, not necessarily causally related to the clinical trial) and serious adverse events (is an adverse event that is fatal or life-threatening, necessitates in-hospital treatment or its prolongation, leads to permanent or serious disability or incapacity or a congenital abnormality or birth defect) which occur during the study visit, are documented in the patient file and the CRF. Serious adverse events are reported to the ethical committee of the MUG.

During the study for this thesis work no adverse events of any kind occurred.

7.11.3 CRF-safety

All CRF's are stored in a lockable cupboard on the vascular surgical unit and are not accessible for unauthorized personal.

7.11.4 Database input

ID of the patients within the trial, clinical data, data from history taking and laboratory data are put into a database. This database contains no direct link to the patients identities like names, addresses or phone numbers.

7.11.5 Database safety

The database is located on a server space of the MUG. Only members of the trial team do have the rights to access this certain server space.

8 Results

8.1 Patient recruitment

From 2009 to 2014 135 PTFE shunt grafts within 112 patients were implanted. 47 of the patients had died before the start of the study. Eight of the considered people declined their participation. Five of them had moved since the implantation and 12 weren't contactable. Another four of them had undergone successful kidney transplantation, thus their shunts were not used any more. Data of 25 patients already existed in the database of the Division of Vascular Surgery and could be used for this study. Seven of these data were collected before 2009 but never the less taken for this study. Another 18 of the interviewed patients agreed to participate. This adds up to 43 participants.

14 of these 43 patients had two shunts and one had three. The other 28 patients had one shunt (Table 2). Therefore a total of 59 shunt prostheses were included in our research.

Table 2: Distribution of the 59 shunts on the 43 patients

patients with one shunt	patients with two shunts	patients with three shunts	Total
28 (65.1 %)	14 (32.6 %)	1 (2.3 %)	43 (100 %)

8.2 Age and gender

43 patients with 59 shunts were evaluable. For patients with more than one shunt, only one of those shunts was taken into account for the statistical evaluation. The selection process was randomized to avoid biasing of the data.

The mean age of the 43 patients at the time of shunt implantation was 63.71 (± 1.62 SE) years, the 95 % confidence interval for mean had a lower bound of 60.44 years and an upper bound of 66.98 years. The 5 % trimmed mean was 64.03 years and the median 65.08 years. The variance was 112.98 years and the standard deviation 10.63 years. The participants were between 40.03 years and

82.10 years old and there was a range of 42.07 years. The interquartile range was 15.63 years, the skewness was -0.47 (± 0.36 SE) and the kurtosis -0.43 (± 0.71 SE) (Table 3). 58.1 % were female and 41.9% male (Table 4).

Table 3: Statistic evaluation of the age of the patients [Y]

Descriptives - Age			
		Statistic [Y]	Std. Error [Y]
Mean		63.71	1.62
95% Confidence Interval for Mean	Lower Bound	60.44	
	Upper Bound	66.98	
5% Trimmed Mean		64.03	
Median		65.08	
Variance		112.98	
Std. Deviation		10.63	
Minimum		40.03	
Maximum		82.10	
Range		42.07	
Interquartile Range		15.63	
Skewness		-0.47	0.36
Kurtosis		-0.43	0.71

Table 4: Summary of the gender in % of the evaluated patients

patients	Female	male
43	58.1 % (25/43)	41.9 % (18/43)

8.3 p-values - Overview

APCR had a significant impact on the PP (p-value = 0.005), but none of the other investigated factors (Table 5).

Table 5: Summary of the laboratory values and their p-values

Laboratory values	p-value
MTHFR heterozygous vs. wild type	0.370
Factor V Leiden mutation	0.141
Prothrombin mutation G20210A	not found
Homocysteine	0.485
Lipoprotein a	0.893
Protein C activity	0.257
Fractionated protein S antigen	0.149
APCR	**0.005**
Lupus aPTT	0.226
Lupus anticoagulant	0.565
anti-cardiolipin antibodies	0.075
ß2-glycoprotein antibodies	0.153

8.4 Overall primary patency

Statistics about the primary patency was evaluated with the Kaplan Meier method.

The mean value for the PP was 18.44 months (± 3.16 SE).

The main period for this study was 2009 to 2014, but also patients with a shunt implanted before 2009 were evaluated (retrospective part of the study). In the 1st year of observation 22 events (shunt thrombosis) happened. Three patients were censored, two because of death and one because of a kidney transplantation. After the 1st year 18 patients had an open shunt. During the 2nd year 7 events happened and one patient died (censored). That left 10 patients to be at risk. In the 3rd year 5 events happened and no patient had to be censored. So 5 patients remained having an open shunt. During the 4th and 5th year no event happened but 3 patients had to be censored during the 4th and one in the 5th year

due to the death of the patients. That left a total of 4 patients at risk after the 4th and 1 after the 5th year (Table 6).

Table 6: Patients at risk and events during the 5 years of observation with censored patients (due to death and kidney transplantation).

Beginning of the time interval [Y]	patients at risk	events	censored patients
0	43	22	3
1	18	7	1
2	10	5	0
3	5	0	1
4	4	0	3
5	1	0	1

The following Figure 1 shows the relative number of open shunts as a function of time (equals PP) and patients at risk for a time interval of 5 years.

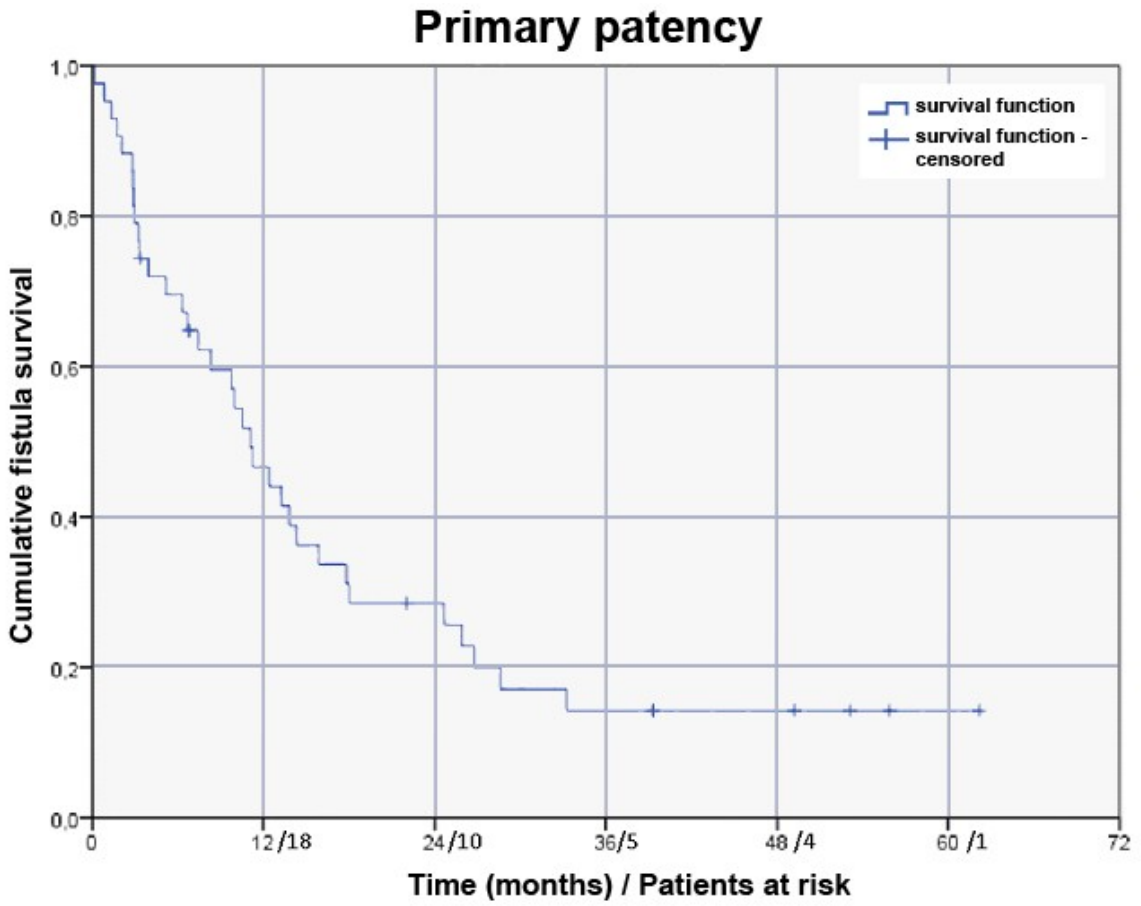

Figure 1: Relative number of open shunts over PP [months] and the patients at risk.

8.5 MTHFR

8.5.1 Frequencies - MTHFR

32.6 % of the 43 patients did not have a MTHFR mutation. 55.8 % were heterozygous and 11.6 % were homozygous for MTHFR (Table 7).

Table 7: Distribution of MTHFR; CC: no mutation, CT: heterozygous, TT: homozygous, n: number of evaluable values

n	CC	CT	TT
43	14	24	5
	(32.6 %)	(55.8 %)	(11.6 %)

8.5.2 PP - MTHFR - correlation

The evaluated values did not show a significant correlation (p = 0.370. 32.6 % of the 43 patients did not have a MTHFR mutation and showed a mean primary patency of 19.6 months (± 4.7 SE). 55.8 % were heterozygous with 15.6 months (± 4.0 SE) and 11.6 % were homozygous with 21.8 months (± 7.2 SE) (Table 8).

Table 8: Primary patency correlation to MTHFR; CC: no mutation, CT: heterozygous, TT: homozygous, PP: mean value of primary patency [M]

Genetic code	PP [M]
CC	19.6 (± 4.7 SE)
CT	15.6 (± 4.0 SE)
TT	21.8 (± 7.2 SE)

8.6 Factor V Leiden thrombophilia

8.6.1 Frequencies - Factor V Leiden thrombophilia

All 43 patients could be evaluated for the Factor V Leiden thrombophilia. The main part (90.7 %) of the 43 patients had no Factor V Leiden thrombophilia. 7.0 % were heterozygous and 2.3 % were homozygous for this mutation, thus 9.3 % of the patients with prostheses had a Factor V Leiden mutation (heterozygous or homozygous) (Table 9).

Table 9: Distribution of Factor V Leiden thrombophilia; RR: no mutation, RQ: heterozygous, QQ: homozygous, RQ + QQ: summation of both forms, n: number of evaluable values

n	RR	RQ	QQ	RR	RQ+QQ
43	39 (90.7 %)	3 (7.0 %)	1 (2.3 %)	39 (90.7 %)	4 (9.3 %)

8.6.2 PP - Factor V Leiden thrombophilia - correlation

Factor V Leiden thrombophilia had a p-value of 0.141. The main part (90.7 %) of the 43 patients had no Factor V Leiden thrombophilia and showed a mean primary patency of 19.6 months (± 3.4 SE). 7.0 % were heterozygous with a mean primary patency of 10.2 months (± 4.3 SE) and 2.3 % were homozygous with 0.8 months (± 0.0 SE).

The difference between the mean value of primary patency of no Factor V Leiden thrombophilia and heterozygous or homozygous mutation was 9.4 M and 18.8 M (Table 10).

Table 10: Primary patency correlation to Factor V Leiden thrombophilia; RR: no mutation, RQ: heterozygous, QQ: homozygous and the difference [M], PP: mean value of primary patency [M]

Genetic code	PP [M]	Difference [M]	
		RR - RQ	RR - QQ
RR	19.6 (± 3.4 SE)	9.4	18.8
RQ	10.2 (± 4.3 SE)		
QQ	0.8 (± 0.0 SE)		

Since there was only one patient detected with homozygous Factor V Leiden mutation, the according PP value is questionable due to lack of statistics. Because of that it was decided to merge the results for heterozygous and homozygous Factor V Leiden mutation. Therefore the patients with a mutation (heterozygous or homozygous) had a mean value of primary patency of 7.9 months (± 3.9 SE). The mean value of primary patency difference between no mutation and a heterozygous or homozygous mutation was 11.7 months (Table 11).

Figure 2 shows the relative number of working shunts for both patient groups, with and without mutation.

Table 11: Difference between the PP value of no Factor V Leiden thrombophilia and heterozygous + homozygous mutation; RR: no mutation, RQ: heterozygous, QQ: homozygous and the difference [M], PP: mean value of primary patency [M]

Genetic code	PP [M]	Difference [M]
RR	19.6 (± 3.4 SE)	11.7
RQ + QQ	7.9 (± 3.9 SE)	

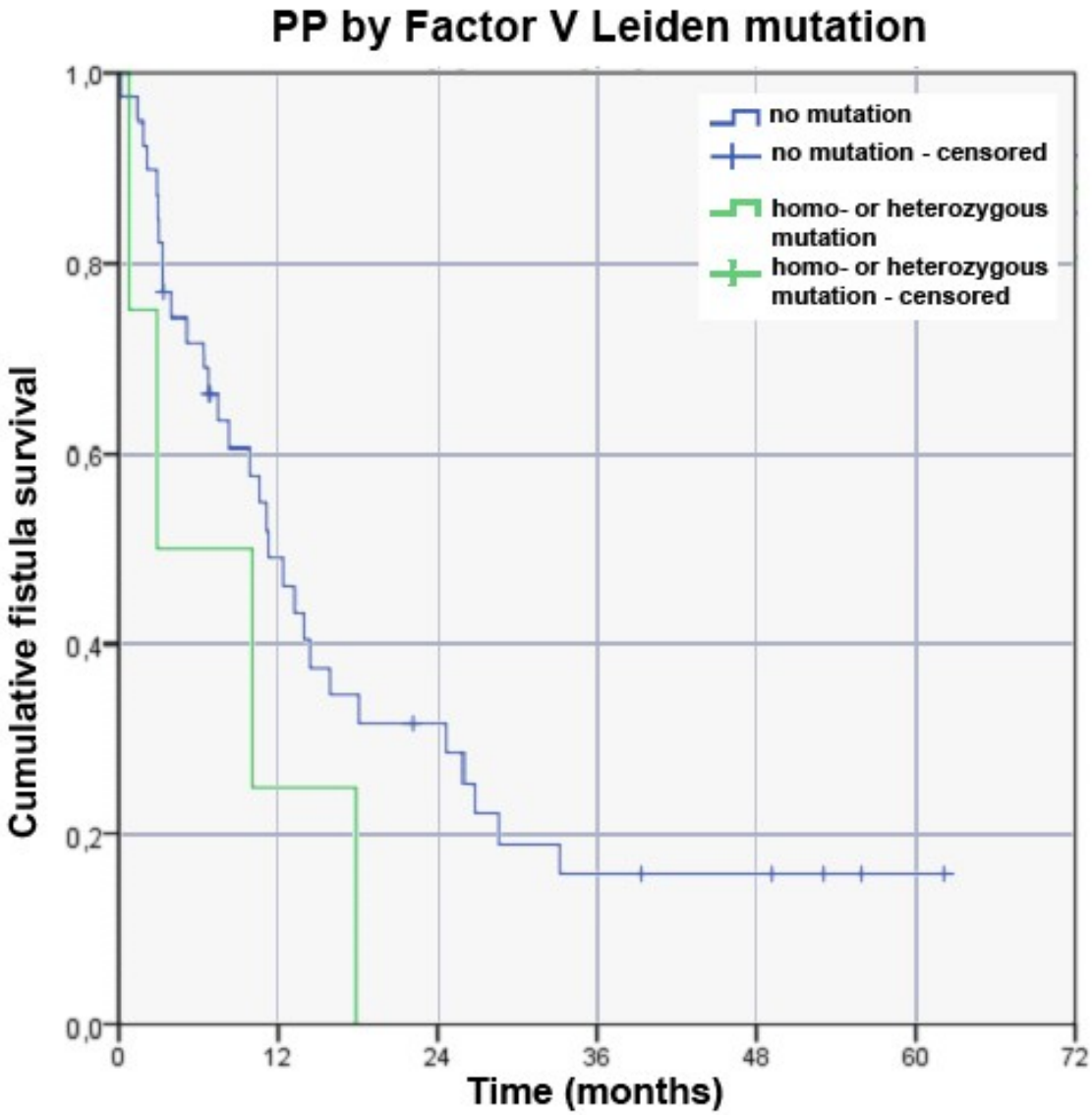

Figure 2: Relative number of working shunts plotted over PP [months] for patients with and without Factor V Leiden mutation. Time: primary patency [M]. Evaluated with Kaplan Meier method

8.7 Prothrombin G20210A mutation

8.7.1 Frequencies - Prothrombin G20210A mutation

No one of the 43 patients had a prothrombin G20210A mutation (Table 12).

Table 12: Distribution of prothrombin G20210A mutation; GG: no mutation, GA: heterozygous, AA: homozygous, n: number of evaluable values

n	GG	GA	AA
43	43 (100.0 %)	0.0	0.0

8.7.2 PP - Prothrombin G20210A mutation - correlation

Since there were no cases with a prothrombin G2021A mutation, an evaluation for this subgroup was not possible.

8.8 Homocysteine

8.8.1 Blood level - Homocysteine

41 patients could be evaluated for homocysteine. For the rest of the patients the according analysis results were not available in the preexisting data. The mean homocysteine blood level of the 41 patients was 21.91 (± 1.30 SE) µmol/dL, the 95 % confidence interval for mean had a lower bound of 19.27 µmol/dL and an upper bound of 24.54 µmol/dL. The 5 % trimmed mean was 21.79 µmol/dL and the median 21.60 µmol/dL. The variance was 69.77 µmol/dL and the standard deviation 8.35 µmol/dL. The values had a minimum of 6.50 µmol/dL and a maximum of 39.00 µmol/dL and there was a range of 32.50 µmol/dL. The interquartile range was 12.60 µmol/dL, the skewness was 0.17 (± 0.37 SE) and the kurtosis -0.62 (± 0.73 SE) (Table 13).

Table 13: Statistic evaluation of homocysteine [µmol/dL]

Descriptives - Homocysteine			
		Statistic [µmol/dL]	Std. Error [µmol/dL]
Mean		21.91	1.30
95% Confidence Interval for Mean	Lower Bound	19.27	
	Upper Bound	24.54	
5% Trimmed Mean		21.79	
Median		21.60	
Variance		69.77	
Std. Deviation		8.35	
Minimum		6.50	
Maximum		39.00	
Range		32.50	
Interquartile Range		12.60	
Skewness		0.17	0.37
Kurtosis		-0.62	0.73

8.8.2 PP – Homocysteine - correlation

The homocysteine level did not show significant correlation with the PP ($p = 0.485$).

8.9 Lipoprotein a

8.9.1 Blood level - Lipoprotein a

All 43 patients had evaluable lipoprotein a values. The mean was 30.51 (± 4.67 SE) mg/dL, the 95 % confidence interval for mean had a lower bound of 21.08 mg/dL and an upper bound of 39.93 mg/dL. The 5 % trimmed mean was 27.35 mg/dL and the median 12.60 mg/dL. The variance was 937.76 mg/dL and the standard deviation 30.62 mg/dL. The values had a minimum of 9.30 mg/dL and a maximum of 115.00 mg/dL and there was a range of 105.70 mg/dL. The interquartile range was 42.90 mg/dL, the skewness was 1.41 (± 0.36 SE) and the kurtosis 0.76 (± 0.71 SE) (Table 14).

Table 14: Statistic evaluation of lipoprotein a [mg/dL]

Descriptives - Lipoprotein a			
		Statistic [mg/dL]	Std. Error [mg/dL]
Mean		30.51	4.67
95% Confidence Interval for Mean	Lower Bound	21.08	
	Upper Bound	39.93	
5% Trimmed Mean		27.35	
Median		12.60	
Variance		937.76	
Std. Deviation		30.62	
Minimum		9.30	
Maximum		115.00	
Range		105.70	
Interquartile Range		42.90	
Skewness		1.41	0.36
Kurtosis		0.76	0.71

8.9.2 PP – Lipoprotein a - correlation

The lipoprotein a level did not show significant correlation with the PP (p = 0.893).

8.10 Protein C activity

8.10.1 Blood level - Protein C activity

38 of 43 patients had an evaluable protein C activity value. For the rest of the patients the according analysis results were not available in the preexisting data. Protein C activity is commonly tested by comparison of the sample to a standardized normal plasma. Therefore values over 100 % are possible. For this study the mean was 111.42 (± 1.86 SE) %, the 95 % confidence interval for mean had a lower bound of 107.65 % and an upper bound of 115.20 %. The 5 % trimmed mean was 112.73 % and the median 116.50 %. The variance was 131.82 % and the standard deviation 11.48 %. The values had a minimum of 67.00 % and a maximum of 120.00 % and there was a range of 53.00 %. The

interquartile range was 16.30 %, the skewness was -1.88 (± 0.38 SE) and the kurtosis 4.66 (± 0.75 SE) (Table 15).

Table 15: Statistic evaluation of the protein C activity [%]

Descriptives - Protein C activity			
		Statistic [%]	Std. Error [%]
Mean		111.42	1.86
95% Confidence Interval for Mean	Lower Bound	107.65	
	Upper Bound	115.20	
5% Trimmed Mean		112.73	
Median		116.50	
Variance		131.82	
Std. Deviation		11.48	
Minimum		67.00	
Maximum		120.00	
Range		53.00	
Interquartile Range		16.30	
Skewness		-1.88	0.38
Kurtosis		4.66	0.75

The results show that 7 patients (16.3 %) had a value below 100 % and 31 patients had a value above or equal 100 %. For a better overview, the group above or equal 100 % was divided into 3 subgroups with the defined intervals of 100 % - 109 %, 110 % - 119 % and above or equal 120 %. 5 patients (11.6 %) showed to have a volume between 100 % and 109 %. 11 patients (25.6 %) were between 110 % and 119 % and over 120 % were 15 patients (34.9 %) (Table 16).

Table 16: Classification of the protein C activity values in groups < 100 and ≥ 100 [%]; < 100, 100 - 109, 110 - 119, and ≥ 120 [%];n: number of evaluable values

n	< 100 %	≥ 100 %	< 100 %	100 - 109 %	110 - 119 %	≥ 120 %
38	7 (16.3 %)	31 (72.1 %)	7 (16.3 %)	5 (11.6 %)	11 (25.6 %)	15 (34.9 %)

8.10.2 PP - Protein C activity - correlation

The protein C activity did not show significant correlation with the PP (p = 0.257).

8.11 Fractionated protein S antigen

8.11.1 Blood level - Fractionated protein S antigen

34 of 43 patients had an evaluable fractionated protein S antigen value. For the remaining patients the according analysis results were not available in the preexisting data. Fractionated protein S antigen is commonly tested by comparison of the sample to a standardized normal plasma. Therefore values over 100 % are possible. In this study the mean was 92.56 (± 2.92 SE) %, the 95 % confidence interval for mean had a lower bound of 86.62 % and an upper bound of 98.50 %. The 5 % trimmed mean was 92.39 % and the median 89.00 %. The variance was 290.01 % and the standard deviation 17.03 %. The values had a minimum of 67.00 % and a maximum of 120.00 % and there was a range of 53.00 %. The interquartile range was 30.50 %, the skewness was 0.38 (± 0.40 SE) and the kurtosis -1.22 (± 0.79 SE) (Table 17).

Table 17: Statistic evaluation of the fractionated protein S antigen [%]

Descriptives - Fractionated protein S antigen			
		Statistic [%]	Std. Error [%]
Mean		92.56	2.92
95% Confidence Interval for Mean	Lower Bound	86.62	
	Upper Bound	98.50	
5% Trimmed Mean		92.39	
Median		89.00	
Variance		290.01	
Std. Deviation		17.03	
Minimum		67.00	
Maximum		120.00	
Range		53.00	
Interquartile Range		30.50	
Skewness		0.38	0.40
Kurtosis		-1.22	0.79

To show their distribution the values were divided into two groups. A threshold at 100 % has been chosen. The evaluation showed that 70.6 % of the patients had a value below 100% and 29.4 % were above or equal 100 % (Table 18).

Table 18: Classification of the fractionated protein S antigen values in groups < 100 and ≥ 100;n: number of evaluable values

n	< 100 %	≥ 100 %
34	24 (70.6 %)	10 (29.4 %)

8.11.2 PP - Fractionated protein S antigen - correlation

The fractionated protein S antigen did not show significant correlation with the PP ($p = 0.149$).

8.12 Activated protein C resistance

8.12.1 Response time - Activated protein C resistance

The activated protein C resistance level in the blood could be gathered from 42 patients. For the one missing value the according analysis results were not available in the preexisting data. This dimensionless value shows the ratio of the aPTT with and without added activated protein C. The mean activated protein C resistance level was 4.04 (± 0.16 SE), the 95 % confidence interval for mean had a lower bound of 3.71 and an upper bound of 4.37. The 5 % trimmed mean was 4.11 and the median 4.10. The variance was 1.13 and the standard deviation 1.06. The values had a minimum of 1.00 and a maximum of 5.60 and there was a range of 4.60. The interquartile range was 1.10, the skewness was -1.21 (± 0.37 SE) and the kurtosis 1.61 (± 0.72 SE) (Table 19).

Table 19: Statistic evaluation of the activated protein C resistance

Descriptives - Activated protein C resistance			
		Statistic	Std. Error
Mean		4.04	0.16
95% Confidence Interval for Mean	Lower Bound	3.71	
	Upper Bound	4.37	
5% Trimmed Mean		4.11	
Median		4.10	
Variance		1.13	
Std. Deviation		1.06	
Minimum		1.00	
Maximum		5.60	
Range		4.60	
Interquartile Range		1.10	
Skewness		-1.21	0.37
Kurtosis		1.61	0.72

To show their distribution the values were divided into two groups. A value of 4.0 was chosen as threshold. 45.2 % of the patients had a value below 4.0 and 54.8 % above or equal 4.0 (Table 20).

Table 20: Classification of the activated protein C resistance values in groups < 4.0 and ≥ 4.0 ;n: number of evaluable values

n	< 4.0	≥ 4.0
42	19 (45.2 %)	23 (54.8 %)

The diagnostic laboratory chose a cutoff at a value of 2.9 to differentiate between healthy and pathologic. 9.5 % of the 42 patients had a pathologic activated protein C resistance level below 2.9 in the blood and 90.5 % had a healthy one above 2.9 (Table 21).

Table 21: Classification of the activated protein C resistance values in groups < 2.9 and ≥ 2.9 ;n: number of evaluable values

n	< 2.9	≥ 2.9
42	4 (9.5 %)	38 (90.5 %)

To compare the activated protein C resistance level in the blood with the Factor V Leiden thrombophilia a contingency table has been made. It showed that all patients with a pathologic activated protein C resistance level in the blood also had a heterozygous or homozygous Factor V Leiden thrombophilia (Table 22).

Table 22: Contingency table between activated protein C resistance and Factor V Leiden thrombophilia; RR: no mutation, RQ: heterozygous, QQ: homozygous

Distribution of Factor V Leiden thrombophilia	Activated protein C resistance		Total
	< 2.9	≥ 2.9	
RR	0	38	38
RQ	3	0	3
QQ	1	0	1
Total	4	38	42

8.12.2 PP - Activated protein C resistance - correlation

Activated protein C resistance (APCR) had a significant p-value of 0.005. To display the effect of the APCR on the PP, APCR values were divided into two groups with a threshold of 4.0. The evaluation showed that the mean value of the primary patency of the patients with APCR values below 4.0 was 9.3 (± 2.0 SE) months and that the patients with APCR values above or equal 4.0 was 24.8 (± 4.9 SE). Therefore the difference between the means of these two groups was 15.5 months (Table 23).

Table 23: Classification of the activated protein C resistance values in groups < 4.0 and ≥ 4.0 with the primary patency and the difference [M]; PP: mean value of primary patency [M]

Group range	PP [M]	Difference [M]
< 4.0	9.3 (± 2.0 SE)	15.5
≥ 4.0	24.8 (± 4.9 SE)	

Figure 3 shows the relative number of working shunts for both patient groups (below 4.0 and above or equal 4.0) over time.

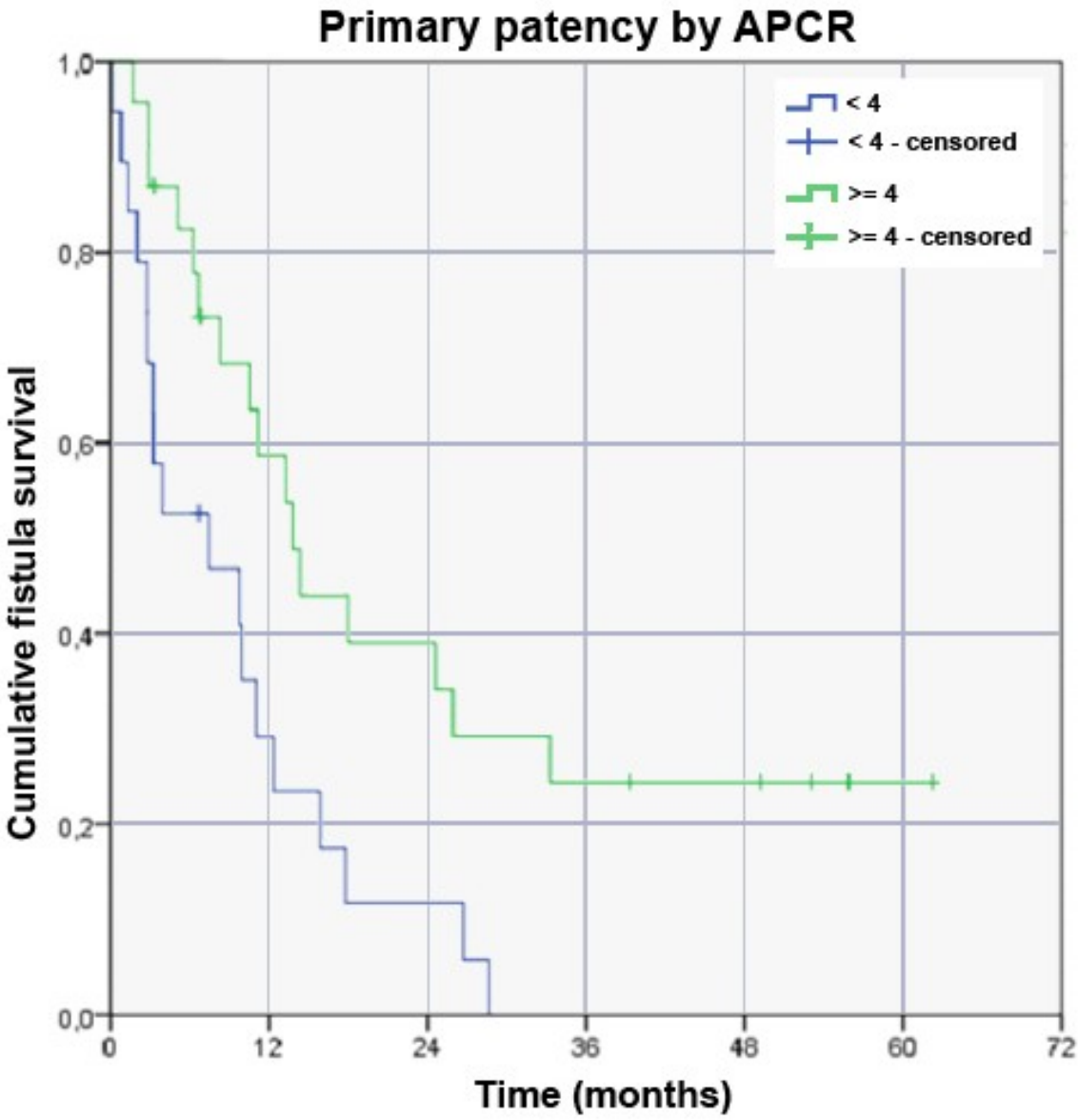

Figure 3: Relative number of working shunts plotted over PP [months] for the activated protein C resistance values divided in groups < 4.0 and ≥ 4.0. Time: primary patency [M]. Evaluated with Kaplan Meier method

8.13 Lupus sensitive activated partial thromboplastin time

8.13.1 Response time - Lupus sensitive activated partial thromboplastin time

The lupus sensitive activated partial thromboplastin time (aPTT) level in the blood could be gathered from 39 patients. For the rest of the patients the according analysis results were not available in the preexisting data. Its dimension is seconds and the mean level was 38.65 (± 1.21 SE) s, the 95 % confidence interval for mean had a lower bound of 36.20 s and an upper bound of 41.09 s.

The 5 % trimmed mean was 38.24 s and the median 37.00 s. The variance was 57.02 s and the standard deviation 7.55 s. The values had a minimum of 25.00 s and a maximum of 61.10 s and there was a range of 36.10 s. The interquartile range was 7.00 s, the skewness was 1.05 (± 0.38 SE) and the kurtosis 1.06 (± 0.74 SE) (Table 24).

Table 24: Statistic evaluation of the lupus sensitive activated partial thromboplastin time [s]

Descriptives - Lupus sensitive activated partial thromboplastin time			
		Statistic [s]	Std. Error [s]
Mean		38.65	1.21
95% Confidence Interval for Mean	Lower Bound	36.20	
	Upper Bound	41.09	
5% Trimmed Mean		38.24	
Median		37.00	
Variance		57.02	
Std. Deviation		7.55	
Minimum		25.00	
Maximum		61.10	
Range		36.10	
Interquartile Range		7.00	
Skewness		1.05	0.38
Kurtosis		1.06	0.74

To show their distribution the values were divided into four groups. There is one group for values below or equal 30 s, one for values between 30 s and 40 s, one for values between 40 s and 50 s and one for values above 50 s. The greater part of the values, with 71.8 %, was in the group between 30 s and 40 s. 5.1 % were below 30 s. 12.8 % were between 40 s and 50 s and the rest of 10.3 % were above 50 s (Table 25).

Table 25: Classification of the lupus sensitive activated partial thromboplastin time values in groups ≤ 30, > 30 - ≤ 40, > 40 - ≤ 50 and > 50; n: number of evaluable values

n	≤ 30 s	>30 - ≤40 s	>40 - ≤50 s	>50 s
39	2 (5.1 %)	28 (71.8 %)	5 (12.8 %)	4 (10.3 %)

8.13.2 PP - Lupus sensitive activated partial thromboplastin time - correlation

The lupus sensitive activated partial thromboplastin time did not show significant correlation with the PP (p = 0.226).

8.14 Lupus anticoagulant

8.14.1 Response time - Lupus anticoagulant

36 of 43 patients had an evaluable lupus anticoagulant value. For the rest of the patients the according analysis results were not available in the preexisting data. The mean was 44.77 (± 1.11 SE) s, the 95 % confidence interval for mean had a lower bound of 42.52 s and an upper bound of 47.02 s. The 5 % trimmed mean was 44.47 s and the median 43.60 s. The variance was 44.31 s and the standard deviation 6.66 s. The values had a minimum of 29.60 s and a maximum of 66.30 s and there was a range of 36.70 s. The interquartile range was 7.30 s, the skewness was 0.93 (± 0.39 SE) and the kurtosis 2.54 (± 0.77 SE) (Table 26).

Table 26: Statistic evaluation of the lupus anticoagulant [s]

Descriptives - Lupus anticoagulant			
		Statistic [s]	Std. Error [s]
Mean		44.77	1.11
95% Confidence Interval for Mean	Lower Bound	42.52	
	Upper Bound	47.02	
5% Trimmed Mean		44.47	
Median		43.60	
Variance		44.31	
Std. Deviation		6.66	
Minimum		29.60	
Maximum		66.30	
Range		36.70	
Interquartile Range		7.30	
Skewness		0.93	0.39
Kurtosis		2.54	0.77

8.14.2 PP - Lupus anticoagulant - correlation

The lupus anticoagulant did not show significant correlation with the PP ($p = 0.565$).

8.15 Anti-cardiolipin antibodies

8.15.1 Blood level - Anti-cardiolipin antibodies

21 of 43 patients had an evaluable anti-cardiolipin antibodies value. For the rest of the patients the according analysis results were not available in the preexisting data. The mean was 2.59 (± 0.27 SE) U/mL, the 95 % confidence interval for mean had a lower bound of 2.04 U/mL and an upper bound of 3.15 U/mL. The 5 % trimmed mean was 2.51 U/mL and the median 2.30 U/mL. The variance was 1.49 U/mL and the standard deviation 1.22 U/mL. The values had a minimum of 0.50 U/mL and a maximum of 6.10 U/mL and there was a range of 5.60 U/mL. The interquartile range was 1.30 U/mL, the skewness was 1.25 (± 0.50 SE) and the kurtosis 2.56 (± 0.97 SE) (Table 27).

Table 27: Statistic evaluation of the anti-cardiolipin antibodies [U/mL]

Descriptives - Anti-cardiolipin antibodies			
		Statistic [U/mL]	Std. Error [U/mL]
Mean		2.59	0.27
95% Confidence Interval for Mean	Lower Bound	2.04	
	Upper Bound	3.15	
5% Trimmed Mean		2.51	
Median		2.30	
Variance		1.49	
Std. Deviation		1.22	
Minimum		0.50	
Maximum		6.10	
Range		5.60	
Interquartile Range		1.30	
Skewness		1.25	0.50
Kurtosis		2.56	0.97

To show their distribution the values were divided into two groups. The threshold was chosen to be 2.5 U/mL. 57.1 % of the patients had a volume below or equal 2.5 U/mL and 42.9 % were above 2.5 U/mL (Table 28).

Table 28: Classification of the anti-cardiolipin antibodies values in groups ≤ 2.5 and > 2.5;n: number of evaluable values

n	≤ 2.5 U/mL	>2.5 U/mL
21	12 (57.1 %)	9 (42.9 %)

8.15.2 PP - Anti-cardiolipin antibodies - correlation

The anti-cardiolipin antibodies had a p-value of 0.075. The values were divided into two groups with a threshold at 2.5 U/mL. The mean of the primary patency for the anti-cardiolipin antibodies values below or equal 2.5 U/mL was 24.9 M (± 6.0 SE) and for above 2.5 U/mL it was 9.4 (± 2.5 SE). Therefore the difference between those means was 15.5 M (Table 29).

Table 29: Classification of the anti-cardiolipin antibodies values in groups ≤ 2.5 and > 2.5 [U/mL] and the difference [M]; PP: mean value of primary patency [M]

Group range [U/mL]	PP [M]	Difference [M]
≤ 2.5	24.9 (± 6.0 SE)	15.5
> 2.5	9.4 (± 2.5 SE)	

Figure 4 shows the relative number of working shunts for both patient groups (below or equal 2.5 and above 2.5) over time.

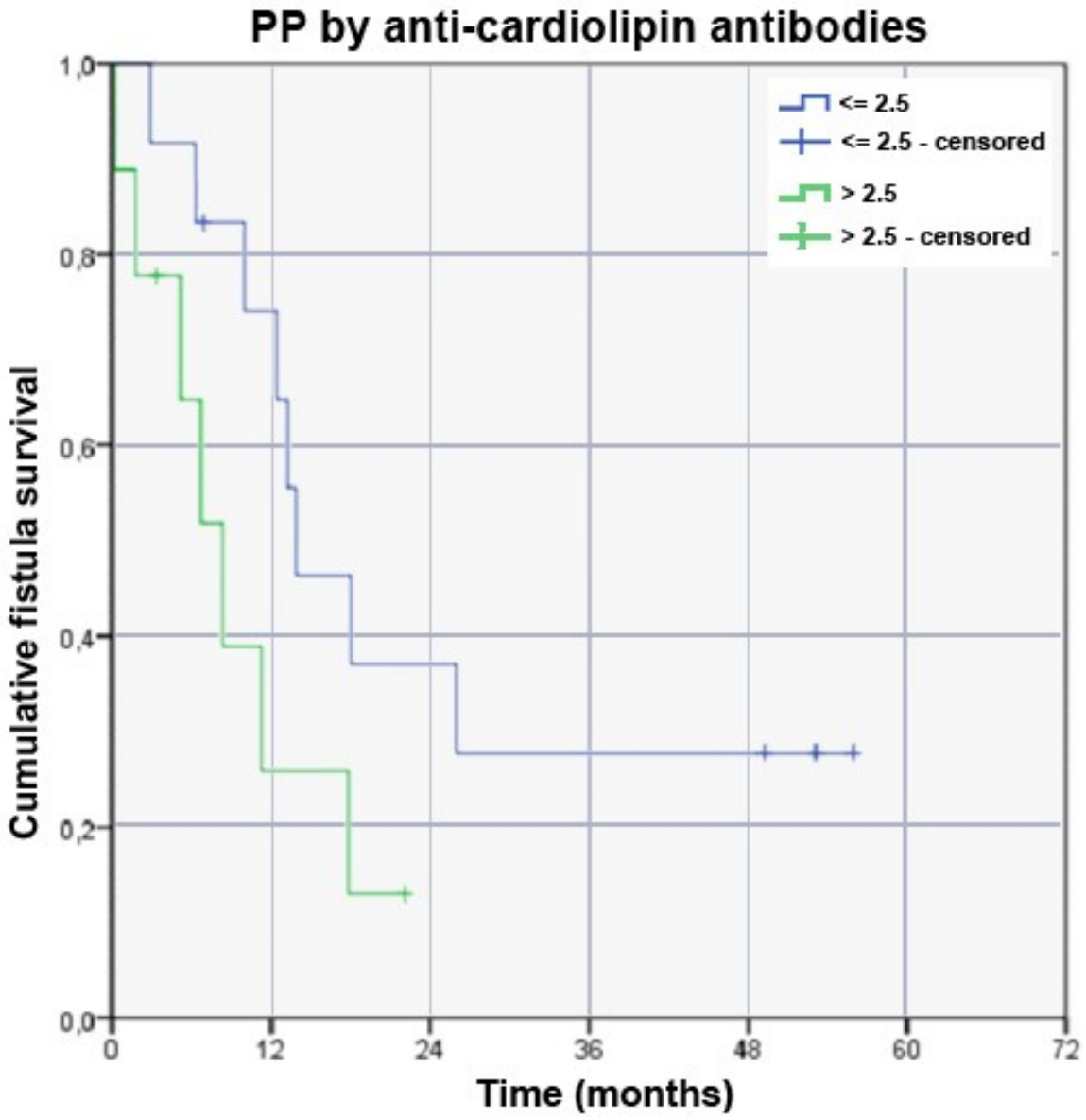

Figure 4: Relative number of working shunts plotted over PP [months] for the anti-cardiolipin antibody values divided in groups ≤ 2.5 and > 2.5 [U/mL]; Time: primary patency [M]. Evaluated with Kaplan Meier method

8.16 ß2-glycoprotein antibodies

8.16.1 Blood level - ß2-glycoprotein antibodies

21 of 43 patients had an evaluable ß2-glycoprotein antibodies value. For the rest of the patients the according analysis results were not available in the preexisting data. The mean was 2.65 (± 0.28 SE) U/mL, the 95 % confidence interval for mean had a lower bound of 2.01 U/mL and an upper bound of 3.24 U/mL. The 5 % trimmed mean was 2.60 and the median 2.60 U/mL. The variance was 1.66 U/mL

and the standard deviation 1.29 U/mL. The values had a minimum of 0.50 U/mL and a maximum of 5.70 U/mL and there was a range of 5.20 U/mL µmol/dL. The interquartile range was 1.90 U/mL, the skewness was 0.50 (± 0.50 SE) and the kurtosis -0.05 (± 0.97 SE) (Table 30).

Table 30: Statistic evaluation of the ß2-glycoprotein antibodies [U/mL]

Descriptives - ß2-glycoprotein antibodies			
		Statistic [U/mL]	Std. Error [U/mL]
Mean		2.65	0.28
95% Confidence Interval for Mean	Lower Bound	2.01	
	Upper Bound	3.24	
5% Trimmed Mean		2.60	
Median		2.60	
Variance		1.66	
Std. Deviation		1.29	
Minimum		0.50	
Maximum		5.70	
Range		5.20	
Interquartile Range		1.90	
Skewness		0.50	0.50
Kurtosis		-0.05	0.97

8.16.2 PP - ß2-glycoprotein antibodies - correlation

The lupus ß2-glycoprotein antibodies did show significant correlation with the PP (p = 0.153).

9 Discussion

In this study we tried to correlate various relevant genetic predispositions and blood parameters with the primary patency of implanted PTFE shunt prostheses. For that goal the available data were statistically evaluated and p-values were calculated. The results will be discussed in the same order as they appear above.

An overall number of 43 patients with 59 shunts were evaluable. For patients with more than one shunt, only one of those shunts was taken into account for the statistical evaluation. The selection process was randomized to avoid biasing of the data which created a lack of precision in evaluating the age of the 43 patients. The mean age of the 43 patients was 63.71 (± 1.62 SE) years at the time of shunt implantation. 58.1 % were female (25/43) and 41.9 % (18/43) male. These results match very well with an already conducted and published study about PTFE grafts and their primary patency (25).

The mean primary patency of the investigated 43 patients (59 shunts) in this study was 18.44 (± 3.16 SE) months. We found a published study about PTFE shunts and PP with which our results correlate very well (25).

We did not succeed in our primary aim to connect the PP with the heterozygous MTHFR mutation. With a p-value of 0.370, it was not significant. An interesting observation can be deducted from Table 8. The mean values for PP for no MTHFR mutation as well as for heterozygous and homozygous mutations are in the same range, when the standard error is taken into account. These findings contradict other studies which indicate that MTHFR mutation is a risk factor for vascular access thrombosis in hemodialysis patients (26,27). In the literature research for this work we found no other publications that specifically combine PTFE shunts with heterozygous MTHFR mutations. Usually a set of various shunt types is evaluated at once, which prohibits a strict differentiation. To our knowledge this study is the first one addressing this particular issue.

Furthermore we found that 55.8 % of the patients were heterozygous for the MTHFR mutation and 11.6 % homozygous (Table 7). Due to another study (28) approximately 50 % of the population in the Netherlands were heterozygous for

the MTHFR mutation and 12 % homozygous. These results match very well with ours.

Also the mean primary patency difference between no Factor V Leiden thrombophilia and heterozygous or homozygous mutation failed statistical significance ($p = 0.141$). 9.3 % of our patients had a Factor V Leiden thrombophilia (heterozygous + homozygous) (Table 9). Again this is in good accordance with another study which shows that Factor V Leiden mutation is very common with a prevalence of 5% in the population (29).

As can be seen in Table 22, all of our patients with a Factor V Leiden mutation (heterozygous or homozygous) showed pathologic activated protein C resistance (APCR) values. It is not too farfetched to conclude that a pathologic APCR value is highly predictive for a Factor V Leiden mutation. There have already been studies about that (30). But there is also another study, which shows that the heterozygous Factor V Leiden mutation does not appear to represent a risk factor for a thrombosis (31). This mutation has to be treated with oral anticoagulants, if there is an event or a risk factor. In our opinion the main conclusion from our study is that a PTFE shunt should be considered as such a risk factor. Therefore we suggest that patients with this mutation and a PTFE shunt prosthesis should be treated with oral anticoagulation.

There were no patients with a prothrombin 20210A mutation, which made it impossible to conduct an evaluation. The incidence for heterozygous prothrombin 20210A mutation in Germany is 2-3 % and for homozygous mutation 0.05 % (32). Due to our sample size it is not surprising that we had no patients with a prothrombin 20210A mutation.

The patients' homocysteine blood level did not significantly influence the PP ($p = 0.485$). Additionally to genetic factors the homocystein level can also be influenced by nutrition, environmental factors and specific medications (33). To find a more reliable homocystein value all those factors need to be taken into account. Another trial with a more sophisticated design is necessary to evaluate the influence of homocysteine on the PP of PTFE shunt prostheses.

Lipoprotein a failed statistical significance (p = 0.893). Most of the evaluated patients exhibited a normal blood level of lipoprotein a. Literature shows that approximately 30 % of the patients with hypercholesterinemia also have a high lipoprotein a. A high lipoprotein a level can increase the risk of thrombosis, heart attack and stroke. Especially the combination of a hypercholesterinemia and a high lipoprotein a level increases the risk for thrombotic events. This combination wasn't reviewed in this study but might have an influence on the primary patency and should be taken into account in further trials (9).

Protein C activity and fractionated protein S antigen are important components of the blood clotting system. A lack of these proteins can cause thrombosis. The mean primary patency correlation with the fractionated protein S antigen failed statistical significance (p = 0.149) as well as the correlation with protein C activity (p = 0.257).

As only evaluated test variable APCR (activated protein C resistance) showed a significant p-value of 0.005 for the correlation with PP. The values in Table 23 indicate a strong increase of PP with a APCR value above or equal a threshold of 4.0. The difference between the groups below 4.0 (19/42 patients) and above or equal 4.0 (23/42 patients) is 15.5 months.

On the one hand the lupus anticoagulants elongate the aPTT but on the other hand cause thromboses. Both lupus aPTT as well as lupus anticoagulant failed statistical significance (p = 0.226 and p = 0.565). Lupus aPTT and lupus anticoagulant are values also determined to diagnose an autoimmune disease (34,35).

The anti-cardiolipin antibodies can be seen in the blood of patients with a primary or secondary antiphospholipid syndrome (34). Anti-cardiolipin antibodies, ß2-glycoprotein antibodies and lupus anticoagulant are antiphospholipid antibodies (36). It was already shown that patients, which had to undergo vascular surgery, exhibited a lower duration of PP, if those antibodies were found in their system (37). We did not find a similar correlation between the antibodies and PP. Neither the anti-cardiolipin antibodies (p = 0.141), the ß2-glycoprotein antibodies (p = 0.153), nor the lupus anticoagulant, as discussed above, showed significance.

Summing up we can say that the main aim, the heterozygous MTHFR mutation, had no significant effect on the PP. Furthermore we can say that all of our patients with a Factor V Leiden mutation (heterozygous or homozygous) showed pathologic activated protein C resistance (APCR) values. > 9 % of the investigated patients had a Factor V Leiden mutation. Thrombectomies are a common complication for a haemodialysis patient with a PTFE shunt. A thrombophilia screening for all shunt prostheses patients could help to decrease the complication rates. None of the other investigated factors showed a significant p-value under 0.05.

10 References

1. Genetics Home Reference. [Online].; 2016 [cited 2016 may 13. Available from: https://ghr.nlm.nih.gov/gene/MTHFR#conditions.

2. Margaglione M, D'Andrea G, d'Addedda M, Giuliani N, Cappucci G, Iannaccone L, et al. The methylenetetrahydrofolate reductase TT677 genotype is associated with venous thrombosis independently of the coexistence of the FV Leiden and the prothrombin A20210 mutation. Thromb Haemost. 1998: p. 907-11.

3. Kluijtmans L, den Heijer M, Reitsma P, Heil S, Blom H, Rosendaal F. Thermolabile methylenetetrahydrofolate reductase and factor V Leiden in the risk of deep-vein thrombosis. Thromb Haemost. 1998: p. 254-8.

4. Arruda V, von Zuben P, Chiaparini L, Annichino-Bizzacchi J, Costa F. The mutation Ala677Val in the methylene tetrahydrofolate reductase gene: a risk factor for arterial disease and venous thrombosis. Thromb Haemost. 1997: p. 818-21.

5. den Heijer M, Koster T, Blom H, Bos G, Briet E, Reitsma P, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis [comments]. N Engl J Med. 1996: p. 759-62.

6. Graham I, Daly L, Refsum H, Robinson K, Brattstrom L, Ueland P, et al. Plasma homocysteine as a risk factor for vascular disease. The European Concerted Action Project. JAMA. 1997: p. 1775-81.

7. Genetics Home Reference. [Online].; 2016 [cited 2016 november 9. Available from: https://ghr.nlm.nih.gov/condition/factor-v-leiden-thrombophilia.

8. Genetics Home Reference. [Online].; 2016 [cited 2016 november 9. Available from: https://ghr.nlm.nih.gov/condition/prothrombin-thrombophilia.

9. Lipoprotein foundation. [Online].; 2016 [cited 2016 november 9. Available from: http://www.lipoproteinafoundation.org/?page=UnderstandLpa.

10. Dove Med. [Online].; 2016 [cited 2016 november 9. Available from: http://www.dovemed.com/common-procedures/procedures-laboratory/activated-protein-c-resistance-blood-test/.

11. Wikipedia. [Online].; 2016 [cited 2016 november 9. Available from: https://en.wikipedia.org/wiki/Lupus_anticoagulant.

12. Wikipedia. [Online].; 2016 [cited 2016 november 9. Available from: https://en.wikipedia.org/wiki/Cardiolipin.

13. Wikipedia. [Online]. [cited 2016 11 29. Available from: https://en.wikipedia.org/wiki/Anti-cardiolipin_antibodies.

14. E.Lazic S. Experimental Design for Laboratory Biologists. 1st ed. Press CU, editor. United Kingdom: Cambridge University Press; 2017.

15. Wikipedia. https://en.wikipedia.org/wiki/Mean. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Mean.

16. WikiHow. http://de.wikihow.com/Konfidenzintervalle-berechnen. [Online]. [cited 2017 02 25. Available from: http://de.wikihow.com/Konfidenzintervalle-berechnen.

17. Köln U. ESWF. [Online]. [cited 2017 02 25. Available from: http://eswf.uni-koeln.de/lehre/stathome/statcalc/v2101b.htm.

18. Wikipedia. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Truncated_mean.

19. Wikipedia. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Median.

20. Wikipedia. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Variance.

21. Wikipedia. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Standard_deviation.

22. Wikipedia. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Interquartile_range.

23. Wikipedia. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Skewness.

24. Wikipedia. [Online]. [cited 2017 02 25. Available from: https://en.wikipedia.org/wiki/Kurtosis.

25. Ravari H, Kazemzade GH, Modaghegh MHS, Khashayar P. Patency rate and complications of polytetrafluoroethylene grafts compared with polyurethane grafts for hemodialysis access. Upsala Journal of Medical Sciences. 2010 Oct: p. 245-248.

26. Fekih-Mrissa N, Klai S, Bafoun A, Nciri B, Hmida J, Gritli N. Role of Thrombophilia in Vascular Access Thrombosis Among Chronic Hemodialysis Patients in Tunisia. Therapeutic Apheresis and Dialysis. 2010: p. 40-43.

27. Fukasawa M, Matsushita K, Kamiyama M, Mikami Y, Araki I, Yamagata Z, et al. The Methylentetrahydrofolate Reductase C677T Point Mutation Is a Risk Factor for Vascular Access Thrombosis in Hemodialysis Patients. American Journal of Kidney Diseases. 2003: p. 637-642.

28. Verhoef P, Kok F, Kluijtmans L, Blom H, Refsum H, Ueland P, et al. The 677C-->T mutation in the methylenetetrahydrofolate reductase gene: associations with plasma total homocysteine levels and risk of coronary atherosclerotic disease. Atherosclerosis. 1997: p. 105-13.

29. Doccheck. [Online].; 2016 [cited 2016 november 10. Available from: http://flexikon.doccheck.com/de/Faktor-V-Leiden-Mutation.

30. Androulakis N, Tzenakis N, Nioti E, Spatharaki P, Vyzoukaki R, Papadopoulou A, et al. Activated Protein C-Resistance Determination and Vascular Access Thrombosis in Populations with High Prevalence of Factor V Leiden. Nephron. 2015: p. 5-10.

31. Födinger M, Mannhalter C, Pabinger I, Koizar D, Rintelen C, Hörl W, et al. Resistance to activated protein C (APC): mutation at Arg506 of coagulation factor V and vascular access thrombosis in haemodialysis patients. Nephrology Dialysis Transplantation. 1996 Apr: p. 668-672.

32. Doccheck. [Online].; 2016 [cited 2016 november 10. Available from: http://flexikon.doccheck.com/de/Prothrombinmutation_G20210A.

33. Emedicine. [Online].; 2016 [cited 2016 november 10. Available from: http://emedicine.medscape.com/article/1952251-overview.

34. Öffentliches Gesundheitsportal Österreichs. [Online].; 2016 [cited 2016 november 10. Available from: https://www.gesundheit.gv.at/Portal.Node/ghp/public/content/labor/referenzwerte/labor-aptt-lupus-sensitiv-apttl.html.

35. Lab Tests Online. [Online].; 2016 [cited 2016 november 10. Available from: https://labtestsonline.org/understanding/analytes/lupus-anticoagulant/tab/test/.

36. The Johns Hopkins Lupus Center. [Online]. [cited 2017 02 27. Available from: https://www.hopkinslupus.org/lupus-tests/antiphospholipid-antibodies/.

37. Taylor LMJ, Chitwood RW, Dalman RL, Sexton G, Goodnight SH, Porter JM. Antiphospholipid antibodies in vascular surgery patients. A cross-sectional study. Annals of Surgery. 1994 Oct: p. 544-551.

11 Titles

Title English long

The impact of methylenetetrahydrofolate reductase (MTHFR) mutations on the primary patency of PTFE haemodialysis shunt prostheses

Title English short

The impact of MTHFR mutations on the primary patency

Titel Deutsch lang

Der Effekt der Methylentetrahydrofolatreduktase (MTHFR) Mutation auf die primäre Offenheit der PTFE Hämodialyse Shunts

Titel Deutsch kurz

Der Effekt der MTHFR Mutation auf die primäre Shuntoffenheit

Titel Deutsch Patienten lang

Einfluss von angeborenen Gerinnungsstörungen auf die Offenheit von Kunststoff-Shunts

Titel Deutsch Patienten kurz

Einfluss von angeborenen Gerinnungsstörungen

12 Appendix

12.1 Informed consent

PatientInneninformation[1] und Einwilligungserklärung zur Teilnahme an der klinischen Studie

Einfluss von angeborenen Gerinnungsstörungen auf die Offenheit von Kunststoff-Shunts

(Englischer Originaltitel: The impact of methylenetetrahydrofolate reductase (MTHFR) mutations on the primary patency of PTFE haemodialysis shunt prostheses)

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Wir laden Sie ein an der oben genannten klinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Ihre Teilnahme an dieser klinischen Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Klinische Studien sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im Klaren sind.

Zu dieser klinischen Studie, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

[1] Wegen der besseren Lesbarkeit wird im weiteren Text zum Teil auf die gleichzeitige Verwendung weiblicher und männlicher Personenbegriffe verzichtet. Gemeint und angesprochen sind – sofern zutreffend – immer beide Geschlechter.

1. Was ist der Zweck der klinischen Studie?

Der Zweck dieser klinischen Studie ist herauszufinden, ob eine bestimmte angeborene Gerinnungsstörung einen Einfluss auf die primäre Shuntoffenheit von Kunststoff-Shunts hat.

2. Wie läuft die klinische Studie ab?

Diese klinische Studie wird an unserer Klinik durchgeführt und es werden insgesamt ungefähr 80 Personen daran teilnehmen. Ihre Teilnahme an dieser klinischen Studie wird voraussichtlich 15 Minuten dauern.

Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:

Es erfolgt eine einmalige Blutabnahme und eine Anamneseerhebung.

3. Worin liegt der Nutzen einer Teilnahme an der Klinischen Studie?

Durch die Teilnahme an dieser Studie erhalten Sie Informationen über Ihre derzeitige Blutgerinnung und ob angeborene Gerinnungsstörungen vorhanden sind. Das Ergebnis der Blutgerinnungsstörung könnte sein, dass Sie eine spezielle Therapie zur Verhinderung von Thrombosen (Bildung von Blutgerinnsel) benötigen.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Im Rahmen der Blutabnahme kann es wie bei anderen Blutabnahmen auch zu einem kurzen Schmerz während des Einstechens kommen. Außerdem kann ein Bluterguss entstehen, der aber innerhalb weniger Tage verschwinden wird.

5. Zusätzliche Einnahme von Arzneimitteln?

Die Teilnahme an dieser Studie hat keinen Einfluss darauf, wann und welche Medikamente Sie einnehmen, dies weder im Vorfeld der Studie, während ihrer Laufzeit.

6. Hat die Teilnahme an der klinischen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Die Teilnahme an dieser Studie hat keine Auswirkungen auf Ihre Lebensführung, es ergeben sich aus ihr keine Verpflichtungen.

7. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten während der Blutabnahme irgendwelche Symptome, Begleiterscheinungen auftreten, müssen Sie diese Ihrem Arzt sofort mitteilen.

8. Wann wird die klinische Studie vorzeitig beendet?

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden ohne dass Ihnen dadurch irgendwelche Nachteile für Ihre weitere medizinische Betreuung entstehen.

Ihr Studienarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur **weiteren** Teilnahme an dieser klinischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Studienarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

a) Sie können den Erfordernissen der Klinischen Studie nicht entsprechen;

b) Ihr Studienarzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Studie nicht in Ihrem Interesse ist;

c) der für diese Studie Hauptverantwortliche (Principal investigator) trifft die Entscheidung, die gesamte klinische Prüfung abzubrechen, oder lediglich Ihre Teilnahme vorzeitig zu beenden.

11. In welcher Weise werden die im Rahmen dieser klinischen Studie gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die Studienärzte und deren Mitarbeiter Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden („personenbezogene" Daten). Weiteres können Beauftragte von inländischen Gesundheitsbehörden, der zuständigen Ethikkommission, sowie – wenn zutreffend – des für diese Studie Hauptverantwortlichen Einsicht in diese Daten nehmen, um die Richtigkeit der Aufzeichnungen zu überprüfen. Diese Personen unterliegen einer gesetzlichen Verschwiegenheitspflicht.

Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken in verschlüsselter (nur „indirekt personenbezogener") oder nicht personenbezogener („anonymisierter") Form, das heißt, Sie werden nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser Studie werden Sie nicht namentlich genannt.

Die Studienärzte und ihre Mitarbeiter unterliegen im Umgang mit den Daten den Bestimmungen des österreichischen Datenschutzgesetzes 2000 in der jeweils geltenden Fassung.

Wenn Sie Ihre Einwilligung zurückziehen und damit Ihre Teilnahme vorzeitig beenden, werden keine neuen Daten mehr über Sie erhoben. Sie haben laut Datenschutzgesetz die Möglichkeit, auch die Verwendung bereits erhobener Daten zu untersagen.

12. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Prüfung entstehen für Sie keine zusätzlichen Kosten. Sie erhalten für die Teilnahme an dieser klinischen Prüfung keine Vergütung.

13. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Studienarzt und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Patient und Teilnehmer an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

Name der Kontaktperson: OA Dr. Peter Konstantiniuk

Ständig erreichbar unter: 0316/385-12804

14. Sollten andere behandelnde Ärzte von der Teilnahme an der klinischen Studie informiert werden?

Eine Information von anderen Ärzten ist nicht erforderlich.

15. Wo kann ich weitere Informationen einholen?

Mag[a]. Renate Skledar
Patientinnenvertretung Steiermark
Friedrichgasse 9
8010 Graz
Tel: 0316 877-3350, -3191, -3318

16. Einwilligungserklärung

Name des Patienten in Druckbuchstaben: .....

Geb.Datum: ..... Code: .....

Ich erkläre mich bereit, an der klinischen Studie *Einfluss von angeborenen Gerinnungsstörungen* teilzunehmen.

Ich bin von Herrn/Frau (Dr. med.) ..... ausführlich und verständlich über mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Studie, sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 5 Seiten umfasst gelesen. Aufgetretene Fragen wurden mir vom Studienarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile für meine weitere medizinische Betreuung entstehen.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte der zuständigen Behörden beim Studienarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

Die Bestimmungen des Datenschutzgesetzes in der geltenden Fassung werden eingehalten.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Studienarzt.

.....
(Datum und Unterschrift des Patienten)

.....
(Datum, Name und Unterschrift des verantwortlichen Arztes)

(Der Patient erhält eine unterschriebene Kopie der Patienteninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Studienarztes.)

12.2 CRF

The impact of MTHFR mutations on the primary patency – CRF

Einfluss von angeborenen Gerinnungsstörungen

Patient: (VN, NN, Geb. Datum)_____ **ID** (fortlaufende Nummer): _____

Telefonnummer:_____ **Aufklärungsdatum**: _____

Geschlecht: männlich O weiblich O

Größe: _____ **Gewicht**: _____ Amputation:_____

Datum des **Shunteinbaues**: _____

Datum des **Shuntverschlusses**: _____

Weitere **Shuntverschlüsse**: _____

Abbruch des Dialyseshunts (Datum und Gründe): _____

Diabetes: kein DM O Diät O Orale Therapie O Insulin O

Rauchverhalten: nie geraucht O früher geraucht O aktiver Raucher O

Packyears: _____

Hypertonus: nein O hyperton ohne Medika O hyperton unter Medika O

normoton unter Medika O

Schlaganfall (Anzahl und Daum): _____

Herzinfarkt (Anzahl und Datum, Vorhofflimmer, Klappenersatz): _____

Thrombosen (Anzahl und Datum, venös/arteriell): _____

Mobilitätseinschränkung: _____

Malignome (was und seit wann): _____

derzeitige **Medikation** (Medikament, Dosierung, Einnahme): _____

_____

_____

_____

GGT (vom OP-Tag): _____ GOT (vom OP-Tag): _____

Sonstiges: _____

_____

_____

Labor

Homocystein: _____µmol/dl

Lp(a): _____mg/dl

APC-Resistenz: _____ (als Zahl ohne Einheit)

Prot-C Akt: _____ %

ProtSAGfr: _____ %

Lupus-APTT: _____s

Lupus_LA1: _____s

LupusRatio: _____ (Zahl ohne Einheit)

MTHFR 677	CC (keine Mutation) O	CT (het) O	TT (hom) O
MTHFR A1298C	AA (keine Mutation) O	AC (het) O	CC (hom) O
FV-Leiden	RR (keine Mutation) O	RQ (het) O	QQ (hom) O
F2-20210A	GG (keine Mutation) O	GA (het) O	AA (hom) O

Cardiolipin AK Screening: _____U/ml

Beta2-Glycoprotein AK Screening: _____U/ml

Sonstiges: _____

_____

_____

_____

Adverse events for details attach separate sheet: _____

Serious adverse events for details attach separate sheet: _____

12.3 Ethic approval

Ethikkommission

Medizinische Universität Graz

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

VOTUM
gültig bis 27.01.2017

EK-Nummer:	28-192 ex 15/16
Studientitel:	The impact of methylenetetrahydrofolate reductase (MTHFR) mutations on the primary patency of PTFE haemodialysis shunt prostheses
Prüfer:	OA Dr. Peter Konstantiniuk MUG
Sponsor:	Univ.Klinik für Chirurgie
Ansprechpartner:	OA Dr. Peter Konstantiniuk, 8036 Graz, Augenbruggerplatz 29
CRO:	-
Antragsteller:	Medizinische Universität Graz
Ansprechpartner:	Stefanie Christine Santler

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 07.01.2016 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 18.12.2015, begutachtet im 'expedited Review' am 07.01.2016		
✓	Antragsformular ECS	18.12.2015
✓	Originalprotokoll study protocol - The impact of MTHFR mutations on the primary patency - Version 02 2015 12 18 02	18.12.2015
	Informed Consent Form Informed Consent - Einfluss von angeborenen Gerinnungsstörungen auf die Offenheit von Kunststoff-Shunts Version 01 2015 12 14 01	14.12.2015
✓	Case Report Form CRF - The impact of MTHFR mutations on the primary patency Version 01 2015 12 14 01	14.12.2015
Dokumente eingegangen am 18.01.2016, begutachtet im 'expedited Review' am 27.01.2016		
✓	Antragsformular ECS Unterschriftenseiten	18.12.2015
✓	Informed Consent Form 02	12.01.2016
✓	Sonstiges: Stellungnahme zur Bearbeitungsmitteilung undatiert	

Die Ethikkommission geht – rechtlich unverbindlich – davon aus, dass es sich um ein Projekt mit genetischen Untersuchungen handelt.

Es handelt sich um eine Studie im Rahmen einer Diplomarbeit.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 27. Jänner 2016

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hermann Toplak
Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!

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