High focused Evaluation of Atherosclerotic risk profile in Retinal Thrombosis: Vascular events Incidence, Sex involvement and Interventional outcomes assessed by Ophthalmologists and internists Network – HEART VISION study protocol

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Abstract

Background and objectives: Retinal vein occlusion (RVO), one of the most relevant causes of vision loss, still represents an open issue in ophthalmology and vascular medicine. Its epidemiology and management approach have not been clearly characterized yet, with several grey zones requiring investigation. Significance of RVO on cardiovascular prognosis is also unclear. "High focused Evaluation of Atherosclerotic risk profile in Retinal Thrombosis: Vascular events Incidence, Sex involvement and Interventional outcomes assessed by Ophthalmologists and internists Network" (HEART VISION) is a longitudinal, prospective, multi-center study which aims at determining the epidemiology, potentially modifiable risk factors and the determinants of RVO in an Italian-based cohort.
Methods: Enrollment of all the eligible patients presenting to recruiting centers (*i.e.* ophthalmology emergency room and thrombosis centers) with suspect of RVO. At baseline, all patients will undergo an opthalmologic evaluation and further investigations about cardiovascular co-morbidities and risk factors. Recruited patients will be followed for a 2-year period.
Outcome measures: Data about adverse cardiovascular events and eye-related outcomes will be recorded.
Discussion: HEART VISION will present data on prevalence and will inform on the prognosis of RVO in an Italian-based cohort. Characterization and prospective evaluation of these patients will be useful in developing novel strategies for management of RVO and their cardiovascular-related risk factors.
Ethics and dissemination: This study protocol (n. 1.0, 01.07.2014) was approved by the Sapienza-University of Rome, Ethics Board (Protocol No. 1076/14). This study will be performed in accordance with the *Declaration of Helsinki*. Dissemination plans include presentations at scientific conferences and publication in scientific journals.
Trial registration: ClinicalTrials.gov Identifier: NCT02257333 on October 6, 2014.

Key words: retinal vein occlusion; vision loss; cardiovascular risk factors; ophthalmology; prospective study

doi: 10.4103/2542-3975.235145
How to cite this article: Basili S, Pacella E, Pacella F, Romiti GF, Visioli G, Antonini LM, Robuffo S, Cangemi R, Mecella M, Proietti M, Raparelli V. High focused Evaluation of Atherosclerotic risk profile in Retinal Thrombosis: Vascular events Incidence, Sex involvement and Interventional outcomes assessed by Ophthalmologists and internists Network – HEART VISION study protocol. Clin Trials Degener Dis. 2018;3(3):101-105.
Funding: This study was funded by Sapienza-University of Rome in 2014 -C26A147HC8.

Introduction

Retinal vein occlusion (RVO) is a highly prevalent cause of unilateral vision loss and the second leading cause of retinal vascular disease after diabetic retinopathy.[1] Nonetheless, the epidemiology, pathophysiology and natural history of this condition have yet to be fully elucidated; besides, due to the lack of definitive data in the literature, the disease management still represents an open issue.[2]

RVO refers to a group of diseases – with different risk factors, prognosis and treatment – all characterized by impaired venous return from the retinal circulation.[3] Depending on the site of occlusion of the retinal vein, it is possible to distinguish two main clinical presentations of RVO: central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), the latter representing most of the cases.[4] A pooled study, which included 11 different cohorts (with a total of 49,869 patients) showed an age and sex- standardized overall prevalence incindence of 0.52% (0.08% for CRVO and 0.42% for BRVO) – which was slightly higher in females, in Asians and Hispanics but with no significant statistical differences – and demonstrated an increased risk with age,[4] probably related to the higher burden of risk factors (RFs) and predisposing

conditions.[5,6]

It has been assumed that RVOs shares the same RFs of cardiovascular disease (*e.g.* arterial hypertension, diabetes, smoking, dyslipidemia, *etc.*).[7-9] However, RVOs, with some differences depending on the type, can also be secondary to other processes such as vasospasm, compression,[10] inflammation[11] and other conditions including thrombophilia,[12] sleep apnea[13,14] or glaucoma[15] could also be associated. In this context, a straightforward definition of cardiovascular RFs in the disease development has not yet been provided and the impact of genetic differences, sex and sociocultural background should not be underestimated.[16] As sex (*i.e.* biological factors) and gender (*i.e.* psycho-social-cultural factors including personality traits, socioeconomic status and social relationship) are not independent, exclusively assessing one or the other fails to account for identified variations in health.[17-20] Therefore, the integration of both sex and gender dimensions is a powerful tool to advance our understanding of the management and outcomes of health disease[18,19] as it has been already proved in patients with acute coronary syndrome.[21]

A deeper knowledge on the impact of traditional and non-traditional RFs in the pathogenesis of RVO would represent a cornerstone in the improvement of primary and secondary prevention strategies, and it could help in developing a personalized management approach for the treatment of RVO patients.

Objectives of the study

The primary objectives of the study are:

1) Creation of RVO patient's national registry to estimate the actual prevalence of the condition.
2) To identify the potentially modifiable RFs and to recognize further potential determinants of the disease related to sex, gender, genetics and socio-cultural background of the population.
3) To verify the real-world management of RVO patients.
4) To gather information for the design of IT application for the management of RVO patients.

Methods/Design

Study design

The "High focused Evaluation of Atherosclerotic risk profile in Retinal Thrombosis: Vascular events Incidence, Sex involvement and Interventional outcomes assessed by Ophthalmologists and internists Network" (HEART VISION) is a longitudinal, prospective, multi-centric study in Italy (**Figure 1**). According to the study design, the first step will consist in the identification of specialized services (*i.e.* ophthalmology emergency room and thrombosis centers) which will enroll patients accessing for suspected RVO. Each center will recruit all the eligible patients, collect written inform consent and all the relevant clinical information according to the study protocol, and will be responsible for the data-entry through the web-based platform. A physician (*i.e.* "local monitor") will be responsible for the adherence to the protocol, standardized operating procedures, and for the management of critical sensitive data in accordance with the current local legislation.

Strengths and limitations

Strengths

- Longitudinal, prospective, multi-center study aimed at determining the epidemiology, potentially modifable risk factors and the determinants of retinal vein occlusion (RVO).
- Real world data on underestimated relevant health problems were obtained to promote high-quality patient-centered care.
- Generating hypothesis on mechanisms underlying RVO and cardiovascular outcomes.

Limitations

- Findings will be country-specific with limited external validity.
- We could not account for all potential confounders or mediating factors in the association between RVO and future cardiovascular outcomes.

In addition, a web-based platform will be developed to enable the management and support to surveys for medical investigation, allowing medical researchers and patients to interact using social features.

Ethical approval

This study protocol (n. 1.0, 01.07.2014) was approved by the Sapienza – University of Rome, Ethics Board (Protocol No. 1076/14). This study will be performed in accordance with the *Declaration of Helsinki*, and it was registered at ClinicalTrials.gov (identifier: NCT02257333).

Study population

All the eligible patients will be consecutively enrolled in the study, according to the inclusion and exclusion criteria defined below.

Inclusion/exclusion criteria

All adults aged > 18 years who access specialized centers with a suspected diagnosis of RVO, and who signed a valid inform consent will be included in the study. Patients would be excluded if a) pregnant, b) affected by a condition which would reduce the life-expectancy to less than the mean time of planned follow-up.

Baseline data collection

At baseline, and after the signature of a valid inform consent, for each patient with suspected RVO the following data will be collected: a) complete personal data and medical history (familiar, past and present) and physical assessment (anthropometric data and vital signs), b) comprehensive ophthalmologic evaluation including eye history and examination, visual acuity, eye fundus examination, optical coherent tomography (OCT) and ocular tonometry, c) data on gender-related variables (including psychosocial factors and socio-economic

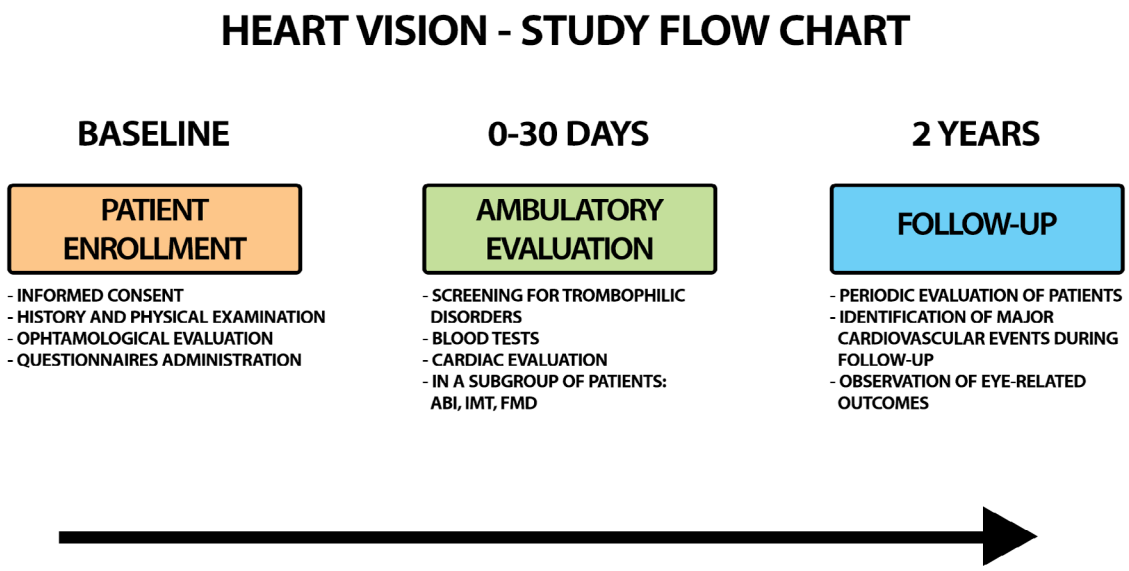

Figure 1: HEART VISION study flow chart.
HEART VISION: High focused Evaluation of Atherosclerotic risk profile in Retinal Thrombosis: Vascular events Incidence, Sex involvement and Interventional outcomes assessed by Ophthalmologists and internists Network; ABI: ankle-brachial index; IMT: intimal-medial thickness; FMD: flow-mediated dilation.

status), d) data on ongoing treatment and questionnaires on medications adherence,[22] demographic and social aspects (including marital status, educational level, income, working status risk taking behaviors)[23] and Mediterranean diet.[24] These data will be recorded on the online registry at baseline. Medical management and prescriptions before the confirmation of the final diagnosis will be also recorded. After 1 month from the index event, the patients will be evaluated through an outpatient examination. During the first month, the patient will undergo a specialist evaluation for the confirmation of the diagnosis (which could also include an evaluation through OCT, microperimetry and retinal fluorescein angiography). Moreover, etiologic factors and a complete evaluation of existing RFs and co-morbidities will be reassessed. At the thrombosis center, the patient will undergo the following instrumental and laboratory investigations:

1) Assessment of the presence/absence of congenital and/or acquired thrombophilic disorders (including antiphospholipid syndrome, hyper-homocysteinemia, Factor V Leiden mutation, prothrombin mutation, protein C and S deficiencies, anti-thrombin III deficiency);

2) Routine blood tests (including whole count cell, creatinine, prothrombin time, liver enzymes);

3) Cardiac evaluation with electrocardiography, transthoracic echocardiography with US-Doppler evaluation (*i.e.* left ventricular hypertrophy screening and cardiac morphology and motility).

A subgroup of patients with an established RVO diagnosis, according to the availability and the consent of the subjects, will be involved in an ancillary evaluation of several markers of subclinical atherosclerosis and endothelial dysfunction, *i.e.*:

1) Ankle-brachial index: at baseline, a measurement of upper and lower limb systolic blood pressure for ankle-brachial index calculation will be performed as previously described and a value equal or inferior to 0.90 will be considered as pathological;

2) Carotid intimal-medial thickness (cIMT): according to the American Society of Echocardiography consensus statement on the use of carotid ultrasound to identify subclinical vascular disease, tracing far wall blood-intima and media-adventitia interfaces using leading edge–to–leading edge method at 1 cm from the carotid bulb will assess cIMT. A value of cIMT above 0.90 mm or the presence of a carotid surrounding thickening more than 1.50 mm will be defined as "pathological cIMT";

3) Brachial artery flow-mediated dilation (FMD): ultrasound assessment of endothelial dependent and independent FMD of brachial artery will be evaluated. Briefly, the study will be performed in a temperature-controlled room (22°C) with the subjects in a resting, supine state between the hours of 8 a.m. and 10 a.m.; brachial artery diameter will be imaged using a 7.5-MHz linear array transducer ultrasound system equipped with electronic callipers, vascular software for two-dimensional imaging, color and spectral Doppler, and internal electrocardiogram; the brachial artery will be imaged at a location 3–7 cm above the ante-cubital crease; to create a flow stimulus in the brachial artery, a sphygmomanometric cuff will be placed on the forearm; the cuff will be inflated at least 50 mmHg above systolic pressure to occlude artery inflow for 5 min; all vasodilatation measurements will be made at the end of diastole; FMD will be expressed as a change in post-stimulus diameter evaluated as a percentage of the baseline diameter;

4) Blood and urine samples collection for the assessment of the hemostatic milieu and redox status: blood samples will be properly maintained until batch analysis in freezers at –80°C. All assays will be performed in a blinded fashion. The samples analyzed by immunoassay methods will be tested in duplicate, and those with concentrations exceeding the standard curve will be assayed again after appropriate dilution. We plan to evaluate the following parameters to study interaction between

platelet function and endothelial dysfunction in RVO patients, including soluble CD40 ligand (sCD40L) and soluble P-selectin, as members of the inflammatory molecules released from platelets, plasma thromboxane B2 and von Willebrand factor as marker of endothelial activation.

Patients in which diagnosis will not be confirmed will be used as controls.

Follow-up and outcomes

Patients with an established diagnosis of RVO will be prospectively followed for 2 years.

After 3 months from the index events, a short-term follow-up will be executed to evaluate the recovery of visual acuity in relation to the type of received treatment according to the ophthalmologist clinical judgement.

Patients will be periodically evaluated with follow-up visits, and a dedicated website will be developed for their management.

The following 2-year follow up events will be collected:

1) Major adverse cardiovascular events including ischemic heart disease (*i.e.* acute coronary syndrome or stable chronic angina), cerebrovascular events (including stroke or transient ischemic attack), cardiovascular death, venous thrombotic events (*i.e.* deep vein thrombosis and/or pulmonary embolism);
2) Eye-related outcomes (*i.e.* outcomes of pharmacological and non-pharmacological management, recurrences).

Data management and statistical analysis

Dataset management and statistical analysis will be performed by both the "UOC Prima Clinica Medica – Atherothrombosis Centre at Policlinico Umberto I – Rome" and the "BioMedical Statistics and Clinical Epidemiology Centre" at Sapienza-University of Rome.

The Wilson method will be used for calculating confidence intervals (CI) for proportions. The Kaplan-Meier estimator will be used to calculate cumulative incidence, with the 95% CI. Multivariate analysis will be used in an attempt to identify determinants of outcomes and to control the effect of confounders (*i.e.* Cox competing risk model and logistic regression).

Likewise, the presence of the center effect will be assessed and eventually, removed. The secondary endpoints will be evaluated with the univariate log-rank test and the Cox model (with time-dependent effects) multivariate analysis. A logistic regression analysis will be performed to establish all clinical sex- and gender- related factors significantly associated with RVO.

Sample size calculation

It is planned to enroll about 1,000 patients for the study (about 50 patients per research center) during a 2-year period. An expected prevalence of 13%, which would produce a CI of 95% with amplitude of 0.043, was used for calculating the dimension of the study population. SPSS and STAT-SOFT Statistical Software will be used for performing statistical analysis.

Discussion

RVO represents an important open issue of concerns for the need of a multidisciplinary approach to patient care. The disease management necessitates the involvement of physicians from a number of different clinical specialties, from ophthalmologists to vascular medicine specialists. At present, lack of definitive data on epidemiology, RFs and their specific contribution to the disease pathogenesis along with the absence of an established treatment algorithm for RVO generates some controversies. HEART VISION study will help to clarify these gray spots and overcome this potential source of pitfalls. It will pursue, as a mandatory objective, to fill in the lack of evidence on the pathogenesis of RVO and, concurrently, to bridge the gap between research and clinical practice with its prognostic and therapeutic implications. Furthermore, it will also represent the starting point for the medical community towards the development of further studies and research.

Trial Status

We are currently recruiting participants.

Additional files

Additional file 1: Ethical Approval Documentation.
Additional file 2: Model consent form.

Author contributions
Study concept and design and manuscript writing: SB, EP, FP, RC, MP, VR; creation of the electronic registry of data and manuscript writing: MM; literature integration and manuscript writing: GFR, GV, LMA, SR. All authors approved the final version of the manuscript.

Conflicts of interest
The authors declare no conflicts of interest.

Financial support
This study was funded by Sapienza-University of Rome in 2014 - C26A147HC8.

Institutional review board statement
This study protocol (n. 1.0, 01.07.2014) was approved by the Sapienza-University of Rome Ethics Board (Protocol No. 1076/14). This study will be performed in accordance with the *Declaration of Helsinki.*

Declaration of patient consent
The authors certify that they will obtain all appropriate patient consent forms. In the form the patients will give their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity will be guaranteed.

Reporting statement
This study followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance for protocol reporting.

Biostatistics statement
The statistical methods of this study were reviewed by Prof. Basili S, Department of Internal Medicine and Medical Specialties, Sapienza-University of Rome, Rome, Italy.

Copyright license agreement
The Copyright License Agreement has been signed by all authors before publication.

Data sharing statement
For data sharing, individual participant data will not be available. However, the study protocol and informed consent form will be made available beginning 3 months and ending 5 years following article publication to investigators whose proposed use of the data has been approved by an independent review committee identified to achieve aims in the approved proposal. In order to gain access, data requestors will need to sign a data access agreement. Proposals should be directed to stefania.basili@uniroma1.it.

Plagiarism check
Checked twice by iThenticate.

Peer review
Externally peer reviewed.

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Manuscript process
Received: June 2, 2018
Peer-review started: June 8, 2018
First decision: July 5, 2018
Revised: July 13, 2018
Accepted: July 20, 2018
Article in press: September 30, 2018

C-Editor: Zhao M; S-Editor: Li CH; T-Editor: Jia Y

Prot. 1076 / 14

Rif. 3351 / 11.09.2014 (nota da citare sempre in qualsiasi corrispondenza)

COMITATO ETICO DELL'UNIVERSITA' "SAPIENZA"
VERBALE DELLA SEDUTA DEL 11.09.2014

Il giorno 11.09.14, alle ore 14.30, si è riunito il Comitato Etico presso la sede del Policlinico Umberto I, con il seguente ordine del giorno:

- comunicazioni del Presidente;
- approvazione verbale del 24.07.2014;
- esame delle sperimentazioni cliniche pervenute;
- varie ed eventuali.

Sono presenti:
Presidente - Prof. Aldo ISIDORI, Dott.ssa Amalia ALLOCCA, Dott.ssa Maria CAPORALE, Dott.ssa Enrica ARDUINI, Dott.ssa Avia CARABELLI, Dott.ssa Anna DALLE ORE, Prof. Giovanni FABBRINI, Prof.ssa Paola FRATI, Dott.ssa Giuseppina DI GIAMMARCO, Dott.ssa Maria Teresa LUPO, Prof. Franco MANDELLI, Dott. Enrico MARINELLI, Dott.ssa Boza MAURO, Dott.ssa Elisabetta SIMONGINI, Dott.ssa Simona GALEASSI, Prof. Giovanni Battista GRASSI, Prof. Paolo MENE', Prof. Lucio MIANO, Prof.ssa Annarita VESTRI, Prof. Pietro SERRA, Prof. Giovanni SPERA, Dott. Ettore TIBERI, Avv. Angelo TUZZA, Prof. Vincenzo ZIPARO.

Assenti giustificati: Prof. Francesco COGNETTI, Prof. Luciano CAPRINO, Prof. Marco SALVETTI, Prof.ssa Marzia DUSE, Dr Lorenzo SOMMELLA, Ing. Remigio TECCHIA, Prof. Massimo VOLPE.

Svolge le funzioni di Segreteria verbalizzante la Dott.ssa Elena Amici.
Il Presidente, constatata la regolarità della convocazione e la presenza del numero legale, dichiara aperta la seduta.
I componenti del Comitato Etico dichiarano che si asterranno dal pronunciarsi su quelle sperimentazioni per le quali possa sussistere un conflitto di interesse di tipo diretto o indiretto.

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Prof. Prof. Stefania BASILI- Dip. Medicina Interna e Specialità Mediche
Sponsor: Sapienza Università di Roma - Azienda Policlinico Umberto I di Roma
Studio HEART-VISION "Valutazione statistica del profilo di rischio aterosclerotico nella trombosi retinica: incidenza di eventi vascolari, coinvolgimento del sesso e esiti delle procedure di intervento da parte di un network di oculisti ed internisti"

Il Comitato Etico, valutati i seguenti documenti: HEART-VISION v1.0-01.07.14, lettera richiesta autorizzazione dello sperimentatore, omissis Consiglio di Dipartimento seduta 11.02.14, CV PI,scheda finanziaria, elenco dei centri partecipanti, sinossi dello studio v1.0-01.07.14, dichiarazione sulla natura osservazionale dello studio, dichiarazione sulla natura no profit dello studio, scheda di arruolamento v1.0-01.07.14, scheda follow-up 1 mese v1.0-01.07.14, foglio informativo e modulo di consenso informato v1.0-01.07.14, informativa privacy v1.0-01.07.14,

Considerato che si tratta di uno studio osservazionale su una popolazione di pazienti affetti da occlusione venosa retinica (RVO), una condizione che come causa di perdita unilaterale della vista è seconda solo alla neuropatia diabetica. Gli obbiettivi dello studio sono infatti: 1) Conoscere la prevalenza italiana della patologia; 2) Individuare i fattori di rischio modificabili e riconoscere ulteriori fattori di rischio legati al genere, alla predisposizione genetica e soprattutto alla condizione socio-economica e culturale nella patogenesi della RVO. Allo scopo di valutare la prevalenza della patologia e l'attuale "clinical practice" gli sperimentatori si propongono di realizzare un registro online tra centri specializzati italiani (pronto soccorso oculistico e centri trombosi) con immediata esportabilità e fruibilità del dato. Ai pazienti che si rivolgono alle strutture sanitarie e che accettano di far parte della survey verrà proposta una visita di follow-up ad 1 mese per la conferma della diagnosi con esami strumentali e l'osservazione per i successivi 2 anni (fuori dall'ambito del

progetto, ma primo caso concreto di uso della piattaforma). Tale periodo osservazionale avrà lo scopo, dal punto di vista medico, di valutare la prevalenza, l'associazione con i fattori di rischio noti e meno noti, e la predittività sugli eventi vascolari, la clinical practice nel management della malattia per identificare possibili nuove strategie di intervento.
I ricercatori prevedono di arruolare 1000 pazienti (50 per centro). Lo studio sarà articolato in 4 fasi: • Fase 1: costituzione della rete: identificazione delle strutture specializzate (pronto soccorso oculistico e centri trombosi) nei quali accedono pazienti per sospetto RVO che parteciperanno alla costituzione del registro online . • Fase 2: attivazione del Registro e reclutamento della coorte di pazienti. • Fase 3: follow-up - programmato (1mese) per esami strumentali di conferma della diagnosi di RVO. • Fase 4: periodo osservazionale mediante registro online supportato da piattaforma web dedicata - per applicabilità nel contesto clinico delle acquisizioni epidemiologiche e di gestione della malattia in tempo reale,

esprime **PARERE FAVOREVOLE** alla conduzione dello studio da effettuarsi sotto la responsabilità dello sperimentatore principale,**Prof. Stefania BASILI,** ritenendo adeguata la struttura dove si svolgerà la ricerca, come garantito dalla Direzione del Dipartimento.

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Si dichiara che il Comitato Etico è organizzato ed opera nel rispetto delle norme di buona pratica clinica (GCP-ICH) e degli adempimenti previsti dall'allegato al D.M. 15/7/97, successivo D.M. 18/03/98, successivo D.Lgs 24/06/2003, successivo D.M. 12/05/2006, successivo D.M. 21/12/2007; D.M. 08/02/2013.

Essendo i punti all'O.d.G. esauriti e null'altro restando da discutere, la seduta è tolta alle 16.30.

La prossima seduta è fissata per il giorno 25.09.2014

Roma, 12.09.2014

COMITATO ETICO DELL'UNIVERSITA' "SAPIENZA"

Il Presidente
Prof. Aldo Isidori

Azienda Policlinico Umberto I
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UMBERTO I
POLICLINICO DI ROMA

PRESA VISIONE DEL PARERE FAVOREVOLE DEL COMITATO ETICO DELL'AZIENDA POLICLINICO UMBERTO I

SI/NON autorizza la conduzione presso questa Struttura dello studio:

"Valutazione statistica del profilo di rischio aterosclerotico nella trombosi retinica: incidenza di eventi vascolari, coinvolgimento del sesso e esiti delle procedure di intervento da parte di un network di oculisti ed internisti" - HEART-VISION

approvato dal Comitato Etico dell'Azienda Policlinico Umberto I nella seduta del 11.09.2014 da attuarsi sotto la responsabilità dello Sperimentatore Principale:

Prof. Stefania BASILI

Il Direttore Generale
Dott. Domenico ALESSIO

Il Direttore Sanitario
Dott.ssa Amalia ALLOCCA

Roma, 12.09. 2014

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SAPIENZA
UNIVERSITÀ DI ROMA

Valutazione specialistica del profilo di rischio aterosclerotico nella trombosi retinica:incidenza di eventi vascolari, coinvolgimento del sesso e esiti delle procedure díntervento da parte di un network di Oculisti ed Internisti

High focused **E**valuation of **A**therosclerotic risk profile in **R**etinal **T**hrombosis: **V**ascular Events **I**ncidence, **S**ex involvement and **I**nterventional outcomes assessed by **O**phthalmologists and internists **N**etwork **(HEART-VISION)**

Foglio di Informazione per il Paziente e Consenso Informato

Struttura: _____ Responsabile: _____

Telefoni: _____ Fax: _____

La patologia trombotica retinica rappresenta un problema emergente di grande impatto sociosanitario.

Lo studio sarà compiuto da specialisti internisti e oculisti che si occupano della gestione di questo problema medico. Lo scopo è di creare un registro di pazienti affetti dalla malattia trombotica retinica per caratterizzarne gli aspetti clinici e diagnostico- terapeutici predominanti nel territorio nazionale. I pazienti verranno seguiti nei due anni successivi per verificare l'andamento della patologia e la comparsa di altre patologie che interessano l'apparato cardiovascolare.

Lo studio prevede la raccolta attraverso la consultazione della cartella clinica da parte del medico del pronto soccorso/reparto/ambulatorio di informazioni cliniche, anamnestiche e strumentali.

Inoltre in un gruppo di pazienti èprevisto anche il prelievo di campioni ematici ed urinari per comprendere meglio il rischio cardiovascolare di pazienti affetti da tale patologia oculare.

In nessun caso comparirà il suo nominativo. I dati che verranno raccolti e inseriti in un sistema computerizzato, saranno del tutto anonimi e riguarderanno esclusivamente i farmaci assunti al momento del ricovero e le malattie di cui è affetto, le terapie somministrate durante la degenza in ospedale e i farmaci che le verranno prescritti alla dimissione.

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UMBERTO I
POLICLINICO DI ROMA

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HEART VISION

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DICHIARAZIONE DI CONSENSO

Io sottoscritto……
DICHIARO :

- di AVER RICEVUTO, nel corso di un colloquio personale con il

Dr./Prof……

INFORMAZIONI comprensibili ed esaurienti circa la natura dello studio.

- di essere a conoscenza della possibilità di REVOCARE il presente consenso in qualsiasi momento.

- di ACCETTARE liberamente, spontaneamente e in piena coscienza l'esecuzione dei prelievi previsti e la relativa raccolta dati.

Firma del paziente ……

Firma e timbro del medico che ha informato ……

Data ……
(rilasciare in copia al paziente debitamente firmato)