



WILL RETINAL AVR AND T_1 PREDICT CARDIOVASCULAR RISK IN HYPERTENSIVE PATIENTS?

The use of retinography (AVR and T_1 parameters) in the cardiovascular risk prediction in newly diagnosed and never-treated hypertensive patients

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INDEX

1. ABREVIATIONS.....	4
2. ABSTRACT	5
3. INTRODUCTION.....	6
3.1. Arterial hypertension.....	6
3.2. Arterial hypertension and the eye – Hypertensive retinopathy	7
3.3. Retinal vascular imaging.....	12
3.4. Artery-to-vein ratio.....	13
3.5. Tortuosity index	14
3.6. Cardiovascular risk stratification.....	16
4. JUSTIFICATION.....	19
5. HYPOTHESIS	21
6. OBJECTIVES	21
6.1. Main objective	21
6.2. Secondary objectives.....	21
7. MATERIAL AND METHODS.....	22
7.1. Study design.....	22
7.2. Participants and setting.....	22
7.3. Inclusion and exclusion criteria.....	22
7.4. Sample selection.....	23
7.5. Sample size.....	23
7.6. Study variables and measure instruments	23
7.6.1. Independent variables (exposure)	23
7.6.2. Dependent variable (outcome)	24
7.6.3. Covariables	25
7.7. Data collection	26
8. STATISTICAL ANALYSIS	27
8.1. Univariate analysis.....	27
8.2. Bivariate analysis	27

8.3. Multivariate analysis.....	27
9. WORK PLAN AND CHRONOGRAM	28
10. ETHICAL AND LEGAL CONSIDERATIONS	31
11. STUDY LIMITATIONS AND BIAS.....	32
12. FEASIBILITY	33
13. BUDGET	34
14. PROJECT IMPACT	36
15. ANNEXES	37
15.1. Annex 1: Initial evaluation and risk stratification of an hypertensive patient....	37
15.2. Annex 2: Following up recommendations for the arterial hypertension	38
15.3. Annex 3: Physical exploration in hypertensive patients	38
15.4. Annex 4: Information sheet	39
15.5. Annex 5: Informed consent.....	41
16. BIBLIOGRAPHY	42

1. ABBREVIATIONS

AHT	Arterial hypertension
ARIC	Atherosclerosis Risk in Communities
AVR	Artery-to-vein ratio
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CABG	Coronary artery bypass graft
CKD	Chronic kidney disease
CVD	Cardiovascular disease
CVMM	Cardiovascular morbimortality
DBP	Diastolic blood pressure
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EKG	Electrocardiogram
HbA _{1c}	Glycosylated haemoglobin
HDL	High density lipoprotein
HR	Hypertensive retinopathy
ICS	Institut Català de la Salut
LDL	Low density lipoprotein
IMT	Intima media thickness
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
PCI	Percutaneous coronary intervention
PCC	Primary Care Center
PWV	Pulse wave velocity
RaVL	R wave in aVL lead
SBP	Systolic blood pressure
T _i	Tortuosity index
TOD	Target organ damage

2. ABSTRACT

TITLE: Will retinal AVR and T_1 predict cardiovascular risk in hypertensive patients?

BACKGROUND: Arterial hypertension (AHT) is the most important and modifiable risk factor for cardiovascular morbimortality (CVMM). The risk stratification tables for cardiovascular disease (CVD) do not include the retinal examination in early stages of AHT although retinal vessel alterations have proved to be associated with higher CVD risk. Retinography shows the state of our microcirculation system in vivo and it could give us information about the CVMM of hypertensive patients. Predicting the CVD risk by the use of retinography is an accessible and non-invasive way to control hypertensive patients during the evolution of this disease. So, AVR and T_1 could become important tools in the stratification risk of CVD and in the prevention of future cardiovascular events.

MAIN OBJECTIVE: Determine whether cardiovascular prognosis could be predicted by the use of retinography (AVR and T_1) in newly diagnosed and never-treated hypertensive patients.

METHODS: It is an observational and prospective cohort study which will include newly diagnosed and never-treated hypertensive patients from Girona attending the CAP's of Anglès and Cassà de la Selva meeting the inclusion criteria. All participants will be following up during a total of 7 years. They will comply the ICS protocol for the AHT monitoring and a part of this; they will be practised a retinography per eye in order to calculate the AVR and the T_1 .

KEY WORDS: Artery-to-vein ratio, tortuosity index, arterial hypertension, cardiovascular morbimortality, hypertensive retinopathy, retinography.

3. INTRODUCTION

3.1. Arterial hypertension (AHT)

Arterial hypertension (AHT) is a global health problem increasing around us and nearly 1 billion people is affected by this disease (1). Expressed in percentages, AHT appears to be around 30-45% over the total population, with a steep increase with ageing (2). Considering its high prevalence, AHT is one of the leading causes of cardiovascular disease (CVD) worldwide and it is one of the most consulted problems at primary care centers (3).

The incidence of AHT in Spain, in women and men, is estimated to be 8.2 and 21.8 for 1.000 persons-years, respectively (4). The last meeting of the Spanish Society of Hypertension define the AHT prevalence by 44.4% in people aged 35-65 and by 67% in people over 65 years old (5). Specifically in Catalunya, the prevalence ranges between 19.7% and 48.4% in the total population older than 14 years (3) and in Girona is about 31.1% in people older than 45 years (6).

According with the *ICS clinical guidelines for hypertension* (3), the *Seventh Report of the Join National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC-7)* (1) and the *2013 ESH/ESC Guidelines for the management of arterial hypertension* (2), AHT is defined as values ≥ 140 mmHg for systolic blood pressure (SBP) and/or ≥ 90 mmHg for diastolic blood pressure (DBP).

BP levels are categorized depending on the SBP and/or DBP values, summarized in the following table:

Category	SBP		DBP
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89

Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110

Table 1: Adapted from '2013 ESH-ESC Guidelines for the management of arterial hypertension' (2)

The AHT diagnosis should be as accurate as possible, meaning that is necessary to practise at least two blood pressure (BP) measurements per visit, in a sitting and calm position, on at least two visits, waiting about 2-3 minutes rest before the measure if necessary (7). For avoiding the white coat effects, it could be interesting to know the regular BP levels measured at home. Depending on the BP levels measured by the sphygmomanometer we can classify the arterial tension according to the **Table 1**.

The AHT treatment has two principal approaches (2,3):

- **Lifestyle changes:** salt restriction, moderation of alcohol consumption, high consumption of vegetables, fruits and low-fat diet, weight reduction and maintenance and regular physical exercise.
- **Pharmacological therapy:** diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers.

Apart from the AHT treatment, it is necessary a rigorous initial examination and follow up of the hypertensive patient for monitoring all the parameters that could be affected by high BP levels (3). For that reason, the ICS establish some recommendations for the initial evaluation in hypertensive patients, their risk stratification and it also explains the following up of hypertensive patients (Annexes 1, 2, 3).

3.2. AHT and the eye - Hypertensive retinopathy (HR)

The eye presents pathophysiological changes in the retinal vessels in response to elevated BP levels and when this occurs we talk about hypertensive retinopathy (HR).

This concept was first described in the 19th century and it is considered as target organ damage (TOD) (1,2,8,9).

The retinal vessels changes (decreased AVR, focal abnormalities of arterioles, arteriolar-venular crossing abnormalities, increase on the T₁, a diminished branching angle at bifurcations, an increased arteriolar length-to-diameter ratio and a reduced microvascular density) reflect lifetime cumulative effects of microvasculature processes and these changes may be used as CVD risk indicators (10–12).

The retinal vessels alterations are divided into different stages, including vasoconstrictive, sclerotic, exudative and malignant AHT phases (13–16). All these changes can be evaluated by retinal imaging, not being necessary a sequence of the events described below (13,14,17,18). The initial response of the retinal circulation to a rise in BP is vasospasm and an increase in vasomotor tone, which is clinically seen as generalised arteriolar narrowing. Subsequently, chronic arteriosclerotic changes, such as intimal thickening, media-wall hyperplasia and hyaline degeneration, develop. These changes are characterized by diffuse and focal areas of arteriolar narrowing, opacification of arteriolar walls (described as silver or copper wiring) and compression of the venules by arterioles at their common adventitial locations (termed arteriovenous nipping or nicking) (13–15).

With more pronounced high BP, the blood-retinal barrier breaks down, resulting in exudation of blood (haemorrhages), lipids (hard exudates) and subsequent ischemia of nerve-fibre layers (known as cotton-wool spots). In the setting of severely high BP, raised intracranial pressure and concomitant optic nerve ischemia can lead to disc swelling (papilledema) and it sometimes drives to a severe or malignant AHT or hypertensive optic neuropathy (13).

The retinal appearance observed by retinography is commonly used to grade the severity of AHT and such features may have prognostic implications in the CV risk prediction (19).

The traditional classification of HR had been originally proposed by Keith – Wagener – Barker on the basis of clinical descriptions by Marcus Gun. Downie LE *et al.* (20) proposed a simplified three-grade classification scheme (*simplified classification*) based

on the strength of the reported associations between hypertensive retinopathy and CV risk (21):

Keith – Wagener – Barker		Simplified classification	
Grade	Features	Grade	Features
1	Mild generalized retinal arteriolar narrowing	None	No detectable signs
2	Definite focal narrowing and arteriovenous nicking	Mild	Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacity ('copper wiring') of arteriolar wall or a combination of these signs
3	Signs of grade 2 plus retinal hemorrhages, exudates and cotton wool spots	Moderate	Retinal hemorrhages (blot shaped, dot shaped or flame shaped), microaneurysms, cotton wool spot, hard exudate or a combination of these signs
4	Severe grade 3 plus papilledema	Malignant	Signs of moderate retinopathy plus swelling of the optic disk

Table 2: Adapted from the Original Article: 'Hypertensive retinopathy: comparing the Keith – Wagener – Barker to a simplified classification. Downie LE et al. (2013)' (20).

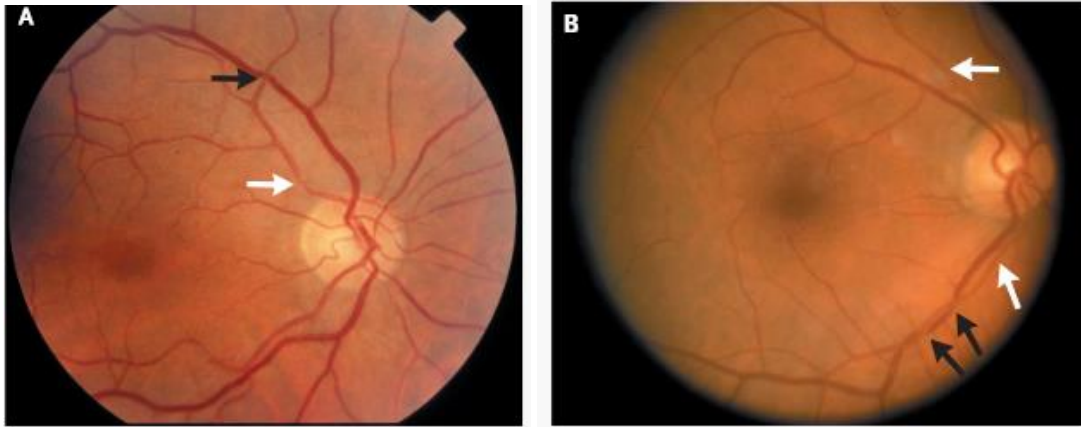


Figure 1: Examples of mild hypertensive retinopathy from '*Hypertensive Retinopathy. Wong, TY & Mitchell P (2004)*'. Panel A shows arteriovenous (black arrow) and focal narrowing (white arrow). Panel B shows arteriovenous nicking (black arrows) and widening of accentuation ('cooper wiring') of the central light reflex of the arterioles (white arrows) (13).

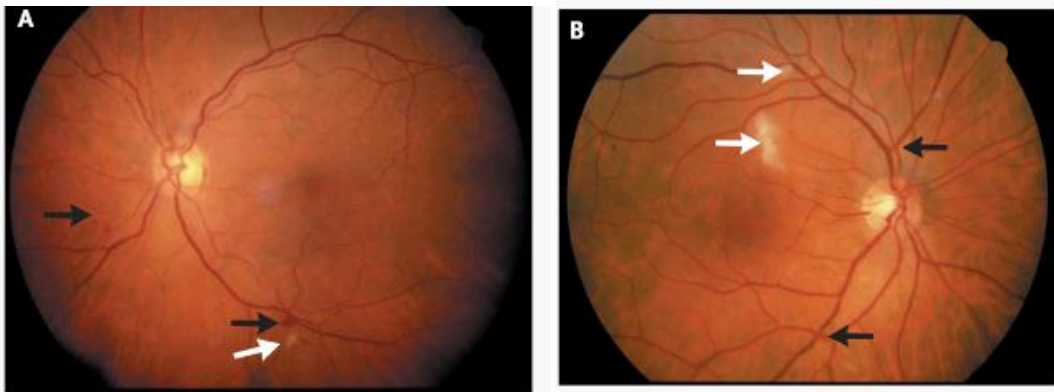


Figure 2: Examples of moderate hypertensive retinopathy from '*Hypertensive Retinopathy. Wong, TY & Mitchell P (2004)*'. Panel A shows retinal haemorrhages (black arrows) and a cotton-wool spot (white arrow). Panel B shows cotton-wool spots (white arrow) and arteriovenous nicking (black arrow) (13).



Figure 3: Example of malignant hypertensive retinopathy from '*Hypertensive Retinopathy. Wong, TY & Mitchell P (2004)*'. Multiple cotton-wool spots (white arrows), retinal haemorrhages (black arrows) and swelling of the optic disk are visible (13).

However, one of the central unresolved issues about the pathophysiology of AHT is whether arteriolar narrowing is antecedent to and contributes to the development of AHT, or whether it is consequential to and represents a secondary adaptation to elevated BP or whether both processes occur (12,16,22,23). In fact, HR signs are detected commonly in people without a known history of AHT so retinal vessels state could predict the risk of having AHT and consecutively prevent it (24).

Some studies have found that retinal arteriolar narrowing is a marker of chronic damage from elevated BP and is associated with current, past and future development of AHT (12,23,25). Besides, Ding J *et. al.* (23) demonstrate that each 20 μm decrease on retinal arteriolar caliber at baseline is associated with a 1.12 mmHg greater increase in SBP over 5 years. These findings are consistent with the hypothesis that generalized microvascular dysfunction, seen in the retinal vasculature, precedes the onset and development of AHT.

According with this, persons with relatively small arteries and arterioles in the retina had the greatest risk of developing severe AHT during the next 10 years (37) and despite having good control of AHT at time of the retinal examination; those with wild and moderate HR were at an increased risk of developing CVD, being the stroke the most common manifestation (36).

Retinal vascular images reflects the cumulative microcirculatory effects of an individual's life-time exposures to lifestyle and environmental factors and the body's response to these exposures, which may be modified by genetic predisposition (26).

These factors are summarized in the following diagram, showing how they can influence the retinal vessel and it also exposes that AHT manifestations can be explained by the use of retinal vascular imaging:

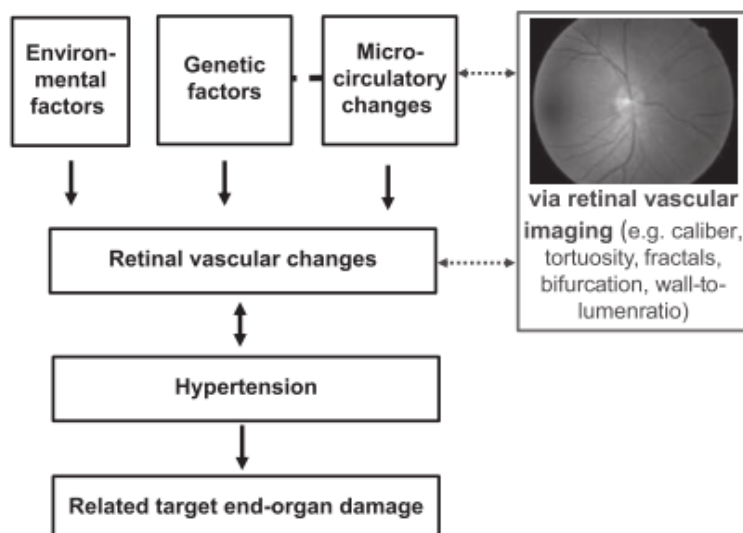


Figure 4: Schematic diagram extracted from Cheung CY *et al.* (2012). *Retinal Microvasculature as a Model to Study the Manifestations of Hypertension* (16). It illustrates the contribution of studying retinal vascular changes to the understanding of the pathogenesis of AHT and related target end-organ damage and CV events.

3.3. Retinal vascular imaging

Retinal vasculature open us a window to explore the microcirculation system and it is a unique biological model to study the manifestations and origins of AHT in vivo (27). Retinal vessels provide interesting information about the functioning of our microvasculature, but there still remain studies objecting this hypothesis (28).

Retinal vascular imaging is currently used in two broad areas of CV research. First, it is an accessible and non-invasive way to examine the pathophysiology of the microvascular system in the development of clinical CVD (15) and second, retinal vascular imaging is a risk stratification tool which identify patients with higher probability of future CVD events (7,15,16,26), but it is still not included in the diagnosis and prognosis evaluation of newly-diagnosed hypertensive patients.

As described, one of the earliest signs of HR is a generalized retinal arteriolar narrowing and for measure it we need to calculate the retinal vessel caliber. The caliber of the retinal blood vessels measure approximately 150-300 μm and provides a model to study correlates and consequences of generalized microvascular dysfunction (9,24,29). This

vessel caliber can be assessed directly and non-invasively from retinal photographs and computer-assisted program approaches (26,30).

The most widely used program to measure retinal vessel caliber in an objective manner was first described in the Atherosclerosis Risk in Communities (ARIC) Study (18). This study developed a computer based method to measure retinal arterioles and venules in a specified zone surrounding the optic disc from retinographies.

The ARIC study demonstrated the association between generalized arteriolar narrowing and concurrent elevated BP (17,18). These measurements were combined into summary indices – the central retinal arteriolar and venular equivalents – which represent the average arteriolar and venular diameters of the eye, respectively (31). These indices were finally expressed as the retinal artery-to-vein ratio (AVR). The ratio compensated for possible magnification differences between eyes and an AVR of 1 indicated that arteriolar diameters were, on average, the same as venular diameters in that eye, while smaller ratio suggested narrower arterioles (31).

Some studies (13,16,30,31) provide strong evidence that retinal vascular caliber measurement can be used in research to understand the relationship between the retinal microvasculature and systemic diseases and it can also be used in clinical practice for AHT assessment and patient tracing.

The two main retinal parameters studied in this project are the AVR and the T_i , both calculated with a retinograph and a computer program called SIRIUS (32,33).

3.4. Artery to vein ratio (AVR)

Retinography permits a direct view of the small retinal vessels and allows the AVR measurement with a computer system called SIRIUS (33). AVR describes the relative size (diameter) of the summarized central retinal artery equivalent over its venous counterpart (10).

The AVR measure is a reliable and standardized method (34) to assess the state of retinal vessels that can be representative for the vessel structure of cerebral and coronary microcirculation and can help predicting the CVD risk (21).

For the definition of decreased AVR we geared to Hubbard *et. al*, who define general arteriolar narrowing by AVR values lower than 0.84 (18) , but there is still not evidence of which is the exact value to consider low AVR (7,33).

AHT conduces to microvascular lesions and it can be detectable in the retina as a progressive reduction of AVR. The Blue Mountain Eye Study concludes that the AVR basal alteration is associated with an increased risk of developing a severe AHT (OR 2.6; IC 95% 1.7-3.9) in 5 years (25) and decreased AVR has shown an association with CVMM (35,36).

Lower AVR is associated with older age, male sex, diabetes, higher glycosylated haemoglobin concentration, higher SBP and DBP, higher body mass index (BMI), higher total cholesterol concentration, cigarette smoking and alcohol consumption, being all them risk factors for AHT and CVMM (27,31).

Taking into account all these risk factors that contribute to an AVR decrease, age is the strongest affector, independently from other factors (34,37,38). This age-dependent influence on the retinal arteriolar diameter can be explained by loss of vasoconstrictive response or media muscular remodelling response on increased BP due to arteriosclerosis (24,29,37,38).

An AVR decrease might be pivotal for AHT management, particularly in patients with initial development of AHT because if they follow the ICS recommendations they will have a higher probability of retinal lesions regression (37). Methodological conclusion points to computed AVR measurement as a fast, reliable and easily feasible parameter to conclude the CV status of hypertensive patients thereby represent the opportunity for considering AVR as a tool to evaluate and control the AHT evolution and the CVMM.

3.5. Tortuosity index (T_1)

The vessel tortuosity is a parameter that measures how and how many times the vessel curves. The higher the value of tortuosity in the arterio-venous tree of a patient, the bigger his CV risk (33).

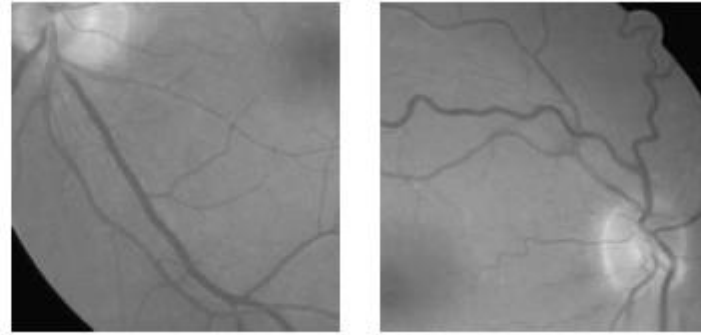


Figure 4: Example of tortuosity levels from *Computer aided diagnosis system for retinal analysis: Automatic assessment of the vascular tortuosity*. Sánchez, L; Barreira, N; Penedo, MG; Coll de Tuero, G. Left: non tortuous vessel. Right: tortuouse vessel (33).

This parameter is calculated as the ratio of the actual length of the vessel segment to the straight-line distance between two connected branching points (19) and for its automatic measure we use the SIRIUS computed program. For this we will need to extract the vessel tree and divide it into segments by looking for vessel end points and join points, then we will obtain the tortuosity value selecting the appropriate menu in the SIRIUS program (33).

One can manually measure tortuosity from a retinography, as Grisan *et al.* porpoise (39), for example between branching points by selecting the vessel length between branches (arc length) and then selecting the shortest distance between these branches (chord length) to calculate simple tortuosity using the following formula (10):

$$\text{Tortuosity} = \frac{\text{Arc length}}{\text{Chord length}}$$

T_1 increases with higher BP levels and is used as a retinal marker of vessel abnormalities, having implications in the CVD risk prognosis, as the AVR. Typically is studied and observed in arteriolar vessels, because venular ones are affected in more advance AHT (19).

Both retinal arteriolar and venular tortuosity are strongly and inversely associated with ageing, so the age has an important impact on reducing retinal vascular tortuosity, in particular for arterioles and retinal arteriolar narrowing. A part from this, retinal vessel

tortuosity is independently associated with BP, variations of the systemic circulation throughout the day and during the cardiac cycle, rendering it a robust measure (10). This suggest that retinal vascular tortuosity may reflect an aspect of vascular structural change different from the associated with retinal vascular caliber change and could provide additional understanding of the relationship between the retinal microvasculature and CVD (40).

It has been speculated that increased retinal vascular tortuosity may be related to increased blood flow and angiogenesis, so that decreased retinal tortuosity may be related to endothelial dysfunction and impairment of perfusion or oxygenation in the microvasculature (40).

3.6. Cardiovascular risk stratification

CVD is a broad term for a range of diseases affecting the blood vessels. A heart attack or stroke may be the first warning of an underlying disease. There are many different types of pathologies defining CVD (41):

- **Heart-related CVD:** acute coronary syndromes, angina, arrhythmia, cardiomyopathy, congenital heart disease, coronary heart disease, heart failure, inflammatory heart disease, ischaemic heart disease, rheumatic heart disease and valvular disease.
- **Brain-related CVD:** cerebrovascular disease (stroke), haemorrhagic stroke and ischaemic stroke.
- **Circulatory system-related CVD:** deep vein thrombosis, hypertensive heart disease, peripheral artery disease and pulmonary embolism.

The majority of CVD is caused by risk factors than can be controlled, treated or modified, such as high BP, cholesterol, overweight/obesity, tobacco use, lack of physical activity and diabetes (3). However, there are also some major CVD risk factors that cannot be controlled as age (the older you are the CVD increase), gender (a man is at greater risk of heart disease than a pre-menopausal woman) and family history (if a first-degree blood relative has had coronary heart disease or stroke before the age 55-

65, the risk increases) (41). In terms of attributable deaths, the leading CVD risk factor is raised BP (to which 13% of global deaths are attributed), followed by tobacco use, diabetes, physical inactivity and obesity (41).

AHT is known as a major risk and modifiable factor for CVD and premature mortality (2). Microvascular dysfunction, characterized by structural and functional abnormalities of small vessels, precedes and may be a causal component of AHT as commented before, but the clinical evidence to support this has been sparse (12,22,23).

The total CV risk can be stratified in different categories, showed in the following table:

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Figure 4: Adapted from '2013 ESH-ESC Guidelines for the management of arterial hypertension' (2)

The risk factors used for the stratification of total CV risk are the following:

Risk factors	<ul style="list-style-type: none"> - Male sex - Age (men ≥55; women ≥65) - Smoking - Dyslipidaemia: <ul style="list-style-type: none"> ✓ Total cholesterol >4.9 mmol/L (190 mg/dL) and/ or ✓ Low density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL) and/or ✓ High density lipoprotein cholesterol: men <1.0 (40 mg/dL) and women <1.2 mmol/L (46 mg/dL) and/or ✓ Triglycerides >1.7 mmol/L (150mg/dL)
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	<ul style="list-style-type: none"> - Fasting plasma glucose 5.6-6.9 mmol/L (102-125 mg/dL) - Abnormal glucose tolerance test - Obesity: IMC ≥ 30 kg/m² (height²) - Abdominal obesity (waist circumference: men ≥ 102 cm; women ≥ 88 cm; in caucasians) - Family history of premature CVD (men aged <55; women aged <65 years)
Asymptomatic organ damage	<ul style="list-style-type: none"> - Pulse pressure (in the elderly) ≥ 60 mmHg - Electrocardiographic LVH (Sokolow-Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or - Electrocardiographic LVH: LVM index men >115 g/m²; women <95 g/m² (BSA) - Carotid wall thickening (IMT >0.9) or plaque - Carotid-femoral PWV >10 m/s - Ankle-brachial index <0.9 - CKD with eGFR 30-60 ml/min/1.73 m² (BSA) - Microalbuminuria (30-300 mg/24h), or albumin-creatinine ratio (30-300 mg/g; 3.4-34 mg/mmol) (preferentially on morning spot urine)
Diabetes mellitus	<ul style="list-style-type: none"> - Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or - HbA_{1c} $>7\%$ (53 mmol/mol), and/or - Post-load plasma glucose >11.0 mmol/L (198 mg/dL)
Established CV or renal disease	<ul style="list-style-type: none"> - CVD: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack - CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG - Heart failure, including heart failure with preserved EF - Symptomatic lower extremities peripheral artery disease - CKD with eGFR <30 mL/min/1.73m² (BSA); proteinuria (>300 mg/24h) - Advanced retinopathy: haemorrhages or exudates, papilloedema

Table 3: Adapted from '2013 ESH-ESC Guidelines for the management of arterial hypertension' (2). BMI, body mass index; BP, blood pressure; BSA, body surface area; CABG, coronary artery bypass graft; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; IMT, intima media thickness; LVH, left ventricular hypertrophy; LVM, left ventricular mass; PCI, percutaneous coronary intervention; PWV, pulse wave velocity.

4. JUSTIFICATION

CVD is the leading cause of death in industrial countries and AHT is the most important and evitable risk factor (2). In 2011, approximately 350.000 deaths were attributable to CVD (41). The retinography offers a possible attractive approach to investigate our microvascular system, by measuring different parameters as the AVR and T_I , which are a reflection of how retinal vessels work. This may complement CV risk stratification, since the retina is a unique site where the in vivo microvasculature can be easily accessible, directly visualized and monitored repeatedly over time (16,26,34).

Large epidemiologic studies have shown that retinal micro and macrovascular signs provide information on microvascular complications, cardiac events and stroke in the general population (12,23,42), but the mechanisms and pathways underlying these associations remain, however, unclear (43).

The present study want to provide further support that retinal imaging may yield significant predictive information for CV prognosis and that retinopathy could become an important tool capable of early detection of atherosclerosis and assist in risk stratification of patients with CVD (12).

Knowing the capacity of AVR evolution to predict future CV events could be an important discover in medicine, because by calculating the AVR we could approximate the CVD risk. Another parameter that may help us in the CVD prognosis is the T_I , which shows the retinal vessel morphology and indicates microvascular abnormalities (10,28).

The need to develop this project lies on the absence of studies demonstrating the ability of the AVR evolution and retinal T_I in the prediction of CV risk in hypertensive patients in long term period (considered at 7 years in our study). The principal problem of the investigation in this field is that the majority of studies are based on 1-year follow and there is no information about this correlation in a longer period. Moreover, recent studies insist in the necessity of further research in order to understand the relationship between retinal vessel diameter and CVD events (7,12,16,26)

Moreover, as commented before, is a non-invasive method and we have to take in mind that current methods to examine the microvasculature system are invasive and can be performed only in highly specialized settings or research, which limits their utility to understand the clinical consequences of microvascular disease (26).

Our study is relevant due to lack of information demonstrating a positive relation between retinal lesions regression and a better CVD prognosis and according with this, we want to incorporate the retinography as a part of the stratification risk for CVD in newly-diagnosed hypertensive patients because the retinography is an accessible tool that shows our in vivo microvascular system in an easier way. Not only this, but it could help with the monitoring of AHT and the anti-AHT treatment modification (22,33).

5. HYPOTHESES

The AVR and T_1 are retinal parameters that reflect our microvasculature function and they could predict the risk of future CV events in newly-diagnosed and never-treated hypertensive patients. To identify how CV prognosis could be explained by both parameters, two potential hypotheses are suggested:

- The regression of retinal lesions, meaning an improvement of AVR and a reduction on retinal T_1 , reduces CVMM at 1, 3 and 7 years in newly-diagnosed hypertensive patients.
- CV risk can be predicted in long-term by the difference of baseline AVR and T_1 and their evolution at 1, 3 and 7 years in newly-diagnosed hypertensive patients.

6. OBJECTIVES

6.1. Main objective

To determine whether CV prognosis could be predicted by the use of retinography (AVR and T_1) in newly diagnosed and never-treated hypertensive patients.

6.2. Specific objectives

- To prove the relationship between baseline AVR and T_1 and their evolution at 1, 3 and 7 years in CVMM prediction in newly-diagnosed and hypertensive patients.
- To find which variables influence the measure and value of AVR and T_1 (baseline and evolution) in the prediction of CV prognosis in newly-diagnosed hypertensive patients
- To investigate the impact of antihypertensive therapy on retinal vascular changes in newly diagnosed hypertensive patients.

7. MATERIAL AND METHODS

7.1. Study design

The present project is an observational and prospective cohort study in which we will analyse if AVR at lower quartiles and a T_1 at higher quartiles could predict the risk of CVMM in newly-diagnosed and never-treated hypertensive patients of Girona.

7.2. Participants and setting

The project will be carried out with patients from the region of Girona, particularly from two primary care centers (PPC): PCC Anglès and PCC Cassà de la Selva. All patients in this study will be newly-diagnosed and never-treated for AHT.

We will conduct a prospective cohort analysis in which standardized measurements of retinal images of both eyes will be performed in our patients. After that, AVR, T_1 measurements and possible occurrence of CV events will be followed up at 1, 3 and 7 years, in order to see if there is any relationship between the regression of retinal lesions and a better CV prognosis.

7.3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">- Aged 15 to 75 years- Recent diagnosis of essential hypertension (primary)- Assessable fundus optic photography	<ul style="list-style-type: none">- Diabetes mellitus (type 1 and 2)- Secondary hypertension- Inability- Previous CV event- Renal insufficiency (serum creatinine >2 mg/dL)- Liver insufficiency- Alcoholism or dual pathology- Psychiatric diseases

Figure 5: Inclusion and exclusion criteria of the study

7.4. Sample selection

A non-probabilistic consecutive sampling-method will be taken. Patients who assist to both PCC's (Cassà de la Selva and Anglès) meeting inclusion criteria will be asked to be included in this project.

The subjects admitted in the study will be followed up during a total of 7 years. All the potential participants will be given an information sheet and an informed consent and they will only be a part of the study after reading and signing said document (Annexes 4, 5).

7.5. Sample size

To calculate the needed sample we use free online software called GRANMO.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, a total of 154 subjects are necessary to recognize as statistically significant a proportion difference, expected to be of 0.20 in patients with worse AVR and T_1 evolution and 0.05 in patients with a better AVR and T_1 evolution, that are those who may have a better CV prognosis. It has been anticipated a drop-out rate of 10%, principally for those retinal images that are not accessible to read and a possible, but not much probable, sample loss.

The study outcomes will be expressed in quartiles because both AVR and T_1 do not follow a linear relationship. All quartiles will be compared regarding CV events at 1, 3 and 7 years. After that, the relationship between these three variables (AVR, tortuosity index and CVD risk) will be established.

7.6. Study variables and measure instruments

7.6.1. Independent variables (exposure): AVR and T_1 . These are quantitative continuous variables but they do not follow a normal distribution, so we will work with quartiles.

All participants will undergo one retinography per eye to evaluate the retinal vessels and calculate the AVR and the T_1 . We will use a retinograph equipped with a non-

mydriatic digital camera with colour images (CANON CR6-45NM, Camera EOS D30). An expert physician, without knowing any patient data, will assess the images and an interactive web application for the management of retinal image screening process (SIRIUS) will be used to measure the AVR and T_1 (32,33).

The AVR and T_1 measurements will be performed at the beginning of the study and then we will take new measurements at 1, 3 and 7 years in order to see the evolution of both parameters and their prediction value for CV risk.

7.6.2. Dependent variable (outcome): CVMM. It is a nominal qualitative variable. Mortality will be defined as deaths/year and for morbidity we will include any of the following manifestations (2,41):

- Exudates, haemorrhages and/or papilla edema: this is macrovascular lesions and they are diagnosed by the use of the funduscopy and an expert physician.
- Retinal thrombosis and/or embolism: diagnosed also by the funduscopy and an expert physician.
- Ischemic heart disease:
 - Angina pectoris: the diagnosis is clinical and it is characterized by a pain, tightness or discomfort in the thoracic region. In the study we include the two different types of angina: *exertional angina* (triggered by circumstances that increase the myocardial oxygen consumption) and the *angina at rest* (it appears spontaneously without any relation with the myocardial oxygen consumption).
 - Heart infarct: diagnosed by the symptoms, the EKG and angiography if it is necessary.
 - Revascularization (angioplasty): meaning patients who need an intervention with stent or myocardial surgery.
- Vascular cerebral disease (stroke): this includes ischemic, haemorrhagic and transitory ischemic accident (TIA).

- Chronic renal disease (glomerular filtration <30 ml/min/ 1.73 m²; 4rt grade) and or proteinuria >300 mg/gr (better calculated in the morning)
- Symptomatic peripheral artery disease: defined as Fontaine stadiums ≥ 2
- Auricular fibrillation (arrhythmia): non valvular/rheumatic
- Congestion heart failure (CHF): this includes both, diastolic and systolic, with a preserved ejection fraction (>50)

7.6.3. Covariables

There are others variables that could affect our dependent and independent variables, but they are not object of our study. As these variables could act as confounders we will have to control them in order to increase the internal and external validity of our study. This confounding effect of these variables can be minimized later with a multivariate analysis.

- Sex: it is a qualitative dichotomous variable (Male or Female).
- Age: it is a quantitative discrete variable (years).
- BMI (body mass index): very severely underweight (<15), severely underweight (15-15.9), underweight (16-18.4), normal weight (18.5-24.9), overweight (25-29.9) and obesity (>30). This is a nominal qualitative variable and it is measured in Kg/m².
- Tobacco use: it is a risk factor of microvascular disease. It is a qualitative nominal variable and we will be defined as: never smoker, past smoker (>1 year without smoking) or smoker (at least 1 cigarette/day/month).
- Alcohol: it is a risk factor of microvascular disease. It is a qualitative nominal variable and will be defined as: never consumption, past consumption (>1 year without consuming) and consumption (at least 1 day/week).
- Cholesterol: having high levels of cholesterol is a potential risk for microvascular disease. We will have into account the total cholesterol, HDL, LDL and

triglycerides, all them expressed in mg/dL. High levels of triglycerides have been related to higher tortuosity index (28).

- Initial retinal lesions: some patients could present at the beginning of the study some retinal lesions as haemorrhages, exudates or others. This mean that there could be important differences in the evolution of the retinal lesions and this could affect our final results.
- Anti-ATH treatment: all patients will be treated from the moment they are diagnosed of AHT. Remember that we have two potential ways to treat AHT: lifestyle changes and pharmacological treatment (RENINA-ANGIOTENSIN SYSTEM: IECA, ARA-II). Depending on the physician decision and the patient's situation they will follow one treatment or another.
- AHT grades: not all the subjects included in the study will present the same AHT values, so there will be ones with a better BP and others with higher values. It will be measured in mmHg.
- Fasting glucose: we expose that patients with DM will be excluded from this project but there are subjects who present higher levels of glucose without having DM, and this is a risk factor for CV events. It will be measured in mg/dL.
- Chronic kidney disease (CKD): AHT affects different organs and one of them is the kidney. For study this covariables we will measure creatinine (mg/dL), glomerular filtration (ml/min/1.73m²) and albumin excretion.

7.8. Data collection

At the beginning of the study all newly hypertensive patients will have an anamnesis, a physical examination (Annexes 1, 3), an electrocardiogram (EKG) and a fundus eye image in both eyes with the retinograph. Then they will be practised the same procedures at 1, 3 and 7 years in order to see if there is a valid association between AVR and T₁ evolution and CV prognosis. All data will be archived in an anonymous way and only the principal researchers will have access to the patient's information. This is detailed in the information sheet (Annex 4).

8. STATISTICAL ANALYSIS

8.1. Univariate description

The AVR and T_I are continuous variables and they do not follow a normal distribution (Gauss Bell), so we will describe our independent variables in quartiles.

For CV morbidity, our dependent variable, results will be expressed as percentages because it is a categorical variable.

8.2. Bivariate analysis

The comparison of AVR and T_I measurements with CV events will be performed using U-Mom-Whitney. Results were considered statistically significant at $p < 0.05$.

8.3. Multivariate analysis

A multivariate logistic regression analysis will be applied to assess the relation between AVR and T_I evolution and the outcome of any CV event conditioned by the presence or absence of covariables that may explain the relationship found between the independent and dependent variables.

9. WORK PLAN AND CHRONOGRAM

Principal researchers: Sandra Perich Coronado (SPC) and Gabriel Coll de Tuero (GCT).

Collaborators: doctors and nursery staff of PCC's Anglès, Cassà de la Selva and Salt, qualified personal on SIRIUS program (Galicia) and the statistics. The present study will last a total of 8 years and it will follow the stages described below:

- Stage 0. Protocol design – 3 months (November 2015-January 2016)

This stage is completed and consisted on bibliographic research, the protocol development and its presentation to a court of teachers in 'Facultat de Medicina de la Universitat de Girona'.

- Stage 1. Ethical evaluation of the protocol – (February 2016)

Study proposal to CEIC and its acceptance.

- Stage 2. Coordination – 8 years (March 2016-December 2023)

Before the patient recruitment, we will have two meetings with the principal researchers and the collaborators where we will plan the timeline of the study and the methods of data collection. We will explain all the procedures that will be taken during the study. During the study we will meet at 1, 3 and 7 years to control the evolution of the project and see if everything is going on.

- Stage 3. Patient recruitment – 8 months (March 2016-October 2016)

The participants of this project will be recruited from PCC's Anglès and Cassà de la Selva. We will collect a total of 154 subjects for developing the study. All patients attending to their correspondent PCC and who meet inclusion criteria will be explained the objective of this study and asked to participate in this study. If they accept they should sign the informed consent in which all the procedures are detailed. It is important to respect the patient's will and freedom and if they do not want to participate they will not be judged or manipulated.

- Stage 4. Data collection – 7 years (November 2016-December 2023)

Each patient included in the study will be subject to the following inspections and tests after being explained all procedures of the study and signing the informed consent:

- ✓ BP measurement by trained nursing staff. The patient should be calm, in a sitting position and at least 2 measures, separated 2-3 minutes, will be taken. We will consider AHT when the median of both measures is SBP ≥ 140 mmHg and DBP ≥ 90 mmHg.
- ✓ General physical examination by the physician.
- ✓ Analysis: glycaemia, creatinine, glomerular filtration, ions, uric acid, cholesterol, triglycerides, HDL, LDL, urine sediment, urinary albumin excretion.
- ✓ EKG by the nursing staff. All the EKG will be interpreted by an expert physician in order to see if there is any pathological sign.
- ✓ Retinography with AVR and T_1 measurement. We will need a retinograph equipped with a non-mydratic digital camera and a computer system called SIRIUS to calculate the AVR and tortuosity index. An expert physician will do and interpret the retinographies and the SIRIUS computed program (available in Galicia) will proceed to the estimation of the AVR and tortuosity index.

All these procedures will be done in the following sequence:

During patient recruitment	March 2016-October 2016
At 1 year from the beginning	October 2017-December 2017
At 3 years from the beginning	October 2019-December 2019
At 7 years from the beginning	October 2023-December 2023

To avoid sample losses, one week before each procedure, the participants will receive a phone call and a text message that will act as a reminder. After each appointment, the database will be filled and all the patient information will be performed and archived in anonymous way.

- Stage 5. Statistical and data analysis – 4 months (January 2024-April 2024)

After the recruitment and data collection, all the information will be analyzed by a qualified statistician who will process the data with the adequate software. A multivariate analysis will be performed using logistic regression models to examine the contribution of confounding variables.

- Stage 6. Results' interpretation and writing – 5 months (May 2024-September 2024)

At this point, the investigators will receive the analyzed data from the statistician and will conduct the interpretation of the obtained results. From these results, they will draft a conclusion and start writing the final formal article.

- Stage 7. Article publication and scientific diffusion – From September 2024

From this stage, the results and conclusions of our work will be presented in national and international conferences. Some of the magazines with international impact there we would like to publish are: Circulation, Hypertension and Journal Hypertension.

TASK	Nov-Jan '16	Feb '16	Mar-Oct '16	Nov '16-Dec '23	Jan-Apr '24	May-Sep '24	From Sep '24
Stage 0: Protocol design							
Stage 1: Ethical evaluation							
Stage 2: Coordination							
Stage 3: Patient recruitment							
Stage 4: Data collection							
Stage 5: Statistical + data analysis							
Stage 6: Results + writing							
Stage 7: Publication + diffusion							

10. ETHICAL AND LEGAL CONSIDERATIONS

Medical research based on data collected from patients should always abide by the basic principles of ethics, which are: autonomy, beneficence, non-maleficence and justice. All they are essential for a proper study procedure.

As it is a non-probabilistic consecutive sampling-method, patients will be asked and explained the purpose and structure of this new project and the importance of their participation in this research field. All this information will be transmitted by the physicians involved in the research project.

The 154 patients who accept to be part of our study will be given an information sheet that details the information transmitted beforehand and an informed consent to be sign as agreement to participate in our project (Annex 5).

This study guarantees the confidentiality of patient's data, so for each patient we will use an identification number for all the data collection form and publishing results. The unique two persons who will have access to personal information will be the main investigators (Sandra Perich Coronado and Gabriel Coll de Tuero). All this is explained also in the informant consent.

The present project will be conducted according to national and international ethics guidelines and laws:

- Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal.
- Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.
- WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, June 1964. Last revision in 64th WMA General Assembly, Brazil, October 2013.

Once this protocol is finished and before starting the project, it will be presented at Comitè d'Ètica d'Investigació Clínica (CEIC) of Hospital Josep Trueta, which is the organ in charge for the evaluation of ethical aspects of research projects made in Girona.

11. STUDY LIMITATIONS AND BIAS

The present study has different limitations we have to take into account in order to obtain profitable results in the future. Something we played in advantage is that AHT is a very common disease and thanks to this our sample is rather simple to obtain. However, our participants were selected from the region of Girona and at time to extrapolate data over the world we assume that there might be differences in demographic factors and epidemiological risk factors for CV diseases.

An important limitation is the lack of previous studies about this theme and the only available study that demonstrate a relationship between an AVR improvement and better CVMM is done with 1 year of evolution (7) and our main goal is to demonstrate if this relationship does exist in long-term (7 years). A part from this, the studies correlating possible association between AVR and CV risk are old and we do not have much recent data about this theme.

We recruit patients using a non-probabilistic consecutive sampling method and this could represent a possible selection bias, as the participants included in the study will be only those who assist to the primary care center and meet the inclusion criteria. But it is true that this rural areas from where this project will recruit the patients, at least 1 day per year approximately the 85% of population consult the PCC.

Another issue is that we study a large range of age (from 15 to 65) and this could interfere in our results. The younger population may not consult the primary care center as much as the median one (>40 years) so, younger population may be underdiagnosed and we could not obtain profitable conclusions in younger patients. Not only this, but older people tend to have more comorbidity having more probability of presenting retinal lesions linked to age that could interfere in our results.

Most of the studies found during the bibliography research talk about retinography, AVR and T_1 measurements as possible future tools to establish CV prognosis in hypertensive patients. These studies emphasize the necessity of further projects to evidence or not the association between the regression of retinal lesions and the reduction of future CV events. This is very interesting, because it means that this project will be something never studied but for me, as a student, it has been difficult the researching process because of the lack of evidence demonstrating the association I want to prove.

Another limitation is the duration of this study (a total of 7 years), because there may be loss of information and/or patients and it could negatively influence our future results. For minimizing this bias we have calculated a total loose of 10%, including the patient, the non-readably and the information loss.

This study has multiple covariables that can modify the final results, so we performed multivariate analyses in order to control them.

Extracting and analyzing a number of parameters from the retinography is a slow and tedious work that specialists have to face. In addition to the large amount of time invested, there is a high degree of subjectivity in this task, so it is common that a discrepancy between the ratings of different experts, or on the same expert evaluations at different times, appear (33). But we have in advantage that we will obtain AVR and T_1 values with the specific method SIRIUS, so in theory we won't have problem in the results interpretations but it is good to take this in mind.

12. FEASIBILITY

In both PCC's, Anglès and Cassà de la Selva, we have all means for developing the study but we also need the PCC of Salt where the retinographies will be taken by the nursing staff and a retinograph.

We will need consulting rooms at PCC's for the different procedures we have to practise to our newly-diagnosed hypertensive patients (BP measurement, general physical

examination, EKG and the retinography). A part from this, the patients will be done a fasting blood and a urine sample in their correspondent PCC's.

For the AVR and T₁ calculation we will use an automatic computer system called SIRIUS, which is available in Galicia. So all the retinographies will be send there with an identification number in order to protect patient's confidentiality.

All the interventions will be performed by doctors and nurses from PCC's Anglès, Cassà de la Selva and Salt. They will be trained in this research area in order to avoid confusions and errors.

There are approximately 110 new cases of AHT per year in rural PCC's and we expect that we will need 8 months to get our sample size. For the patient recruitment is very important to follow the inclusion and exclusion criteria and the informed consent signature ensuring that the patient has understood everything.

13. BUDGET

Study budget	Costs
<p style="text-align: center;">Material costs</p> <ul style="list-style-type: none"> • EKG: 4 EKG will be done per patient (at baseline, 1, 3 and 7 years), so a total of 616 EKG will be required. 10€/EKG • Retinography; Camera CANON CR6-45NM: this camera is available in PCC Salt and no extra money will be needed. • Clinical revisions: 4 per patient during these 7 years. No extra costs will be needed. 	6160€
<p style="text-align: center;">Statistician services</p> <ul style="list-style-type: none"> • 30€/h x 80h 	2400€

<p style="text-align: center;">Coordination meetings</p> <ul style="list-style-type: none"> • At the beginning of the study: 2 meetings • During the study: 3 meetings (at 1, 3 and 7 years) <p>Approximately: 200€/meeting</p>	1000€
<p style="text-align: center;">Redaction and publication</p> <ul style="list-style-type: none"> • Manuscripts (400€/revision and 2000€/open-access). American Journal Hypertension, Journal Hypertension, Hypertension 	7000€
<p style="text-align: center;">Diffusion and conferences participation</p> <ul style="list-style-type: none"> • 2 international and 2 national conferences. <p>National: 500€/inscription. International: 800€/inscription</p> <p>Flights and accommodation: 800€ national and 1300€ international</p>	6800€
<p style="text-align: center;">Staff services</p> <ul style="list-style-type: none"> • 2 physicians: 1 of PCC Anglès and 1 of PCC Cassà de la Selva. No extra cost will be needed. • 2 nurses: 1 of PCC Anglès and 1 of PCC Cassà de la Selva. No extra cost will be needed. • 2 nurses: both of PCC Salt, who practises the retinographies. We will pay 25€/h/nurse. The estimated time per retinography is 5 minutes and a total of 4 retinographies will be done per patient during the study. 	1030€
Total	24390€

14. PROJECT IMPACT

We want to prove whether the disappearance of retinal lesions is related to an improvement in CVMM. This would be a great scientist advance, because from the optical test at baseline we could predict how an hypertensive patient is at risk of CV events by calculating the AVR and T_1 evolution over time.

There are no long-term studies demonstrating the relationship between retinal lesions regression and a CVD risk improvement, so if we obtain a positive association between our independent and dependent variables, retinographies could be integrated in the initial evaluation of AHT, being an essential part in the daily diagnoses and monitoring of hypertensive patients.

Future proposals will be the availability of retinographs in the primary care centers, becoming an important tool in the follow up of AHT and for preventing the CVD risk.

15. ANNEXES

15.1. Annex 1: Initial evaluation and risk stratification of a newly diagnosed hypertensive patient (ICS guideline)

Avaluació inicial i estratificació del risc

Grau de recomanació	
C	L'estudi inicial del pacient hipertens consta d'exploració física cardiovascular, anàlisi (glucèmia, creatinina, estimació del filtrat glomerular, ions, àcid úric, colesterol, TGC, HDL, LDL, sediment urinari, excrecció urinària d'albúmina) i electrocardiograma.
C	Per estratificar el risc cardiovascular dels pacients hipertensos es proposa la taula de risc de les societats europees d'hipertensió arterial i cardiologia.
C	Per determinar el risc coronari en pacients sense antecedents de malaltia cardiovascular es proposa l'equació de Framingham calibrada a la població espanyola (REGICOR).
C	Es recomana el tractament amb estatines a les persones malaltes hipertenses sense antecedents de malaltia cardiovascular a partir d'un risc coronari >10% segons les Taules REGICOR, malgrat les modificacions de l'estil de vida durant, almenys tres mesos.
A	Es recomana començar amb modificacions de l'estil de vida a les persones hipertenses Grau 1.
D	A les persones hipertenses Grau 1 de risc moderat (1 o 2 factors de risc CV afegits), es recomana afegir-los tractament amb fàrmacs si no es normalitza la PA en un termini de 6 setmanes.
D	A les persones hipertenses Grau 1 de risc baix (sense altres factors de risc CV afegits), es recomana afegir-los tractament amb fàrmacs si no es normalitza la PA en un termini de 6 mesos.
A	El tractament farmacològic immediat associat a MEV és obligat per a tots els pacients que presentin de forma persistent xifres superiors o iguals a 180 mmHg de PAS i/o superiors o iguals a 110 mmHg de PAD.
A	Igualment els pacients hipertensos amb evidència de malaltia cardiovascular o renal han de rebre tractament farmacològic associat a MEV.
A	Es recomana tractament farmacològic a totes les persones hipertenses de Grau 2 (xifres superiors iguals a 160 mmHg de PAS i/o superiors o iguals a 100 mmHg de PAD) i a les persones hipertenses de Grau 1 que siguin d'alt risc (LOD, diabetis, síndrome metabòlica associació de 3 o més FRCV).

15.2. Annex 2: Following up recommendations for the hypertensive patient (ICS guideline)

Seguiment

Grau de recomanació	
B	El pacient hipertens ben controlat ha de ser atès pel personal d'infermeria d'atenció primària cada 6 mesos i pel personal mèdic d'atenció primària una vegada a l'any.
D	La freqüència de les visites pot ser més elevada en determinades situacions com ara: mal control reiterat de la PA, sospita o evidència de mala adherència al tractament, aparició d'efectes secundaris, tractament complex o canvis en les pautes farmacològiques, associació d'altres factors de risc cardiovascular o malalties concomitants, si la persona no ha consolidat els mínims establerts pel que fa a les habilitats, coneixements i la seva capacitat d'autocura.

15.3. Annex 3: Physical exploration in hypertensive patients (ICS guideline)

3.1.3. Exploració física (GR D):

Inclou les exploracions següents:

- Mesura correcta de la PA (vg. l'Annex I). S'ha de determinar el braç de control, en què la PA sigui més alta.
- Pes, talla i perímetre abdominal. Càlcul de l'índex de massa corporal (IMC). A la Taula 4, es detallen les definicions de les alteracions del pes i del perímetre abdominal.
- Aspectes morfològics: distribució del greix, estries.
- Exploració del coll: polsos i bufos carotidis, estasi jugular, goll.
- Exploració cardíaca: freqüència, ritme, augment del 2n soroll en focus aòrtic, 3r i 4t sorolls (indicatius de disfunció ventricular), bufos.
- Extremitats: edemes, polsos perifèrics. És recomanable la determinació de l'índex turmell braç (ITB) en pacients amb absència de polsos tibials o si hi ha evidències de malaltia vascular a d'altres nivells.
- Exploració abdominal: visceromegàlies, masses i bufos abdominals.
- Fons d'ull: està indicat en els casos de diabetis, HTA Grau III o urgències hipertensives. Cal considerar-lo en la resta de persones hipertenses que no tinguin cap lesió d'òrgan diana i si hi ha l'opció de la retinografia.

15.4. Annex 4: Information sheet

FULL INFORMATIU PEL PARTICIPANT/PACIENT

Li preguem llegeixi amb atenció aquest full informatiu on s'expliquen els motius de dur a terme aquest projecte i els procediments que s'hi realitzaran. El motiu pel qual se li ha estès aquest full informatiu és perquè vostè pateix hipertensió arterial i ens interessaria comptar amb la seva participació per l'avenç de la medicina.

Estudi: *'La raó arteria-vena retiniana i l'índex de tortuositat com a factors pronòstics de risc cardiovascular en pacients recentment diagnosticats d'hipertensió arterial'*

Lloc de realització: Centres d'Atenció Primària de Girona (Cassà de la Selva i Anglès)

Objectius de l'estudi: conèixer si la raó artèria-vena retiniana i l'índex de tortuositat mesurats mitjançant una retinografia tenen capacitat predictiva de la possibilitat d'aparició de fenòmens cardiovasculars en pacients diagnosticats recentment d'hipertensió arterial. L'objectiu d'aquest estudi és observar les possibles alteracions retinianes que poden presentar els pacients hipertensos i determinar si la disminució d'aquestes estaria associat amb una millora cardiovascular, tant en morbiditat com en mortalitat.

Beneficis per el pacient: millora en el coneixement de les comorbiditats que inclou la hipertensió arterial, possible millora en el maneig de la patologia hipertensiva i un control més exhaustiu incloent la retinografia com a eina diagnòstica i pronòstica.

Procediments a realitzar: el pacient recentment diagnosticat d'hipertensió arterial seguirà el protocol general establert per l'Institut Català de la Salut (ICS) i a part se li realitzarà una retinografia al CAP de Salt, que és on disposen d'un retinograf. És convenient el control a casa de la tensió arterial, ja que és més precisa que no la mesurada al CAP.

Extensió i durada: l'estudi durarà 7 anys en total, des de el moment d'inclusió. Durant aquest temps, el pacient seguirà el protocol de l'ICS i als 1, 3 i 7 anys es realitzarà un

control mèdic, una retinografia, un electrocardiograma i la mesura de la tensió arterial per el personal d'infermeria.

Per què han pensat en incloure'l a l'estudi? El seu metge de capçalera o el personal d'infermeria ha detectat que pateix una malaltia anomenada hipertensió arterial. Al ser un diagnòstic recent, sense haver estat encara tractat (farmacològica i no farmacològicament), això ens ajudaria molt a determinar si la raó arteria-vena i l'índex de tortuositat mesurats en la retinografia tenen valor pronòstic per la morbimortalitat cardiovascular. Vostè compleix els requisits per ser inclòs en l'estudi: edat entre 15-65 anys i diagnòstic recent d'hipertensió essencial o primària

Què demanem que faci? La seva participació en l'estudi és voluntària i només serà inclòs si vostè hi està d'acord després de llegir-se el full informatiu i haver entès totes les parts. Si vostè accepta formar part de l'estudi haurà d'assistir als controls que de forma rutinària es farien pel control de la seva hipertensió arterial, però a part una prova més que no s'inclou en el protocol de l'ICS. Aquesta prova s'anomena retinografia, un procés indolor i no invasiu que consisteix en realitzar una fotografia a la retina dels seus ulls. Aquesta prova se l'haurà de fer 4 vegades en total, una al principi, una al cap d'un any, una altre al cap de tres anys i la definitiva al cap de 7 anys.

Protecció de dades i drets del pacient: el present estudi es regeix per les lleis de l'Estat en lo referent a matèria d'investigació mèdica: Ley Orgánica 15/1999 de protección de datos de carácter personal y Ley 41/2002 básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. Aquest estudi ha estat aprovat per el Comitè Ètic d'Investigació Clínica (CEIC) de l'Hospital Universitari Josep Trueta de Girona.

Vostè té el dret a revocar el consentiment en qualsevol moment, sense perjudici en el seu tractament i controls posteriors. Totes les seves dades personals seran confidencials i es tractaran de manera anònima, només hi tindran accés els dos investigadors principals del projecte i es garantitza que cap dada personal vostre serà exposada ni publicada en aquest estudi.

15.5. Annex 5: Informed consent

CONSENTIMENT INFORMAT PEL PACIENT

Títol de l'estudi: *'La raó arteria-vena retiniana i l'índex de tortuositat com a factors pronòstics de risc cardiovascular en pacients recentment diagnosticats d'hipertensió arterial'*

Centre:

Dades del pacient/participant (nom i cognoms, DNI):

Jo,confirmo que:

- He rebut i llegit el full informatiu pel pacient i totes els dubtes que m'han sortit al llegir-me'l han estat resposos de manera satisfactòria i entenedora.
- Se m'ha explicat les característiques i objectius de l'estudi, els beneficis, possibles riscos i la importància de la meva contribució per l'avenç de la medicina.
- He entès que la meva participació és voluntària i que puc abandonar l'estudi en qualsevol fase d'aquest sense que això repercuteixi en la meva atenció sanitària.
- He comprès que la meva participació és confidencial i les meves dades seran eliminades del registre un cop finalitzat l'estudi.
- Estic d'acord en que s'utilitzin les meves dades per a l'estudi indicat i els possibles estudis que en puguin derivar d'aquest.

Data: Nom i cognoms

Firma:

Confirmo que he explicat al participant el caràcter i el propòsit del projecte d'investigació.

Firmat(membre de l'equip del projecte).

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