Universidade de Aveiro Departamento de Ciências Médicas
2019

Clarinda Maria de Castro Neves

Valor prognóstico da Monitorização Ambulatória da Pressão Arterial numa população Portuguesa com evento cardiovascular prévio

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Ciências e Tecnologias da Saúde, realizada sob a orientação científica do Doutor José Mesquita Bastos, Professor Adjunto Convidado da Escola Superior de Saúde da Universidade de Aveiro, e do Doutor Jorge Junqueira Polónia, Professor Associado da Faculdade de Medicina da Universidade do Porto

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palavras-chave

monitorização ambulatória da pressão arterial; predição cardiovascular; acidente vascular cerebral; isquemia do miocárdio; prognóstico.

resumo

A Monitorização Ambulatória da Pressão Arterial (MAPA) tem valor preditor de eventos cardiovasculares em doentes sem evento prévio. No entanto, o valor preditor para eventos secundários não foi ainda estabelecido na comunidade médica.

Neste trabalho, investigamos o valor preditivo da MAPA em doentes com evento cardiovascular prévio, considerando as variáveis seguintes: pressão arterial (PA) de 24 horas, diurna e noturna, queda noturna, pressão de pulso diurno e noturno e frequência cardíaca.

Realizámos um estudo observacional numa população de adultos com evento cardiovascular prévio, referenciado para MAPA entre 1996 e 2017 no Centro Hospitalar do Baixo Vouga. Foram avaliados um total de 391 registos de MAPA de 295 doentes hipertensos, dos quais 72.6% eram homens, 37.6% eram diabéticos e 19.2% eram fumadores. Os eventos cardiovasculares prévios incluíram: 235 eventos coronários, 140 acidentes vasculares cerebrais isquémicos, 11 acidentes vasculares cerebrais hemorrágicos e cinco cirurgias vasculares carotídeas e periféricas. Durante um follow-up de 4.5 ± 5.2 anos, foram observados 93 eventos recorrentes, dos quais 42 acidentes vasculares cerebrais isquémicos, 38 eventos coronários, sete acidentes vasculares hemorrágicos, cinco cirurgias arteriais periféricas e uma endarterectomia carotídea.

O estudo permitiu concluir que: (1) a MAPA teve valor preditivo para eventos cardiovasculares recorrentes em doentes com evento cardiovascular prévio; (2) de entre os valores da MAPA, o valor preditivo dos valores sistólicos e diastólicos diurnos foram superiores aos de 24 horas, e que os valores noturnos não têm valor preditivo para eventos cardiovasculares recorrentes; (3) os limites da MAPA para predição de eventos recorrentes foram mais baixos que os usados para predição primária (4) ; a MAPA teve um valor preditivo de eventos recorrentes superior nos doentes < 65 anos relativamente aos doentes ≥ 65 anos e em doentes com < 65 anos, o valor preditivo dos valores sistólicos (24 horas, diurnos e noturnos) foi superior ao dos respetivos valores diastólicos; (5) os valores da MAPA antes do evento para depois do evento diminuem na sua globalidade.

keywords

ambulatory blood pressure monitoring; cardiovascular prediction; stroke; myocardial ischaemia; prognosis.

abstract

Ambulatory blood pressure monitoring (ABPM) is a predictor of cardiovascular outcomes in patients without previous cardiovascular events. However, the same predictive value for secondary events is not yet established in the medical community.

In this work, we investigate the predictive value of ABPM for patients with prior cardiovascular events, considering the following variables: 24-hour blood pressure (BP), daytime and night-time BP, BP dipping, daytime and night-time pulse pressure and heart rate.

We conducted an observational study on a population of adults with previous cardiovascular events, referenced for ABPM between 1996 and 2017 at Centro Hospitalar do Baixo Vouga. A total of 391 ABPM records from 295 hypertensive patients, from which 72.6% were men and 37.6% were diabetic, were evaluated. Previous cardiovascular events included 235 coronary events, 140 ischemic strokes, 11 hemorrhagic strokes and five carotid and peripheral artery surgeries. During a mean follow-up of 4.5 ± 5.2 years, 93 recurrent cardiovascular events were observed, namely 42 ischemic strokes, 38 coronary events, seven hemorrhagic strokes, five peripheral artery surgeries and one carotid endarterectomy.

The present work allowed us to conclude that (1) ABPM has predictive value for recurrent cardiovascular events in patients with previous cardiovascular events; (2) the predictive value of systolic and diastolic blood pressure values obtained from ABPM were superior to the 24 hour, and that night-time has no predictive value for recurrent events; (3) ABPM thresholds that predict the second event are lower than those used for predicting first events; (4) ABPM has a stronger prediction value for recurrent events in patients < 65 years when comparing to patients ≥ 65 years old; in patients with < 65 years old, the predictive value of the systolic blood pressure values (24h, daytime and night-time) was superior to the respective diastolic values; (5) ABPM values from before the event and after the event decrease overall.

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List of acronyms

ACC/AHA – American College of Cardiology / American Heart Association

ACS – acute coronary syndrome

BMI – body mass index

BP – blood pressure

CABG – coronary artery bypass grafting

CAD – coronary artery disease

COPD – chronic obstructive pulmonary disease;

CV - cardiovascular

DBP – diastolic blood pressure

MI – myocardial infarction

NRI - net reclassification index

NSTEMI - non ST-segment elevation myocardial infarction

NT-proBNP – N-terminal pro b-type natriuretic peptide;

PAD – peripheral artery disease

PCI - previous percutaneous coronary intervention

SBP – systolic blood pressure

SD – standard deviation

SNPs - single-nucleotide polymorphisms

STEMI - ST-segment elevation myocardial infarction

1 Introduction

1.1 Context and motivation

The population of cardiovascular (CV) event survivors is increasing. More than 85 million patients alive in Europe in 2015 (see Figure 1) and over 92 million in the United States (2011-2014) have established CV disease (1)(2). In developing countries, it is becoming a major public health problem (3).

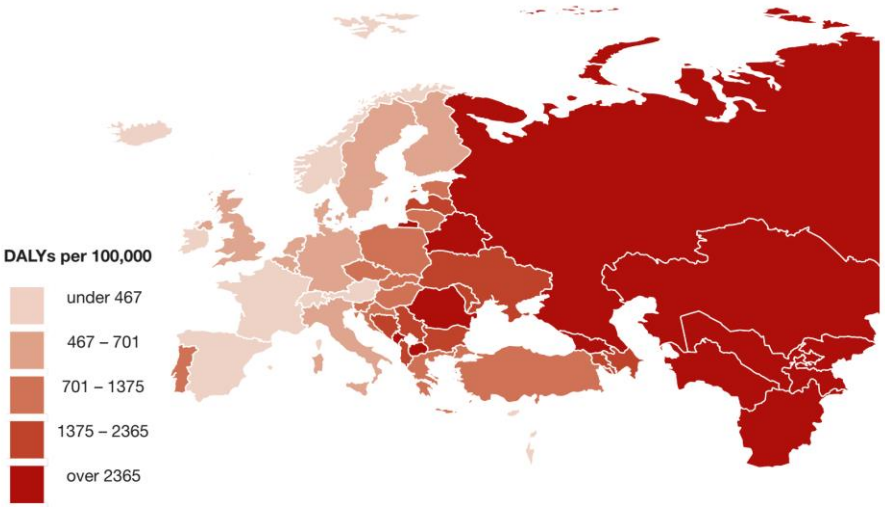


Figure 1 - Age-standardised disability-adjusted life years rate for stroke, 2015, Europe (from: European Cardiovascular Disease Statistics. 2017 edition. European Heart Network)

The high prevalence of CV disease requires a major effort in treatment and prevention of recurrent events. The enhancement of secondary risk stratification may provide guidance for better allocation of resources to patients at true high risk, and to prevent patients with lower risk from intensive therapy side effects and rigorous surveillance.

Currently, the risk stratification strategies recommended for recurrent events and proper validated are directed to the short-term. Significant predictors and consensual prediction models of recurrent events for stable and established CV disease are still lacking (4)(5). The clinical practice would benefit from the availability of an accurate and validated prediction tool with reliable predictors to better stratify patients with established CV disease.

The gap concerning blood pressure use in recurrent event prediction

Blood pressure (BP) is a known CV risk factor and one of the most powerful predictors of events in primary prediction. The role of BP in the prediction of recurrent CV events is still uncertain. There is discrepancy in literature concerning BP as a solid predictor of second event. Most studies use the diagnosis of hypertension or the measurement of BP at baseline as candidate predictor. Ambulatory blood pressure monitoring (ABPM) provides more amount of information and is a stronger predictor of events than office BP in primary prediction. There is little knowledge concerning the value of ABPM in secondary prediction (6).

1.2 Previous work at CHBV and new contributions

The "Cardiovascular prognostic value of ambulatory monitoring in a Portuguese hypertensive population" study was developed from 1991 to 1998 and followed a cohort of 1200 patient without previous CV disease and referred for ABPM for 8.9 years (7)(8)(9). This study was developed in Centro Hospitalar do Baixo Vouga and Hospital Pedro Hispano and was the first study of a Portuguese hypertensive population to evaluate the prognostic value of ABPM for total CV, stroke and coronary events. The study was able to show the higher predictive value of ABPM comparing with office BP for first CV event. This project led to the question if ABPM was also superior to office BP in the prediction of recurrent CV events.

In connection to the results attained in the project, we faced the question whether ABPM would also have value in the prediction of recurrent CV events. This question motivated and is the corner-stone of the present work.

The patients with CV event in the prior cohort were selected and shaped the initial population sample for the work we present here; other patients were included to extend the cohort, considering the information in clinical records up to 2018.

1.3 Research questions

The aim of this work is to study the value of ABPM and its variables in the prediction of recurrent CV events for a population with established CV disease, selected from regular clinical practice at an acute care hospital. The main proposed contributions were to ascertain the possible role of ABPM in the secondary prediction and to demonstrate the benefit of ABPM for the stratification of risk of patients with previous event.

The five research questions that led the present work were the following:

1. Does ABPM have any predictive value for recurrent cardiovascular disease?
2. Which ABPM variables have the highest predictive value for recurrent cardiovascular events, if any?
3. Will the limits of BP that best predict the first CV events be identical to those that predict the second events?
4. ABPM prediction values for recurrent cardiovascular events are they different between distinct age groups?
5. How far and how much ABPM data change from before through after the event?

1.4 Thesis structure

The present text is structured as follows:

- Chapter 1 introduces the present work, the research goals and existing context.
- In chapter 2, 3 and 4 we review the background concepts and the state of the art, focusing on secondary prediction, the development of prediction scores and the characteristics of its

variables, the role of blood pressure in secondary event long-term prediction and a literature review concerning the predictive value of ABPM in primary and secondary prediction.

- In chapter 5, we describe the Methods, reporting in detail the methodology and statistical analysis used in the present work.
- In chapter 6, we present the results, structured according to the research questions.
- In chapter 7, we offer a critical appraisal of the results, comparing and relating to the published literature, and giving potential explanations for some findings.
- In chapter 8, we summarize our main findings and propose new research directions.

2 Secondary prediction of cardiovascular events: literature review

2.1 Introduction

CV disease is a major public health issue. In Europe there were over 5,700,000 new cases of ischemic heart disease and over 1,500,000 new strokes during 2015 (10). In United States there 580,000 new and 210,000 recurrent myocardial infarction (2), and 610,000 new and 185,000 recurrent strokes (2).

Patients who survived CV events have different recurrent event risk. The stratification of these patients could identify those who would most benefit from aggressive risk factor modification, stricter surveillance and individualized optimal treatment (11) (12) (13).

These patients need continued effective and long-term care (14), tight surveillance, and lifelong periodical exams, consultations and medication. This burden raises the costs with treatment, prevention, rehabilitation, novel medications and follow-up. Additional costs come also from disability, work absence, lack of productivity and quality of life, highlighting the relevance of CV disease in terms of public health decisions (15).

Prediction of CV events allows the recognition of the individuals most at risk and the focus on preventive measures to avoid or delay the onset of a new event (16). According to current international guidelines (17) (18) and most commonly used prediction scores (19) (20) (21), the survivors of a CV event have the highest CV risk, but it is the same level of risk for all these patients. If so, this means they will all benefit equally of the same treatment. However, physicians intuitively feel this is not accurate (15) and their heterogeneous risk spectrum is nowadays recognized (22).

Choices like intense platelet inhibition (23), highly expensive treatments as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (24) or implantable cardioverter-defibrillator therapy (25) could benefit some patients, while others need a more conservative approach with obvious reduction in side effects. Intensive therapy side effects such as hypotension, bleeding, rhabdomyolysis or cardiac rhythm disturbances, may be avoided by a better stratification (26). Other important reasons are the patient personal need for information on his health and risk status (15), motivation to lifestyle changes and medication compliance(17), and an enhanced randomisation for future clinical trials (27)(28).

Several cohorts with established CV disease have and are being studied. The REACH (REduction of Atherothrombosis for Continued Health) registry is an international project started in 2003, of patients with established vascular disease and/or at least three atherothrombotic risk factors (29). The SMART cohort (30) includes patients with clinically manifest atherosclerotic disease and the Framingham registry (31) has a secondary event subpopulation.

The identification of features that enables the occurrence of events allows the development of models and algorithms (19,21,32–35) that calculate the probability of an event in a given period of time (36). For long term prediction, single variables usually do not allow good accuracy for the individual, and multivariate models are required (37).

Several entangled issues influence the development and performance of recurrent CV risk scores, becoming a highly complex area.

We present an overview of CV secondary prediction models developed for long term (≥ 3 years), and elaborate on their development, validation and implementation.

2.2 Methods

A literature search was performed on the Medline database for studies which developed multivariate (minimum 2 or more variables) prediction models for long-term (≥ 3 years) CV events or mortality in patients with previous CV disease. The later was defined as previously diagnosed angina pectoris, myocardial infarction, previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), stroke or transient ischaemic attack, diagnosed peripheral artery disease (PAD), or carotid atherosclerosis. Models predicting outcome for specific subgroups (i.e. selected populations with specific comorbidities or submitted to specific procedures) which do not reflect the broader CV disease population were excluded. Models developed to a specific decision making (use or not of certain drug or procedure, for example) were not considered. Only studies which examined one or more of the following endpoints were selected: mortality (total or CV), sudden death, CV event or combinations of any of these. The search was limited to studies written in English.

The literature search was performed on 4th September 2017, using a combination of key words ((secondary OR recurrent) AND (score* OR model) AND (cardiovascular OR cardiac OR vascular OR atherosclerosis) AND predict*) and free text. From a total of 3285 articles, 55 articles were selected by title and abstract. From these, 18 articles matched the inclusion parameters. By further exploring the refence lists and citations, another 22 articles were identified and selected. A total of 40 papers fulfilled the inclusion criteria.

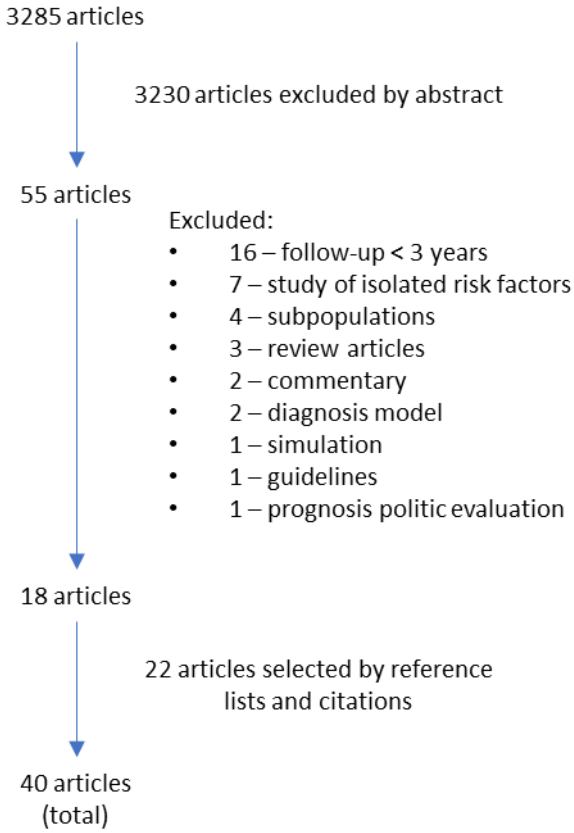
The following data were retrieved from each paper: description of the underlying objectives, aspects of the developed prediction model including inclusion and exclusion criteria, cohort features, number of events, outcome definition, risk predictor selection, missing data, model-building strategies and performance variables were collected. The CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) was used to guide data recollection (38).

Moreover, reviews, editorials, and several articles were reviewed, through reference lists, citations and free search, and issues and features concerning secondary CV prediction were compiled and addressed.

2.3 Results

The 55 references identified were read in full: 18 were selected and 37 were excluded (Figure 2). Additional 22 articles were selected through reference lists and manual searches.

Figure 2 - Selection of articles



A total of 40 references was selected, describing 56 models. Five of these models had more than one type of presentation (e.g. mathematical equation, risk chart, sum score) (Table 1). The populations selected in each article had different primary vascular events: 26 studies evaluated patients with coronary disease (14 with acute coronary syndrome, 12 with established coronary heart disease), seven studies evaluated patients with atherosclerotic disease in different vascular beds, one study evaluated patients with atherosclerotic disease or diabetes (even without CV event), three evaluated patients with stroke, one study evaluated patients with stroke and coronary heart disease, one study evaluated patients with CV disease (no definition of CV disease was given) and one study evaluated patients with PAD. The definition of established CV disease was different between studies (seven included only patients with acute myocardial infarction, seven included patients with acute coronary syndrome (ACS) including unstable angina, seven included patients with atherosclerotic disease, and one included patients with established atherosclerotic event or diabetes). Nine studies addressed the validation of former models: four for coronary disease patients (39)(40)(41)(42), three for stroke populations (43)(44)(45) and two for atherosclerotic disease patients (46)(47). Of the nine, five were for validation for longer term of a score previously developed for shorter term (39) (40)(41)(42) (43), one was for validation of a specific risk class of guidelines (47), one for validation of scores previously validated for the primary event population (46), one for validation of a diagnosis score for long term prognosis (45), one studied two different scores (one developed previously for primary event with patients with a specific comorbidity; another short term secondary prediction score) and evaluated their performance for secondary event long term prediction in patients (44). Some studies made adaptations from previous known and validated scores (48)(49)(50). Three studies developed a score with external validation (51)(4)(52) and from the 28 developing studies, 17 presented internal

validation (seven by bootstrapping, five by split data, four by cross-validation and one by bootstrapping and cross-validation).

The dates of the studies were different (spanning from 1985 to 2011).

Population samples were distinct: average age ranges between 57 and 72 years old, male percentage between 54,3-86.1%, prior stroke between 2-36%, diabetes between 9-48%, and tobacco disorder between 10-82%.

Table 1 – Selected papers with long-term recurrent cardiovascular events scores and key facts

Name	Pop	Dev/ Val	Age	Study dates	Outcome	Time of prediction	Sample size	Int val	Ext Val	Final model given
Plakht 2012 (53)	AMI	Dev	*	2002-2004	all-cause mortality	5	2772	✓		✓
Marchioli 2001 (54)	AMI	Dev	59	1993-1995	all-cause mortality	4	11248	✓		✓
Bohula 2016 (26)	CAD	Dev	59		CV death, MI, ischaemic stroke	3	8598	✓		✓
Dorresteijn 2013 (15)	Ather D.	Dev	60	1996-2010	CV death, MI, ischaemic or haemorrhagic stroke	7 (10)[¥]	5788	✓		✓
Papavasileiou 2013 (43)	Isch stroke	Val	72	1998-2010	functional outcome and mortality	5	1520			✓
Ganz 2016 (51)	CAD	Dev	67	2000-2002	MI, stroke, heart failure, all-cause mortality	4	912		✓	✓
Beatty 2015 (4)	CAD	Dev		2000-2002	composite (time to first nonfatal MI, stroke, CV death)	5	912	✓	✓	
Battes 2013 (55)	CAD	Dev	60	1997-2000	single: MI, CABG, PCI, non-CV death; composite 1 (CV death, nonfatal MI, resuscitated cardiac arrest), composite 2 (CV death, non-CV death, MI, CABG, PCI, resuscitated cardiac arrest)	4	12218	✓		
Kleber 2014 (56)	CAD	Dev	65	1997-2000	all-cause mortality	10	1275	✓		✓
Goliasch 2012 (52)	CAD	Dev	64	1999-2000	all-cause mortality	10	547	✓	✓	✓
Tang 2007 (39)	ACS	Val	64.9	2000-2002	all-cause mortality	4	1057			✓
Fox 2014 (48)	ACS	Dev	*		all-cause mortality	3	1274		✓	✓
Marschner 2001 (57)	ACS	Dev	62	1989	CAD death or nonfatal MI	5	8557	✓		✓

Name	Pop	Dev/ Val	Age	Study dates	Outcome	Time of prediction	Sample size	Int val	Ext Val	Final model given
Sprengers 2009 (58)	PAD	Dev	58	1996-2007	CV death, MI, ischaemic or haemorrhagic stroke	5	800	✓		✓
Ingle 2013 (49)	CVD	Dev	66.4	1998-2004	CV death	**	1372			
Tragante 2013 (59)	Ather D.	Dev	60.6	1996-2007	all CV events / MI	**	8446			
De Bacquer 2013 (60)	CAD	Dev	*	1995-1996	all-cause mortality	5	5216			✓
Uthoff 2010 (46)	Ather D.	Val	67.7	1999-2000	SMART: CV death, MI, ischaemic or haemorrhagic stroke; PROCAM: CAD; FRAMINGHAM: developing coronary death, MI, angina pectoris or coronary insufficiency; SCORE: CV death	6	96			
Van den Berg 2017 (47)	Ather D.	Val	60.1	1996-2004	CV death, MI, ischaemic or haemorrhagic stroke	10	SMART-7216; REACH – 48322			
Deckers 2006 (61)	CAD	Dev	60	1997 – 2000	Composite (CV death, MI, resuscitated cardiac arrest)	10	12218			✓
Rizza 2015 (50)	Ather D.	Dev	*	2005	nonfatal stroke, nonfatal MI, peripheral vascular surgery	4	298			✓
Andersen 2015 (44)	Stroke	Val	*	2003-2012	stroke, death, CV events	5	42182			
Lau 2017 (45)	Stroke	Val	*	2004-2014	stroke, ischaemic stroke, intracerebral haemorrhage	**	2002		✓	
Blankenberg 2006 (62)	Ather D and diabetics	Dev	*	1993	MI (fatal and nonfatal), stroke, CV death	**	3199			
Mega 2015 (63)	AMI	Dev	*	**	CAD	**	CARE: 2878 / PROVE-IT – 1999			✓
Vaara 2016 (64)	ACS	Dev	66.8	2006	single: recurrent ACS; composite: CAD death, ACS	5	2090			✓
Wassink 2011 (65)	Ather D.	Dev	59	1996	any CV event (CV death, ischaemic stroke, MI)	3	3679			

Name	Pop	Dev/ Val	Age	Study dates	Outcome	Time of prediction	Sample size	Int val	Ext Val	Final model given
D'Agostino 1998 (31)	CAD and stroke	Dev	*	1968	single: CAD events (MI, angina pectoris, coronary insufficiency, sudden CAD death, non-sudden CAD death); composite	4	1176			✓
Plakht 2015 (66)	AMI	Dev	66.6	2002	all-cause mortality	10	2763			
Clayton 2005 (67)	ACS	Dev	*	1996	death, MI, disabling stroke	5	7311	✓		✓
Chen 2016 (68)	CAD	Dev	63.6	2008	all-cause and CV mortality	4	1911	✓		✓
Atwater 2009 (69)	CAD	Dev	*	1985	sudden cardiac death	10	37258	✓	✓	✓
Hsia 2008 (70)	CAD	Dev	64	2000	sudden cardiac death	4	8290	✓		✓
Cui 2009 (71)	ACS	Dev	63	1990	CVD event (MI, stroke, CVD-related death), follow-up	5	55654	✓		✓
Rapsomaniki 2013 (72)	CAD	Dev	68.9	2000	all-cause mortality; composite (non-fatal MI or coronary death)	5	102023	✓	✓	✓
Plankht 2012 (42)	AMI	Val	*	2002	all-cause mortality	10	2772			✓
Fox 2010 (40)	ACS	Val	66	1999	all-cause mortality and MI	5	3721			
Cui 2010 (73)	AMI	Dev	**	1990	recurrence of MI event and the time from randomisation to MI event	**	8557			
Truong 2009 (41)	AMI	Val	57	1986	death, recurrent MI, CHF, composite (death or recurrent MI), composite (death or CHF)	3	3153			
van Peet 2013 (74)	Ather D.	Dev	85	1997	CV morbidity and CV mortality composite (incident fatal and non-fatal MI, incident fatal and non-fatal stroke or any other CV mortality)	5	282	✓		✓

* characteristics not given for the total of the population
** not specified
ɣ models fitted for 7 years and extrapolated for 10 years
ACS – Acute coronary syndrome; AMI – acute myocardial infarction; Ather – Atherosclerotic; CABG – coronary artery bypass grafting; CAD – coronary artery disease; CV – cardiovascular; CVD – Cardiovascular Disease; D. – Disease; Dev – Development; MI – myocardial infarction; PAD – Peripheral artery disease; PCI – percutaneous coronary intervention; Val- Validation

Concerning developing scores, eleven studies were based in randomised trials populations, with subsequent stricter inclusion and exclusion criteria, and twenty from cohorts. The time enrolment in

relation to the first event was different among studies: five studies enrolled patients at discharge, one enrolled within three months after the event, one after two and one after four weeks, seven after three months, four after six, one study did not present defined criteria for time of enrolment (from acute event to many years after) and one study had two cohorts with different time of enrolment. Nine studies did not provide objective information or reference to previous description about time for enrolment after the event (two of these were community-based samples). Seven studies had age restriction, six studies excluded patients with heart failure or renal impairment, six excluded patients with unfavourable short-term prognosis or terminal malignancy, three used place of residence or willing to move away as exclusion criteria, two excluded patients with hepatic disease, one had no exclusion criteria. Ten studies had no reference to exclusion criteria. Inclusion criteria of patients were different between studies, and even some definitions also differed. Inclusion criteria of angiographic evidence of coronary artery disease (CAD) varied between 50% to 75% stenosis. Some studies included patients without proven event if they had evidence of ischaemia in stress tests (five studies), electrocardiogram (ECG) changes consistent with ACS (one study) or diabetes (one study). Twelve studies were based on one centre population, and 19 were multicentre. Most studies (90,3%) did not mention patients lost for follow-up, and 35,5% did not address missing data. From those who did, 65% of them excluded patients with missing data from analysis. Sample size ranged from a minimum of 282 patients to a maximum of 102 023 (five studies with population samples below 1000 patients, 20 with population samples between 1000-10000 patients, and five with population sample over 10000 patients). Follow up ranged from 3 to 11.3 years, and the event per candidate predictor ratio was <10 in 22.6% of the studies, and over 20 in 58.1%. In three studies there was no sufficient information to calculate the ratio. Table 2 presents the candidate versus selected predictors found more frequently.

Table 2 - Candidate and selected variables for prediction models more frequently found in the reviewed papers

Variables	Candidate (n)	Selected (n)
Medication[۲]	27	4
Age	24	21
Tobacco use disorder	24	18
Diabetes	21	16
Gender	21	11
Renal disease (creatinine / eGFR)*	20 (6/8)	15 (5 /3)
SBP	20	11
Prior CAD (MI)**	16 (11)	7 (6)
BMI	16	4
HDL cholesterol	15	12
Prior stroke	15	12
Total cholesterol	15	10
Hypertension	14	5
PAD	9	7
comorbidities[۲۲]	9	7
Heart rate	9	5

Variables	Candidate (n)	Selected (n)
DBP	9	3
Statin/lipid lowering agents	9	2
History of heart failure	8	4
hs-CRP	8	3
LVEF	7	5
glucose	7	5
Ethnic group	7	1
aspirin	7	1
revascularization	6	5
Malignant neoplasm	5	3
LDL cholesterol	5	3
Leucocytes	5	3
Triglycerides	5	2
Diuretics	5	2
Angina	5	2
Family history of CV disease	5	1
NT-proBNP	4	4
COPD	4	3
Angina grade	4	3
History of CABG	4	1
Intermittent claudication	4	1
Alcohol or drug addiction	3	2
Qualifying event	3	2
Abdominal obesity	3	2
Moderate to severe mitral regurgitation	3	2
Atrial fibrillation	3	1
hypertriglyceridemia	3	1
Nitrates	3	1
Angina duration	3	1
LVH	3	1
PCI	2	2
CABG	2	2
Thrombolysis	2	2
Plasma sodium	2	2

Variables	Candidate (n)	Selected (n)
uACR	2	2
hs-cTnT	2	2
Severe LV dysfunction	2	2
Fibrinogen	2	1
Physical activity	2	1
Years since first vascular event	2	1
Nationality / country of residence	2	1
Homocysteine	2	1
STEMI	2	1
Previous angiography	2	1
No of diseased coronary arteries	2	1
sVCAM-1	2	1
sICAM-1	2	1
Moderate to severe pulmonary hypertension	2	1
Echo missing	1	1
Acute LV failure in hospital	1	1
No premature ventricular beats	1	1
Arrhythmias	1	1
Results of exercise stress test	1	1
cIMT and carotid stenosis	1	1
Waist-hip ratio	1	1
AAA	1	1
Surgery of arterial disease	1	1
Social deprivation	1	1
PCI/CABG within 6 months of event	1	1
Depression / anxiety	1	1
No lipid lowering therapy	1	1
Angina each additional drug	1	1
Angina attack >= 1/week	1	1
QT interval	1	1
Non-STEMI	1	1
Haemoglobin	1	1
sTNFR1	1	1
Symptomatic CAD	1	1

Variables	Candidate (n)	Selected (n)
ST depression	1	1
Not having in hospital PCI	1	1
Psychological distress	1	1

ϒ Each drug was counted once (except aspirin, diuretics and lipid-lowering agents) (e.g. ACEI or ARB, anti-coagulants, beta-blockers, CCB, digitalis)

ϒϒ Each comorbidity was counted once (neurological disorders, gastrointestinal haemorrhage, anaemia, schizophrenia or psychosis, chronic liver disease) (except malignant neoplasm)

* Total of candidate predictors of renal disease or renal lesion, including those evaluated by level of plasma creatinine and those by eGFR (in parenthesis those defined specifically by creatinine or eGFR, included in the total)

** Total of candidate predictors of established CAD (in parenthesis those defined specifically by previous MI, included in the total)

AAA – abdominal aortic aneurysm; ACEI – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blockers; BMI – body mass index; CABG – coronary artery bypass grafting; CAD – coronary artery disease; CCB- calcium channel blockers; cIMT – carotid intima-media thickness; COPD – chronic obstructive pulmonary disease; CV – cardiovascular; DBP – diastolic blood pressure; eGFR- estimated glomerular filtration rate; HDL – high density lipoproteins; hs-cTNT – high sensitive cardiac troponin T; hsCRP – high sensitivity C-reactive protein; LDL – low density lipoproteins; LV – left ventricular; LVEF – left ventricular ejection fraction; LVH – left ventricular hypertrophy; MI – myocardial infarction; NT-proBNP – N-terminal pro b-type natriuretic peptide; PAD – peripheral arterial disease; PCI – percutaneous coronary intervention; SBP – systolic blood pressure; STEMI – ST-segment elevation myocardial infarction; sICAM-1 – soluble intercellular cell adhesion molecule 1; sVCAM-1 – soluble vascular cell adhesion molecule 1; sTNFR1 – soluble tumor necrosis factor receptor 1; uACR – urine albumin to creatinine ratio

The selected variables for recurrent prediction models in studies with populations with coronary artery event or atherosclerotic event are presented in Table 3, divided by outcome.

Table 3 – Variables selected for recurrent events prediction models by population sample and outcomes

Population sample		**Outcome: All-cause mortality**	**Outcome: CV death, MI or stroke**
	n (total studies)	9	8
ACS + AMI + coronary heart disease	22	9/22 Age – 8 Echocardiographic changes – 6 Heart rate – 5 Creatinine – 4 Gender -3 Renal disease-3 Anaemia-3 COPD-3 Malignant neoplasm-3 HTN – 3 Plasma sodium-2 Alcohol or drug addiction-2 Schizophrenia or psychosis -2 Neurological disorders – 2 Diabetes-2 HDL cholesterol – 2	3/22 Age – 3 Smoking – 3 Diabetes – 3 Previous stroke – 3 Gender – 2 Ejection fraction – 1 Leucocytes – 1 Glucose – 1 Creatinine – 1 Angina attack ≥ 1/week – 1 Previous angiography – 1 No lipid lowering drugs -1 QT interval – 1 SBP – 1 Each drug for angina – 1 Previous MI – 1

Population sample		Outcome: All-cause mortality	Outcome: CV death, MI or stroke
		Leucocytes -2 Fasting glucose -2 PAD – 2 HgA1c – 2 Smoking – 2 CABG-1 PCI and/or thrombolysis-1 Obesity-1 GI haemorrhage-1 Electrical instability-1 Residual myocardial ischaemia-1 Intermittent claudication – post-MI smokers –1 Fibrinogen -1 ST deviation – 1 SBP – 1 Killip class – 1 Cardiac arrest at admission – 1 Biomarkers of necrosis – 1 Diabetes without renal or peripheral circulation changes – 1 NT-proBNP – 1 Cystatin C – 1 Renin – 1 25OH-vitD3 – 1 Deprivation – 1 ACS subtype – 1 Recent revascularizations – 1 Previous MI – 1 Use of long acting nitrates – 1 Lipids – 1 Heart failure – 1 Atrial fibrillation – 1 Stroke – 1 Chronic liver disease – 1 Depression – 1 Anxiety – 1 Serum cholinesterase -1	HTN – 1 CHF – 1 Prior CABG, PAD or other vascular disease – 1 eGFR - 1

Population sample		Outcome: All-cause mortality	Outcome: CV death, MI or stroke
		Total cholesterol -1 LDL cholesterol - 1	
Atherosclerotic disease	6	0/6	4/6 Gender – 4 Age – 3 Diabetes – 3 Smoking – 3 HDL cholesterol – 3 SBP – 2 Total cholesterol – 2 hsCRP – 2 previous CAD, CVD, PAD or AAA – 2 Fasting glucose - 2 Triglycerides – 2 proBNP – 2 HTN – 2 yrs since 1st vascular event – 1 eGFR – 1 cIMT – 1 presence of carotid stenosis – 1 Ramipril – 1 Waist-hip ratio – 1 LDL/HDL cholesterol – 1 Lipid lowering drugs – 1 Microalbuminuria – 1 Creatinine – 1 Waist circumference – 1 Prior MI, stroke or arterial surgery – 1 MDRD – 1 Homocysteine – 1

AAA – abdominal aortic aneurysm; ACS – acute coronary syndrome; AMI – acute myocardial infarction; CABG - coronary artery bypass grafting; CAD – coronary artery disease; cIMT – carotid intima-media thickness; CHF – chronic heart failure; COPD – chronic obstructive pulmonary disease; CV – cardiovascular; CVD – cardiovascular disease; eGFR – estimated glomerular filtration rate; GI – gastrointestinal; HgA1c – Haemoglobin A1c; hsCRP – high sensitivity C reactive protein; HTN – hypertension; SBP – systolic blood pressure; MDRD – Modification of Diet Renal Disease equation; MI – myocardial infarction; NT-proBNP – N-terminal pro b-type natriuretic peptide; PAD – peripheral artery disease; PCI – percutaneous coronary intervention; yrs – years

The preferred method for model development was Cox regression (77,4%). Variable selection methods were used in 29% (backward) and 6.5% (forward) of the studies. Other methods like choosing all significant variables from univariate analysis or omission of the latest weakest predictors were used in 12.9% and 3,2%, respectively. Discrimination was addressed in 77,4% of the developing models' studies (C statistic ranged from 0.61 to 0.85). From the models published after 2008, 25.8% presented measures of reclassification. The presentation of the models to allow its use by others was given in 71% of the studies. Of these, 10 studies gave a mathematical formula, and one of them did not give an alternative way of scoring (ex: sum points, risk chart, app). Seven of the developing model studies had external validation.

2.4 Discussion

The development and reporting of prediction models is a growing field. However, different reviews point out the poor quality of reporting and development issues (Table 4) (75) (76). Many studies do no report important information to assess its quality, reproduction or validation. In recent years, several publications aimed at providing tools to improve the development, validation, reporting and reviewing of prediction models (77). Some examples are the PROGRESS series on prognostic models research (78), the CHARMS checklist (38) and the TRIPOD statement (79), amongst others.

Table 4 - Methodological issues found in cardiovascular recurrent events prediction scores development and implementation

- Multiple scores published without practical implementation
- Poor quality of reporting
- Different criteria for population inclusion
- Different types of selection of population
- Higher proportion of men
- Dates of enrolment
- Population from single centre vs multicentre
- Ethnicity and geographical origin of the population sample
- Time of enrolment in relation to the first event
- Time and number of assessments of the population characteristics
- Candidate variables chosen
- Treatment control of a variable in follow-up
- Comorbidities, psychological and social features less studied
- Age-bias by its prediction power
- Difference of predictors according to age
- Choice of outcomes
- EPV ratio
- Performance quality
- External validation
- Emphasis in global risk
- Primary event risk factors may not work as well in the secondary setting
- New biomarkers / proteomics
- Genomics
- Cost benefit analysis
- Bias by decision-making
- Index event bias
- Confounders by indication
- Presentation of score model / apps / webpage
- Little studies from small investigators team versus joined researchers and data

Patients with established CV disease have nowadays an increased life expectancy, for which prognostic scores need to have a longer time of prediction than most models were built for. In secondary prediction, the time interval for risk prediction is much lower when compared to the usual 5 to 10 years for primary event. This may lead to an underestimation of the risk in the patients with lower secondary risk. A lower risk at two years could become higher at 10. If the patient in question has a long life expectancy, a more relaxed clinical approach to this patient could lead to a disastrous outcome (80). In our analysis, only seven scores had prediction time of five or more years.

2.4.1 The development of the model

The models analysed were developed for different populations (e.g. ACS (57), atherosclerotic disease (15), stroke (43), PAD (58)), have different inclusion criteria, different moments of enrolment and assessment of features in relation to the first event, and different chosen candidate variables and outcomes. All these factors contribute to different models for different outcomes with different performances for the same populations.

Differences in population samples are huge and this has direct influence on which patients apply the developed score. There are major differences between hospital admission cohorts, community population samples (like the Framingham cohort) or clinical trial samples. The latter has usually stricter inclusion criteria, less comorbidities and a better compliance (81). An example is high risk patients which usually are poorly represented in trials (39). Extrapolation of these scores to the real-life patient must be done with care. Registries with little exclusion criteria and consecutive selected patients (39), like the Global Registry of Acute Coronary Events (GRACE) registry (82), may unravel different prognosis features for which highly chosen population may not.

Scores developed in different populations lead to different sets of selected variables. The study of prediction variables may vary if the developing population has previous CV event in any vascular bed (15)(30), or just coronary disease (55) (4) or stroke (43). Even with the same vascular bed affected as inclusion criteria, populations can be quite different. A score derived from the ACTION trial cohort, with ACS, had 56% of patients with previous MI and 5% with previous stroke (67), whereas the LIPID cohort, with ACS, from which long term secondary scores were also derived, had 38.4% with previous MI and 21.8% with previous stroke (57).

All scores had a higher proportion of men, with over 80% in 11 of them. This raises issues when applying them in women (4). The recurrent event score developed from the Framingham cohort developed a different score for men and women (31).

Also risk scores may behave differently in distinct populations. In healthier populations or with better socio-economic status, prediction scores may overestimate risk, while in sicker populations, could be underestimated (83).

The dates of enrolment of population samples are also highly different (57) (68). Disease definitions, diagnosis and management approaches have changed in the last decades, and long periods of enrolment may cause big heterogeneity (84). Given the advance of medical knowledge and clinical practice, CV risk tended to reduce over the last decades. Thus, risk scores based in old data skew by overestimation of the risk (85), along with models which are outdated from contemporary clinical practice, which can under or overestimate the present risk (54)(86). Also, redefinition of endpoints over the years may affect data collection and, consequently, the results. The new emergence of biomarkers, genomics and proteomics may outdate some scores.

Scores developed using population samples from a single centre, like the SMART cohort (30), may differ from those which arose from a multicentre cohort (29). Also, scores developed in population from a specific ethnic group (54), may not apply to other ethnic groups. East Asian patients have similar or less rate of ischaemic events during antiplatelet therapy after PCI and a higher risk of bleeding when compared to Caucasian patients (87).

One possible limitation is the inclusion of patients promptly after the occurrence of the event, since these patients have greater risk of recurrent events in the first weeks to months after the event (26) (53) (68). The timing of patient selection after the event can directly influence the final model. In addition, patient characteristics are usually assessed only at baseline, not considering the clinical management and treatment effect in the follow up, which can influence the outcome (4)(39) (88).

In our analysis the selected variables are different between models, although coronary populations scores were more prevalent than atherosclerosis populations (22 versus 5). Scores from populations with coronary heart disease included more often age (78%), smoking disorder (63.2%), diabetes (57.9%), prior stroke (47.4%), gender (42.1%), renal disease (36.8%), left ventricular dysfunction (36.8%), prior revascularization (36.8%), hypertension (36.5%) and PAD (31.6%). Scores from populations with atherosclerotic disease (with proportions of coronary heart disease between 38% and 85%) privileged high-density-lipoprotein cholesterol (100%), smoking disorder (80%), diabetes (80%), renal dysfunction (80%), age (60%), gender (60%), total cholesterol (60%), systolic blood pressure (SBP) (60%) and triglycerides (60%). Cholesterol levels appear to have more significance for the stratification of events of atherosclerotic cause. Age, events in other vascular beds and organ damage features are more prevalent in scores for coronary patients. Other risk factors like NT-proBNP, which seems to have a promising role in secondary risk stratification, do not frequently appear as candidate variable. Some explanations may be related to cost, not being a relevant biomarker at the time the score was developed or laboratory availability. In our analysis, NT-proBNP was selected for the final score every time it was a candidate. Different choices of candidate variables will lead to different prediction scores, improving or worsening the final score prediction (4).

Different comorbidities appear to have a considerable impact in secondary setting, particularly for longer term. This is probably related to the recovery of CV events in an older population (which gives comorbidity a higher weight (81)), meddling with CV therapy intolerance and dysfunction of other systems. Some examples are renal disease (89) (selected 75% the times it was evaluated), chronic obstructive pulmonary disease (COPD)(selected 75% the times) and anaemia (90)(selected 100% the times). These comorbidities are usually not studied as candidate variables (53), and their true value is yet to be validated. Patients with COPD have an increased risk of death after MI than those without COPD (91) (92) (93). In patients with ACS and with the same GRACE score, those with COPD have 30% higher risk of death than non-COPD patients (94). Introducing COPD as a predictive variable in the GRACE score would reclassify 33.9% from low risk to moderate risk (3% to 3%-6%) and 64.3% of the moderate risk were reclassified as high risk (>6%). This probably would change a different endeavour in the management of a considerable part of COPD and ACS patients. Anaemia has also been associated with a worst prognosis in CV patients (90). Some studies found the highest CV recurrent event rates in patients with chronic kidney disease (47) and impaired renal function at admission (47)(39).

Medication use was sometimes not chosen as a candidate variable, for its leaning to confounding by indication (55) (15). The fact that most patients with established CV disease were already with most of the recommended drugs will eventually diminish its prediction power and clinical applicability (15).

Some studies evaluated medication as a post-hoc analysis and showed no interference with the estimation of prediction in the final model (55) (4).

Other examples of variables less studied are social deprivation (72), psychological distress (49) and quality of life evaluation (this one addressed in a study outside this scope for a shorter period of prediction, still worth mentioning (95)).

Age is one of the most powerful predictors. The increase in risk by age alone deludes into the suggestion that the potential benefits of therapeutic interventions are higher in the elderly than in younger patients. And this may lead to the decision in favour of the elderly, leaving the younger and the lower risk population with less stringent goals (54). Still, the costs of preventive measures to the young population with longer life expectancy have to be taken into account (54). Also, predictor variables may vary between younger and older patients. In a retrospective study (66) based on the SAMI cohort (53), two groups (≤ 65 years and > 65 years of age) were compared. Some factors had a stronger association with mortality in the younger group (renal diseases, previous MI, CABG treatment, hyponatraemia, anaemia and malignant neoplasm) and other in the older (significant 3-vessel or left main coronary diseases, left atrial dilation and neurological disorders).

The choice of the outcomes influences the model development (55). Nonfatal events are usually more frequent than fatal events and ACS will include angina attack and acute coronary infarction will not.

The number of candidate variables along with the number of outcomes may be important to prevent overfitting. A minimum of ten events per variable has been considered the minimum for preventing overfitting (96) (97). In the present analysis, 7% of the models did not achieve this minimum, at the risk of overfitting.

Performance measures like C statistics and net reclassification index (NRI) are important to access quality performance. The C statistic is a measure of discrimination: it measures how well a model differentiates patients with or without the outcome. A C statistic of 0.75 means that in 75% of patients with and without the event, the patient with the event had a higher predicted probability than the patient without the event. NRI was introduced in 2008 (98) aiming to measure the improvement that a marker could provide to the prediction power of a model towards a given outcome. Since then, some published models provide NRI, showing the pool of patients that would be reclassified and therefore supposedly better stratified by the new model. This is a comparative measure of performance, only well applied when two models are compared. Given that in the secondary setting there are no generally accepted risk categories for long term mortality, one should note that this comparison is made with other published models (52). In our analysis, 82.5% of the models had measures of discrimination (between 0.61 and 0.94). High C-statistics, although apparently better, may conceal a problem of overfitting of the model, in which an optimistic performance of the model towards the data set from which was developed. These models perform well in that population sample but will perform poorly in other cohorts. Only 25.8% of the models published after 2008 presented measures of reclassification. The comparisons were: to the same model but restricted to demographic factors (72), to a model with only age and gender (65), to a single risk factor (47), to a traditional risk factors model developed in the same article (74), compared to a refit Framingham model (51), compared to a previous developed score (56) (52).

Accuracy (the degree to which a predicted case match an observed one) and generalizability (the capacity of accurate predictions in a different set of patients (54) are essential performance features. Validation allows to demonstrate the model accuracy in a population other than the one it was built for, it allows distinction between patients with and without the outcome (discrimination) and allows

agreement between prediction and observation of risks rates in groups with the similar risk prediction (99). External validation, which is to evaluate the performance of the model in a population different from the developing cohort is essential to the model generalisation. Most scores in our analysis lack internal validation and only seven had external validation (see Table 1).

The presentation of the score to be used by other professionals is also important. Many studies do not present their models (55) (4) (65), while others developed apps (48), online datasheets and models (15) (72), as seen in Table 1.

2.4.2 Adaptation and validation of scores developed with different aims

Some studies evaluated scores validated for short term prognosis but for the long-term prognosis. The GRACE registry gave rise to prediction scores, from in-hospital mortality (100) to mortality prediction at six months for patients with ACS, including STEMI (82), to several other adaptations. Several studies for longer term were published using the GRACE score (39) (40) or an adaptation of it (48). In the later, creatinine values and Killip class were substituted by history of renal dysfunction and diuretic usage, respectively (48), and an electronic tool providing absolute percentage risks was developed and externally validated.

Several studies approached the Framingham risk score and adjusted in order to improve prediction and discrimination in the secondary setting: adding lifestyle changes (49) or different biomarkers (51)(50).

A study evaluated scores commonly used in primary prevention (SCORE, PROCAM, FRAMINGHAM) concluding they had no power to predict recurrent events (46).

Another study evaluated the prediction power of the CHA2DS2VASc score and of the Essen Stroke Risk Score to predict stroke, death and CV events recurrence in a first ever stroke population without atrial fibrillation (44).

2.4.3 Current guidelines

Current European Society of Cardiology guidelines consider all patients with a previous CV event to be at very high risk for CV mortality (17) using SCORE (19) to predict the 10 year risk of fatal CV disease (≥ 10% mortality risk). American guidelines classify patients with previous events as having high risk (10 year risk ≥ 7.5% of coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke) (101), leaving the very high risk classification to patients with established CV disease and multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially current smoking), multiple risk factors of the metabolic syndrome (especially dyslipidaemia) or progression of CAD (102). The SMART and the REACH cohorts risk was classified according to an adapted American College Cardiology/American Heart Association very high risk criteria by choosing some risk factors (current smokers, diabetes, dyslipidaemia, recent recurrent vascular event) (47). Other very high-risk factors were also selected from literature (polyvascular disease, PAD, abdominal aortic aneurysm, congestive heart failure and presence of atrial fibrillation, and other possible very high-risk factors were also considered like severe obesity, therapy resistant hypertension, hyperlipidaemia or chronic kidney disease). In these cohorts with patients with clinical established atherosclerotic disease, 57% in the SMART and 64% of the REACH cohorts were classified as very high risk (47). Events rate were higher in these strata (2.7 vs.2.0/100 patients-years and 5.9 vs 3.9/100 patients-years in SMART and REACH, respectively) but its discriminative predictive power was low (C statistic of 0.54 and 0.56 in

SMART and REACH). In the former, about two thirds of the patients had an expected 10-year risk prediction of recurrent events <30%, and risk factors not considered in the ACC/AHA criteria like eGFR<45 ml/min/1.73m^2, polyvascular disease or age >70 years had similar or better discriminative power of prediction than the ACC/AHA. Apart from the progression of coronary heart disease, the ACC/AHA criteria had relative low incidence rates. The criteria selected younger patients, and they were modifiable (quit smoking, dyslipidaemia treatment) leading to a higher range of outcomes which diminished its prediction power and lead to lower absolute risks (47). The authors concluded that current guidelines do not provide powerful tools to accurately discriminative the risk profile of patients with established CV disease.

2.4.4 Other issues concerning recurrent prediction

Traditional risk factors for primary event (smoking, cholesterol levels, hypertension or diabetes) play an important role. In our analysis, age, gender, diabetes and tobacco use disorder are among the most frequent selected variables (Table 2). Gender, total and low-density-lipoprotein cholesterol were selected half the times they were evaluated, hypertension a third of the times and BMI a quarter of times. But they may lose predictive power in the secondary prediction (4). A valid reason may be their better control after the first event (72). Some authors advocate that event specific lesions of CV end organ damage may probably improve recurrent risk score (103). These predictors may allow better discrimination than traditional risk factors, measuring disease burden, hemodynamic stress, myocardial or renal damage. Some examples are biomarkers (4) (104) like natriuretic peptides (105), high sensitive C-reactive protein (106), high sensitive cardiac troponin (107) or albuminuria (108) or the number of symptomatic arterial beds affected (109). Other risk modifiers are usually not taken into account in several scores: potential prognostic variables in clinical history and examination, pharmacologic therapy, exercise, social deprivation, ethnicity, central obesity, several biomarkers, psychosocial features and family history of premature CV disease (85) (110).

Proteomics is a major tool in the study of biomarkers. The possibility of analysing systemic proteins in large scale and applying these techniques to cohorts of CV risk studies followed for several years, may unravel new pathways of research. Ganz et al followed this approach, presenting a 4-year risk score for secondary event in stable coronary heart disease patients based on levels of nine proteins (51). The levels of 1130 proteins were measured, and, in a timeline of 4 years, 200 proteins had prognostic value for CV events (145 positively and 55 negatively). The final model based on nine proteins was compared to a refit Framingham secondary event risk model (the variables of the Framingham secondary event risk model readjusted to the Heart and Soul derivation cohort) (31). Proteomics appears to be a promising course in the prediction model investigation. A strong current limitation in the present time is that most of the proteins identified are not available in the traditional clinical setting, and cost-benefit factors need to improve. The comparison with more widely available biomarkers, as high sensitivity troponin or natriuretic peptide (111), has yet to be established.

Gene investigation has associated several loci and single-nucleotide polymorphisms with atherosclerosis development and CAD (112) (113) . The CARDIoGRAMplusC4D Consortium identified 15 new loci with genome-wide significance, and over 100 single-nucleotide polymorphisms (SNPs) with a strong association to CAD, which could explain 10.6% of CAD heredity (114). The development of risk scores based on the discovered SNP's (64), with each SNP with weighted number of risk alleles, has been associated with recurrent events independently from risk factors. However, they were not associated with composite coronary death and recurrent ACS. The authors suggest that the background for STEMI and NSTEMI are different: Gene risk scores are associated to atherosclerosis,

multivessel disease, CAD and NSTEMI, while thrombosis has an important role in MI, associated with smoking and probably STEMI (64).

A cost-benefit analysis is essential when considering possible candidate variables. Balance between the variables required to improve secondary risk prediction and their costs must be considered. High costs could undermine general use, for example in primary care or developing countries. Complicated, long tests which need more specialised exams are also more time-consuming.

When selecting variables, bias by decision making needs to be considered. In a study for development of risk prediction models for patients with coronary heart disease (55), outcomes such as CABG and PCI worsened the discrimination power. One explanation is the high influence of the physician decision for revascularization or medical treatment. In some studies, older patients with renal dysfunction are less often submitted to therapeutic interventions, contributing to the mortality risk increase (115). The therapeutic approach to older patients is more often conservative by physician choice (25) and lesser times based in objective criteria or validated risk scores, unlike younger patients (116). This is true concerning invasive procedures like CABG or PCI and target goals for hypertension or dyslipidaemia treatment.

Index event bias (117) plays an important tole, yet most studies and published scores fail to address this matter. This may unravel several known paradoxes in the recurrent event research. Factor V Leiden is an undoubted risk factor for first-time deep vein thrombosis, although in patients with previous event, its role has been described as apparently not important (118); smoking is an important risk factor for first CV event, but it seems to have a paradoxical beneficial role in patients with previous myocardial infarction (119); the aspirin paradox, in which patients on aspirin for primary prevention had lower risk for first event, but it was associated with slightly higher rates of recurrence (120); and the case of obesity, associated with better outcomes after the first myocardial infarction, although is a proven risk factor for CAD (121). In the study of the general population, the different risk factors for a first event are not associated with each other. Thus, to relate each risk factor with the event does not involve a prior biased selection of population. When we select a population based on a first event, the risk factors are already present in a hypothetically big part of this population, biasing the study towards the null (117). This bias may be different according to the intraindividual variability of the risk factor (122). For example, the control of a certain risk factor like blood pressure or cholesterol level after the event, may affect its association with recurrence. Also, unmodifiable factors will have a higher index event bias since they do not change and are maintained in the studied population. In addition, possible unknown and unmeasured risk factors, due to the selection of the population, may have also negative associations, affecting the accuracy of predictive models of recurrence risk (122). Some authors point out that markers of end-organ damage may be better predictors for recurrent events than clinical risk factors (4), which may be biased by the population selection.

Confounders by indication are another known bias which may affect secondary prediction. The selection of patients with a specific feature which obligates certain terms (like selection of patients with coronary heart disease which are mostly prescribed with aspirin), may induce a misleading association between these later terms and some of the studied predictors which may have nothing to do with the terms, but with features that were inclusion criteria in the first place. So, several associations may not be real (86).

Some scores were developed aiming simplicity of use (54) and practical availability in clinical practice (56) (68) and primary care (80). There are scores which were developed only with simple clinical characteristics of real life clinical practice (26) (53). Collection of data from electronic health records may be a faster way to analyse data, and some scores have been developed using this strategy (72).

This allows also to study real-life patients rather than data from selected trial cohorts. Other studies aimed targeting community based cohorts with few inclusion criteria aiming developing scores based in real life population (53).

The use of web calculators, web datasheets or apps is a major tool for the wide diffusion of a score. The use of a prognostic model to stratify patients with a wide range of clinical data already available in real world health records without the need of extra exams is very appealing (72). The initial stratification could be made in a simple way, and then only a smaller part of the patients with CV disease would be selected for more sophisticated, time and human resources consuming and costly examinations.

Finally, the abundance of prediction models is overwhelming. A systematic review of clinical prediction models published from 1990 to mid-2012 (123) referred 215 for patients with CAD, 78 for stroke and 25 for sudden death. The authors noticed that they probably underestimated the total number, given they excluded all that did not predict a clinical outcome measure, all that were exclusive validations and all that did not provide enough information to calculate the individual risk probability. The number of prediction models made *de novo* is increasing over time, but the clinical application remains low. We are seeing a bigger effort in optimizing statistical performance than answering clinical decision questions (123). The pressure for publication, associated with the preference by the publishers for positive studies, lead to important publication bias (37). Is important to overcome publication bias originated by many small positive studies which mislead meta-analysis and systematic reviews with low grade positive associations. Different methodological procedures and statistics can affect the results, by enhancing, attenuating or abolishing associations (110). Also omission of some details, analysis and outcomes, and enhancing the importance of the findings is a major concern (110). This is an important issue, since it changes present knowledge and future directions of investigation.

Whether the use of risk scores has a vital role in clinical decision-making is of utmost importance (83). If its use can help change how we treat patients and benefit the course of the disease is critical for its implementation in clinical practice. Although risk markers of deleterious outcomes are intuitively the focus of treatment, they are not necessarily the way to improve outcomes (124). Also, risk markers become more relevant when there are interventions to improve outcomes.

Impact of research is a fundamental issue. External validations are needed. Information about the conditions in which the studies are made and how dependent are of those conditions is fundamental for the consideration of implementing the score in another setting (125).

Some authors defend that researchers should join for critical mass; a larger amount of data would provide more solid prognostic research, instead of having many papers on small cohorts (110). Data sharing (123) and joint research may be strategic to improve the quality and validation of clinical prediction models, to minimize duplicate research and maximize the impact in patient outcomes. Nowadays, electronic databases provide a large amount of data from different populations and ethnic groups, which could be used by a confluence of researchers, and provide the means to develop a multivariate model with sound accuracy and the means to validate in other populations. This could lead to a single or at least few prediction models, validated in several populations, instead of innumerable competing models to the same problem (99).

We should stress the need to study the impact of prognosis research. This is highly forgotten, yet a core area, since it could change the way we inform patients about their status and future decisions and clinical decision making (110).

2.5 Final remarks

The major purpose of a clinical prediction model should be to aid physicians in decision making by estimating the probability of diagnostic or prognostic event. A model with an outstanding discrimination power would fail the desired clinical impact and clinical outcomes improvement if it does not help in clinical decision-making.

Several issues concerning the development, the validation, the report, all the potential bias, the analysis cost-benefit, the implementation and the evaluation of its use are still unresolved, despite all the publications and investigation done. A methodologically irreprehensible study by a joint group of researchers worldwide could help overcoming some of the main issues pointed out and to improve patient stratification and consequently their treatment and quality of life.

3 Blood pressure and prediction of secondary cardiovascular events: literature review

3.1 Introduction

High BP is an unquestionable risk factor for CV events (17)(126)(127). Lowering high BP has a direct impact in diminishing first CV events (128)(129)(130).

In the secondary prediction, high BP remains an important CV risk factor, and several published prediction scores for recurrent events include BP or hypertension diagnosis in their selected variables (31)(54)(58)(72). Still, there are a considerable number of scores in which BP variables did not achieve significance for prediction for recurrent events (14)(55)(60) Hypertension control with high use on anti-hypertensive drugs could undermine hypertension relevance in secondary prediction(14)(55)(60). This could explain why some recurrent event scores developed from populations with strong use of anti-hypertensive drugs do not have hypertension, BP or anti-hypertensive treatment in their selected variables in the final score (14)(55)(60). In addition, BP in patients who developed heart failure after a CV event could become lower thereafter, and this may affect the predictive power of BP (54)(60). Some authors add that traditional risk factors like hypertension may have a diminished power for prediction of the recurrent event than in primary prediction, and that lesions of CV end organ damage or biomarkers are better predictors (46) (4)(74). The population with established CV disease has high proportion of traditional CV risk factors, much higher than the general population. So, the first and the recurrent events have the same risk factors, but in the population with previous events, the high proportion of patients with the risk factors, undermines its predictive value (117). The prediction of high-risk patients for recurrent events in this population may benefit from specific markers of the true cause of the disease, and not indirect markers like the traditional risk factors.

Furthermore, most studies, from trials to observational, assess the predictive power in short term. Although it is important to identify the patients who need intensive surveillance and care in the short-range (14), this may lead to a devaluation of patients who seem to have a low risk in short term, but may have a far greater risk in the long term. The underestimation of risk in these patients may lead to a relaxed approach which may lead to a less fortunate outcome (80).

To address this issue, we performed a systematic review of medical literature to investigate the long-term predictive power of BP for recurrent CV events.

3.2 Methods

The development was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (131). Randomised trials, observational studies, post-hoc analysis of trials data and meta-analysis of patients with established CV disease (i.e. previous myocardial infarction, angina pectoris, unstable angina, cardiac revascularization, stroke, PAD, carotid stenosis or endarterectomy) were included. The articles were required to study the predictive value of BP, hypertension or other variables related to BP for recurrent CV event or death (i.e. all-cause mortality, CV mortality, myocardial infarction, angina pectoris, unstable angina, cardiac revascularization, stroke, PAD, carotid stenosis, endarterectomy) with a mean follow up of at least five years or more. Studies with reference only to statistical differences between populations, or with patients without prior CV

event were excluded. All types of BP measurements were admitted. Eligible articles were in English and concerning adults of 18 or more years. Pregnancy was an exclusion criterion.

PICO (Population, Intervention, Comparison, Outcome) approach was used for the search strategy (see Table 5). The search strategy included combinations of the following keywords (MeSH (Medical Subject Headings) terms and truncated): myocardial infarction, myocardial ischemia, myocardial reperfusion, myocardial revascularization, coronary artery disease, stroke, peripheral arterial disease, atherosclerosis, carotid stenosis, carotid endarterectomy, cardiovascular diseases, survival analysis, prospective studies, prognosis, risk assessment, proportional hazard models, recurren*, secondary, predict*, blood pressure and hypertension. The search was limited to articles in English.

Table 5 - PICO question of BP and prediction review

Population	Intervention	Outcome
– adults, non-pregnant – cardiovascular disease – atherosclerotic disease – acute coronary syndrome – myocardial infarction – CABG – PCI – STEMI – nonSTEMI – stroke – carotid stenosis – endarterectomy	– blood pressure – hypertension – ambulatory blood pressure monitoring – prediction – risk factor	– secondary cardiovascular event – recurrent cardiovascular event – death – mortality

CABG – coronary artery bypass grafting; PCI – percutaneous coronary intervention; STEMI – ST elevation myocardial infarction; NSTEMI – non-elevation myocardial infarction

During August 2018, a systematic search was performed in Ovid Medline and Cochrane databases from inception. Articles were selected based on titles and abstracts, according to inclusion and exclusion criteria. When a title or abstract raised doubts, the article was read in full. Data collected included: type of study, target population, dates of study, inclusion and exclusion criteria, outcomes, baseline characteristics of population, medication, time of retrieved information, type of statistical test of prediction, definition of hypertension, time of measurement of BP, description of the technique used, variable of prediction, adjustment and quantification.

The risk of bias was assessed by the Quality in Prognostic Studies (QUIPS) tool (132), which was adapted for prognostic factor review questions and evaluated for inter-rater reliability (133).

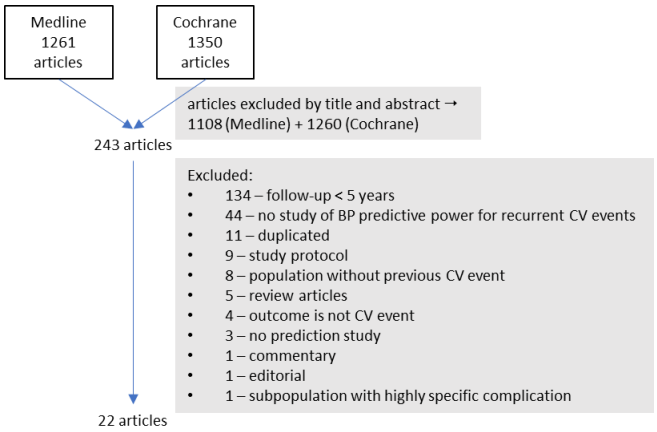
Analyses by type of BP variable were described. A high degree of heterogeneity between the studies was found: different dates leading to different variable definitions and therapy approaches, different type of selection and baseline characteristics of populations, distinct definitions of outcomes, BP variables as well as the time of measurement. These reasons lead to a preferred narrative synthesis of this review.

3.3 Results

A total of 2611 articles were screened mainly by title, selecting 243 articles which were screened by abstract and full text when needed (Figure 3). From these, a total of 22 articles matched the inclusion

criteria (see Table 6). This corresponded to 68169 patients with mean follow-up between 5 and 9.8 years.

Figure 3 - Search strategy for the BP and prediction review



Seven studies corresponded to post-hoc analysis of randomized clinical trials populations, 13 to observational studies (nine prospective and four retrospective), one cross-sectional and one meta-analysis. Ten studies were with population with coronary ischemic disease (four with population with acute event and one with population submitted to PCI), nine with population with stroke (four with ischemic, three with stroke, one with population with haemorrhagic stroke, and one with patients with lacunar stroke), two with population with CV disease (stroke, coronary, peripheral) and one study with population submitted to carotid endarterectomy. Table 6 describes several features of different studies.

Table 6 - Characteristics of the different studies concerning blood pressure and prediction review

Study	**Type of study**	**Population selected**	**Follow-up (years)**	**Nº patients**	**BP definition**	**BP technique**	**Outcome**
Bangalore 2017 (134)	Post-hoc an	MI	5	8658	No	✓	Composite (coronary death, nonfatal MI, resuscitated cardiac arrest, revascularization or angina)
Schmidt 2016 (135)	Obs Ret	Haemorrhagic stroke	5	15270	No	No	Recurrent haemorrhagic stroke
Hayden 2015 (136)	Obs Pro	Stroke	5	177	No	No	All-cause mortality
Kielbergerová 2015 (137)	Cross sect	Stroke	5.4	341	No	✓	All-cause mortality
Beatty 2015 (4)	Obs Pro	Stable CHD	6.6	912	✓	✓	Composite (time to first nonfatal MI, stroke or CV death)
Lau 2014 (Neur) (138)	Obs Pro	Stroke	6.3	632	✓	✓	All-cause mortality, CV mortality, nonfatal recurrent stroke, nonfatal ACS
Williams 2014 (139)	Obs Ret	Carotid endart	5.2	79	✓	No	Restenosis
Konishi 2014 (140)	Obs Ret	PCI	9.8	4294	✓	No	Composite (all-cause mortality, ACS)

Study	Type of study	Population selected	Follow-up (years)	Nº patients	BP definition	BP technique	Outcome
Park 2014 (141)	Obs Ret	Ischemic stroke	7.6	426	✓	✓	Ischemic stroke recurrence
Lau 2014 (AJH) (142)	Obs Pro	Lacunar stroke	6.5	281	✓	✓	All-cause mortality; CV mortality; recurrent stroke; ACS
Cui 2009 (71)	Post-hoc an	ACS	6	5654	No	No	CV death, MI, stroke
Fagard 2008 (143)	Meta an	CV disease*	6.8	302	✓	✓	All-cause mortality
Kaplan 2006 (144)	Obs Pro	Ischemic stroke	5.4	254	✓	No	Recurrent stroke
Kammersgaard 2006 (145)	Obs Pro	Ischemic stroke	5	905	✓	No	All-cause mortality
Mason 2004 (146)	Post-hoc an *	CV disease**	6.5	5218	✓	✓	Composite (MI, stroke, revascularization, endarterectomy, peripheral artery surgery, angina pectoris, TIA)
Staaf 2001 (147)	Obs Pro	Ischemic stroke	6.5	178	✓	No	All-cause mortality
Marschner 2001 (57)	Post-hoc an	ACS	6	8557	No	No	CHD death or nonfatal MI
Herlitz 1996 (148)	Obs Pro	MI	5	860	✓	✓	All-cause mortality
Berger 1992 (149)	Obs Pro	MI	5.1	363	✓	No	Recurrent MI
CDPRG 1984 (150)	Post-hoc an	MI	5	2789	✓	✓	All-cause mortality
West 2002 (151)	Post-hoc an	ACS	6	9014	✓	No	Ischemic stroke
Wilhelmsen 2001 (152)	Post-hoc an	MI	5.4	3005	No	No	Death of any cause

CDPRG – The Coronary Drug Project Research Group; post-hoc an – post-hoc analysis of a clinical trial; Obs Pro – observational prospective; obs ret – observational retrospective; Meta an – meta-analysis; AJH – American Journal of Hypertension; Neur – Neurology; CHD – coronary heart disease; MI – myocardial infarction; ACS- acute coronary syndrome; endart – endarterectomy; PCI – percutaneous coronary intervention; CV- cardiovascular; TIA – transient ischemic attack;

*- coronary heart disease; cerebrovascular disease; congestive heart failure

** - self-reported history of myocardial infarction, angina pectoris, coronary revascularization, stroke, transient ischemic attack, carotid endarterectomy, peripheral artery surgery

- age categorized (by interval, by outcome, by both)

The proportion of men ranged from 44% to 95.7%, excluding two studies that were exclusively one with male (150) and one with female patients (146). The prevalence of diabetes ranged from 4.4% to 33.3% and smoking from 9% to 40%. Table 7 describes several characteristics of the population samples.

Table 7 - Clinical characteristics of the different studies concerning blood pressure and prediction review

Study	Patients (n)	Mean age (years)	Men (%)	Diabetes (%)	Hypertension (%)	Smoking (%)	Time of assessment of medication	Antihypertensive drugs statistics	Statins (% defined)	Antiplatelets (% defined)

Bangalore 2017	8658	#	81	11.9	32.9	20.4	Discharge	✓		✓
Schmidt 2016	15270	#	52.3	4.7	**	No data	Pre-event	✓	✓	
Hayden 2015	177	76.5	46	8.6	78	40	Pre-event	✓	✓	✓
Kielbergerová 2015	341	69	58.9	*	*	15.8	6 months after event	✓	✓	
Beatty 2015	912	#	82.2	31.8	77.4	19.6				
Lau 2014 (EJNeur)	632	71	53	38	73	15	Discharge	✓		
Williams 2014	79	73	79	44	92	24				
Konishi 2014	4294	36.1	95.7	33.3	47.8	30.5	Discharge	✓	✓	✓
Park 2014	426	72	60	23	48	21	Baseline			
Lau 2014 (AJH)	281	70	52	39	74	32		✓		
Cui 2009	5654	63	84	9.25	44.34	9.5	Pre-event		✓	✓
Fagard 2008	302	69.2	50.3	14.9	100	9.3		✓		
Kaplan 2006	254	78.6	44	29	80	9	Baseline	✓	✓	✓
Kammersgaard 2006	905	73.7	51.9	21.2	34	47.1	Baseline			
Mason 2004	5218	62.1	0	16.4	64	16.8		✓	✓	✓
Staaf 2001	178	72.5	59.55	15.2	52.2	28.1				
Marschner 2001	8557	62	83	9	42	10			✓	٢
Herlitz 1996	860	#	67.62	11.36	34	34		✓		
Berger 1992	363	67.2	64.1	17.63	48.3	35.6	baseline	✓		✓
CDPRG 1984	2789	52.4	100	No data	No data	No data		٢		
West 2002	9014	#	83.2	8.7	41.7	9.6			✓	
Wilhelmsen 2001	3005	#	81.4	4.4	23.5	26.9			✓	

CDPRG – The Coronary Drug Project Research Group; AJH – American Journal of Hypertension; EJNeur – European Journal of Neurology;
* no data on diabetes or hypertension; 22.3% of population was treated with antidiabetics, 88.3% with anti-hypertensive drugs
** - no data on hypertension; 37.5% of population treated with antihypertensive drugs
٢ - showed multivariate analysis associated to tis medication, but not % of patients usage

BP measurement

Five studies used the BP measurement done at the beginning of follow-up for the analysis of prediction value. Two studies did not provide definition and two other did not describe the measurement technique. One study assumed hypertension by self-reporting of patients through questionnaire. Definitions, measurement techniques and outcomes are quite different (Table 8). In two studies, the measurement of BP did not reveal statistical power for prediction. Studies without quantification values were not presented (150), but the statistical analysis of elevated BP (SBP ≥ 140 or DBP ≥ 90 mmHg) were not significant.

Table 8 - Studies with blood pressure measurement

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% CI	p

Kielbergerová 2015	No data	6 month after fisrt stroke	✓	SBP ≥ 140 and/or DBP≥90 mmHg		death	Multivar cox model	HR	0.77	0.48-1.21	0.255
				SBP ≥ 140 and/or DBP≥90 mmHg	Including BNP in the model	death	Multivar cox model	HR	0.86	0.54-1.39	0.549
				SBP ≥ 140 and/or DBP≥90 mmHg		CV death	Multivar cox model	HR	0.83	0.49-1,4	0.485
				SBP ≥ 140 and/or DBP≥90 mmHg	Including BNP in the model	CV death	Multivar cox model	HR	0.96	0.55-1.66	0.875
Kaplan 2006	Prior physician diagnosis or anti-HTN drugs	8 month after first stroke		SBP ≥ 160		**Recurrent stroke**	**Multivar cox model**	**HR**	**1.86**	**0.76-4.59**	**0.04**
						CHD	Multivar cox model	HR	1.22	0.58-2.57	0.44
						Combined vascular events	Multivar cox model	HR	1.27	0.67-2.42	0.12
						All-cause mortality	Multivar cox model	HR	0.74	0.45-1.21	0.91
Mason 2004	Self reported meas in questinnaire	baseline		SBP (per ↑ 10 mmHg)	Only age adjust	CV events*	Multivar cox model	RR	1.09	1.09-1.15	
				DBP (per ↑ 10 mmHg)		CV events*	Multivar cox model	RR	1.06	0.97-1.16	
				MAP (per ↑ 10 mmHg)	**Only age adjust**	**CV events***	**Multivar cox model**	**RR**	**1.22**	**1.14-1.29**	
				MAP (per ↑ 10 mmHg)		**CV events***	**Multivar cox model**	**RR**	**1.10**	**1.02-1.18**	
				PP (per ↑ 10 mmHg)	**Only age adjust**	**CV events***	**Multivar cox model**	**RR**	**1.18**	**1.12-1.23**	
				PP (per ↑ 10 mmHg)		**CV events***	**Multivar cox model**	**RR**	**1.10**	**1.03-1.15**	
West 2002	**Anti-HTN drugs or >160-95 mmHg**	**baseline**		**SBP 126-140 mHg**		**Non-hemorrhagic stroke**	**Multivar cox model**	**RR**	**1.48**	**1.11-1.97**	**0.004**
				SBP > 140 mmHg		**Non-hemorrhagic stroke**	**Multivar cox model**	**RR**	**1.63**	**1.21-2.18**	**0.004**
Wilhelmsen 2001	No data	baseline		SBP ≥ 146 mmHg	Placebo group	Coronary events	Logistic regression	RR	0.99	0.8-1.21	0.21
				DBP	Placebo group	Coronary events	Logistic regression	RR	1.14	0.91-1.43	0.18

BNP – brain natriuretic peptide; BP – blood pressure; CI – confidence interval; CV – cardiovascular; DBP – diastolic blood pressure; HR – hazard ratio; HTN - hypertension MAP – median arterial pressure; Meas – measurement; multivar – multivariate; PP – pulse pressure; RR – relative risk; stat – statistic; SBP – systolic blood pressure

Hypertension

Previous diagnosis of hypertension was evaluated in several articles (Table 9). Definition of hypertension is not homogeneous between studies, and six studies did not provide definition. Six

studies fail to show that hypertension has predictive power for the recurrent event. Studies without quantification values were not presented (4), but the statistical analysis of hypertension was not significant. On study addressed the outcome survival instead of death, but it was considered (139).

Table 9 - Studies that assessed previous diagnosis of hypertension

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% CI	p
Hayden 2015	No data	baseline	No data	HTN		death	univar	HR	1.68		0.06
Williams 2014	HTN: BP≥ 140/90 or anti-HTN drugs	baseline	No data	HTN		survival	multivar	HR	0.78	0.24-3.51	0.72
Konishi 2014	HTN: BP≥ 140/90 or anti-HTN drugs	baseline	No data	HTN		Composite (all-cause death, ACS)	univar	HR	1.87	0.59-6.37	0.28
Park 2014	No data	2 weeks after first stroke	No data	HTN		All-cause death	univar	HR	0.862	0.619-1.202	0.381
Lau 2014 (EJNeur)	HTN: BP≥ 140/90 or anti-HTN drugs	baseline	✓	HTN		All-cause mortality	Cox multiv analysis	HR	0.71	0.41-1.24	
						CV mortality	Cox multiv analysis	HR	0.59	0.20-1.70	
						Recurrent stroke	Cox multiv analysis	HR	0.91	0.42-1.95	
						ACS	Cox multiv analysis	HR	1.08	0.31-3.72	
Cui 2009	**No data**	**baseline**	**No data**	**HTN**	**Cox with polynomial**	**CV death, MI, ischemic or haemorrhagic stroke**	**Cox multiv analysis**	**HR**	**1.18**	**1.04-1.35**	
					Cox model with no lab data	**CV death, MI, ischemic or haemorrhagic stroke**	**Cox multiv analysis**	**HR**	**1.21**	**1.06-1.38**	
Kammersgaard 2006	HTN: BP≥ 160/95 or anti-hypertensive drugs	baseline	No data	HTN		All-cause death	Multiv	HR	NS	NS	0.54
Staaf 2001	**No data**	**baseline**	**No data**	**HTN**		**Recurrent stroke**	**univariate**	**No data**	**No data**	**No data**	**< 0.05**
						Recurrent stroke	**Cox multiv analysis**	**No data**	**No data**	**No data**	**0.025**
Marschner 2001	**No data**	**baseline**	**No data**	**HTN**		**Coronary death or nonfatal MI**	**Cox multiv analysis**	**HR**	**1.14**	**1.01-1.28**	**0.035**
Herlitz 1996	Self-reported	baseline	Self-reported	HTN	Adjusted for age, sex, previous MI, angina, DM,	All-cause death	Multivar logistic regression	No data	No data	No data	NS

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% CI	p
					HTN, CHF, smoking						
					Adjusted for age, sex, previous MI, angina, DM, HTN, CHF, smoking, coronary unit admission	**All-cause death**	**Multivar logistic regression**	**No data**	**No data**	**No data**	**0.048**
					Adjusted for age, sex, HTN	**Recurrent MI**	**Multivar logistic regression**	**No data**	**No data**	**No data**	**< 0.05**
Berger 1992	**HTN: BP > 160/95 or anti-HTN drugs**	**baseline**	**No data**	**HTN**		**Recurrent MI (men)**	**Logistic regression adjusted to sex**	**OD**	**2.3**	**1.1-4.8**	
West 2002	**HTN: BP > 160/95 or anti-HTN drugs**	**baseline**	**No data**	**HTN**		**Non-haemorrhagic stroke**	**Cox multiv analysis**	**RR**	**1.35**	**1.08-1.69**	**< 0.008**
Wilhelmsen 2001	**No data**	**baseline**	**No data**	**HTN**	**Placebo group***	**Coronary events**	**Multivar logistic regression**	**RR**	**1.23**	**1.03-1.46**	**0.024**
					Simvastatin group*	**Coronary events**	**Multivar logistic regression**	**RR**	**1.35**	**1.07-1.71**	**0.013**

ACS – acute coronary syndrome; BP – blood pressure; CHF – congestive heart failure; CI – confidence interval; CV – cardiovascular; DM – diabetes *mellitus*; HTN – hypertension; meas – measurement; MI – myocardial infarction; multivar – multivariate; NS – nonsignificant; RR – relative risk; Stat – statistic; Univar – univariate;
*4S trial (Scandinavian Simvastatin Survival Study (152), double blind randomized placebo controlled trial for long-term simvastatin or placebo in coronary heart disease patients

Anti-hypertensive treatment

Anti-hypertensive treatment was used as a synonym of diagnosis of hypertension in several studies (138)(145)(151). In our sample, only one study evaluated its long-term predictive power (Table 10).

Table 10 - Studies that assessed previous anti-hypertensive treatment

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% IC	p
Schmidt 2016	No data	Baseline	No data			Intracerebral haemorrhage	Multivar Poisson regression	Rate ratio	0.78	0.66-0.91	

BP – blood pressure; CI – confidence interval; HTN – hypertension; meas – measurement; multivar – multivariate; Stat – statistic

Ambulatory blood pressure monitoring

ABPM 24 hours was evaluated in two studies, an observational retrospective study (141) and a metanalysis (143), and several variables measured by the ABPM were evaluated (Table 11).

Table 11 - Studies that assessed ambulatory blood pressure monitoring 24 hours

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% CI	p
Park 2014	Nocturnal systolic fall, dipper, non-dipper, extreme dipper, reverse dipper	2 weeks after ischemic first stroke	✓	**Daytime mean SBP**	**Adjusted for extreme dipper**	**Recurrent ischemic stroke**	**Cox multiv analysis**	**HR**	**1.014**	**1.002-1.026**	**0.017**
				Extreme dipper	Adjusted for daytime mean SBP	Recurrent ischemic stroke	Cox multiv analysis	HR	1.833	0.655-5.124	0.248
				Daytime mean SBP		All-cause death	univar	HR	1.001	0.992-1.1010	0.776
				Nighttime SBP	Adjusted for reverse dipper	All-cause death	Cox multiv analysis	HR	1.001	0.990-1.011	0.878
				Reverse dipper	**Adjusted for night-time SBP**	**All-cause death**	**Cox multiv analysis**	**HR**	**1.676**	**1.155-2.433**	**0.007**
				Daytime mean DBP		**All-cause death**	**univar**	**HR**	**0.980**	**0.966-0.994**	**0.05**
Fagard 2008	✓	✓	✓	24 h SBP	Adjusted for office BP	All-cause death	Cox multiv analysis	HR	1.09	0.84-1.43	
				Nighttime SBP	Adjusted for office BP	All-cause death	Cox multiv analysis	HR	1.24	0.99-1.56	
				Daytime SBP	Adjusted for office BP	All-cause death	Cox multiv analysis	HR	0.97	0.74-1.28	
				24 h SBP	Unadjusted for office BP	All-cause death	Cox multiv analysis	HR	1.12	0.88-1.44	
				Nighttime SBP	**Unadjusted for office BP**	**All-cause death**	**Cox multiv analysis**	**HR**	**1.26**	**1.02-1.56**	**≤ 0.05**
				Daytime SBP	Unadjusted for office BP	All-cause death	Cox multiv analysis	HR	1.01	0.87-1.39	
				24 h SBP	Adjusted for office BP	CV death	Cox multiv analysis	HR	1.23	0.88-1.71	
				Nighttime SBP	**Adjusted for office BP**	**CV death**	**Cox multiv analysis**	**HR**	**1.41**	**1.06-1.87**	**≤ 0.05**
				Daytime SBP	Adjusted for office BP	CV death	Cox multiv analysis	HR	1.06	0.75-1.49	
				24 h SBP	Unadjusted for office BP	CV death	Cox multiv analysis	HR	1.23	0.91-1.66	
				Nighttime SBP	**Unadjusted for office BP**	**CV death**	**Cox multiv analysis**	**HR**	**1.40**	**1.08-1.81**	**≤ 0.01**
				Daytime SBP	Unadjusted for office BP	CV death	Cox multiv analysis	HR	1.09	0.79-1.50	
				24 h SBP	Adjusted for office BP	CV events	Cox multiv analysis	HR	1.20	0.91-1.58	

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% CI	p
				Nighttime SBP	**Adjusted for office BP**	**CV events**	**Cox multiv analysis**	**HR**	**1.34**	**1.06-1.69**	**≤ 0.01**
				Daytime SBP	Adjusted for office BP	CV events	Cox multiv analysis	HR	1.03	0.77-1.36	
				24 h SBP	Unadjusted for office BP	CV events	Cox multiv analysis	HR	1.19	0.92-1.53	
				Nighttime SBP	**Unadjusted for office BP**	**CV events**	**Cox multiv analysis**	**HR**	**1.32**	**1.06-1.65**	**≤ 0.01**
				Daytime SBP	Unadjusted for office BP	CV events	Cox multiv analysis	HR	1.04	0.80-1.36	
				Nighttime SBP	**Adjusted for daytime SBP**	**All-cause death**	**Cox multiv analysis**	**HR**	**1.41**	**1.07-1.85**	**≤ 0.01**
				Nighttime SBP	**Adjusted for daytime SBP**	**CV death**	**Cox multiv analysis**	**HR**	**1.57**	**1.12-2.19**	**≤ 0.01**
				Nighttime SBP	Adjusted for daytime SBP	CV events	Cox multiv analysis	HR	1.49	1.13-1.98	
				Nighttime DBP	**Adjusted for daytime DBP**	**All-cause death**	**Cox multiv analysis**	**HR**	**1.32**	**1.00-1.74**	**≤ 0.05**
				Nighttime DBP	**Adjusted for daytime DBP**	**CV death**	**Cox multiv analysis**	**HR**	**1.43**	**1.03-2.00**	**≤ 0.05**
				Nighttime DBP	**Adjusted for daytime DBP**	**CV events**	**Cox multiv analysis**	**HR**	**1.38**	**1.04-1.83**	**≤ 0.05**

BP – blood pressure; CI – confidence interval; CV- cardiovascular; DBP – diastolic blood pressure; HTN – hypertension; HR – hazard ratio; meas- measurement; multivar – multivariate; SBP – systolic blood pressure; stat- statistic

BP variability

BP variability was addressed in several studies (Table 12). Definitions and calculations are different, according to literature.

Table 12 - Studies that assessed blood pressure variability

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% IC	p
Bangalore 2017	SBPV – average of absolute difference between successive values	Month 3 and 6 after first , and 6/6 months thereafter (5 years)		**SBPV by average**	**Adjustment: trial treatment, LDL variability, baseline charact**	**Composite coronary death, nonfatal MI, resuscitate cardiac arrest, revascular, angina**	**Cox multiv analysis**	**HR**	**1.07**	**1.04-1.11**	**0.0001**
				SBPV by average	**Adjustment: trial treatment, LDL variability, baseline charact**	**Any CV event**	**Cox multiv analysis**	**HR**	**1.08**	**1.05-1.11**	**0.0001**

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% IC	p
				SBPV by average	**Adjustment: trial treatment, LDL variability, baseline charact**	**Death**	**Cox multiv analysis**	**HR**	**1.2**	**1.14-1.25**	**0.0001**
				SBPV by average	**Adjustment: trial treatment, LDL variability, baseline charact**	**Fatal and non fatal stroke**	**Cox multiv analysis**	**HR**	**1.33**	**1.2-1.47**	**0.0001**
				DBPV by average	**Adjustment: trial treatment, LDL variability, baseline charact**	**Composite CHD death, nonfatal MI, resuscitate cardiac arrest, revascular, angina**	**Cox multiv analysis**	**HR**	**1.11**	**1.06-1.16**	**0.0001**
				DBPV by average	**Adjustment: trial treatment, LDL variability, baseline charact**	**death**	**Cox multiv analysis**	**HR**	**1.29**	**1.20-1.39**	**0.0001**
Lau 2014 (AJH)	HTN ≥ 140/90 mmHg or anti-hypertensive drugs; BPV by the coefV	Follow up visits 3-4/3-4 months	✓	**coefV SBPV (last quartil)**		**CV death**	**Bivariate (mean BP)**	**HR**	**2.77**	**1.23-6.23**	
				coefV SBPV (3rd quartil)		CV death	Bivariate (mean BP)	HR	1.70	0.72-4.06	
				coefV SBPV (last quarti)		**CV death**	**Cox multiv analysis**	**HR**	**2.36**	**1.02-5.49**	
				coefV SBPV (3rd quartil)		CV death	Cox multiv analysis	HR	1.64	0.68-3.98	
				coefV DBPV (last quartil)		CV death	Bivariate (mean BP)	HR	1.25	0.57-2.75	
				coefV DBPV (3rd quartil)		CV death	Bivariate (mean BP)	HR	1.69	0.80-3.59	
				coefV DBPV		CV death	Cox multiv analysis	HR	1.49	0.69-3.20	

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% IC	p
				(last quartil)							
				coefV DBPV (3rd quartil)		CV death	Cox multiv analysis	HR	1.20	0.54-2.67	
				coefV SBPV (last quartil)		**All-cause death**	**Bivariate (mean BP)**	**HR**	**1.79**	**1.16-2.75**	
				coefV SBPV (3rd quartil)		All-cause death	Bivariate (mean BP)	HR	1.23	0.77-1.95	
				coefV SBPV (last quartil)		All-cause death	Cox multiv analysis	HR	1.46	0.88-2.43	
				coefV SBPV (3rd quartil)		All-cause death	Cox multiv analysis	HR	1.18	0.77-1.80	
				coefV DBPV (last quartil)		All-cause death	Bivariate (mean BP)	HR	1.18	0.77-1.95	
				coefV DBPV (3rd quartil)		All-cause death	Bivariate (mean BP)	HR	0.89	0.57-1.39	
				coefV DBPV (last quartil)		All-cause death	Cox multiv analysis	HR	1.03	0.62-1.69	
				coefV DBPV (3rd quart)		All-cause death	Cox multiv analysis	HR	0.88	0.52-1.48	
Lau 2014 (EJNeur)	HTN ≥ 140/90 mmHg or anti-hypertensive drugs; BPV by the coefV drugs; BPV by the coefV	Follow up visits 3-4/3-4 months	✓	**SBP SD (3rd tert >17.5 mmHg)**		**All-cause death**	**Cox multiv* analysis**	**HR**	**1.97**	**1.02-3.80**	**< 0.05**
				SBP SD (2nd tert 13-17.5 mmHg)		All-cause death	Cox multiv* analysis	HR	1.47	0.74-2.90	
				SBP SD (3rd tert >17.5 mmHg)		**CV death**	**Cox multiv* analysis**	**HR**	**7.64**	**1.65-35.41**	**< 0.01**
				SBP SD (2nd tert 13-17.5 mmHg)		CV death	Cox multiv* analysis	HR	2.00	0.36-11.21	

Study	BP / HTN definition	Time meas	Meas technique	BP variable meas	Notes	Outcome	Adjusted	Stat	Stat value	95% IC	p
				SBP SD (3rd tert >17.5 mmHg)		Recurrent stroke	Cox multiv* analysis	HR	1.14	0.51-2.56	
				SBP SD (2nd tert 13-17.5 mmHg)		Recurrent stroke	Cox multiv* analysis	HR	0.95	0.41-2.19	
				SBP SD (3rd tert >17.5 mmHg)		ACS	Cox multiv* analysis	HR	2.13	0.62-7.35	
				SBP SD (2nd tert 13-17.5 mmHg)		ACS	Cox multiv* analysis	HR	0.95	0.41-2.19	

ACS – acute coronary syndrome; AJH – American Journal of Hypertension; BPV – blood pressure variability; CI – confidence interval; charact – characteristics; DBPV – diastolic blood pressure variability; coefV – coefficient of variation; EJNeur – European Journal of Neurology; HR – hazard ratio; stat- statistic; LDL – low-density-lipoprotein cholesterol; multiv – multivariate; ; SBPV – systolic blood pressure variability; SD – standard deviation; tert – tertile
* with mean SBP and mean DBP

3.4 Discussion

There is consistent evidence that BP values are a main risk factor for primary (126)(127) and secondary CV events (153)(154)(155) and treatment of hypertension for prevention of secondary outcomes is mandatory. But whether hypertension or BP values have a place in secondary predicting scores is less clear.

Our selection has a wide range of differences: in basic populations (nine with coronary heart disease, nine with stroke, two with established CV disease, one after carotid endarterectomy and one after PCI). A considerable part (31.8%) did not give BP variable definition, and more than half (54.0%) did not describe the technique, raising limitations to accurately compare studies. Some of the older studies used hypertension criteria of 160/90 mmHg, which changes the stratification of the population and its correlation with events. The lack of complete information concerning the measurement methodology of BP in research papers is a bias for the accurate comparison of results (156).

Characteristics heterogeneity such as age, sex, comorbidities and medication highly influence the statistical significance of the studied variables. Medication was not quantitively addressed in 45.5% (11/22) for anti-hypertensive treatment, 54.5% (12/22) for statins and 63.6% (14/22) for the use of anti-platelets agents. Lack of information of control of BP values throughout follow-up is a major issue. No study addressed this matter, and this could help to understand differences between the value of predictive power concerning BP. In addition, the studies were developed in a wide time range, during which medical knowledge, behaviours and therapeutic strategies changed, which also influences the role of predictive values.

In our analysis, several studies have not found an established predictive value for history of hypertension or BP levels. Eight studies (36.4%) did not find any predictive power for the variables of BP studied (4)(135)(136)(137)(139)(140)(145)(152). Others had significant results found for specific

outcomes, like SBP≥ 160 mmHg for stroke (but not for coronary events, all CV events or all-cause mortality) (144) or for variability visit-to-visit, but not for the diagnosis of hypertension (142).

In some scores, the use of hypertension as a predictive variable did not affect the model performance (54) or had no predictive power(139)(140) in survival analysis. This does not change the fact it remains an undoubted risk factor which must be controlled in secondary prevention.

The use of BP values, although an established strategy in many primary prediction scores (19)(20), is not as well supported in the secondary practice (137)(144)(152). To use the BP measured in one unique medical appointment, for example at baseline, which happens in several studies, as a predictor for recurrent events not be the best option. The use of measured BP values from hypertensive treated patients may underestimate the true value of associated risk (54)(157). Also, in our analysis, the use of hypertension as a variable reached statistical significance for risk of recurrence in several articles(57) (71)(147) (148)(149)(151)(152), but not for six others (136) (138)(139)(140)(141)(145).The first set mostly included older studies and all except one were based on ischemic heart disease patients. The second set globally comprised more recent studies and all but one were based on stroke or carotid disease populations. This may point that hypertension and BP have an important role in some specific CV events, but less strong in others.

The concept that statistical performance may be worked to improve statistical significance is also relevant. The work by Herlitz et all (148) shows that hypertension is not predictive in a specific multivariate model, by adding whether or not admission in intensive care unit changed the significance of the predictive value of hypertension. Sometimes the focus is mainly in highlighting the statistical performance of the models (123), but this undermines the ability to truly find the best predictive variables for recurrent events.

Using ABPM 24 hours allows to evaluate BP along the 24 hours, including the nocturn pattern. In our sample, two studies qualified for long term prediction. One, based on stroke patients, found significance in the daytime mean SBP, daytime mean DBP and the reverse dipper pattern (141), in univariate and multivariate analysis (adjustments seen in Table 11). A meta-analysis of 3 studies with patients with CV disease (coronary, cerebrovascular, peripheral) found a consistent significance in nocturnal SBP for all-cause mortality, CV death and CV events (143). In this way, to measure BP in office for stratifying patients will fall short, and to evaluate the night pattern may be a more accurate tool.

Variability of BP is being studied as a main CV risk for several years (126). In our analysis three studies based on two populations, one with previous myocardial infarction (134) and one with previous stroke (138)(142) associated variability of visit-to-visit SBP to secondary outcomes. Evaluations by average of absolute difference between successive values, coefficient of variation and standard-deviation (SD) were used, to predict all-cause mortality and CV death. Coefficient of variation and SD only showed significance in their higher values (last quartile and tercile)(138) (142).

The concept of index event bias competing risks may also have a stronger role in secondary setting, since several risk factors conglomerate highly in patients with established CV disease (117). Instead of traditional risk factors maintaining the gold standard in secondary prediction, as in the primary setting, some authors defend that specific disease organ lesions and targeted biomarkers may be of higher importance in secondary prediction (158)(56)(104).

Limitations for this study are the criteria for inclusion of articles only written in English may have discarded some papers, but the long-follow-up is somehow difficult to attend and may have attenuate this limitation. Also, the inclusion in the search strategy of at least one of “survival analysis,

prospective studies, prognosis, risk assessment, proportional hazard models" may have excluded articles which were not classified with none of these. The highly different methods, definitions, populations, items measured, and outcomes limits the true comparison between studies.

3.5 Final Remarks

The literature reports a wide variety on results concerning the predictive power of BP, hypertension or associated variables, with respect to recurrent CV events prediction at long term. Although BP is a strong undisputed CV risk factor, which is mandatory to be controlled, its place in prediction models for recurrent events may need further evaluation. BP may remain important for prediction in specific target lesion populations, but it may weaken the predictive power in others. The use of prior diagnosis of hypertension or the BP measurement of one single visit may not be the best way to use the information given by BP in secondary prediction. Other methods like ABPM or variability should be considered. Further investigation of BP contribution to recurrent events prediction can benefit from aggregating information from several existing trials, as well from the prospectively study of information given by traditional risk factors, including BP, along with new specific end organ lesion or biomarkers.

4 Role of ABPM in prediction of cardiovascular events: literature review

Arterial hypertension is one of the major risk factors for CV disease (159)(160)(161). It is largely associated with stroke (162) and coronary heart disease (163). CV disease is a global wide public health problem, and in Portugal is the first cause of death (164). In 2015, in Portugal the death rates for stroke and ischaemic heart disease were, respectively, 58.4 and 51.5 deaths per 100,000 people (164).

The association between hypertension and CV disease has mostly been investigated using office BP. The reduction of BP has been associated with a decrease in CV events (165)(166).

There are some known issues in relation to office BP being ABPM the most accurate way of evaluating BP, concerning technical issues, white-coat effect and variability (167) (168)(169). Several authors alert to the importance of the errors in BP determination in routine clinical office, and advocate out-of-office BP measurement, particularly ABPM, as the preferred method to evaluate and approach BP (156)(170).

ABPM is a recognized method for the diagnosis of hypertension, to assess the efficacy of treatment and the long term control of BP values (171). It has other advantages over office BP: it provides greater information considering the 24 hour pattern on systolic and diastolic blood pressure, heart rate and measures of variability in the patient usual daily environment and permits the recognition of masked and white-coat hypertension (168).

It is nowadays well known the better performance of ABPM concerning prediction of hypertension mediated organ damage (172) and CV events (173)(174)(175). Recent guidelines and position papers stated the superiority of ABPM over office BP measurement in the prediction of CV morbidity and mortality (126)(176) (177). Several articles addressed the higher predictive value of ABPM for death or CV events in several populations: general patients in primary care (174) and population based studies (178)(173)(179), hypertensive patients (7)(180)(181)(175), treated hypertensive patients (182), elderly patients (183)(184), resistant hypertension (185)(186), patients with isolated SBP (187), untreated patients (188), diabetics (189) and patients on haemodialysis (190).

In primary prediction, the ABPM variables and patterns most associated with worst outcomes have been identified.

Night-time BP appears to be a better predictor of outcomes than daytime (7)(191)(192). The dipping pattern and the night-time/daytime BP ratio are significant and independent predictors of CV events (8)(193), stroke (180), and coronary events (180). Non-dipping (8)(176), reverse dipping (194) and extreme dipping (195) have been associated to a higher risk for CV events than dipping. Extreme dipping has been associated also to silent cerebral lesions (184).

Increase in SBP (24 hours, daytime and night-time) has been associated in several studies with increased stroke, CV mortality, total mortality and cardiac events (196)(197). Other ABPM variables have significant predictive value for CV outcomes: increased BP night-time variability (198)(199), increased systolic and diastolic 24-hour variability (200), increased pulse pressure (196)(201) and increased morning surge (202)(203)(204), but their significance for clinical practice has not well defined in recent guidelines (126).

In patients with established CV disease, studies addressing the predictive value of ABPM to CV events are scarce. Some address to the relevance of night-time (143), the dipping pattern (141), and the variability (205), but results are not conclusive.

A study evaluating high-risk patients and comparing differences between office BP and ABPM variables showed a high prevalence of non-dipping pattern in high-risk patients when comparing with lower risk patients (206).

Fagard et al performed a meta-analysis of 302 patients with established CV disease (143). There was an association between night-time BP and death and recurrent CV events, and the night-day BP ratio and the dipping pattern were associated with CV outcomes (143).

In patients with stroke, high 24-hour SBP has been associated as an independent predictor for CV events (6)(207). Non-dipping pattern was associated with higher risk for stroke, in a observational study comparing stroke survivors with controls (208). In patients with lacunar stroke, high risk of brain microbleeds was associated to 24-hour, day and night SBP and DBP (209). In another study in patients with lacunar ischemic lesions, high 24 hour SBP and 24 hour DBP, night-time BP and a lower nocturnal BP dip were related with silent ischemic cerebral lesions and stroke (210). Also SBP and dipping patterns have been associated with cognitive impairment and dementia in patients with previous stroke (207)(211).

Night-time SBP has been related with CV event in a cohort of high-risk patients, but only nearly 30% of them had previous CV event (212)

In some studies, ABPM variability in stroke patients did not show association with recurrent stroke (205) or CV events (213). A study comparing diabetic and non-diabetic stroke survivors, found association of BP variability for CV outcomes in non-diabetic stroke patients, but not in the diabetic (214). Another study related several measures of ABPM variability (coefficient of variation, standard-deviation, average real variability) with small vessel disease progression (215).

Mean 24 hour DBP and mean 24 hours heart rate has been associated with CV events in a study with acute myocardial infarction patients (216). ABPM was performed 3 weeks after the first acute event and variables associated with risk at 1 year were introduced in a score to identify high-risk populations (216).

ABPM is associated with CV events, and there is association between several variables and outcomes in primary prediction. In secondary prediction, the studies are few and inconclusive, although some studies indicate a clear association between ABPM variables and CV outcome. More studies are needed in order to evaluate if ABPM could be a reliable predictor for high risk patients that already had a CV event.

5 Methods

Between 1991 and 2007, a cohort of 1200 patients without established CV disease and previously referred for ABPM was followed for CV events. The description of the methods and results of this study was previously published (7). In brief, 1200 hypertensive patients referred to ABPM were followed for 8.2 ± 3.1 years, with 152 CV events being reported. These patients were subsequently reviewed. Those who repeated 24 hour-ABPM after the event and fulfil the remaining inclusion criteria were selected.

To these selected patients were added all patients with prior CV event and referred to ABPM at Centro Hospitalar do Baixo Vouga between 1996 and 2017.

The inclusion criteria comprised:

- aged 18 years and older;
- confirmed CV event (myocardial infarction, unstable angina with hospital admission, myocardial revascularization, stroke, endarterectomy or bypass surgery for PAD, carotid endarterectomy);
- referred to ABPM at any point after the event;
- possibility of obtaining updated and accurate clinical information by August 2018, including death cause if applicable; the allowed sources of information were: normal scheduled clinical appointment, by the individual physician of each patient and clinical records;
- ABPM valid information of 85% or more.

Exclusion criteria were:

- pregnancy;
- patients who could not be further evaluated in follow-up examination.

The ABPM records between 2013 and 2014 were lost due to a failure in the hospital information system and these two years could not be included. Between 1996-2012 and 2015-2017, a total of 3928 24-hours ABPM was performed.

The following clinical data at the time of ABPM were retrieved: age, sex, body mass index (BMI), CV risk factors (smoking, dyslipidaemia, atrial fibrillation, diabetes *mellitus*, hypertension, sleep apnoea obstructive syndrome) and CV medication (renin-angiotensin inhibitors, calcium antagonists, diuretics, nitrates, statins, anti-platelet agents, anti-coagulation). Smoking was defined as ever smoking or never smoking. The CV risk factors were considered when written in the patient medical record. Basic blood chemistry (haemoglobin, leukocytes, fasting glycaemia, glycosylated haemoglobin, creatinine, fasting total cholesterol, fasting high-density-lipoprotein-cholesterol, fasting low-density-lipoprotein-cholesterol, fasting triglycerides) and echocardiographic parameters were retrieved from electronic clinical records. All blood chemistry and echocardiographic data were retrieved from the normal clinical evaluation of the patients by their physician. Data retrieved was the closest possible in time from the ABPM date. The patients' medical records were reviewed for further occurrence of CV events.

The study was approved by the local ethical committee and all patients gave their informed consent.

Twenty-four hour ABPM was performed during a working day with SpaceLabs 90207 (Space Labs Inc., Redmond, Washington, USA) as described earlier (217). The monitor was mounted on the

nondominant arm between 08:00 and 09:00 hours until 2007 and after that it was during the morning period and was removed 24 hours later. The proper calibration of ABPM was made according to guidelines in force. The patients were instructed to perform their usual daily activities and to report the time they went to bed and time they got up in the morning, as well all unusual events that happened during the day. Each patient was given a diary for the day which helped with this self-reporting. BP was recorded every 20 minutes during the day (between 07:00 – 23:00 h) and every 30 minutes at night (between 23:30-06:30 h). Only ABPM with over 85% of valid information was admitted. Pulse pressure was calculated as SBP minus diastolic BP (DBP). The nocturnal SBP fall (%) was calculated as 100 x (1-night SBP/day SBP ratio) and the nocturnal DBP fall (%) was calculated as 100 x (1-awake DBP/day DBP ratio). The periods considered as representatives of the awake and night-time resting BPs were the periods reported by the patient and registered in the device. Patients were classified by the nocturnal SBP fall as: extreme dippers (ED) if SBP fall ≥20%, dippers if nocturnal SBP fall was 10% or more and less than 20%, non-dippers if nocturnal SBP fall was between 0 and 9.9% and reverse dippers if nocturnal SBP fall was below 0%. The same equation and definitions were applied to DBP. Morning surge was defined by the mean nocturnal systolic values recorded in the first two hours upon waking up minus the mean nocturnal systolic values recorded immediately before, during and after the lowest SBP value of night-time.

Follow-up was performed from ABPM until 2018. The presence or absence of CV events was assured by the examination of the patients' medical records or phone call until the end of the follow-up period. CV events were diagnosed by the patient hospital physician or by medical records. In all cases, the diagnosis of CV events was objectively confirmed by an external expert who examined the patient's records and diagnostic procedures. CV events were classified as fatal or nonfatal. Fatal events were subdivided in CV and non-CV. Cause of death was confirmed by medical records. If the cause of death was not confirmed, it was considered undetermined. CV events consisted of ischemic stroke, haemorrhagic stroke, transient ischemic attack, myocardial infarction, hospitalization by angina pectoris, coronary bypass, coronary angioplasty, carotid endarterectomy or surgery for PAD. For analysis, event by stroke, haemorrhagic stroke, ischemic stroke and transient ischemic attack were all considered integrating cerebrovascular disease; event by coronary disease, myocardial infarction, coronary revascularization and hospitalization for unstable angina were all considered coronary heart disease, and carotid endarterectomy and PAD were all considered other. The analysis was limited up to the first event after ABPM, considered the end of the follow-up. In the case of patients with more than one 24-hour ABPM between the two events, each ABPM was considered a separate entry for the database.

Statistical analysis was performed using the SPSS software (version 25.0 Inc., Armonk, NY: IBM Corp). Missing values were excluded from the sample. Values of continued variables are presented as the mean + standard deviation (SD) or as percentages. Categorical variables were presented as percentages. Continuous variables were compared using non-parametric (Wilcoxon-Mann-Whitney test) and categorical using χ^2. Cox proportional hazards regression analysis was performed to evaluate the prognostic significance of the various BP measurements, after testing the proportional hazards assumption. The hazard ratio (HR) corresponds to the risk of having a total CV events, stroke and coronary events associated with a 1-SD increment or a 10 mmHg increment in BP values. In a multivariate cox regression analysis, the risk associated with a 1-SD increment in BP and to 10 mmHg increment was evaluated without and with adjustment for age, smoking, body mass index (BMI), diabetes, dyslipidaemia and office blood pressure. Adjustments for casual BP, 24-h BP, daytime BP and night-time BP were made when appropriated. Statistical tests for collinearity, with analysis of variance inflation factor, were conducted to assess the quality relationship among the predictor variables. Cox

analysis of tertiles of BP was performed. The receiver operating characteristic (ROC) curve was performed with evaluation of the area under the curve and the point of effectiveness, concerning sensibility and specificity was calculated. Kaplan Meier survival curves concerning cut-off values of BP thresholds were performed. Comparison was made based on log-rank. Cox regression analysis uni and multivariate was performed in several analyses. Statistical significance was considered for a p value < 0.05.

6 General Results

From the first cohort, 29 ABPM sere selected. Between 1997 and 2017 (excluding years 2013 until 2015) were performed a total of 3928 ABPM, and 431 ABPM were selected from patients with previous CV event. These 460 ABPM were reviewed according to the inclusion and exclusion criteria, and 69 were excluded.

6.1 Baseline characteristics of the population

A total of 391 ABPM from 295 patients met the inclusion criteria. The first events were: 235 coronary events (from which 95 were revascularization procedures), 140 ischemic strokes, 11 haemorrhagic strokes, and five carotid and PAD procedures. The mean follow-up was 4.5 ± 5.2 (range 0.0-24.3), with a total of 1768 patient-years. Overall, medium age of 65.9 ± 10.4 years, 72.6% were men, 37.6% were diabetics, 19.2% had smoking habits and all had hypertension. All patients were Caucasian. Baseline characteristics of the population are described in Table 13.

No difference concerning BMI, diabetes, smoking or medication was found between the recurrent event group and the non-recurrent event. Atrial fibrillation was found in 11.5% of the total cohort, and 77.3% of the patients with atrial fibrillation was on anticoagulants.

There were 93 recurrent CV events, none fatal, and 21 non-cardiovascular deaths. The recurrent events were 42 ischemic strokes, 38 coronary events (15 of which were coronary revascularization procedures), seven haemorrhagic strokes, five PAD surgeries and one carotid endarterectomy.

Table 13 - Baseline characteristics of the population

	All (n=391)	**No Event** (n=298)	**With Event** (n=93)	**p value**
Age (mean, years)	65.9 ± 10.4	66.5 ± 10.3	64.0 ± 10.6	0.085
Male, n (%)	284 (72.6%)	214 (71.8%)	70 (75.3%)	0.514
BMI (kg/m2)	28.3 ± 3.7	28.1 ± 3.5	29.0 ± 4.4	0.186
Diabetes *mellitus*, n (%)	147 (37.6%)	111 (37.3%)	36 (38.7%)	0.321
Smoking, n (%)	75 (19.2%)	55 (18.5%)	20 (21.5%)	0.514
Dyslipidaemia, n (%)	318 (81.3%)	253 (84.9%)	65 (69.9%)	0.071
Atrial Fibrillation, n (%)	45 (11.5%)	29 (9.7%)	16 (17.2%)	**0.018**
Total Cholesterol (mg/dl)	164.1 ± 38.2	167.3 ± 37.7	152.4 ± 38.1	**0.005**
Serum Creatinine (mg/dl)	1.14 ± 0.41	1.12 ± 0.38	1.24 ± 0.50	**0.011**
Fasting Glycaemia (mg/dl)	124.7 ± 45.1	123.9 ± 45.4	127.2 ± 44.4	0.420
Echo TT – LA A (cm^2)	22.4 ± 4.8	22.1 ± 4.6	24.4 ± 5.6	0.089
Echo LVIDs (mm)	35.0 ± 9.8	33.9 ± 6.2	39.7 ± 17.9	0.583
Echo LVPWD (mm)	10.9 ± 1.5	10.8 ± 1.4	11.6 ± 1.4	**0.005**
ACEI/ARBs, n (%)	341 (87.2%)	269 (90.3%)	72 (77.4%)	0.144

	All (n=391)	No Event (n=298)	With Event (n=93)	p value
Diuretics, n (%)	215 (55.0%)	162 (54.4%)	53 (57.0%)	0.123
Statins, n (%)	331 (85.7%)	260 (87.2%)	71 (76.3%)	0.574
Anti-Platelets, n (%)	248 (63.4%)	201 (67.4%)	47 (50.5%)	**0.046**
Anti-coagulants, n (%)	45 (11.5%)	30 (10.1%)	15 (16.1%)	**0.047**
Office SBP (mmHg)	147.1 ± 24.1	145.9 ± 24.1	150.9 ± 23.7	0.080
Office DBP (mmHg)	85.0 ± 14.5	83.6 ± 13.4	89.4 ± 16.6	**0.009**
24 H SBP (mmHg)	129.2 ± 15.5	127.8 ± 15.2	133.7 ± 15.7	**0.001**
24h DBP (mmHg)	72.8 ± 10.0	71.8 ± 9.3	76.1 ± 11.3	**0.002**
24 h PP (mmHg)	56.6 ± 13.6	56.3 ± 13.7	58.0 ± 13.0	0.257
24 h HR (ppm)	66.1 ± 9.8	65.8 ± 9.4	67.2 ± 11.2	0.161
SD 24 h SBP (mmHg)	15.2 ± 3.9	15.1 ± 3.9	15.5 ± 3.9	0.452
Daytime SBP (mmHg)	133.6 ± 15.9	132.2 ± 15.5	138.1 ± 16.3	**0.001**
Daytime DBP (mmHg)	76.4 ± 10.6	75.3 ± 10.1	79.6 ± 11.4	**0.001**
Daytime PP (mmHg)	57.4 ± 13.8	57.0 ±13.9	58.7 ± 13.4	0.275
Daytime HR (ppm)	68.6 ± 10.8	68.3 ± 10.2	69.7 ± 12.6	0.252
SD Daytime SBP (mmHg)	14.2 ± 4.1	14.1 ± 4.1	14.4 ± 3.9	0.644
Night-Time SBP (mmHg)	121.4 ± 17.2	119.9 ± 17.1	126.2 ± 16.5	**0.002**
Night-Time DBP (mmHg)	66.5 ± 10.1	65.5 ± 9.2	69.8 ± 12.0	**0.006**
Night-time PP (mmHg)	55.1 ± 14.3	54.6 ± 14.6	56.9 ± 13.1	0.137
Night-Time HR (ppm)	61.5 ± 9.3	61.2 ± 9.0	62.7 ± 10.0	0.104
SD Night-time SBP (mmHg)	12.3 ± 4.2	12.1 ± 4.2	12.7 ± 4.2	0.122
Night-Time/Daytime of SBP (%)	9.5 ± 10.2	9.8 ± 10.9	8.5 ± 7.6	0.274
Night-Time/Daytime of DBP (%)	12.9 ± 9.4	13.0 ± 9.8	12.5 ± 8.0	0.657
Systolic morning surge (mmHg)	23.4 ± 20.7	22.7 ± 21.2	25.6 ± 18.9	0.588

ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, BMI - body mass index, CI – confidence interval, DBP - diastolic blood pressure, Echo TT - transthoracic echocardiogram, h – hours, HR – heart rate, LA A - left auricular area, LVIDs - left ventricular internal diameter in systole, LVPWD - left ventricular posterior wall dimensions, PP - pulse pressure, SBP - systolic blood pressure

Comparison between patients with and without recurrent events had no statistical difference concerning several risk factors: age, sex, diabetes, smoking and dyslipidaemia. Patients without recurrent event had higher total cholesterol and lower serum creatinine.

6.2 Research questions

In this section, we structure the presentation of the results after each research question.

6.2.1 "Does ABPM have any predictive value for recurrent cardiovascular disease?" and "Which ABPM variables have higher predictive value for recurrent cardiovascular events, if any"?

Table 14 shows univariate analysis (and 95% confidence interval) of the population characteristics and ABPM variables in relation to total CV events.

Table 14 - Univariate analysis of the population for total cardiovascular events

	HR	95% CI	p value
Age	**1.031**	**1.009-1.053**	**0.006**
Gender	1.311	0.815-2.111	0.264
BMI	1.045	0.987-1.107	0.132
Diabetes	1.137	0.730-1.771	0.571
Smoking	1.316	0.802-2.161	0.277
Dyslipidaemia	1.640	0.908-2.965	0.101
Atrial fibrillation	1.666	0.961-2.890	0.069
Total cholesterol	**0.987**	**0.979-0.996**	**0.006**
creatinine	1.165	10.634-2.139	0.623
Fasting glycaemia	0.999	0.993-1.005	0.691
Echo TT – LA A	1.037	0.963-1.117	0.339
Echo LVIDs	0.987	0.964-1.011	0.276
Echo LVPWD	**1.393**	**1.055-1.841**	**0.020**
ACEI/ARBs	0.661	0.304-1.440	0.297
Diuretics	1.131	0.707-1.812	0.607
Statins	1.505	0.722-3.139	0.275
Anti-platelets	0.887	0.564-1.394	0.602
Office SBP	1.001	0.992-1.010	0.894
Office DBP	0.995	0.980-1.010	0.494
24h SBP	**1.014**	**1.000-1.027**	**0.047**
24h DBP	1.001	0.980-1.023	0.913
24 h PP	**1.020**	**1.003-1.036**	**0.018**
24 h heart rate	1.010	0.989-1.032	0.339
SD 24 h SBP	1.039	0.989-1.092	0.125
Daytime SBP	**1.015**	**1.002-1.029**	**0.024**
Daytime DBP	1.004	0.983-1.024	0.730

	HR	95% CI	p value
Daytime PP	**1-020**	**1-004-1.037**	**0.013**
Daytime heart rate	1.011	0.999-1.023	0.256
SD Daytime SBP	1.029	0.982-1.078	0.231
Night-Time SBP	1.011	0.999-1.023	0.068
Night-Time DBP	1.004	0.984-1.024	0.715
Night-time PP	**1.017**	**1.002-1.033**	**0.026**
Night-time heart rate	1.009	0.987-1.032	0.412
SD Night- time SBP	1.045	0.998-1.094	0.061
Night-Time/Daytime of SBP	0.996	0.971-1.022	0.779
Night-Time/Daytime of DBP	1.001	0.977-1.025	0.930
Systolic morning surge	1.005	0.992-1.019	0.427

ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, BMI - body mass index, CI – confidence interval, h – hours; DBP - diastolic blood pressure, Echo TT - transthoracic echocardiogram, HR – hazard ratio; LA A - left auricular area, LVIDs - left ventricular internal diameter in systole, LVPWD - left ventricular posterior wall dimensions; PP - pulse pressure, SBP - systolic blood pressure

In Table 15 is presented the multivariate Cox analysis of SBP and DBP, with further adjustments to other continuous ABPM variables in relation to total CV events

Table 15 - Multivariate analysis of continuous blood pressure variables for total cardiovascular outcomes

	HR (IC 95%)ˠ	HR (CI 95%) ˠ and for 24 h DBP	HR (CI 95%) ˠ and for daytime DBP	HR (CI 95%) ˠ and for night-time SBP	HR (CI 95%) ˠ and for night-time DBP	HR (CI 95%) ˠ and for daytime SBP	HR (CI 95%) ˠ and for 24 h SBP
24-hour SBP	**1.032 (1.008-1.057)***	1.021 (0.993-1.050)		§		§	
Daytime SBP	**1.045 (1.019-1.071)***		**1.034 (1.004-1.064)****	**1.052 (1.018-1.088)***			§
Night-time SBP	1.015 (0.998-1.033)				1.007 (0.984-1.030)	0.992 (0.970-1.015)	§
24-hour DBP	**1.055 (1.011-1.100)****		§		§		1.048 (0.998-1.099)
Daytime DBP	**1.064 (1.022-1.107)***				**1.064 (1.013-1.118)****	**1.054 (1.008-1.102)****	
Night-time DBP	1.029 (0.997-1.062)	§	1.000 (0.961-1.039)	1.026 (0.984-1.069)			

CI – confident interval; DBP – diastolic blood pressure; h- hour; HR – hazard ratio; SBP – systolic blood pressure
ˠ adjusted for age, sex, BMI, diabetes, smoking status, dyslipidaemia and office BP
* p<0.01; ** p<0.05
§ High collinearity (≥ 4)

In our study, 24-hour and daytime SBP, and 24-hour and daytime DBP significantly predicted total CV events. Daytime SBP and daytime DBP persisted significantly after further adjustment (daytime SBP adjusted for daytime DBP or night-time SBP; daytime DBP adjusted for night-time DBP or daytime

SBP). Night-time never showed significant increased risk, and 24-hour SBP and 24-hour DBP lost strength when adjusted respectively to 24-hour DBP and 24-hour SBP. Daytime variables provide additional predictive information over 24-hour and over night-time.

Table 16 shows the hazard ratio associated with each 1-SD increment and 10 mmHg increment of BP.

Analysing by 1 SD increment, 24-hours SBP significantly predicted CV events, but lost its significance when adjusted for 24-hour DBP. Daytime SBP significantly predicted CV events, adjusted for confounding factors, maintaining its significance when adjusted for daytime DBP and night-time SBP. For each SD increment, 24-hour and daytime SBP, 24-hour and daytime DBP significantly predicted risk for CV events, when adjusted for several confounders and office BP (model 2). After further adjustment, only daytime SBP and daytime DBP maintained significance.

For each 10 mmHg increment, 24 hour SBP, daytime SBP, 24 hour DBP and daytime DBP were significant predictors of risk for CV events, when adjusted for several confounders (model 2). Daytime SBP and 24-hour DBP persisted significantly, even after further adjustment for night-time SBP and 24-hour SBP (models 3b, 3e and 3d). Daytime SBP is more significant than night-time BP for total CV events in multivariate analysis.

Table 16 - Multivariate analysis for total cardiovascular events by 1 SD increment and by 10 mmHg increment

	Cardiovascular events (95% CI)	**Collinearity**		**Cardiovascular events (CI 95%)**	**Collinearity**
Systolic BP	HR		**Systolic BP**	HR	
1 SD office SBP			**10 mmHg office SBP**		
Model 1	1.018 (0.821-1.262)		**Model 1**	0.998 (0.910-1.093)	
1 SD 24 h SBP			**10 mmHg 24 h SBP**		
Model 1	**1.239 (1.000-1.535)***		**Model 1**	1.127 (0.988-1.287)	
Model 2	**1.456 (1.932-2.055)****	1.695	**Model 2**	1.258 (0.998-1.585)	1.849
Model 3a	1.239 (0.841-1.825)	2.215	**Model 3a**	1.115 (0.856-1.454)	2.628
1 SD daytime SBP			**10 mmHg daytime SBP**		
Model 1	**1.243 (1.020-1.515)****		**Model 1**	**1.164 (1.026-1.319)****	
Model 2	**1.797 (1.255-2.572)***	2.031	**Model 2**	**1.603 (1.248-2.057)***	2.051
Model 3b	**1.575 (1.058-2.347)****	2.525	**Model 3b**	**1.514 (1.136-2.018)***	2.793
Model 3e	**1.845 (1.198-2.842)***	3.142	**Model 3e**	**1.755 (1.279-2.409)***	3.754
1 SD night-time SBP			**10 mmHg night-time SBP**		
Model 1	1.180 (0.977-1.424)		**Model 1**	1.126 (0.999-1.269)	
Model 2	1.243 (0.940-1.642)	1.360	**Model 2**	1.147 (0.966-1.361)	1.408
Model 3c	1.135 (0.815-1.580)	2.136	**Model 3c**	1.083 (0.880-1.334)	2.242
Model 3f	0.963 (0.687-1.349)	2.105	**Model 3f**	0.902 (0.725-1.123)	2.452
Diastolic BP			**Diastolic BP**		
1 SD casual DBP			**10 mmHg casual DBP**		
Model 1	0.960 (0.782-1.179)		**Model 1**	0.926 (0.798-1.074)	
1 SD 24 h DBP			**10 mmHg 24 h DBP**		
Model 1	1.032 (0.844-1.262)		**Model 1**	1.032 (0.844-1.262)	
Model 2	**1.545 (1.086-2.199)****	2.284	**Model 2**	**1.545 (1.086-2.199)****	2.284
Model 3d	1.486 (0.993-2.224)	2.977	**Model 3d**	**1.529 (1.032-2.265)****	3.055

(Continued from last page)

	Cardiovascular events (95% CI)	Collinearity		Cardiovascular events (CI 95%)	Collinearity
Diastolic BP			**Diastolic BP**		
1 SD daytime DBP			**10 mmHg daytime DBP**		
Model 1	1.040 (0.838-1.290)		**Model 1**	1.025 (0.844-1.244)	
Model 2	**1.638 (1.139-2.357)***	2.411	**Model 2**	**1.566 (1.094-2.240)****	2.649
Model 3 f	**1.505 (1.021-2.219)****	2.818	**Model 3 f**	1.386 (0.940-2.045)	3.379
Model 3 c	**1.607 (1.051-2.456)****	3.369	**Model 3 c**	1.515 (0.997-2.301)	3.719
1 SD night-time DBP			**10 mmHg night-time DBP**		
Model 1	1.019 (0.837-1.241)		**Model 1**	1.019 (0.837-1.241)	
Model 2	1.254 (0.926-1.698)	1.610	**Model 2**	1.254 (0.926-1.698)	1.610
Model 3 e	1.197 (0.837-1.711)	2.477	**Model 3 e**	1.195 (0.833-1.715)	2.439
Model 3 b	1.031 (0.728-1.462)	2.250	**Model 3 b**	1.054 (0.746-1.489)	2.260

CI – confident interval; DBP – diastolic blood pressure; h- hour; HR – hazard ratio; SBP – systolic blood pressure; SD- standard deviation
Model 1 – without adjustment
Model 2 – after adjustment for age, sex, BMI, smoking status, dyslipidaemia, diabetes, and office BP
Model 3 – as model 2 plus adjustment for: (a) 24 h DBP; (b) daytime DBP; (c) night-time DBP; (d) 24 h SBP; (e) night-time SBP; (f) daytime SBP
Significance of hazard ratios: *p<0.01, **p<0.05

- *Analysis of the subgroup with coronary first event*

We performed an analysis of the subgroup with coronary disease events including coronary revascularization, comparing the ones with recurrent event with those without. From a total of 235 ABPM with coronary event as first event, 61 had recurrent event. The follow-up was 4.5 ± 5.1 years.

esults are presented in Table 17.

Table 17 - Baseline characteristics of the subgroup with coronary event (first event)

	All (n=235)	No Event (n=174)	With Event (n=61)	p value
Age (mean, years)	66.8 ± 10.3	67.7 ± 10.4	64.3 ± 9.5	**0.022**
Male, n (%)	195 (83.0%)	139 (79.9%)	56 (91.8%)	**0.033**
BMI (kg/m2)	28.3 ± 3.6	28.1 ± 3.5	28.6 ± 4.0	0.707
Diabetes, n (%)	101 (43.0%)	75 (43.1%)	26 (42.6%)	0.551
Smoking, n (%)	54 (23.0%)	35 (20.1%)	19 (31.1%)	0.078
Dyslipidaemia, n (%)	206 (87.7%)	158 (90.8%)	48 (78.7%)	0.543
Atrial Fibrillation, n (%)	28 (11.9%)	21 (12.1%)	7 (11.5%)	0.881
Total Cholesterol (mg/dl)	155.5 ± 33.8	159.3 ± 35.1	140.9 ± 23.5	**0.015**
Serum Creatinine (mg/dl)	1.22 ± 0.46	1.20 ± 0.43	1.31 ± 0.57	0.072
Fasting Glycaemia (mg/dl)	134,8 ± 50.9	136.3 ± 52.2	130.9 ± 48.0	0.750
Echo TT – LA A (cm^2)	22.8 ± 4.5	22.7 ± 4.5	23.3 ± 4.4	0.729
Echo LVIDs (mm)	36.6 ± 11.4	34.9 ± 5.8	42.4 ± 20.7	0.802
Echo LVPWD (mm)	10.7 ± 1.4	10.6 ± 1.4	11.1 ± 1.4	0.207
ACEI/ARBs, n (%)	211, (89.8%)	161 (92.5%)	50 (82.0%)	0.726

	All (n=235)	No Event (n=174)	With Event (n=61)	p value
Diuretics, n (%)	136 (57.9%)	96 (55.2%)	40 (65.6%)	**0.015**
Statins, n (%)	213 (90.6%)	161 (92.5%)	52 (82.5%)	0.690
Anti-Platelets, n (%)	172 (73.2%)	140 (80.5%)	32 (52.5%)	**0.001**
Office SBP (mmHg)	148.0 ± 22.9	146.9 ± 22.2	151.2 ± 24.4	0.290
Office DBP (mmHg)	83.1 ± 13.9	81.5 ± 12.9	87.7 ± 15.7	**0.010**
24 H SBP (mmHg)	129.1 ± 14.8	127.1 ± 13.9	134.7 ± 16.1	**0.001**
24h DBP (mmHg)	71.0 ± 9.1	69.6 ± 8.1	74.9 ± 10.6	**0.001**
24 h PP (mmHg)	58.4 ± 13.6	57.7 ± 13.6	60.5 ± 13.5	0.191
24 h HR (ppm)	63.7 ± 9.1	63.4 ± 8.2	64.5 ± 11.2	0.468
SD 24 h SBP (mmHg)	15.1 ± 4.0	15.0 ± 4.0	15.4 ± 4.1	0.561
Daytime SBP (mmHg)	133.3 ± 15.5	131.4 ± 14.4	138.8 ± 17.0	**0.002**
Daytime DBP (mmHg)	74.3 ± 9.8	73.0 ± 9.1	78.1 ± 10.8	**0.001**
Daytime PP (mmHg)	59.3 ± 13.9	58.6 ± 13.9	61.3 ± 13.8	0.200
Daytime HR (ppm)	65.8 ± 9.8	65.5 ± 8.7	66.5 ± 12.4	0.583
SD Daytime SBP (mmHg)	14.2 ± 4.2	14.1 ± 4.2	14.4 ± 4.1	0.750
Night-Time SBP (mmHg)	121.7 ± 16.5	119.7 ± 16.1	127.4 ± 16.2	**0.002**
Night-Time DBP (mmHg)	65.1 ± 9.3	63.7 ± 8.0	69.1 ± 11.3	**0.003**
Night-time PP (mmHg)	57.0 ± 14.2	56.2 ± 14.3	59.3 ± 13.5	0.150
Night-Time HR (ppm)	59.9 ± 8.8	59.7 ± 8.4	60.7 ±9.9	0.384
SD Night-time SBP (mmHg)	12.0 ± 4.0	11.8 ± 4.0	12.7 ± 4.15	0.111
Night-Time/Daytime of SBP (%)	9.0 ± 10.2	9.4 ± 10.9	7.9 ± 7.7	0.311
Night-Time/Daytime of DBP (%)	12.5 ± 10.31	12.9 ± 10.9	11.5 ± 8.3	0.357
Systolic morning surge (mmHg)	24.3 ± 20.8	23.8 ± 20.7	25.4 ± 21.1	0.489

ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, BMI - body mass index, CI – confidence interval, DBP - diastolic blood pressure, Echo TT - transthoracic echocardiogram, h – hours, HR – heart rate, LA A - left auricular area, LVIDs - left ventricular internal diameter in systole, LVPWD - left ventricular posterior wall dimensions, PP - pulse pressure, SBP - systolic blood pressure, SD – standard deviation

The subgroup of patients with coronary first event were younger, with lower serum fasting cholesterol and with predominance of male gender. They also had higher prevalence of use of diuretics and a significant lower use of anti-platelets. In this subgroup, systolic and diastolic BP (24-hour, daytime and night-time) were significantly higher in the patients with recurrent event versus the non-recurrent event patients.

The univariate Cox analysis is presented in Table 18.

Table 18 - Univariate analysis for recurrent cardiovascular events (subgroup with first coronary event)

	HR	95% CI	p value
Office SBP	1.003	0.991-1.015	0.601
Office DBP	0.999	0.980-1.018	0.904
24h SBP	1.018	1.001-1.036	**0.042**
24h DBP	1.005	0.977-1.034	0.737
24 h PP	1.026	1.005-1.047	**0.015**
24 h heart rate	1.016	1.987-1.045	0.283
SD 24 h SBP	1.034	0.980-1.092	0.224
Daytime SBP	1.018	1.001-1.035	**0.041**
Daytime DBP	1.003	0.977-1.030	0.812
Daytime PP	1.026	1.006-1.047	**0.013**
Daytime heart rate	1.018	0.993-1.045	0.164
SD Daytime SBP	1.029	0.979-1.081	0.264
Night-Time SBP	1.016	0.999-1.032	0.062
Night-Time DBP	1.010	0.983-1.038	0.486
Night-time PP	1.021	1.002-1.042	**0.034**
Night-time heart rate	1.007	0.978-1.037	0.633
SD Night- time SBP	1.049	0.991-1.111	0.098
Night-Time/Daytime of SBP	0.995	0.965-1.026	0.752
Night-Time/Daytime of DBP	0.993	0.965-1.022	0.620
Systolic morning surge	1.003	0.988-1.019	0.666

CI – confident interval; DBP – diastolic blood pressure; h- hour; HR – hazard ratio; PP – pulse pressure; SBP – systolic blood pressure; SD – standard deviation

In the univariate analysis only 24-hour SBP and daytime SBP persisted with significant risk.

- *Analysis of the subgroup with cerebrovascular event as first event*

The analysis of the subgroup with stroke as first event, evaluated 151 patients and we performed the comparison between the group with recurrent event and the group without recurrent event. The follow-up was of 4.6 ± 5.3 years, and there were 32 recurrent events.

In Table 19 we show the baseline characteristics of this subgroup.

Table 19 - Baseline characteristics of the subgroup with cerebrovascular event (first event)

	All (n=151)	No Event (n=119)	With Event (n=32)	p value
Age (mean, years)	64.5 ± 10.5	64.9 ± 9.9	63.3 ± 12.5	0.753
Male, n (%)	85 (56.3%)	71 (59.7%)	14 (43.8%)	0.107
BMI (kg/m2)	28.5 ± 3.9	28.1 ± 3.5	29.8 ± 5.1	0.110
Diabetes, n (%)	45 (29.8%)	35 (29.4%)	10 (31.3%)	0.537
Smoking, n (%)	18 (11.9%)	17 (14.3%)	1 (3.1%)	0.084

	All (n=151)	No Event (n=119)	With Event (n=32)	p value
Dyslipidaemia, n (%)	108 (71.5%)	91 (76.5%)	17 (53.1%)	**0.038**
Atrial Fibrillation, n (%)	16 (10.6%)	7 (5.9%)	9 (28.1%)	**0.000**
Total Cholesterol (mg/dl)	179.0 ± 41.1	181.3 ± 38.5	171.1 ± 49.3	0.211
Serum Creatinine (mg/dl)	1.02 ± 0.3	1.00 ± 0.27	1.10 ± 0.31	0.131
Fasting Glycaemia (mg/dl)	114.1 ± 35.8	111.8 ± 34.5	122.6 ± 39.9	0.343
Echo TT – LA A (cm^2)	21.8 ± 5.31	21.1 ± 4.6	26.6 ± 7.2	0.069
Echo LVIDs (mm)	32.6 ± 6.4	32.6 ± 6.7	33.2 ± 4.1	0.324
Echo LVPWD (mm)	11.2 ± 1.4	11.0 ± 1.4	12.4 ± 1.1	**0.003**
ACEI/ARBs, n (%)	126 (83.4%)	104 (87.4%)	22 (68.8%)	0.069
Diuretics, n (%)	78 (51.7%)	65 (54.6%)	13 (40.6%)	0.372
Statins, n (%)	114 (75.5%)	95 (79.8%)	19 (59.4%)	0.680
Anti-Platelets, n (%)	73 (48.3%)	58 (48.7%)	15 (46.9%)	0.827
Anti-coagulants, n (%)	20 (13.2%)	12 (10.1%)	8 (25.0%)	**0.026**
Office SBP (mmHg)	146.3 ± 25.9	145.3 ± 26.6	150.1 ± 22.6	0.203
Office DBP (mmHg)	88.2 ± 14.8	87.0 ± 13.6	92.8 ± 18.2	0.225
24 h SBP (mmHg)	129.7 ± 16.6	129.1 ± 16.9	131.9 ± 15.3	0.306
24 h DBP (mmHg)	75.7 ± 10.7	75.0 ± 10.2	78.3 ± 12.5	0.280
24 h PP (mmHg)	54.0 ± 13.2	54.3 ± 13.8	52.9 ± 10.5	0.798
24 h HR (ppm)	69.6 ± 9.6	68.9 ± 9.5	72.3 ± 9.6	0.067
SD 24 h SBP (mmHg)	15.4 ± 3.7	15.3 ± 3.7	15.7 ± 3.7	0.579
Daytime SBP (mmHg)	134.4 ± 16.7	133.7 ± 17.1	137.0 ± 15.0	0.207
Daytime DBP (mmHg)	79.6 ± 11.5	78.8 ± 10.8	82.9 ± 11.9	0.12
Daytime PP (mmHg)	54.8 ± 13.3	55.0 ± 13.8	53.7 ± 11.2	0.75
Daytime HR (ppm)	72.8 ± 10.7	72.1 ± 10.5	75.7 ± 10.8	0.099
SD Daytime SBP (mmHg)	14.1 ± 3.8	14.1 ± 3.9	14.3 ± 3.7	0.772
Night-Time SBP (mmHg)	121.2 ± 18.1	120.5 ± 18.5	123.8 ± 17.0	0.428
Night-Time DBP (mmHg)	68.9 ± 10.9	68.2 ± 10.0	71.2 ± 13.4	0.433
Night-time PP (mmHg)	52.5 ± 14.1	52.5 ± 14.8	52.3 ± 10.9	0.79
Night-Time HR (ppm)	63.8 ± 9.04	63.0 ± 8.9	66.6 ± 9.2	**0.043**
SD Night-time SBP (mmHg)	12.6 ± 4.3	12.6 ± 4.4	12.7 ± 4.2	0.542
Night-Time/Daytime of SBP (%)	10.2 ± 10.2	10.4 ± 10.9	9.6 ± 7.4	0.745
Night-Time/Daytime of DBP (%)	13.4 ± 7.8	13.1 ± 7.9	14.4 ± 7.2	0.447
Systolic morning surge (mmHg)	21.6 ± 20.6	20.6 ± 22.0	25.9 ± 12.3	0.54

ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, BMI - body mass index, , CI – confidence interval, DBP - diastolic blood pressure, Echo TT - transthoracic echocardiogram, h – hours, HR – heart rate, LA A - left auricular area, LVIDs - left ventricular internal diameter in systole, LVPWD - left ventricular posterior wall dimensions, PP - pulse pressure, SBP - systolic blood pressure

In the subgroup with first event stroke, patients with recurrent event had higher prevalence of atrial fibrillation and similar level of anti-coagulation. In the analysis of ABPM variables, only night-time heart rate was statistically different between the recurrent event group and those without recurrent event.

The univariate Cox analysis of the ABPM variables showed no statistical difference in any of the variables (Table 20).

Table 20 - Univariate analysis for recurrent cardiovascular events (subgroup with first cerebrovascular event)

	HR	95% CI	p value
Office SBP	0.996	0.981-1.012	0.658
Office DBP	0.991	0.965-1.018	0.527
24h SBP	1.005	0.983-1.028	0.649
24h DBP	0.997	0962-1.034	0.887
24 h PP	1.005	0.977-1.034	0.733
24 h heart rate	1.022	0.985-1.062	0.248
SD 24 h SBP	1.076	0.967-1.198	0.181
Daytime SBP	1.011	0.988-1.034	0.364
Daytime DBP	1.008	0.972-1.045	0.660
Daytime PP	1.007	0.979-1.036	0.636
Daytime heart rate	1.021	0.987-1.056	0.221
SD Daytime SBP	1.042	0.936-1.161	0.454
Night-Time SBP	1.004	0.985-1.023	0.711
Night-Time DBP	0.996	0.964-1.029	0.808
Night-time PP	1.007	0.980-1.034	0.625
Night-time heart rate	1.025	0.987-1.066	0.203
SD Night- time SBP	1.043	0.962-1.131	0.309
Night-Time/Daytime of SBP	1.008	0.965-1.052	0.734
Night-Time/Daytime of DBP	1.026	0.982-1.071	0.250
Systolic morning surge	1.010	0.982-1.039	0.467

CI – confident interval; DBP – diastolic blood pressure; h- hour; HR – hazard ratio; PP – pulse pressure; SBP – systolic blood pressure; SD – standard deviation

6.2.2 "Will the limits of BP that best predict the first CV events be identical to those that predict the second events?"

We studied SBP and DBP (24-hour, daytime and night-time) pattern, and divided each variable in tertiles of value of BP (Table 21). The univariate Cox analysis of each tertile showed unadjusted higher risk for 24-hour SBP ≥ 135 mmHg, night-time SBP (between 115-127 mmHg) and night-time DBP (between 62-70 mmHg).

Table 21 - Tertiles of systolic blood pressure and diastolic blood pressure in relation to risk of total cardiovascular events

	HR	95% CI
24 h SBP (≤ 123 mmHg)	ref	
24 h SBP (124-134 mmHg)	1.748	0.992-3.081
24 h SBP (≥ 135 mmHg)	**1.823**	**1.017-3.271***
Daytime SBP (≤ 127 mmHg)	ref	
Daytime SBP (128-137 mmHg)	1.436	0.821-2.512
Daytime SBP (≥ 138 mmHg)	1.722	0.992-2.990
Night-time SBP (≤ 114 mmHg)	ref	
Night-time SBP (115-127 mmHg)	**1.767**	**1.036-3.013***
Night-time SBP (≥ 128 mmHg)	1.567	0.916-2.680
24 h DBP (≤ 67 mmHg)	ref	
24 h DBP (68-77 mmHg)	0.789	0.456-1.364
24 h DBP (≥ 78 mmHg)	0.833	0.501-1.384
Daytime DBP (≤ 71 mmHg)	ref	
Daytime DBP (72-81 mmHg)	1.048	0.608-1.807
Daytime DBP (≥ 82 mmHg)	0.996	0.592-1.676
Night-time DBP (≤ 61 mmHg)	ref	
Night-time DBP (62-70 mmHg)	**0.490**	**0.279-0.860***
Night-time DBP (≥ 71 mmHg)	0.818	0.503-1.330

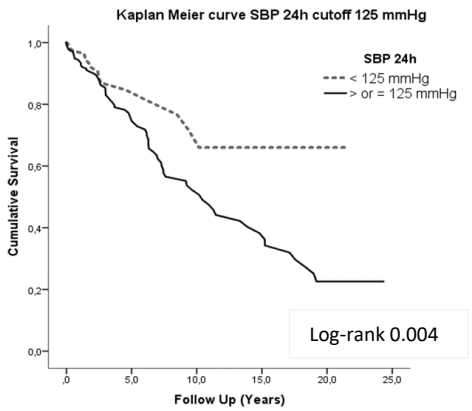
CI – confidence interval, DBP – diastolic blood pressure, h – hours, HR – hazard ratio, SBP – systolic blood pressure
*p<0.05

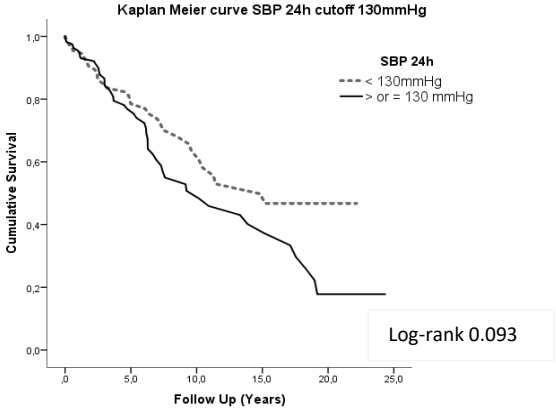
The receiver operating characteristic (ROC) curve of SBP 24 hours with an area under the curve (AUC) of 0.614 was analysed for the best value of effectiveness, concerning both sensibility and specificity, for recurrent event risk prediction, which was 125 mmHg (82% sensitivity, 46% specificity). We evaluated the ROC curve for daytime SBP (AUC 0.613) and night-time SBP (AUC 0.604) and the best cut-offs values were, respectively, 131 mmHg (73% sensitivity, 49% specificity) and 112 mmHg (sensitivity 85%, specificity 33%). The Kaplan Meier survival curves were applied to these cut-offs and compared to the established guidelines ABPM cut-offs of diagnosis of hypertension (see The survival curve of patients divided by mean 24-hour SBP < 130 mmHg and ≥ 130 mmHg, daytime < 135 mmHg and ≥ 135 mmHg and night-time < 120 mmHg and ≥ 120 mmHg, had respectively log-ranks of 0.093, 0.138 and 0.411. The survival curves using the thresholds of 125 mmHg for 24-hour SBP and 131 mmHg for daytime SBP showed a log-rank of 0.004 and 0.007, respectively.

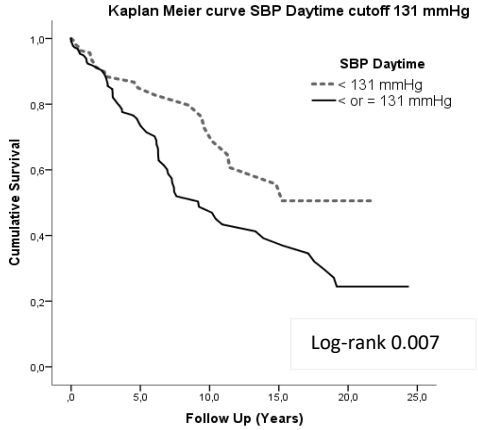
Figure 4).

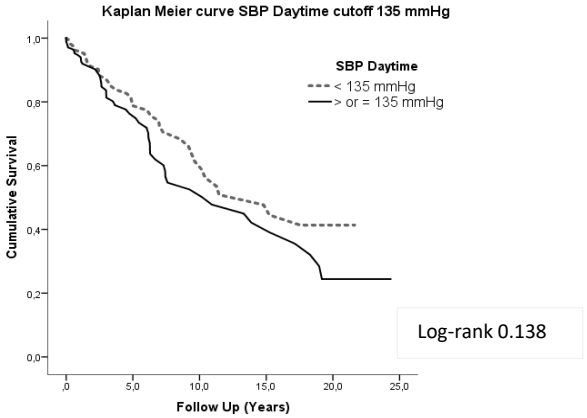
The survival curve of patients divided by mean 24-hour SBP < 130 mmHg and ≥ 130 mmHg, daytime < 135 mmHg and ≥ 135 mmHg and night-time < 120 mmHg and ≥ 120 mmHg, had respectively log-ranks of 0.093, 0.138 and 0.411. The survival curves using the thresholds of 125 mmHg for 24-hour SBP and 131 mmHg for daytime SBP showed a log-rank of 0.004 and 0.007, respectively.

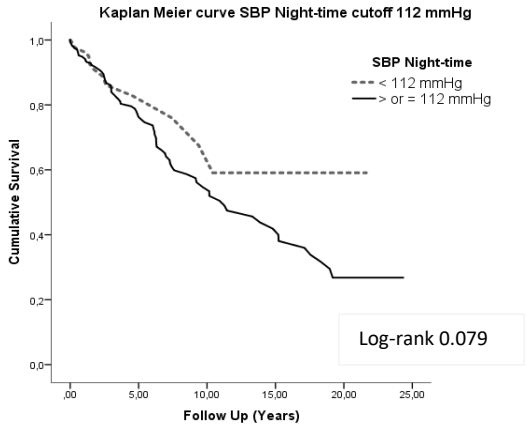
Figure 4 - Kaplan Meier survival curves of different systolic blood pressure thresholds for total cardiovascular events

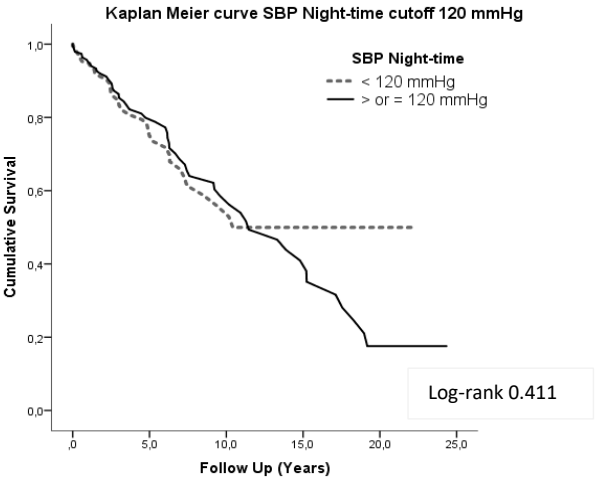












The Cox regression analysis of these thresholds is showed in Table 22 in comparison with the current established guidelines cut-offs of 130 mmHg, 135 mmHg and 120 mmHg for mean 24-hour SBP, mean daytime SBP and mean night-time SBP, respectively. The threshold of 125 mmHg for mean 24-hour SBP and 131 mmHg for mean daytime SBP, were statistically significant, when adjusted for age, sex, body mass index, diabetes, dyslipidaemia, smoking and office SBP.

Table 22 - Analysis of different systolic blood pressure thresholds and hazard risk for recurrent cardiovascular events

	HR (unadjusted)	p value	HR *	95% CI	p value
24 h SBP (130 mmHg)	1.417	0.095	1.604	0.912-2.823	0.101
24 h SBP (125 mmHg)	2.130	**0.005**	2.957	1.500-5.827	**0.002**
Daytime SBP (135 mmHg)	1.360	0.140	1.713	0.972-3.019	0.063
Daytime SBP (131 mmHg)	1.852	**0.008**	2.626	1.402-4.917	**0.003**
Night-time SBP (120 mmHg)	1.189	0.412	1.218	0.725-2.046	0.456
Night-time SBP (112 mmHg)	1.660	0.082	1.807	0.902-3.620	0.095

* adjusted for age, sex, body mass index, diabetes, dyslipidaemia, smoking, and office SBP

CI – confident interval; DBP – diastolic blood pressure; HR – hazard ratio; SBP – systolic blood pressure

6.2.3 "ABPM prediction values for recurrent cardiovascular events are they different between distinct age groups?"

In our sample, mean age is 65.9 years and median 65 years. We divided our sample in patients under 65 years old, and above 65 years old, and studied their characteristics and ABPM variables, to find if they would be more associated to risk in a given age.

There were 179 patients < 65 years, and 212 with age ≥ 65 years. Patients < 65 years old had 50 CV events, over a mean follow-up of 6.3 ± 6.3 years (medium 3.6 years). Patients ≥ 65 years had 43 events over a mean follow up of 3.0 ± 3.2 years (medium 1.9 years).

In Table 23 we compared baseline characteristics between patients under 65 years and patients ≥ 65 years.

Table 23 – Baseline characteristics of patients <65 years and ≥ 65 years

	All (n=391)	< 65 years (n=179)	≥ 65 years (n=212)	p value
Age (mean, years)	65.9 ± 10.4	56.7 ± 6.1	73.6 ± 6.0	**0.000**
Male, n (%)	284 (72.6%)	143 (79.9%)	141 (66.5%)	**0.003**
BMI (kg/m2)	28.3 ± 3.7	29.0 ± 4.0	27.8 ± 3,4	**0.008**
Diabetes *mellitus*, n (%)	147 (37.6%)	60 (33.5%)	87 (41%)	0.199
Smoking, n (%)	75 (19.2%)	50 (27.9%)	25 (11.8%)	**0.000**
Dyslipidaemia, n (%)	318 (81.3%)	133 (74.3%)	185 (87.3%)	**0.002**
Atrial Fibrillation, n (%)	45 (11.5%)	12 (6.7%)	33 (15.6%)	**0.009**
Total Cholesterol (mg/dl)	164.1 ± 38.2	167.8 ± 43.5	161.4 ± 33.6	0.489
Serum Creatinine (mg/dl)	1.14 ± 0.41	1.08 ± 0.26	1.19 ± 0.49	0.392
Fasting Glycaemia (mg/dl)	124.7 ± 45.1	126.4 ± 52.1	122.9 ± 36.6	0.433
Echo TT – LA A (cm^2)	22.4 ± 4.8	21.9 ± 4.5	22.6 ± 5.0	0.231

	All (n=391)	< 65 years (n=179)	≥ 65 years (n=212)	p value
Echo LVIDs (mm)	35.0 ± 9.8	37.2 ± 13.1	33.5 ± 6.5	0.562
Echo LVPWD (mm)	10.9 ± 1.5	10.9 ± 1.6	10.9 ± 1.4	0.636
ACEI/ARBs, n (%)	341 (87.2%)	152 (84.9%)	189 (89.2%)	0.635
Diuretics, n (%)	215 (55.0%)	98 (54.7%)	117 (55.2%)	0.743
Statins, n (%)	331 (84.7%)	140 (78.2%)	191 (90.1%)	**0.002**
Anti-Platelets, n (%)	248 (63.4%)	106 (59.2%)	142 (67.0%)	0.227
Anti-coagulants, n (%)	45 (11.5%)	11 (6.1%)	34 (16.0%)	**0.003**
Office SBP (mmHg)	147.1 ± 24.1	144.7 ±24.1	149.0 ± 24.0	**0.037**
Office DBP (mmHg)	85.0 ± 14.5	90.7 ± 14.7	80.2 ± 12.4	**0.000**
24 H SBP (mmHg)	129.2 ± 15.5	128.9 ± 16.7	129.4 ± 14.5	0.377
24h DBP (mmHg)	72.8 ± 10.0	78.0 ± 9.8	68.4 ± 7.8	**0.000**
24 h PP (mmHg)	56.6 ± 13.6	51.1 ± 12.5	61.1 ± 12.8	**0.000**
24 h HR (ppm)	66.1 ± 9.8	68.9 ± 10.2	63.7 ± 8.9	**0.000**
SD 24 h SBP (mmHg)	15.2 ± 3.9	14.5 ± 3.5	15.8 ± 4.1	**0.002**
Daytime SBP (mmHg)	133.6 ± 15.9	133.2 ± 16.8	133.9 ± 15.2	0.363
Daytime DBP (mmHg)	76.4 ± 10.6	81.6 ± 10.4	71.9 ± 8.6	**0.000**
Daytime PP (mmHg)	57.4 ± 13.8	51.8 ± 12.6	62.0 ± 13.0	**0.000**
Daytime HR (ppm)	68.6 ± 10.81	71.6 ± 11.3	66.1 ± 9.9	**0.000**
SD Daytime SBP (mmHg)	14.2 ±4.1	13.3 ± 3.5	14.9 ± 4.4	**0.000**
Night-Time SBP (mmHg)	121.4 ± 17.2	120.6 ± 18.1	122.0± 16.4	0.236
Night-Time DBP (mmHg)	66.5 ± 10.1	71.1 ± 10.4	62.6 ± 8.0	**0.000**
Night-time PP (mmHg)	55.1 ± 14.3	49.8 ± 12.9	59.5 ± 14.0	**0.000**
Night-Time HR (ppm)	61.5 ± 9.3	63.8 ± 9.2	59.6 ± 9.0	**0.000**
SD Night-time SBP (mmHg)	12.3 ± 4.2	11.6 ± 4.0	12.8 ± 4.3	**0.004**
Night-Time/Daytime of SBP (%)	9.5 ± 10.2	9.5 ± 7.6	9.5 ± 12.0	0.769
Night-Time/Daytime of DBP (%)	12.9 ± 9.4	12.7 ± 8.4	13.0 ± 10.2	0.796
Systolic morning surge (mmHg)	23.4 ± 20.7	23.9 ± 16.3	22.8 ± 24.06	0.902

ACEI - angiotensin converting enzyme inhibitors, ARB - angiotensin receptor blockers, BMI - body mass index, CI – confidence interval, DBP - diastolic blood pressure, Echo TT - transthoracic echocardiogram, h – hours, HR – heart rate, LA A - left auricular area, LVIDs - left ventricular internal diameter in systole, LVPWD - left ventricular posterior wall dimensions; PP - pulse pressure, SBP - systolic blood pressure

The two populations have major differences, not just because they are different age groups, but also in most of comorbidities. Patients under 65 years have higher prevalence of men, higher BMI and dyslipidaemia and higher prevalence of patients with smoking habits. Although the group ≥ 65 years had 41% of diabetics, the comparison between the two groups was not statically significant. Older

patients had a much higher prevalence of atrial fibrillation. There was no difference between groups concerning medication, except for statins. Although patients under 65 years old had a higher prevalence of dyslipidaemia, had also a smaller prevalence of use of statins.

In the group of patients < 65 years old, the mean 24-hour SBP for those with recurrent event versus no recurrent event was 135.3 ± 16.9 mmHg versus 126.4 ± 15.9 (p 0.000). In the group of patients ≥ 65 years old, the mean 24-hour SBP for those with recurrent event versus no recurrent event was 131.9 ± 14.3 versus 128.8 ± 14.5 (p 0.309).

We performed univariate and multivariate Cox analysis, adjusted for age, gender, diabetes, smoking status, dyslipidaemia and office BP. Table 24 shows the HR of the relation of several ABPM variables and the risk of total CV outcome.

Table 24 - Univariate and multivariate analysis of patients < 65 years and ≥ 65 years old for total cardiovascular events

		Univariate HR (CI 95%)	Multivariate* HR (CI 95%)	p value
Office SBP	< 65 years	1.000 (0.988-1.012)		
	≥ 65 years	0.998 (0.984-1.012)		
Office DBP	< 65 years	0.994 (0.973-1.015)		
	≥ 65 years	1.011 (0.985-1.037)		
24h SBP	< 65 years	**1.021 (1.004-1.039)**	**1.066 (1.026-1.107)**	**0.001**
	≥ 65 years	1.000 (0.980-1.021)	1.010 (0.976-1.046)	0.565
24h DBP	< 65 years	1.022 (0.991-1.054)	**1.065 (1.014-1.118)**	**0.011**
	≥ 65 years	1.005 (0.967-1.044)	1.021 (0.969-1.076)	0.440
24 h heart rate	< 65 years	1.017 (0.989-1.046)	1.007 (0.971-1.045)	0.714
	≥ 65 years	1.022 (0.986-1.059)	1.010 (0.971-1.050)	0.631
SD 24 h SBP	< 65 years	0.986 (0.914-1.075)	0.950 (0.848-1.063)	0.371
	≥ 65 years	1.048 (0.985-1.116)	1.074 (0.984-1.172)	0.111
Daytime SBP	< 65 years	**1.020 (1.003-1.038)**	**1.072 (1.030-1.116)**	**0.001**
	≥ 65 years	1.006 (0.986-1.027)	1.029 (0.992-1.068)	0.122
Daytime DBP	< 65 years	1.017 (0.987-1.048)	**1.053 (1.007-1.102)**	**0.023**
	≥ 65 years	1.019 (0.984-1.055)	1.042 (0.994-1.094)	0.089
Daytime heart rate	< 65 years	1.017 (0.992-1.042)	1.009 (0.978-1.040)	0.589
	≥ 65 years	1.021 (0.988-1.055)	1.008 (0.971-1.046)	0.682
SD Daytime SBP	< 65 years	0.994 (0.913-1.083)	0.917 (0.808-1.040)	0.178
	≥ 65 years	1.023 (0.963-1.086)	1.017 (0.934-1.108)	0.691
Night-Time SBP	< 65 years	**1.021 (1.006-1.037)**	**1.048 (1.017-1.079)**	**0.002**
	≥ 65 years	0.996 (0.978-1.014)	0.996 (0.971-1.021)	0.742
Night-Time DBP	< 65 years	**1.028 (1.001-1.056)**	**1.059 (1.017-1.103)**	**0.006**
	≥ 65 years	0.987 (0.950-1.025)	0.989 (0.942-1.038)	0.658
Night-time heart rate	< 65 years	1.013 (0.982-1.045)	1.009 (0.968-1.051)	0.673
		1.024 (0.990-1.060)	1.018 (0.981-1.056)	0.354

		Univariate HR (CI 95%)	Multivariate* HR (CI 95%)	p value
SD Night- time SBP	< 65 years	1.028 (0.959-1.102)	1.000 (0.915-1.093)	0.997
	≥ 65 years	**1.048 (0.983-1.117)**	**1.091 (1.006-1.183)**	**0.036**
Night-Time/Daytime of SBP	< 65 years	0.969 (0.934-1.006)	0.971 (0.924-1.021)	0.255
	≥ 65 years	1.017 (0.990-1.045)	1.021 (0.992-1.052)	0.156
Night-Time/Daytime of DBP	< 65 years	0.972 (0.940-1.004)	0.981 (0.942-1.021)	0.336
	≥ 65 years	**1.028 (1.003-1.054)**	**1.030 (1.003-1.058)**	**0.029**
Systolic morning surge	< 65 years	1.004 (0.985-1.023)	0.997 (0.976-1.018)	0.767
	≥ 65 years	1.006 (0.988-1.024)	1.010 (0.989-1.031)	0.372

* adjusted for age, gender, diabetes, smoking status, dyslipidaemia, BMI, office BP
CI – confident interval; DBP – diastolic blood pressure; h – hour; HR – hazard ratio; SBP – systolic blood pressure; SD- standard deviation

The group < 65 years had significant HR in multivariate analysis for BP 24-hour, daytime and night-time. Patients ≥ 65 years only had significant result for diastolic nocturnal dip and SD of the night-time SBP.

6.2.4 "How far and how much ABPM data change from before through after the event?"

From our cohort, 46 patients had ABPM before the first event, but in three, there were not enough values to compare.

We compared the ABPM from 43 patients, from before the first event and after the first event.

The mean follow-up between first ABPM and the first event was 6.5 ± 4.6 years, and the mean follow up between the first event and the second ABPM was 2.7 ± 2.0 years.

These 43 patients had a lower mean age than the total cohort (61.9 ± 9.7 versus 65.9 ± 10.4), a lower proportion of men (60.5% versus 72.6%), lower proportion of diabetics (34.9% versus 37.6%), of patients with smoking habits (5.7% versus 19.2%) and a lower use of statins (74.4% versus 91.4%).

Overall, 21 had coronary event and 22 had stroke as first event.

ABPM paired variables comparison are presented in Table 25.

Table 25 - Comparison between ABPM before first event and ABPM after first event

	n	1st ABPM	2nd ABPM	Paired samples test
		Mean ± SD	Mean ± SD	Wilcoxon
Office SBP (mmHg)	42	161.4 ± 24.4	144.8 ± 24.8	**0.002**
Office DBP (mmHg)	42	100.5 ± 13.2	87.2 ± 16.4	**0.001**
24 h SBP (mmHg)	43	138.7 ± 16.3	131.7 ± 14.1	**0.008**
24 h DBP (mmHg)	43	84.2 ± 10.3	76.7 ± 10.2	**0.002**
24 h PP (mmHg)	39	54.2 ± 13.5	53.9 ± 12.0	0.896
24 h HR (bpm)	43	71.3 ± 7.8	69.6 ± 11.0	0.267

	n	1st ABPM	2nd ABPM	Paired samples test
24 h SD SBP	43	15.9 ± 3.6	14.9 ± 3.9	0.111
Daytime SBP (mmHg)	43	143.4 ± 16.4	139.3 ± 14.4	**0.009**
Daytime DBP (mmHg)	43	88.4 ± 10.4	80.8 ± 10.8	**0.003**
Daytime PP (mmHg)	39	54.9 ± 13.9	54.3 ± 11.7	0.816
Daytime HR (bpm)	43	74.1 ± 8.9	72.4 ± 11.7	0.216
Daytime SD SBP	43	14.2 ± 3.8	13.5 ± 4.2	0.398
Night-Time SBP (mmHg)	43	127.7 ± 17.2	123.4 ± 16.6	0.122
Night-Time DBP (mmHg)	43	74.9 ± 10.6	69.5 ± 10.8	**0.010**
Night-Time PP (mmHg)	39	52.6 ± 13.2	53.1 ± 13.5	0.982
Night-Time SD SBP	43	13.3 ± 3.9	12.2 ± 3.5	0.378
Morning surge SBP (%)	28	24.3 ± 17.5	20.1 ± 19.7	0.502
Night-time/daytime SBP (%)	40	10.4 ± 7.2	11.1 ± 15.7	0.536
Night-time/daytime DBP (%)	37	14.6 ± 9.0	14.8 ± 8.1	0.789

ABPM – ambulatory blood pressure monitoring; DBP – diastolic blood pressure; HR – heart rate; PP – pulse pressure; SBP – systolic blood pressure; SD – standard deviation

Comparing both ABPM, 24-hour SBP and DBP, daytime SBP and DBP, and night-time DBP had significant differences. The mean values in the ABPM before the event are higher than the ABPM after the event.

We further evaluated differences between paired ABPM in the coronary event patients (Table 26) and cerebrovascular patients (Table 27). There were 21 patients with first event as coronary and 22 patients with first event as cerebrovascular.

Table 26 - Comparison between paired ABPM (before and after the event) - coronary disease patients

Coronary disease	1st ABPM	2nd ABPM	Paired Samples Test
	Mean ± SD	Mean ± SD	Wilcoxon
Office SBP (mmHg)	160.1 ± 24.1	145.4 ± 21.1	0.067
Office DBP (mmHg)	100.3 ± 13.7	87.1 ± 18.5	**0.033**
24 h SBP (mmHg)	136.6 ± 17.7	129.2 ± 10.4	**0.032**
24 h DBP (mmHg)	83.0 ±11.6	73.7 ± 7.8	**0.023**
24 h PP (mmHg)	54.6 ± 12.4	54.8 ± 12.8	0.906
24 h HR (bpm)	68.2 ± 5.2	67.3 ± 9.6	0.732
24 h SD SBP (mmHg)	16.1 ± 2.9	14.8 ± 3.3	0.079
Daytime SBP (mmHg)	142.2 ± 17.8	134.4 ± 9.9	**0.020**
Daytime DBP (mmHg)	87.9 ± 11.4	78.3 ± 9.4	**0.038**
Daytime PP (mmHg)	55.4 ± 12.5	55.2 ± 12.0	0.868

Coronary disease	1st ABPM	2nd ABPM	Paired Samples Test
Daytime HR (bpm)	71.1 ± 5.9	70.0 ± 10.5	0.668
Daytime SD SBP (mmHg)	13.6 ± 2.5	13.2 ± 2.7	0.768
Night-time SBP (mmHg)	123.3 ± 18.1	119.4 ± 15.4	0.254
Night-time DBP (mmHg)	71.7 ± 10.7	65.1 ± 7.1	**0.040**
Night-time PP (mmHg)	52.7 ± 13.5	53.8 ± 15.6	0.836
Night-time HR (bpm)	62.2 ± 4.1	62.6 ± 8.4	0.717
Night-time SD SBP (mmHg)	13.9 ± 5.0	11.9 ± 3.4	0.259
Morning surge SBP (%)	25.6 ± 10.8	26.3 ± 9.4	0.650
Night-time/daytime SBP (%)	12.6 ± 6.7	11.4 ± 8.9	0.557
Night-time/daytime DBP (%)	17.3 ± 7.0	16.8 ± 8.2	0.687

ABPM – ambulatory blood pressure monitoring; DBP – diastolic blood pressure; HR – heart rate; PP – pulse pressure; SBP – systolic blood pressure; SD – standard deviation

Table 27 - Comparison between paired ABPM (before and after the event) - cerebrovascular disease patients

Cerebrovascular disease	1ste ABPM	2nd ABPM	Paired Samples Test
	Mean ± SD	Mean ± SD	Wilcoxon
Office SBP (mmHg)	162.7 ± 25.1	144.2 ± 6.2	**0.014**
Office DBP (mmHg)	100.6 ± 13.0	87.4 ± 3.2	**0.005**
24 h SBP (mmHg)	140.7 ± 15.0	134.0 ± 3.6	0.055
24 h DBP (mmHg)	85.4 ± 9.0	79.7 ± 2.5	**0.027**
24 h PP (mmHg)	53.9 ± 14.8	53.1 ± 2.5	0.903
24 h HR (bpm)	74.1 ± 8.8	71.7 ± 2.6	0.269
24 h SD SBP (mmHg)	15.7 ± 4.2	15.0 ± 1.0	0.570
Daytime SBP (mmHg)	144.6 ± 15.4	138.1 ± 3.8	0.057
Daytime DBP (mmHg)	88.9 ± 9.7	83.2 ± 2.5	**0.029**
Daytime PP (mmHg)	54.4 ± 15.3	53.5 ± 2.6	0.767
Daytime HR (bpm)	77.0 ± 10.3	74.6 ± 2.7	0.178
Daytime SD SBP (mmHg)	14.7 ± 4.8	13.8 ± 1.1	0.426
Night-time SBP (mmHg)	131.9 ± 15.5	127.1 ± 3.7	0.338
Night-time DBP (mmHg)	77.9 ± 9.8	73.6 ± 2.6	0.150
Night-time PP (mmHg)	52.6 ± 13.2	52.4 ± 2.6	0.848
Night-time HR (bpm)	69.0 ± 8.7	66.3 ± 2.7	0.385
Night-time SD SBP (mmHg)	12.7 ± 2.4	12.5 ± 0.8	0.910

Cerebrovascular disease	1ste ABPM	2nd ABPM	Paired Samples Test
Morning surge SBP (%)	23.3 ± 22.1	14.7 ± 6.4	0.281
Night-time/daytime SBP (%)	8.6 ± 7.2	10.8 ± 4.2	0.910
Night-time/daytime DBP (%)	11.9 ± 10.0	12.9 ± 1.8	0.573

ABPM – ambulatory blood pressure monitoring; DBP – diastolic blood pressure; HR – heart rate; PP – pulse pressure; SBP – systolic blood pressure; SD – standard deviation

Overall there is a decrease in the mean values of ABPM. Significant differences are systolic and diastolic 24 hour and daytime BP in coronary, but only diastolic reached significance in cerebrovascular patients.

7 Discussion

The baseline characteristics of our population are similar to other populations of studies in secondary prediction (22)(4). The follow up has a wide range of dispersion (SD of 5.2 years, range 0.0-24.3 years), since we did not apply any criteria of timing between ABPM and event. The purpose was to study patients of daily real clinical practice and not a chosen population with several exclusion criteria and highly specific features.

Comparing the groups with and without recurrent event, there was no statistical difference concerning, age, gender, BMI, dyslipidaemia, diabetes or smoking. One reason for this lack of differentiation is that they all are high-risk patients, with established CV disease.

The population selected had a high preponderance of CV risk factors at baseline. Patients with atrial fibrillation were also included, given that some published studies comparing patients with and without atrial fibrillation did not find significant difference in both ABPM and office BP (218) suggesting that accuracy of ABPM is preserved in these patients. In addition, from the recent European ABPM guidelines there is no reason to exclude these patients from evaluation by ABPM in atrial fibrillation patients (126). Atrial fibrillation is associated with prevalence of CV disease (219). Atrial fibrillation was significantly more common in the recurrent event group, along with the use of anticoagulants. The use of anti-coagulants in the group of patients with atrial fibrillation and no recurrent event (74.2% of these were under anticoagulants) was higher than in atrial fibrillation group with event, which is likely to result in a more efficient protection to these patients. However, the atrial fibrillation prevalence increasing with age (220), could explain that in our study it occurred more often in older patients (≥ 65 years, see Table 23).

There was no difference on the use of ACE inhibitors or ARBs, statins or diuretics between the recurrent event group and the non-recurrent event. The use of anti-platelets was significantly higher in the non-recurrent event group (Table 13). Such effect may be attributed to the well-known protection of aspirin in secondary prevention of CV outcome. This difference was not seen when we divided the population by age. The patients that had a first coronary event (Table 17) kept the difference.

In our study, the baseline population had a higher proportion of coronary first events than cerebrovascular one. However, regarding recurrent events, stroke had higher prevalence than coronary events (49 versus 38). It is known that any CV event (coronary or stroke) potentiates the occurrence of a new CV event. In Portugal, however, the prevalence of stroke is higher than coronary events and the rule of probability may elicit an increase of stroke as a second event after a coronary one, given that globally the risk of stroke for the Portuguese population is higher.

7.1 Does ABPM have any predictive value for recurrent cardiovascular disease? Which ABPM variables have higher predictive value for recurrent cardiovascular events, if any?

In our population, daytime SBP significantly predicted total CV events independently from casual BP and other confounding factors and it was the most significant and consistent variable associated with increased risk of total CV events (see Table 15). Such a prediction persisted when analysed by its SD

increments and 10 mmHg increments (see Table 16). Daytime DBP showed significant predictive value for recurrent event when adjusted for office DBP and other confounding factors when evaluated as a continuous variable and by SD increment, only loosing significance when analysed by 10 mmHg. Nonetheless, daytime BP is most significant than night-time. Such data suggest that daytime SBP and DBP are the most significant variables for prediction of recurrent CV events.

In our study 24-hour SBP and 24-hour DBP are both associated with increased risk but less strongly than daytime SBP and DBP (see Table 15 and Table 16). Daytime SBP association with risk persisted through several adjustments to other variables, which did not happen with 24-h SBP and 24-hour DBP. Night-time SBP and DBP were not associated with increased risk in our population of patients with previous CV event. Since in the univariate analysis (see Table 14), night/day ratios and morning surge were not associated with risk, we did not further evaluate these with the multivariate analysis.

Night-time BP has been shown to have the highest predictive value in relation to the first CV events (7). We may speculate that any CV event introduces changes in the autonomic regulation of the circadian BP rhythm that prevent the normal manifestation the night-time BP load. Also, we cannot exclude that any more aggressive therapy introduced after the event may change the spontaneous feature of night-time BP.

To our knowledge, there are just few studies that evaluated the predictive value of ABPM for recurrent events. Fagard et al (143) performed a meta-analysis of 302 patients with established CV disease, and night-time BP was the most significant for risk prediction of CV mortality and major CV events. Night-day ratio was also predictive of outcome, which was not the case in our sample. Our population has higher prevalence of men, smoking and diabetes. Also, our sample has lower mean values of BP (for example 134 versus 144 mmHg for daytime SBP, 121 versus 133 mm for night-time SBP, respectively) which could influence the results. In other studies in patients with stroke, higher 24-hour SBP (207) and higher 24 hour SBP and DBP (210) have been associated with worst outcomes. So, the lower BP values of our population may reduce the power of night-time BP to predict recurrent events. Some studies evaluated patients with CV event by using ABPM few weeks after the event, what could also influence the results (209)(210)(216) and explained the differences versus our study.

In our cohort, the evaluation of patients with coronary event as a first event (see Table 17 and Table 18) showed significant risk of a second event associated with daytime SBP, and daytime and night-time pulse pressure. The group with recurrent event had higher values of all BP variables throughout 24 hours. A study which evaluated patients with ABPM three weeks after recent myocardial infarction found associated risk with lower levels of mean 24-hour DBP (216). In our subgroup, this was not found. The timing of performance of ABPM within 3 weeks of event may have changes related to acute changes that had not yet stabilized.

The evaluation of our subgroup of patients with cerebrovascular events (see Table 19 and Table 20), unlike other studies (207)(208)(209), did not show any association with risk of any ABPM variables. In other studies, independent risk has been associated with 24-hour SBP (6)(207) and non-dipping pattern associated with risk of stroke in stroke survivors (208). In patients with lacunar stroke, 24-hour, daytime and night-time SBP and DBP have been associated with risk of microbleeds (209), and 24-hour SBP and DBP, night-time BP and lower night-time/day ratio were associated with silent ischemic cerebral lesions and stroke (210). In our cohort we failed to reproduce these published positive significant relations. The fact that our population had a better level of BP control of that found in these studies may contribute to explain such differences between studies.

7.2 Will the limits of BP that best predict the first CV events be identical to those that predict the second events?

A growing part of the general population has survived a CV event, and the control of risk factors is then mandatory. Most recent international guidelines of arterial hypertension recommend lower BP below 130/80 mmHg to patients with coronary artery disease (126)(177)(221). The European guidelines also recommend this threshold to patients with lacunar stroke patients, preserving that the correct BP target is not certain (126). The implied measurement technique for these thresholds is office BP.

The number of studies in secondary prediction concerning the better BP threshold of risk with 24-hour BP measurement is scarce. The role of out-of-office BP in the improvement of risk stratification is still not well established, as well as the accuracy of the out-of-office BP treatment thresholds (126). This is more evident if we are referring to patients with previous CV event.

We hypothesized that the ABPM thresholds of event risk for patients with CV disease may be different from the limits of diagnosis established for patients without previous event.

In Portugal, CV diseases are the first cause of death and cerebrovascular disease has a much higher prevalence and mortality rate than cardiac ischemic disease (164).

In our study, the baseline population had a higher proportion of coronary first events than cerebrovascular (see Table 13). Regarding recurrent events, stroke had higher prevalence than coronary events (49 versus 38). Comparing the patients with and without recurrent event, there was no statistical difference in terms of age, gender, BMI, diabetes, dyslipidaemia or smoking. This could be explained by the fact that they all are high-risk patients, with previous CV event. In fact, all the population had high preponderance of CV risk factors at baseline including dyslipidaemia, which affected 85% of the patients without recurrent event and 70% of the patients with event recurrence. Also, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, statins, diuretics and anti-platelets showed no difference in prevalence between the two groups. So, all patients were heavily treated and with high CV risk at baseline.

Considering ABPM variables, SBP was significantly higher in patients with second event when comparing to the ones without second event, whether for 24-hour, daytime or night-time SBP. DBP had also significant differences between these populations, being higher in those with recurrent event. It is expected that higher burden of cardiovascular disease, namely higher blood pressure, would be associated with higher probability of event.

The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) evaluated 5682 patients without established CV disease for 9.7 years (222) and determined ABPM thresholds which corresponded to the 10-year CV risks associated with BP thresholds in guidelines of arterial hypertension. The ABPM corresponding limits for hypertension were 131.0 / 79.4 mmHg for 24-hour, 138.2 / 86.4 mmHg for daytime and 118.5 / 70.8 mmHg for night-time (222). The optimal ABP values for 24-hour, daytime and night-time were respectively 116.8 / 64.2 mmHg, 121.6 / 78.9 mmHg and 100.9 / 65.3 mmHg; for normal ABP were 123.9 / 76.8 mmHg, 129.9 / 82.6 mmHg and 110.2 / 68.1 mmHg. Authors concluded that the best threshold for optimal and normal BP was lower than the ones recommended by hypertension guidelines. The 2013 European Position Paper on ABPM raises the question whether the current thresholds apply to all ages and conditions (168).

In our cohort, the univariate cox regression analysis (Table 14), SBP was associated with increased CV risk. The tertiles analysis (Table 21) showed a clear increase in risk with increasing SBP. However, DBP

showed a tendency for increased risk with lower values (HR of 0.833 for 24 h-DBP ≥ 78 mmHg comparing to 24 h DBP ≤ 67 mmHg; similar results in daytime DBP and night-time DBP) (see Table 21). This result was not significant, but low DBP has been associated with increased CV risk (223) in other studies, namely because coronary perfusion depends on DBP, and this could be an explanation for this tendency.

In our cohort, the better threshold for prediction of increased recurrent event risk is lower than the current guidelines limits. For 24-hour SBP the value was 125 mmHg, for daytime SBP was 131 mmHg and for night-time SBP was 112 mmHg. The Kaplan Meier survival curves (see The survival curve of patients divided by mean 24-hour SBP < 130 mmHg and ≥ 130 mmHg, daytime < 135 mmHg and ≥ 135 mmHg and night-time < 120 mmHg and ≥ 120 mmHg, had respectively log-ranks of 0.093, 0.138 and 0.411. The survival curves using the thresholds of 125 mmHg for 24-hour SBP and 131 mmHg for daytime SBP showed a log-rank of 0.004 and 0.007, respectively.

Figure 4) showed a significant increase in years free of event for patients with mean 24-hour SBP < 125 mmHg. The survival curve using the threshold of the guidelines (130 mmHg) was not significant. The daytime SBP showed the same difference in the survival curves (131 mmHg versus 135 mmHg). Night-time survival curve did not show statistical significance both with the 120 or 112 mmHg values. This suggests that there is a better cut-off for prediction of risk at lower levels of BP than the ones established for treatment. The multivariate Cox regression (Table 22) also presented a significant increase for CV events with the thresholds of 125 and 131 mmHg, in comparison with 130mmHg and 135 mmHg (24-hour SBP and daytime SBP, respectively). In patients with previous CV event heavily treated and highly controlled, a significant prediction of risk may be attainable at lower values. Also, a decay in the general conditions, associated a multiple risk factors and high burden of disease, could influence a decrease in BP.

Several studies have found a decrease of CV events with the lowering of BP below the established thresholds (224)(128). Recent European hypertension guidelines have decreased the threshold for treatment for patients with previous stroke or ischemic heart disease (126). A recent meta-analysis concerning 26863 patients with very high-risk by symptomatic CV disease found benefit in reducing BP even in the normotensive individuals (225). This was found mainly by stroke reduction, independently of the drug class used. In populations with high prevalence and mortality by stroke, this could indicate a possible change in BP limits for starting medication. To the best of our knowledge, there is no prior study with ABPM in patients with previous CV events evaluating the best cut-off for risk prediction. Our findings are in line with published studies using office BP.

Finally, low DBP (<70 mmHg) has been associated with higher CV event risk (226)(227), particularly for patients with coronary heart disease (223). However, stroke does not seem to increase with low DBP (228)(229). This points for different levels of target organ by low DBP, or to different mechanisms and higher cerebroprotection towards low BP (224). Some argue that lower BP targets than the ones established currently could not be of benefit for all patients of high risk, except perhaps for populations at high risk, with a high prevalence of stroke (230).

7.3 ABPM prediction values for recurrent cardiovascular events are they different between distinct age groups?

Several features associated with age may enable differences in BP regulation. Younger people are more physically active than older patients (231) and changes in the circadian pattern are important in

elderly (232) Some studies have addressed changes in ABPM values in different ages (231) and in the elderly (232). We evaluated if ABPM predictive value is different according to age. The choice of the cut-off value was driven by the value of median (65 years) of our sample. It is also the value for which the World Health Organization marks the threshold of the old age.

In our population, the patients under 65 years had higher prevalence of CV risk factors than the older patients: male gender (79.9% versus 66.5%), BMI (28.9% versus 27.8%) and smoking (27.9% versus 11.8%). Use of statins (78.2% versus 90.1%), dyslipidaemia (74.3% versus 87.3%) and atrial fibrillation (6.7% versus 15.5%) had a significant higher prevalence in the older group (see Table 23). The group < 65 years old had a higher 24 hours, daytime and night-time DBP and a smaller pulse pressure when compared to the group ≥ 65 years old. DBP usually increases with aging until the fifth decade and starts to decay from the sixth decade forward until at least 84 years old (233).

We used univariate and multivariate Cox regression to evaluate the possible risk of total CV events. Table 24 shows the HR of the relationship between ABPM variables and outcome. In the group < 65 years, the 24-hour, daytime and night-time SBP and DBP were significantly associated with risk of CV events, in multiple adjusted model. The differences in comorbidities between the groups could have an influence in these results, although the multivariate analysis was adjusted for several of them. Also, there was a difference in mean DBP value between them, but more importantly the mean BP values of the patients < 65 years with recurrent event were significantly higher than those with no recurrent event. In the group of patients ≥ 65 years, there was no significant difference between the BP values of those with and without event. The higher values of BP in the younger patients could provide a higher CV risk for recurrent event, and this could also influence our results. Since age is one of the most powerful risk factors which increases known CV risk scores (19)(20), this could lead to a devaluating of risk in the younger patients, and by addition a decreasing in intensive therapy.

In the group ≥ 65 years, diastolic night-time/day ratio was significantly associated with higher risk (see Table 24). Although systolic night-time/day ratio hazard ratio was also high, it did not reached statistically significance. The median diastolic night-time/day ratio of the elderly group was of 13.0 mmHg (see Table 24) and was associated with higher CV risk (176). Although the value of the group < 65 years old is also high (12.7 mmHg), older people are much more susceptible to high BP dipping, increasing risk (234), as described previously.

7.4 How far and how much does ABPM data change at before and after the event?

In our cohort, 43 patients had ABPM from before and after the event. We performed the comparison between paired ABPM to address possible changes over time.

These 43 patients had a lower median age than the total cohort (61.9 ± 9.7 versus 65.9 ± 10.4), a lower proportion of men (60.5% versus 72.6%), lower proportion of diabetics (34.9% versus 37.6%), of patients with smoking habits (5.7% versus 19.2%) and a lower use of statins (74.4% versus 91.4%). The mean follow-up between first ABPM and the first event was 6.5 ± 4.6 years, and the mean follow up between the first event and the second ABPM was 2.7 ± 2.0 years.

The comparison of 43 paired ABPM between before and after the event showed a significant decrease of BP mean values in the ABPM after the first event (see Table 25): 24-hour SBP and DBP, daytime SBP and DBP, and night-time DBP. This could be explained by a better risk control after the event with an increase in therapy leading to a better control of BP.

From this subgroup, we further analysed the patients with coronary events and with stroke. In the patients with coronary events, there was a significant decrease in 24-hour SBP and DBP, daytime SBP and DBP, night-time DBP. Intensive therapy after the event and control of risk factors may be the main reasons for these changes. In the stroke patients, only 24-hour DBP and daytime DBP decreased significantly.

To the best of our knowledge, this is the first Portuguese study that evaluated paired ABPM from before and after a CV event. We observed a decrease in all variables, which could be a consequence of more rigorous therapy from event, a higher adherence to therapy. Also, reverse causality should be bear in mind in patients with high burden of disease. Older age, end organ damage like heart failure or general frailty could be part of an overall poor health status, in which low systolic or diastolic blood pressure may be a consequence of the disease and not the cause (235).

There are limitations to this study. This study evaluated patients of daily clinical practice. The purpose was to study patients of daily real clinical practice and not a chosen population with several exclusion criteria and highly specific features. This implies a poor control over several conditions that interfere in the results. It is an observational study, with lack of control of several confounders, including comorbidities through follow-up. Management of medication through follow-up was not considered and it could interfere with outcome. The ABPM date in relation to first event is not homogeneous among our population, adding to the problem of ABPM reproducibility. The limited number of recurrent strokes (in patients with previous stroke) prevented further analysis.

8 Conclusion

8.1 Overall conclusions

Just a few published studies evaluated the predictive value of ABPM for the occurrence of CV events after a previous event. Our study aimed at bringing new contributions to the field.

- We found that ABPM clearly have a strong predictive value for recurrent CV disease and that among all ABPM data, the daytime SBP and daytime DBP had the highest predictive value for recurrent CV events. In our population with well controlled BP and heavily treated, daytime BP may become more relevant and less modifiable by other influences on circadian control of BP.
- We found that the ABPM limits that predict the second events are much lower than those predicting first events which may be related with more aggressive treatments and more vulnerable general conditions.
- We found that ABPM has a stronger prediction value for recurrent CV events in patients < 65 old when comparing to patients ≥ 65 years old. This predictive value is associated to 24-hour systolic and diastolic BP and to pulse pressure. In our population of high-risk, higher prevalence of comorbidities and less intensity of treatment in younger patients with previous event may be related to higher values of BP and increased ABPM predictive value.
- We found that the main changes in ABPM from before to after the event, in our population, was a decrease in BP values globally. This decrease was more evident in coronary patients than in stroke patients. Increased therapy and control of risk factors may have a huge influence in these results.

8.2 Future directions

The work we present here is a modest contribution to address the existing research gap with respect to the role of ABPM-related variables in the prediction of cardiovascular events in the long-term, for patients that already suffered from a previous event.

Although our findings offer relevant insights for the Portuguese population, the work is certainly not concluded. The research will benefit from a larger sample population and addition control of confounding factors. The number of patients in each event group would need to increase to understand whether the ABPM alterations are caused by a type of event or concerns the entire cardiovascular spectrum.

It was our believing, at the beginning of the thesis project, that the field requires additional research; after this work, our conviction is even stronger. We heartily support the need for randomized, prospective studies with sound methodological approaches to further investigate the promising role of ABPM in secondary event prediction.

9 References

1. Wilson E, Wilson L, Wickramasinghe K, et al. European Cardiovascular Disease Statistics 2017. Brussels; 2017.
2. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. Circulation. 2018 Mar 20;137(12):e67–492.
3. Teo KK, Dokainish H. The Emerging Epidemic of Cardiovascular Risk Factors and Atherosclerotic Disease in Developing Countries. Can J Cardiol. 2017 Mar;33(3):358–65.
4. Beatty AL, Ku IA, Bibbins-Domingo K, et al. Traditional Risk Factors Versus Biomarkers for Prediction of Secondary Events in Patients With Stable Coronary Heart Disease: From the Heart and Soul Study. J Am Heart Assoc. 2015 Jul 6;4(7):e001646.
5. Lindholm D, Lindbäck J, Armstrong PW, et al. Biomarker-Based Risk Model to Predict Cardiovascular Mortality in Patients With Stable Coronary Disease. J Am Coll Cardiol. 2017 Aug 15;70(7):813–26.
6. Castilla-Guerra L, Fernandez-Moreno MDC. Chronic Management of Hypertension after Stroke: The Role of Ambulatory Blood Pressure Monitoring. J stroke. 2016 Jan 31;18(1):31–7.
7. Mesquita-Bastos J, Bertoquini S, Polónia J. Cardiovascular prognostic value of ambulatory blood pressure monitoring in a Portuguese hypertensive population followed up for 8.2 years. Blood Press Monit. 2010 Oct;15(5):240–6.
8. Bastos JM, Bertoquini S, Polónia J. Prognostic value of subdivisions of nighttime blood pressure fall in hypertensives followed up for 8.2 years. Does nondipping classification need to be redefined? J Clin Hypertens (Greenwich). 2010 Jul 1;12(7):508–15.
9. Bastos JM, Bertoquini S, Polónia J. Prognostic significance of ambulatory arterial stiffness index in hypertensives followed for 8.2 years: its relation with new events and cardiovascular risk estimation. Rev Port Cardiol. 2010 Sep;29(9):1287–303.
10. European Cardiovascular Disease Statistics 2017 edition.
11. Nissen SE. Effect of intensive lipid lowering on progression of coronary atherosclerosis: evidence for an early benefit from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. Am J Cardiol. 2005 Sep 5;96(5A):61F–68F.
12. Betancourt M, Van Stavern RB, Share D, et al. Are patients receiving maximal medical therapy following carotid endarterectomy? Neurology. 2004 Dec 14;63(11):2011–5.
13. Appel LJ, Wright JT, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010 Sep 2;363(10):918–29.
14. Wilson PWF, D'Agostino R, Bhatt DL, et al. An international model to predict recurrent cardiovascular disease. Am J Med. 2012;125:695–703.e1.
15. Dorresteijn JAN, Visseren FLJ, Wassink AMJ, et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart. 2013;12(99):866–72.
16. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by re. Eur Heart J. 2012 Jul;33(13):1635–701.
17. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2016 Jul 27;23(11):NP1-NP96.

18. Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. J Am Coll Cardiol. 2014 Jul 1;63(25):2935–59.

19. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003 Jun;24(11):987–1003.

20. D'Agostino RB, Vasan RS, Pencina MJ, et al. General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743–53.

21. Hippisley-Cox J, Coupland C, Robson J, et al. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ. 2010 Jan;341:c6624.

22. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative Determinants of 4-Year Cardiovascular Event Rates in Stable Outpatients at Risk of or With Atherothrombosis. JAMA. 2010 Sep 22;304(12):1350.

23. Bonaca MP, Bhatt DL, Cohen M, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. N Engl J Med. 2015 May 7;372(19):1791–800.

24. Bergeron N, Phan BAP, Ding Y, et al. Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition. Circulation. 2015 Oct 27;132(17):1648–66.

25. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction. N Engl J Med. 2002 Mar 21;346(12):877–83.

26. Bohula EA, Bonaca MP, Braunwald E, et al. Atherothrombotic Risk Stratification and the Efficacy and Safety of Vorapaxar in Patients With Stable Ischemic Heart Disease and Previous Myocardial Infarction. Circulation. 2016 Jul 26;134(4):304–13.

27. Weimar C, Benemann J, Michalski D, et al. Prediction of recurrent stroke and vascular death in patients with transient ischemic attack or nondisabling stroke: a prospective comparison of validated prognostic scores. Stroke. 2010;41:487–93.

28. Stahrenberg R, Niehaus C-F, Edelmann F, et al. High-sensitivity troponin assay improves prediction of cardiovascular risk in patients with cerebral ischaemia. J Neurol Neurosurg Psychiatry. 2013 May;84(5):479–87.

29. Ohman EM, Bhatt DL, Steg PG, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. Am Heart J. 2006 Apr;151(4):786.e1-10.

30. Simons PC, Algra A, Van De Laak MF, et al. Second manifestations of ARTerial disease (SMART) study: rationale and design. Eur J Epidemiol. 1999 Oct;15(9):773–81.

31. D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham study. Am Heart J. 2000 Feb;139(2 Pt 1):272–81.

32. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. 2007 Feb 14;297(6):611–9.

33. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998 May 12;97(18):1837–47.

34. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. Circulation. 2008 Nov 25;118(22):2243–51, 4p following 2251.

35. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. Circulation. 2002 Jan 22;105(3):310–5.

36. Moons KGM, Kengne AP, Woodward M, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012 May;98(9):683–90.

37. Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: Prognostic Factor Research. PLoS Med. 2013 Feb 5;10(2):e1001380.

38. Moons KGM, de Groot JAH, Bouwmeester W, et al. Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies: The CHARMS Checklist. PLoS Med. 2014 Oct 14;11(10):e1001744.

39. Tang EW, Wong C-K, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. Am Heart J. 2007 Jan;153(1):29–35.

40. Fox KAA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J. 2010 Nov 2;31(22):2755–64.

41. Truong QA, Cannon CP, Zakai NA, et al. Thrombolysis in Myocardial Infarction (TIMI) Risk Index predicts long-term mortality and heart failure in patients with ST-elevation myocardial infarction in the TIMI 2 clinical trial. Am Heart J. 2009 Apr;157(4):673–9.e1.

42. Plakht Y, Shiyovich A, Weitzman S, et al. Soroka acute myocardial infarction (SAMI) score predicting 10-year mortality following acute myocardial infarction. Int J Cardiol. 2013 Sep 10;167(6):3068–70.

43. Papavasileiou V, Milionis H, Michel P, et al. ASTRAL score predicts 5-year dependence and mortality in acute ischemic stroke. Stroke. 2013 Jun 1;44(6):1616–20.

44. Andersen SD, Gorst-Rasmussen A, Lip GYH, et al. Recurrent Stroke. Stroke. 2015 Sep;46(9):2491–7.

45. Lau KK, Li L, Schulz U, et al. Total small vessel disease score and risk of recurrent stroke. Neurology. 2017 Jun 13;88(24):2260–7.

46. Uthoff H, Staub D, Socrates T, et al. PROCAM-, FRAMINGHAM-, SCORE- and SMART-risk score for predicting cardiovascular morbidity and mortality in patients with overt atherosclerosis. VASA. 2010;39:325–33.

47. van den Berg MJ, Bhatt DL, Kappelle LJ, et al. Identification of vascular patients at very high risk for recurrent cardiovascular events: validation of the current ACC/AHA very high risk criteria. Eur Heart J. 2017 Nov 14;38(43):3211–8.

48. Fox KAA, Fitzgerald G, Puymirat E, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. BMJ Open. 2014 Feb 21;4(2):e004425.

49. Ingle L, Carroll S, Stamatakis E, et al. Benefit of adding lifestyle-related risk factors for prediction of cardiovascular death among cardiac patients. Int J Cardiol. 2013 Feb 20;163(2):196–200.

50. Rizza S, Copetti M, Cardellini M, et al. A score including ADAM17 substrates correlates to recurring cardiovascular event in subjects with atherosclerosis. Atherosclerosis. 2015 Apr;239(2):459–64.

51. Ganz P, Heidecker B, Hveem K, et al. Development and Validation of a Protein-Based Risk Score for Cardiovascular Outcomes Among Patients With Stable Coronary Heart Disease. JAMA. 2016 Jun 21;315(23):2532–41.

52. Goliasch G, Kleber ME, Richter B, et al. Routinely available biomarkers improve prediction of long-term mortality in stable coronary artery disease: the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score. Eur Heart J. 2012 Sep 2;33(18):2282–9.

53. Plakht Y, Shiyovich A, Weitzman S, et al. A new risk score predicting 1- and 5-year mortality following acute myocardial infarction Soroka Acute Myocardial Infarction (SAMI) Project. Int J Cardiol. 2012 Jan 26;154(2):173–9.

54. Marchioli R, Avanzini F, Barzi F, et al. Assessment of absolute risk of death after myocardial infarction by use of multiple-risk-factor assessment equations: GISSI-Prevenzione mortality risk chart. Eur Heart J. 2001 Nov 15;22(22):2085–103.

55. Battes L, Barendse R, Steyerberg EW, et al. Development and Validation of a Cardiovascular Risk Assessment Model in Patients With Established Coronary Artery Disease. Am J Cardiol. 2013;112(1):27–33.

56. Kleber ME, Goliasch G, Grammer TB, et al. Evolving biomarkers improve prediction of long-term mortality in patients with stable coronary artery disease: the BIO-VILCAD score. J Intern Med. 2014 Aug;276(2):184–94.

57. Marschner IC, Colquhoun D, Simes RJ, et al. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. LIPID Study Investigators. J Am Coll Cardiol. 2001 Jul;38(1):56–63.

58. Sprengers RW, Janssen KJM, Moll FL, et al. Prediction rule for cardiovascular events and mortality in peripheral arterial disease patients: data from the prospective Second Manifestations of ARTerial disease (SMART) cohort study. J Vasc Surg. 2009;50:1369–76.

59. Tragante V, Doevendans PAFM, Nathoe HM, et al. The impact of susceptibility loci for coronary artery disease on other vascular domains and recurrence risk. Eur Heart J. 2013 Oct 1;34(37):2896–904.

60. De Bacquer D, Dallongeville J, Kotseva K, et al. Residual risk of cardiovascular mortality in patients with coronary heart disease: the EUROASPIRE risk categories. Int J Cardiol. 2013 Sep 30;168(2):910–4.

61. Deckers JW, Goedhart DM, Boersma E, et al. Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk. Eur Heart J. 2006 Apr 1;27(7):796–801.

62. Blankenberg S, McQueen MJ, Smieja M, et al. Comparative impact of multiple biomarkers and N-Terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. Circulation. 2006 Jul 18;114(3):201–8.

63. Mega JL, Stitziel NO, Smith JG, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet. 2015 Jun 6;385(9984):2264–71.

64. Vaara S, Tikkanen E, Parkkonen O, et al. Genetic Risk Scores Predict Recurrence of Acute Coronary SyndromeCLINICAL PERSPECTIVE. Circ Cardiovasc Genet. 2016 Apr;9(2):172–8.

65. Wassink AM, van der Graaf Y, Janssen KJ, et al. Prediction model with metabolic syndrome to predict recurrent vascular events in patients with clinically manifest vascular diseases. Eur J Prev Cardiol. 2012 Dec 18;19(6):1486–95.

66. Plakht Y, Shiyovich A, Gilutz H. Predictors of long-term (10-year) mortality postmyocardial infarction: age-related differences. Soroka Acute Myocardial Infarction (SAMI) Project. J Cardiol. 2015 Mar;65(3):216–23.

67. Clayton TC, Lubsen J, Pocock SJ, et al. Risk score for predicting death, myocardial infarction, and stroke in patients with stable angina, based on a large randomised trial cohort of patients. BMJ. 2005 Oct 15;331(7521):869.

68. Chen Q, Ding D, Zhang Y, et al. Prediction of the risk of mortality using risk score in patients with coronary heart disease. Oncotarget. 2016 Dec 6;7(49):81680–90.

69. Atwater BD, Thompson VP, Vest RN, et al. Usefulness of the Duke Sudden Cardiac Death risk score for predicting sudden cardiac death in patients with angiographic (>75% narrowing) coronary artery disease. Am J Cardiol. 2009 Dec 15;104(12):1624–30.

70. Hsia J, Jablonski KA, Rice MM, et al. Sudden Cardiac Death in Patients With Stable Coronary Artery Disease and Preserved Left Ventricular Systolic Function. Am J Cardiol. 2008 Feb 15;101(4):457–61.

71. Cui J, Forbes A, Kirby A, et al. Laboratory and non-laboratory-based risk prediction models for secondary prevention of cardiovascular disease: the LIPID study. Eur J Cardiovasc Prev Rehabil. 2009 Dec;16(6):660–8.

72. Rapsomaniki E, Shah A, Perel P, et al. Prognostic models for stable coronary artery disease based on electronic health record cohort of 102 023 patients. Eur Heart J. 2014 Apr 1;35(13):844–52.

73. Cui J, Forbes A, Kirby A, et al. Semi-parametric risk prediction models for recurrent cardiovascular events in the LIPID study. BMC Med Res Methodol. 2010 Apr 1;10(1):27.

74. van Peet PG, Drewes YM, de Craen AJM, et al. NT-proBNP best predictor of cardiovascular events and cardiovascular mortality in secondary prevention in very old age: the Leiden 85-plus Study. Sen U, editor. PLoS One. 2013 Nov 21;8(11):e81400.

75. Damen JAAG, Hooft L, Schuit E, et al. Prediction models for cardiovascular disease risk in the general population: systematic review. BMJ. 2016 May 16;353:i2416.

76. Fahey M, Crayton E, Wolfe C, et al. Clinical prediction models for mortality and functional outcome following ischemic stroke: A systematic review and meta-analysis. Quinn TJ, editor. PLoS One. 2018 Jan 29;13(1):e0185402.

77. Debray TPA, Damen JAAG, Snell KIE, et al. A guide to systematic review and meta-analysis of prediction model performance. BMJ. 2017 Jan 5;356:i6460.

78. Steyerberg EW, Moons KGM, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. PLoS Med. 2013 Feb 5;10(2):e1001381.

79. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement. Ann Intern Med. 2015 Jan 6;162(1):55.

80. Poppe KK, Doughty RN, Wells S, et al. Developing and validating a cardiovascular risk score for patients in the community with prior cardiovascular disease. Heart. 2017 Jun;103(12):891–2.

81. Singh M, Reeder GS, Jacobsen SJ, et al. Scores for post-myocardial infarction risk stratification in the community. Circulation. 2002 Oct 29;106(18):2309–14.

82. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004;291:2727–33.

83. Anderson JL. Improving secondary cardiovascular risk prediction: taking a few steps along the long path from probability toward certainty. Eur Heart J. 2017 Nov 14;38(43):3219–21.

84. Singh M, Holmes DR, Lennon RJ, et al. Development and validation of risk adjustment models for long-term mortality and myocardial infarction following percutaneous coronary interventions. Circ Cardiovasc Interv. 2010 Oct 1;3(5):423–30.

85. Redon J. Global Cardiovascular Risk Assessment: Strengths and Limitations. High Blood Press Cardiovasc Prev. 2016 Jun 18;23(2):87–90.

86. Bavry AA, Kumbhani DJ, Gong Y, et al. Simple integer risk score to determine prognosis of patients with hypertension and chronic stable coronary artery disease. J Am Heart Assoc. 2013 Aug 15;2(4):e000205.

87. Levine GN, Jeong Y-H, Goto S, et al. World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol. 2014 Oct 26;11(10):597–606.

88. Liew SM, Doust J, Glasziou P. Cardiovascular risk scores do not account for the effect of treatment: a review. Heart. 2011 May 1;97(9):689–97.

89. Anavekar NS, McMurray JJV, Velazquez EJ, et al. Relation between Renal Dysfunction and Cardiovascular Outcomes after Myocardial Infarction. N Engl J Med. 2004 Sep 23;351(13):1285–95.

90. Hasin T, Sorkin A, Markiewicz W, et al. Prevalence and prognostic significance of transient, persistent, and new-onset anemia after acute myocardial infarction. Am J Cardiol. 2009 Aug 15;104(4):486–91.

91. Andell P, Koul S, Martinsson A, et al. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. Open Hear. 2014 Feb 3;1(1):e000002.

92. Bursi F, Vassallo R, Weston SA, et al. Chronic obstructive pulmonary disease after myocardial infarction in the community. Am Heart J. 2010 Jul;160(1):95–101.

93. Rothnie KJ, Yan R, Smeeth L, et al. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. BMJ Open. 2015 Sep 11;5(9):e007824.

94. Rothnie KJ, Smeeth L, Pearce N, et al. Predicting mortality after acute coronary syndromes in people with chronic obstructive pulmonary disease. Heart. 2016 Sep 15;102(18):1442–8.

95. Pocock SJ, Huo Y, Van de Werf F, et al. Predicting two-year mortality from discharge after acute coronary syndrome: An internationally-based risk score. Eur Hear journal Acute Cardiovasc care. 2017 Aug 1;2048872617719638.

96. Concato J, Peduzzi P, Holford TR, et al. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. J Clin Epidemiol. 1995 Dec;48(12):1495–501.

97. Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol. 1995 Dec;48(12):1503–10.

98. Pencina MJ, D'Agostino RB, D'Agostino RB, et al. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med. 2008 Jan 30;27(2):157–72.

99. Ahmed I, Debray TPA, Moons KGM, et al. Developing and validating risk prediction models in an individual participant data meta-analysis. BMC Med Res Methodol. 2014 Jan 8;14(1):3.

100. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of Hospital Mortality in the Global Registry of Acute Coronary Events. Arch Intern Med. 2003 Oct 27;163(19):2345.

101. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Circulation. 2014 Jun 24;129(25 suppl 2):S1–45.

102. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2011 Update. J Am Coll Cardiol. 2011 Nov 29;58(23):2432–46.

103. Antoni ML, Hoogslag GE, Boden H, et al. Cardiovascular mortality and heart failure risk score for patients after ST-segment elevation acute myocardial infarction treated with primary percutaneous coronary intervention (Data from the Leiden MISSION! Infarct Registry). Am J Cardiol. 2012 Jan 15;109(2):187–94.

104. Sabatine MS, Morrow DA, de Lemos JA, et al. Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. Circulation. 2012 Jan 17;125(2):233–40.

105. Kragelund C, Grønning B, Køber L, et al. N-Terminal Pro–B-Type Natriuretic Peptide and Long-Term Mortality in Stable Coronary Heart Disease. N Engl J Med. 2005 Feb 17;352(7):666–75.

106. Sabatine MS, Morrow DA, Jablonski KA, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation. 2007 Mar 27;115(12):1528–36.

107. Omland T, de Lemos JA, Sabatine MS, et al. A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease. N Engl J Med. 2009 Dec 24;361(26):2538–47.

108. Solomon SD, Lin J, Solomon CG, et al. Influence of albuminuria on cardiovascular risk in patients with stable coronary artery disease. Circulation. 2007 Dec 4;116(23):2687–93.

109. Steg PG, Bhatt DL, Wilson PWF, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA. 2007 Mar 21;297(11):1197–206.

110. Hemingway H, Riley RD, Altman DG. Ten steps towards improving prognosis research. BMJ. 2009 Dec 30;339(dec30 1):b4184–b4184.

111. Sabatine MS. Using Aptamer-Based Technology to Probe the Plasma Proteome for Cardiovascular Disease Prediction. JAMA. 2016 Jun 21;315(23):2525–6.

112. Samani NJ, Erdmann J, Hall AS, et al. Genomewide Association Analysis of Coronary Artery Disease. N Engl J Med. 2007 Aug 2;357(5):443–53.

113. Coronary Artery Disease (C4D) Genetics Consortium JF, Hopewell JC, Saleheen D, et al. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. Nat Genet. 2011 Mar 6;43(4):339–44.

114. Deloukas P, Kanoni S, Willenborg C, et al. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet. 2013 Jan 2;45(1):25–33.

115. Moscucci M, Kline-Rogers E, Share D, et al. Simple bedside additive tool for prediction of in-hospital mortality after percutaneous coronary interventions. Circulation. 2001 Jul 17;104(3):263–8.

116. Carro A, Kaski JC. Myocardial infarction in the elderly. Aging Dis. 2011 Apr;2(2):116–37.

117. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. JAMA. 2011 Feb 23;305(8):822–3.

118. Christiansen SC, Cannegieter SC, Koster T, et al. Thrombophilia, Clinical Factors, and Recurrent Venous Thrombotic Events. JAMA. 2005 May 18;293(19):2352.

119. Barbash GI, Reiner J, White HD, et al. Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol. 1995 Nov 1;26(5):1222–9.

120. Rich JD, Cannon CP, Murphy SA, et al. Prior Aspirin Use and Outcomes in Acute Coronary Syndromes. J Am Coll Cardiol. 2010 Oct 19;56(17):1376–85.

121. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? J Am Coll Cardiol. 2002 Feb 20;39(4):578–84.

122. Smits LJM, van Kuijk SMJ, Leffers P, et al. Index event bias-a numerical example. J Clin Epidemiol. 2013 Feb;66(2):192–6.

123. Wessler BS, Lai YH L, Kramer W, et al. Clinical Prediction Models for Cardiovascular Disease. Circ Cardiovasc Qual Outcomes. 2015 Jul;8(4):368–75.

124. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med. 1989 Aug 10;321(6):406–12.

125. Grant A, Treweek S, Wells M. Why is so much clinical research ignored and what can we do about it? Br J Hosp Med. 2016 Oct;77(Sup10):554–5.

126. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. J Hypertens. 2018 Oct;36(10):1953–2041.

127. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA - J Am Med Assoc. 2014;311(5):507–20.

128. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. J Hypertens. 2014 Dec;32(12):2285–95.

129. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. Br Med Bull. 1994 Apr;50(2):272–98.

130. Brunström M, Carlberg B. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels. JAMA Intern Med. 2018 Jan 1;178(1):28.

131. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339:b2535.

132. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006 Mar 21;144(6):427–37.

133. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing Bias in Studies of Prognostic Factors. Ann Intern Med. 2013 Feb 19;158(4):280.

134. Bangalore S, Fayyad R, Messerli FH, et al. Relation of Variability of Low-Density Lipoprotein Cholesterol and Blood Pressure to Events in Patients With Previous Myocardial Infarction from the IDEAL Trial. Am J Cardiol. 2017 Feb 1;119(3):379–87.

135. Schmidt LB, Goertz S, Wohlfahrt J, et al. Recurrent Intracerebral Hemorrhage: Associations with Comorbidities and Medicine with Antithrombotic Effects. Baron J-C, editor. PLoS One. 2016 Nov 10;11(11):e0166223.

136. Hayden DT, Hannon N, Callaly E, et al. Rates and Determinants of 5-Year Outcomes After Atrial Fibrillation-Related Stroke: A Population Study. Stroke. 2015 Dec;46(12):3488–93.

137. Kielbergerová L, Mayer O, Vaněk J, et al. Quality of life predictors in chronic stable post-stroke patients and prognostic value of SF-36 score as a mortality surrogate. Transl Stroke Res. 2015 Oct 15;6(5):375–83.

138. Lau K-K, Wong Y-K, Teo K-C, et al. Long-term prognostic implications of visit-to-visit blood pressure variability in patients with ischemic stroke. Am J Hypertens. 2014 Dec 1;27(12):1486–94.

139. Williams WT, Assi R, Hall MR, et al. Metabolic syndrome predicts restenosis after carotid endarterectomy. J Am Coll Surg. 2014 Oct;219(4):771–7.

140. Konishi H, Miyauchi K, Kasai T, et al. Long-term prognosis and clinical characteristics of young adults (≤40 years old) who underwent percutaneous coronary intervention. J Cardiol. 2014 Sep;64(3):171–4.

141. Park J-H, Lee H-S, Kim JH, et al. Reverse dipper and high night-time heart rate in acute stage of cerebral infarction are associated with increased mortality. J Stroke Cerebrovasc Dis. 2014 May;23(5):1171–6.

142. Lau KK, Wong YK, Chang RSK, et al. Visit-to-visit systolic blood pressure variability predicts all-cause and cardiovascular mortality after lacunar infarct. Eur J Neurol. 2014 Feb;21(2):319–25.

143. Fagard RH, Thijs L, Staessen JA, et al. Prognostic significance of ambulatory blood pressure in hypertensive patients with history of cardiovascular disease. Blood Press Monit. 2008;13:325–32.

144. Kaplan RC, Tirschwell DL, Longstreth WT, et al. Blood pressure level and outcomes in adults aged 65 and older with prior ischemic stroke. J Am Geriatr Soc. 2006 Sep;54(9):1309–16.

145. Kammersgaard LP, Olsen TS. Cardiovascular Risk Factors and 5-Year Mortality in the Copenhagen Stroke Study. Cerebrovasc Dis. 2006;21(3):187–93.

146. Mason PJ, Manson JE, Sesso HD, et al. Blood Pressure and Risk of Secondary Cardiovascular Events in Women. Circulation. 2004 Apr 6;109(13):1623–9.

147. Staaf G, Lindgren A, Norrving B. Pure motor stroke from presumed lacunar infarct: long-term prognosis for survival and risk of recurrent stroke. Stroke. 2001 Nov;32(11):2592–6.

148. Herlitz J, Bång A, Karlson BW. Five-year prognosis after acute myocardial infarction in relation to a history of hypertension. Am J Hypertens. 1996 Jan;9(1):70–6.

149. Berger CJ, Murabito JM, Evans JC, et al. Prognosis after first myocardial infarction. Comparison of Q-wave and non-Q-wave myocardial infarction in the Framingham Heart Study. JAMA. 268(12):1545–51.

150. Blood pressure in survivors of myocardial infarction. The Coronary Drug Project Research Group. J Am Coll Cardiol. 1984 Dec;4(6):1135–47.

151. West MJ, White HD, Simes RJ, et al. Risk factors for non-haemorrhagic stroke in patients with coronary heart disease and the effect of lipid-modifying therapy with pravastatin. J Hypertens. 2002 Dec;20(12):2513–7.

152. Wilhelmsen L, Pyörälä K, Wedel H, et al. Risk factors for a major coronary event after myocardial infarction in the Scandinavian Simvastatin Survival Study (4S). Impact of predicted risk on the benefit of cholesterol-lowering treatment. Eur Heart J. 2001 Jul 1;22(13):1119–27.

153. Zonneveld TP, Richard E, Vergouwen M DI, et al. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. Cochrane Database Syst Rev. 2018 Jul 19;7:CD007858.

154. Katsanos AH, Filippatou A, Manios E, et al. Blood Pressure Reduction and Secondary Stroke Prevention. Hypertension. 2017 Jan;69(1):171–9.

155. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation. 2016 Nov 8;134(19):1419–29.

156. Stergiou GS, Parati G, Mcmanus RJ, et al. Guidelines for blood pressure measurement: development over 30 years. J Clin Hypertens. 2018;20:1089–91.

157. Friday G, Alter M, Lai S-M. Control of hypertension and risk of stroke recurrence. Stroke. 2002 Nov;33(11):2652–7.

158. Fadl YY, Zareba W, Moss AJ, et al. History of hypertension and enhanced thrombogenic activity in postinfarction patients. Hypertens (Dallas, Tex 1979). 2003 Apr;41(4):943–9.

159. Ezzati M, Lopez AD, Rodgers A, et al. Selected major risk factors and global and regional burden of disease. Lancet. 2002 Nov 2;360(9343):1347–60.

160. Forouzanfar MH, Liu P, Roth GA, et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. JAMA. 2017 Jan 10;317(2):165–82.

161. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet (London, England). 2002 Dec 14;360(9349):1903–13.

162. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet (London, England). 2016 Aug 20;388(10046):761–75.

163. Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep;364(9438):937–52.

164. Direção Geral de Saúde. Programa Nacional para as Doenças Cérebro-Cardiovasculares. Saúde em Números. Portugal; 2017.

165. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet (London, England). 1990 Apr 7;335(8693):827–38.

166. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009 May 19;338(may19 1):b1665–b1665.

167. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. N Engl J Med. 2006 Jun 1;354(22):2368–74.

168. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring. J Hypertens. 2013 Sep;31(9):1731–68.

169. Armitage P, Fox W, Rose GA, et al. The variability of measurements of casual blood pressure. II. Survey experience. Clin Sci. 1966 Apr;30(2):337–44.

170. O'Brien E, Dolan E. Ambulatory Blood Pressure Monitoring for the Effective Management of Antihypertensive Drug Treatment. Clin Ther. 2016 Oct;38(10):2142–51.

171. O'Brien E, White WB, Parati G, et al. Ambulatory blood pressure monitoring in the 21st century. J Clin Hypertens. 2018 Jul;20(7):1108–11.

172. Gaborieau V, Delarche N, Gosse P. Ambulatory blood pressure monitoring versus self-measurement of blood pressure at home: correlation with target organ damage. J Hypertens. 2008 Oct;26(10):1919–27.

173. Sega R, Facchetti R, Bombelli M, et al. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation. 2005 Apr 12;111(14):1777–83.

174. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. N Engl J Med. 2018 Apr 19;378(16):1509–20.

175. Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med. 2003 Jun 12;348(24):2407–15.

176. Parati G, Stergiou G, O'Brien E, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014 Jul;32(7):1359–66.

177. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2018 May 15;71(19):e127–248.

178. Hansen TW, Jeppesen J, Rasmussen S, et al. Ambulatory Blood Pressure and Mortality. Hypertension. 2005 Apr;45(4):499–504.

179. Ohkubo T, Imai Y, Tsuji I, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. J Hypertens. 1997 Apr;15(4):357–64.

180. ABC-H Investigators GC, Roush GC, Fagard RH, et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. J Hypertens. 2014 Dec;32(12):2332–40; discussion 2340.

181. Khattar RS, Swales JD, Banfield A, et al. Prediction of coronary and cerebrovascular morbidity and mortality by direct continuous ambulatory blood pressure monitoring in essential hypertension. Circulation. 1999 Sep 7;100(10):1071–6.

182. Verdecchia P, Reboldi G, Porcellati C, et al. Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. J Am Coll Cardiol. 2002 Mar 6;39(5):878–85.

183. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. J Hum Hypertens. 2005 Oct 16;19(10):801–7.

184. Kario K, Matsuo T, Kobayashi H, et al. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. Hypertens (Dallas, Tex 1979). 1996 Jan;27(1):130–5.

185. Salles GF, Cardoso CRL, Muxfeldt ES. Prognostic Influence of Office and Ambulatory Blood Pressures in Resistant Hypertension. Arch Intern Med. 2008 Nov 24;168(21):2340.

186. Redon J, Campos C, Narciso ML, et al. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. Hypertens (Dallas, Tex 1979). 1998 Feb;31(2):712–8.

187. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. JAMA. 1999 Aug 11;282(6):539–46.

188. Li Y, Wei F-F, Thijs L, et al. Ambulatory Hypertension Subtypes and 24-Hour Systolic and Diastolic Blood Pressure as Distinct Outcome Predictors in 8341 Untreated People Recruited From 12 Populations. Circulation. 2014 Aug 5;130(6):466–74.

189. Najafi MT, Khaloo P, Alemi H, et al. Ambulatory blood pressure monitoring and diabetes complications. Medicine (Baltimore). 2018 Sep;97(38):e12185.

190. Mayer CC, Matschkal J, Sarafidis PA, et al. Association of Ambulatory Blood Pressure with All-Cause and Cardiovascular Mortality in Hemodialysis Patients: Effects of Heart Failure and Atrial Fibrillation. J Am Soc Nephrol. 2018 Sep;29(9):2409–17.

191. Fagard RH, Celis H, Thijs L, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertens (Dallas, Tex 1979). 2008 Jan;51(1):55–61.

192. Kikuya M, Ohkubo T, Asayama K, et al. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. Hypertens (Dallas, Tex 1979). 2005 Feb;45(2):240–5.

193. Fagard RH, Thijs L, Staessen JA, et al. Night–day blood pressure ratio and dipping pattern as predictors of death and cardiovascular events in hypertension. J Hum Hypertens. 2009 Oct 19;23(10):645–53.

194. Mancia G, Verdecchia P. Clinical Value of Ambulatory Blood Pressure. Circ Res. 2015 Mar 13;116(6):1034–45.

195. Salles GF, Reboldi G, Fagard RH, et al. Prognostic Effect of the Nocturnal Blood Pressure Fall in Hypertensive Patients: The Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) Meta-Analysis. Hypertens (Dallas, Tex 1979). 2016 Apr;67(4):693–700.

196. Balietti P, Spannella F, Giulietti F, et al. Ten-year changes in ambulatory blood pressure: The prognostic value of ambulatory pulse pressure. J Clin Hypertens. 2018 Sep;20(9):1230–7.

197. Conen D, Bamberg F. Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: a systematic review and meta-analysis. J Hypertens. 2008 Jul;26(7):1290–9.

198. Verdecchia P, Angeli F, Gattobigio R, et al. Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. Am J Hypertens. 2007 Feb;20(2):154–61.

199. Pringle E, Phillips C, Thijs L, et al. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. J Hypertens. 2003 Dec;21(12):2251–7.

200. Hansen TW, Thijs L, Li Y, et al. Prognostic value of reading-to-reading blood pressure variability over 24 hours in 8938 subjects from 11 populations. Hypertens (Dallas, Tex 1979). 2010 Apr;55(4):1049–57.

201. Björklund K, Lind L, Zethelius B, et al. Prognostic significance of 24-h ambulatory blood pressure characteristics for cardiovascular morbidity in a population of elderly men. J Hypertens. 2004 Sep;22(9):1691–7.

202. Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation. 2003 Mar 18;107(10):1401–6.

203. Amici A, Cicconetti P, Sagrafoli C, et al. Exaggerated morning blood pressure surge and cardiovascular events. A 5-year longitudinal study in normotensive and well-controlled hypertensive elderly. Arch Gerontol Geriatr. 2009 Sep;49(2):e105–9.

204. Pierdomenico SD, Pierdomenico AM, Coccina F, et al. Prognostic Value of Nondipping and Morning Surge in Elderly Treated Hypertensive Patients With Controlled Ambulatory Blood Pressure. Am J Hypertens. 2017 Feb;30(2):159–65.

205. Tao Y, Xu J, Song B, et al. Short-term blood pressure variability and long-term blood pressure variability: which one is a reliable predictor for recurrent stroke. J Hum Hypertens. 2017 Sep 27;31(9):568–73.

206. Gorostidi M, Sobrino J, Segura J, et al. Ambulatory blood pressure monitoring in hypertensive patients with high cardiovascular risk: a cross-sectional analysis of a 20,000-patient database in Spain. J Hypertens. 2007 May;25(5):977–84.

207. Yamamoto Y, Akiguchi I, Oiwa K, et al. Twenty-four-hour blood pressure and MRI as predictive factors for different outcomes in patients with lacunar infarct. Stroke. 2002 Jan;33(1):297–305.

208. Phillips RA, Sheinart KF, Godbold JH, et al. The association of blunted nocturnal blood pressure dip and stroke in a multiethnic population. Am J Hypertens. 2000 Dec;13(12):1250–5.

209. Staals J, van Oostenbrugge RJ, Knottnerus ILH, et al. Brain microbleeds relate to higher ambulatory blood pressure levels in first-ever lacunar stroke patients. Stroke. 2009 Oct;40(10):3264–8.

210. Yamamoto Y, Akiguchi I, Oiwa K, et al. Adverse effect of nighttime blood pressure on the outcome of lacunar infarct patients. Stroke. 1998 Mar;29(3):570–6.

211. Coca A, Camafort M, Doménech M, et al. Ambulatory Blood Pressure in Stroke and Cognitive Dysfunction. Curr Hypertens Rep. 2013 Jun 11;15(3):150–9.

212. de la Sierra A, Banegas JR, Segura J, et al. Ambulatory blood pressure monitoring and development of cardiovascular events in high-risk patients included in the Spanish ABPM registry: the CARDIORISC Event study. J Hypertens. 2012 Apr;30(4):713–9.

213. Webb AJS, Mazzucco S, Li L, et al. Prognostic Significance of Blood Pressure Variability on Beat-to-Beat Monitoring After Transient Ischemic Attack and Stroke. Stroke. 2018 Jan;49(1):62–7.

214. Chen B-X, Tian J-P, Wang H-X, et al. Effect of blood pressure variability on cardiovascular outcome in diabetic and nondiabetic patients with stroke. J Stroke Cerebrovasc Dis. 2014 Oct;23(9):2450–7.

215. Yamaguchi Y, Wada M, Sato H, et al. Impact of ambulatory blood pressure variability on cerebral small vessel disease progression and cognitive decline in community-based elderly Japanese. Am J Hypertens. 2014 Oct 1;27(10):1257–67.

216. Antonini L, Pasceri V, Greco S, et al. Ambulatory blood pressure monitoring early after acute myocardial infarction: development of a new prognostic index. Blood Press Monit. 2007 Apr;12(2):69–74.

217. Groppelli A, Omboni S, Parati G, et al. Evaluation of noninvasive blood pressure monitoring devices Spacelabs 90202 and 90207 versus resting and ambulatory 24-hour intra-arterial blood pressure. Hypertens (Dallas, Tex 1979). 1992 Aug;20(2):227–32.

218. Almeida L, Amado P, Vasconcelos N, et al. [Is ambulatory blood pressure monitoring reliable in hypertensive patients with atrial fibrillation?]. Rev Port Cardiol. 2001 Jun;20(6):647–50.

219. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet (London, England). 2015 Jul 11;386(9989):154–62.

220. Haim M, Hoshen M, Reges O, et al. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. J Am Heart Assoc. 2015 Jan 21;4(1):e001486.

221. Zanchetti A, Liu L, Mancia G, et al. Blood pressure and low-density lipoprotein-cholesterol lowering for prevention of strokes and cognitive decline: a review of available trial evidence. J Hypertens. 2014 Sep;32(9):1741–50.

222. Kikuya M, Hansen TW, Thijs L, et al. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. Circulation. 2007 Apr 24;115(16):2145–52.

223. Vidal-Petiot E, Ford I, Greenlaw N, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet (London, England). 2016 Oct 29;388(10056):2142–52.

224. Kjeldsen SE, Berge E, Bangalore S, et al. No evidence for a J-shaped curve in treated hypertensive patients with increased cardiovascular risk: The VALUE trial. Blood Press. 2016 Mar 3;25(2):83–92.

225. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. J Hypertens. 2017 Nov;35(11):2150–60.

226. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med. 2006 Jun 20;144(12):884–93.

227. McEvoy JW, Chen Y, Rawlings A, et al. Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events: Implications for Blood Pressure Control. J Am Coll Cardiol. 2016 Oct 18;68(16):1713–22.

228. Bangalore S, Messerli FH, Wun C-C, et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. Eur Heart J. 2010 Dec 1;31(23):2897–908.

229. Böhm M, Schumacher H, Teo KK, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. Lancet. 2017 Jun 3;389(10085):2226–37.

230. Mancia G, Kjeldsen SE, Zappe DH, et al. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. Eur Heart J. 2016 Mar 21;37(12):955–64.

231. Conen D, Aeschbacher S, Thijs L, et al. Age-Specific Differences Between Conventional and Ambulatory Daytime Blood Pressure Values. Hypertension. 2014 Nov;64(5):1073–9.

232. Burr ML, Dolan E, O'brien EW, et al. The value of ambulatory blood pressure in older adults: the Dublin outcome study. Age Ageing. 2008;37:201–6.

233. Pinto E. Blood pressure and ageing. Postgrad Med J. 2007 Feb;83(976):109.

234. Kario K, Pickering TG, Matsuo T, et al. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertens (Dallas, Tex 1979). 2001 Oct;38(4):852–7.

235. Mancia G, Grassi G. Aggressive blood pressure lowering is dangerous: the J-curve: pro side of the arguement. Hypertens (Dallas, Tex 1979). 2014 Jan;63(1):29–36.