Ana Cristina Gaspar Cabral

Evaluation of risk factors associated with uncontrolled blood pressure of hypertensive patients under pharmacological antihypertensive treatment

Doctoral Thesis in Pharmaceutical Sciences, specialization in Pharmacology and Pharmacotherapy, supervised by Professor Isabel Vitória Figueiredo and by Professor Fernando Fernandez-Llimos and presented to the Faculty of Pharmacy of the University of Coimbra

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Universidade de Coimbra

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Esta dissertação, mais do que um projeto de investigação, mostrou ser um teste às minhas capacidades e uma prova de resistência. Não poderia terminar esta etapa sem agradecer às pessoas que contribuíram para esta vitória.

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Abstract

Hypertension is one of the world's most prevalent diseases and its management is a timely topic and one of interest world-wide. Despite the amount of research done in this field, blood pressure goals are still far from being achieved, with almost half of hypertensive population with blood pressure levels above the recommended, despite being under pharmacological treatment. In this research we aimed to identify objective and measurable factors associated with risk of uncontrolled blood pressure in hypertensive patients under pharmacological therapy.

First we performed a systematic review of literature about poor control of blood pressure in patients under pharmacological treatment. Gender, health insurance, adherence to therapy, obesity and diabetes were identified as having a negative influence on the control of blood pressure in patients under pharmacological antihypertensive treatment. The impact of diabetes as comorbidity is the most important, being 2 times higher than adherence to therapy and 3 times higher than obesity. Outcome switching and the use of different core outcome sets hindered the performance of the expected meta-analysis once there was no results comparability in several studies.

Our aim was, not only identify factors associated with poor blood pressure control in treated hypertensive patients, but also to understand the needs in this area in Portugal, identify what research has been done, and how we can add knowledge in this field. As so, we decided to further research one of the factors with more pharmaceutical interventions possibilities found in the systematic review, adherence to medication.

In Portugal, although increasing importance has been assigned to adherence, few robust investigation exist. The only validated instrument to assess antihypertensive drugs adherence before our work was Medida de Adesão ao Tratamento (MAT), developed in 2001, it's a questionnaire with good internal consistency but has the disadvantage of being a national instrument, which prevents cross comparisons with studies from other countries.

We seek in the literature which would be the best instrument to use. In fact, no gold standard exist concerning adherence questionnaires, but one clearly stands out, the 8-items Morisky Medication Adherence Scale (MMAS-8). However, the MMAS-8 scoring system is not intuitive which may result in potential discrepancies in the application of the instrument. Therefore, we performed a systematic review and meta-analysis to assess heterogeneity associated with the use of MMAS-8, finding that, despite the demonstrated reliability and internal consistency, the use of this instrument is associated to high heterogeneity.

We hypothesize that one of the possible causes for MMAS-8 high heterogeneity may be validation problems regarding psychometric properties and cross-cultural adaptation of MMAS-8 to other languages, so we decided to develop and validate the European-Portuguese adaptation of the 8-Items Morisky Medication Adherence Scale in a Portuguese hypertensive patient's sample. We obtained a Portuguese version of MMAS-8, with an acceptable internal consistency and good convergent and concurrent validity.

As important as having the best instrument to assess adherence, is designing the right intervention to improve it, and better and more effective interventions could be developed if adherence is treated as a the complex concept that it is. As so we research in published literature the existent tools available to assess reasons for non-adherence and, among the several self-report instruments, the Maastricht Utrecht Adherence in Hypertension Questionnaire (MUAH) stands out. MUAH measures 4 adherence-related dimensions such as positive attitude towards health care and medication, lack of discipline, aversion towards medication and active coping with health problems. Thus, we decided to translate it and validate it to Portuguese. While evaluating the questionnaire psychometric properties some difficulties in the methodological implementation arise and the lack of a global score that allows adherence classification appears as one major gap in this instrument. Therefore, we developed a short version of MUAH (MUAH-16). MUAH-16 we developed, evaluates the same dimensions than the original MUAH, with the advantage of having a global score of adherence. It can be easily applied in clinical practice, giving health professionals more extended information about the patient's reasons for poor adherence.

During the systematic review analysis, in addition to medication adherence, other variable stood out. Being an important contributor to blood pressure control, and also a growing

area of intervention in community pharmacies, patient's knowledge about hypertension disease was one of the aims of our research. Although it has been recognized that interventions in order to improve knowledge about hypertension contribute to an improvement in blood pressure control, validated instruments, that properly assess knowledge, and subsequently allow the design of more targeted interventions, are scarce. After a literature search, the Hypertension Knowledge Test (HKT) revealed to be an easy-to-use questionnaire covering several items related to the disease as the etiology, diagnosis, treatment and prevention methods, and has demonstrated good psychometric properties, namely internal consistency. So we decided to develop and validate the Portuguese adaptation of the Hypertension Knowledge Test questionnaire in a hypertensive patient's population. We obtained a Portuguese version of with an acceptable internal consistency, discriminatory capacity, and predictive power regarding adherence.

Resumo

A hipertensão arterial é uma das doenças mais prevalentes no mundo e a efetividade do seu tratamento é um tema atual e de interesse mundial. Apesar da intensa investigação desenvolvida nesta aérea, os valores de pressão arterial (PA) dos doentes hipertensos estão ainda longe dos valores recomendados, com quase metade da população hipertensa a apresentar níveis de PA acima dos objetivos terapêuticos estipulados. Com este projeto pretendemos identificar fatores de risco objetivos e mensuráveis associados ao não controlo da pressão arterial de doentes hipertensos sob tratamento farmacológico.

Numa primeira fase foi realizada uma revisão sistemática da literatura sobre o não controlo da PA em doentes hipertensos sob tratamento farmacológico, tendo sido encontrados 5 grandes fatores de risco: sexo, seguro de saúde, adesão ao tratamento, obesidade e diabetes. O impacto da diabetes como comorbilidade foi o mais significativo, sendo 2 vezes maior do que a adesão à terapêutica e 3 vezes maior do que a obesidade. A presença de fenómenos como *outcome switching* e a utilização de diferentes *core outcome sets* impossibilitou a realização das metanálises esperadas.

Além de identificar fatores de risco de descontrolo da pressão arterial, outro objetivo deste trabalho foi entender as necessidades nesta área em Portugal, perceber que investigação tem sido feita e como podemos acrescentar conhecimento neste campo. Como tal, decidimos aprofundar um dos fatores com mais potencialidade para o desenvolvimento de intervenções farmacêuticas encontrado na revisão sistemática, a adesão à terapêutica.

Em Portugal, apesar da importância crescente que tem sido atribuída à adesão, existe ainda uma falha relativamente ao desenho de investigações robustas nesta área. O único instrumento validado para avaliar a adesão à terapêutica anti-hipertensora, antes do nosso trabalho, era o questionário Medida de Adesão ao Tratamento (MAT). O MAT apresenta boa consistência interna, mas tem a desvantagem de ser um instrumento nacional, o que impede comparações transversais com estudos de outros países. Assim decidimos realizar uma pesquisa na literatura sobre qual o melhor instrumento a utilizar. Apesar de não termos encontrado nenhum *gold standard*, um questionário destacou-se claramente, o 8-item Morisky Medication Adherence Scale (MMAS-8). No entanto, o seu sistema de

pontuação não é intuitivo, o que pode resultar em potenciais discrepâncias na aplicação do instrumento. Para avaliar este pressuposto foi realizada uma revisão sistemática e meta-análises para avaliar a heterogeneidade associada ao uso do MMAS-8, concluindo-se que, apesar da fiabilidade e consistência interna demonstradas, a utilização deste instrumento está associada a uma elevada heterogeneidade.

Colocámos a hipótese de que uma das possíveis causas para a elevada heterogeneidade do MMAS-8 podem ser problemas associados à validação das propriedades psicométricas e ao processo de adaptação transcultural do MMAS-8 para outros idiomas, por isso, decidimos desenvolver e validar a adaptação para português europeu do MMAS-8 numa amostra de doentes hipertensos portugueses. Obtivemos uma versão portuguesa com uma consistência interna aceitável e boa validade convergente e concorrente.

Tão importante como ter o melhor instrumento para avaliar a adesão, é desenvolver uma boa intervenção para poder melhorar este parâmetro. Melhores e mais eficazes intervenções poderiam ser desenhadas se a adesão, em vez e ser tratada como um conceito único, for avaliada em todas as suas dimensões. Assim, nós pesquisámos na literatura as ferramentas existentes para avaliar as razões para a não-adesão e, entre os vários instrumentos, o Maastricht Utrecht Adherence in Hypertension Questionnaire (MUAH) destacou-se. O MUAH mede 4 dimensões relacionadas com a adesão: atitude positiva em relação aos medicamentos e cuidados de saúde, falta de disciplina, aversão à medicação e gestão ativa de problemas de saúde. Assim, decidimos traduzir e validar este questionário para português. Ao avaliar as suas propriedades psicométricas algumas dificuldades de aplicação metodológica e a falta de uma pontuação global que permita a classificação da adesão apareceram como uma lacuna importante neste instrumento. Por isso, propusemos desenvolver uma versão curta do MUAH, o MUAH-16. O MUAH-16 avalia as mesmas dimensões que o MUAH original, com a vantagem de ter uma pontuação global de adesão. Pode ser facilmente aplicado na prática clínica, dando aos profissionais de saúde informações mais alargadas sobre as causas para a baixa adesão dos doentes.

Na análise da primeira revisão sistemática, além da adesão à terapêutica, destacou-se outra variável. Dando um importante contributo para o controlo da PA, e sendo uma potencial área de intervenção em farmácias comunitárias, o conhecimento do doente sobre

hipertensão arterial foi um dos focos da nossa investigação. Embora seja amplamente reconhecido que as intervenções com o objetivo de melhorar o conhecimento sobre a doença contribuem para uma melhoria no controlo da PA, há uma falta de instrumentos devidamente validados, que avaliem adequadamente o conhecimento e, posteriormente, permitam o desenho de intervenções mais específicas. Depois de uma pesquisa bibliográfica, o Hypertension Knowledge Test (HKT) revelou ser um questionário de fácil utilização, que abrange vários conceitos relacionados com a doença, como a etiologia, diagnóstico, tratamento e prevenção, tendo demonstrado boas propriedades psicométricas. Desta forma decidimos desenvolver e validar a adaptação para português do questionário Hypertension Knowledge Test numa população de doentes hipertensos portugueses. Obtivemos uma versão portuguesa com uma consistência interna aceitável, e com capacidade discriminatória e poder preditivo em relação a adesão.

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List of acronyms and abbreviations

ABPM.....Ambulatory blood pressure measurement
ACE-I.....Angiotensin-converting enzyme inhibitors
AntiHTA .....Antihypertensive drugs
ARB.....Angiotensin receptor blockers
BMI.....Body Mass Index
BP .....Blood pressure
CCB.....Calcium channel blockers
CFA .....Confirmatory factor analysis
CFI .....Comparative fit index
CHD .....Coronary Heart Disease
CI.....Confidence interval
CKD .....Chronic kidney disease
COS.....Core Outcome Set
DBP .....Diastolic blood pressure
DGS .....Direção Geral de Saúde
EFA .....Exploratory factor analysis
ESC .....European Society of Cardiology
ESH .....European Society of Hypertension
HBPM .....Home blood pressure measurement
HDL.....High density lipoprotein
HKT .....Hypertension Knowledge Test questionnaire
HTA .....Hypertension
iNOS.....Inducible nitric oxide synthase
LVH.....Left Ventricular Hypertrophy
MAT .....Medida de Adesão aos Tratamentos [Measure Treatment Adherence]
MI .....Myocardial Infarction
MMAS-4 .....4-Item Morisky Medication Adherence Scale
MMAS-8 .....8-item Morisky Medication Adherence Scale
MOA .....Mode of administration
MUAH .....Maastricht Utrecht Adherence in Hypertension Questionnaire

MUAH-16 .....Maastricht Utrecht Adherence in Hypertension Questionnaire short version

NHS .....National Health System

OBPM .....Office blood pressure measurement

OR.....Odds Ratio

RAS-I.....Renin–angiotensin system inhibitor

RMSEA .....Root mean square error of approximation

SBP .....Systolic blood pressure

SRMR .....Standardised root-mean-square residual

WHO .....World Health Organization

General Introduction

General Introduction

A global brief on hypertension

Hypertension (HTA) is a major public health issue. Demographic ageing, rapid urbanization, and the globalization of unhealthy lifestyles are increasing conditions that lead hypertension to be one of the most prevalent diseases in the world.

The number of patients diagnosed with hypertension has been increasing over the years. In 2008, worldwide, approximately 40% of adults aged 25 and above had been diagnosed with hypertension and the number of people with the condition rose from 600 million in 1980 to 1 billion in 2008[1]. World Health Organization (WHO) estimates that the number of adults with hypertension in 2025 increase by about 60% to a total of 1.56 billion[2].

The prevalence of this disease is different between different regions of the world. The major differences appear between low- and high-income countries. From the 972 million adults with hypertension worldwide in 2000, 333 million were from economically developed countries and 639 million from economically developing countries[2]. The absolute numbers of hypertensive patients in the developing world are considerably higher because there is a much larger population in these countries, but if we analyse the global prevalence of hypertension in population aged 20 years or older, we find that hypertension is present in approximately 35% of the Latin American population, 25%-30% of the Chinese and Indian population, 20%-30% in Sub-Saharan African countries and about 20% in USA and Canada[2, 3]. The prevalence of hypertension is increasing in developing countries, probably due to urbanization, which is often associated with increased income and adoption of an unhealthy lifestyle such as unhealthy food habits with the transition from traditional rural diets (with a low glycaemic index and a higher fibre content) to a diet rich in salt, saturated fats, and poor-quality carbohydrates (such as fast foods) and reduced physical activity and sedentary occupations[4].

Assessing economically developed countries, and although heterogeneity existed, as a group, the European countries uniformly had higher blood pressure (BP) measurements than United States and Canada[5]. North America has lower rates of hypertension, with

values of around 28% for adults between 35 and 64 years, while in Europe this numbers reaches 44%[5].

According to 2008 data, WHO reported that in Portugal 34.5% of men and 24.3% of women over 25 years have high blood pressure[6] and for the last 30 years, Portugal has been among the countries with the highest levels of mean blood pressure[7].
Several Portuguese studies have explored prevalence, awareness, treatment and control of hypertension in Portugal. Going back ten years, mostly of the studies published cover only one region of the country, but there are 3 studies using representative samples at national level[8-10]. Table 1.1 summarizes the results obtained in these 3 studies.

Table 1.1 - Prevalence, Awareness, Treatment and Control of hypertension in Portugal through the years.

Study	Year	Prevalence	Awareness	Treatment	BP control in hypertensive patients	BP control in treated hypertensive patients	Mean SBP in treated hypertensive patients (mmHg)	Mean DBP in treated hypertensive patients (mmHg)
PAP	2003	42.1%	45.7%	38.9%	11.2%	28.6%	152.1	85.3
VALSIM	2004	42.6%	-	89.7%	-	-	-	-
PHYSA	2012	42.2%	76.8%	74.9%	42.6%	55.6%	136.5	76.9

BP - blood pressure; SBP - Systolic blood pressure; DBP - Diastolic blood pressure.

We can observe that the prevalence of the disease remain unchanged, with about 42% of Portuguese being hypertensive patients, but there is a significant improvement either in the diagnosis, treatment and in control of HTA. A recent systematic review concluded that from 1975 to 2005, mean systolic blood pressure (SBP) decreased in men after middle-aged and women at all ages, and diastolic blood pressure (DBP) remained constant in younger adults and decreased in middle-aged and older adults, more strongly with advancing age[11].

In fact, according to Direção Geral de Saúde (DGS), since 2008 there has been a maintained growth in the use of antihypertensive drugs in Portugal, with the number of antihypertensive packages sold in National Health System (NHS) increasing from 20.569.489 in 2008 to 26.798.800 in 2013 (Figure 1)[12].

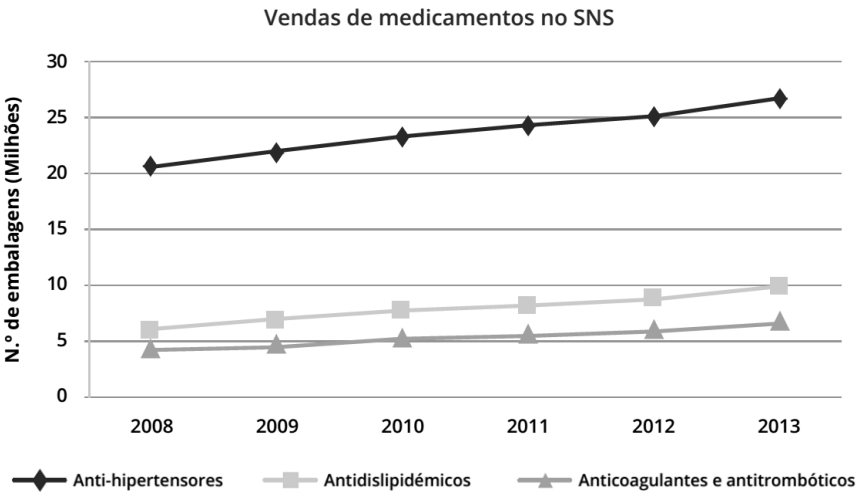


Figure 1 *- Drug sales in NHS (number of packaging) in Portugal (2008-2013) Subgroups selected from Pharmacotherapeutic Groups Cardiovascular system and Blood. Adapted from Direção Geral de Saúde, Portugal - Doenças Cérebro-Cardiovasculares em números 2014 [12].*

In the last years, there has been an effort from health authorities to improve the diagnosis, treatment and control of HTA, having been released several standards and regulations to establishes the procedures desirable to be adopted by health professionals and setting priorities as early detection of HTA, proper therapeutic management (pharmacological and non-pharmacological) and monitoring of blood pressure control over the years[13-15].

These numbers suggest that increasing awareness translates into a higher treatment proportion, resulting in a decrease in blood pressure level, however, in spite all the efforts, almost half of hypertensive patients still do not achieve the therapeutic targets[10].

Burden of blood pressure control

The lack of control of blood pressure values is not a purely national situation. Worldwide, the results remain below expectations. In Wolf-Maier *et al.* (2004) study[16], hypertension control rates in treated hypertensives across Europe range between 49,4% in Spain and 73,1% in England. Canada and United States presents higher success in hypertension treatment, reaching 84% of blood pressure control. Differences in hypertension aetiology between blacks and whites, associated with economic problems in developing countries, that forbid the acquisition of needed pharmacological treatment, lead to lower rates of BP control in Sub-Saharan African populations, with rates of control ranging from 5% to 10%[4, 17].

Actually, according to ESH/ESC 2013 guidelines for the management of arterial hypertension from European Society of Hypertension (ESH) and European Society of Cardiology (ESC)[18], blood pressure is considered to be under control if SBP is below 140 mmHg and DBP is below 90mmHg in low-to-moderate risk hypertensive patients, having establish different targets to specific population as elderly, diabetic patients or patients with chronic kidney disease (CKD) (Table 1.2).

The concept that "the lower the SBP and DBP achieved the better the outcome", defended by Lewington *et al.* (2002)[19] is outdated, having tendentiously been replaced by the hypothesis of a J-shaped relationship, according to which the benefits of reducing SBP or DBP to markedly low values are smaller than for reductions to more moderate values[20]. This, associated with a large number of randomized trials of antihypertensive treatment in the elderly which were unable to observe benefits by lowering average SBP to lower values than 140 mmHg, allow the definition of new targets to elderly patients, with less strict control[18, 21, 22].

Table 1.2 - Guidelines comparison of goal BP.		
Guideline	Population	Goal BP (mmHg)
2014 Hypertension Guideline	General ≥ 60 years	< 150/90
	General < 60 years	< 140/90
	Diabetes	< 140/90
	CKD	< 140/90
ESH/ESC 2013	General nonelderly	< 140/90
	General elderly < 80 years	< 150/90
	General elderly ≥ 80 years	< 150/90
	Diabetes	< 140/85
	CKD no proteinuria	< 140/90
	CKD + proteinuria	< 130/90
CHEP 2014	General < 80 years	< 140/90
	General ≥ 80 years	< 150/90
	Diabetes	< 130/80
	CKD	< 140/90
ADA 2016	General Diabetes	< 140/90
	Diabetes younger patients, albuminuria and/or atherosclerotic cardiovascular disease risk factors	≤ 130/80
KDIGO 2012	CKD no proteinuria	≤ 140/90
	CKD + proteinuria	≤ 130/80
NICE 2011	General < 80 years	< 140/90
	General ≥ 80 years	< 150/90
ISHIB 2010	Black, lower risk	< 135/85
	Target organ damage or CVD risk	< 130/80

2014 Hypertension Guideline[22] - Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8); ESH/ESC 2013[18] - Guidelines for the management of arterial hypertension from European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC); CHEP 2014[21] - The 2014 Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension; ADA 2016[23] - Standards of Medical Care in Diabetes by American Diabetes Association; KDIGO 2012[24] - Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease; NICE 2011[25] - Clinical management of primary hypertension in adults by National Institute for Health and Clinical Excellence and ISHIB 2010[26] - International Society on Hypertension in Blacks consensus statement.

Another important current discussion is which BP measure is more valuable to evaluate blood pressure control, office BP measurement (OBPM), home BP measurement (HBPM) or ambulatory BP measurement (ABPM).

Office BP measurement is the usual care or gold standard for hypertension diagnosis and treatment. It has been assumed that the controlled measurement of BP made in clinical setting represent the average level of BP that occurs between clinic visits. However, several studies have pointed some limitations to this technique, especially errors associated with an increase in BP attributable to the "white coat effect"[27, 28]. Defined as clinic BP readings disproportionately greater than home or ambulatory BP averages[25], white coat effect may lead patients to receive more antihypertensive medication that they need. In fact, in this case, the BP rise is a short-lived effect, with blood pressure dropping to normality after or near the end of the consultation. Consequently, a patient may present as uncontrolled hypertensive in clinic but be controlled otherwise. Withal the reduce number of measures that OBPM provides, does not reflect the reality of the patient.
As so, BP is actually accepted as a continuous variable, impossible to characterize accurately except by multiple readings under various conditions and several guidelines recognized multiple out-of-office measurements as essential for accurate management and control of HTA[18, 21, 22, 25].

Home BP measurement involves self-measurement of BP[22]. Yields multiple measurements over several days, or even longer periods, taken in the individual's usual environment meaning a larger number of BP measurements away from the medical environment and from clinical office interference. The procedure should be adequately explained to the patient, with verbal and written instructions and in addition requires appropriate training under medical supervision. However, BP values reported by the patient may not always be reliable and does not provide BP data during routine, day-to-day activities and during sleep.

Ambulatory BP measurement is performed with the patient wearing a portable BP measuring device, usually on the non-dominant arm, for a 24–25 h period, so that it gives information on BP during daily activities and at night during sleep[22]. The patient is instructed to engage in normal activities but to refrain from strenuous exercise and, at the

time of cuff inflation, to stop moving and talking and keep the arm still with the cuff at heart level. Measurements should be made at the same frequency during the day and night, for example every 20 min throughout. The major advantage of this methodology is its ability to measure nocturnal BP, being more accurate for prognosis. Otherwise, of the three methodologies discussed it's the most expensive.

Advantages and disadvantages of each measuring techniques are presented in Table 1.3.

Table 1.3 - Relative qualities of BP measuring techniques.

	OBPM	HBPM	ABPM
Cost	+	++	-
Need for training	-	+	+
Accuracy	-	+	++
Identification of white coat HTA	-	+	+
Nocturnal readings	-	-	++
Prognostic ability	+	++	++
Recognition of control	-	+	+
Improve adherence	-	+	?

- Less favourable; + Favourable; ++ Greatly favourable

Adapted from Kaplan's Clinical Hypertension[33].

Several studies have studied the relationship between theses 3 measurement types, demonstrating that HBPM is as good as ABPM and superior to OBPM in regard to their association with preclinical organ damage[29] and that adjustment of antihypertensive treatment based on HBPM instead of OBPM led to less intensive drug treatment and marginally lower costs, but also to less BP control[30].

Therefore, Office BP measurement still the gold standard for blood pressure evaluation but, in some specifically situations, out-of-office BP measurements are an important adjunct for diagnostic purposes and control assessment (Table 1.4).

Table 1.4 - Clinical indications for out-of-office blood pressure measurement for diagnostic purposes.
Clinical indications for HBPM or ABPM
• Suspicion of white-coat hypertension
- Grade I hypertension in the office
- High office BP in individuals without asymptomatic organ damage and at low total CV risk
• Suspicion of masked hypertension
- High normal BP in the office
- Normal office BP in individuals with asymptomatic organ damage and at high total CV risk
• Identification of white coat effect in hypertensive patients
• Considerable variability of office BP over the same or different visits
• Autonomic, postural, post-prandial, siesta- and drug-induced hypotension
• Elevated office BP or suspected pre-eclampsia in pregnant women
• Identification of true or false resistant hypertension
Specific indications for ABPM
• Marked discordance between office BP and home BP
• Assessment of dipping status
• Suspicion of nocturnal hypertension or absence of dipping, such as in patients with sleep apnoea, CKD, or diabetes
• Assessment of BP variability
CKD - chronic kidney disease; CV - cardiovascular. Modified from ESH/ESC 2013[18] - Guidelines for the management of arterial hypertension from European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).

Social and economic impact of uncontrolled blood pressure

The risks of elevated BP have been determined from large scale epidemiologic surveys. In 1993, Stamler *et al.* (1993)[31], after reviewing data from United States prospective population studies of the past 20 years on SBP and DBP, conclude that high levels of BP have continuous, graded, strong, independent, and etiologically significant relationships with the onset of cardiovascular events. Vasan *et al.* (2001)[32] found a stepwise increase in cardiovascular event rates in persons with higher baseline blood pressure categories, suggesting an association between hypertension and risk of cardiovascular disease.

Hypertension is associated with structural changes in small-vessels, high levels of blood pressure leads to hardening and thickening of the walls of arterioles, conducting to the development of arteriosclerosis that is responsible for much of the target organ damage seen in long-standing hypertension[33]. Therefore, etiologically speaking, hypertensive patients have a higher risk of cardiovascular diseases than normotensive, being HTA pointed as a major risk factor for cardiovascular events (Figure 2).

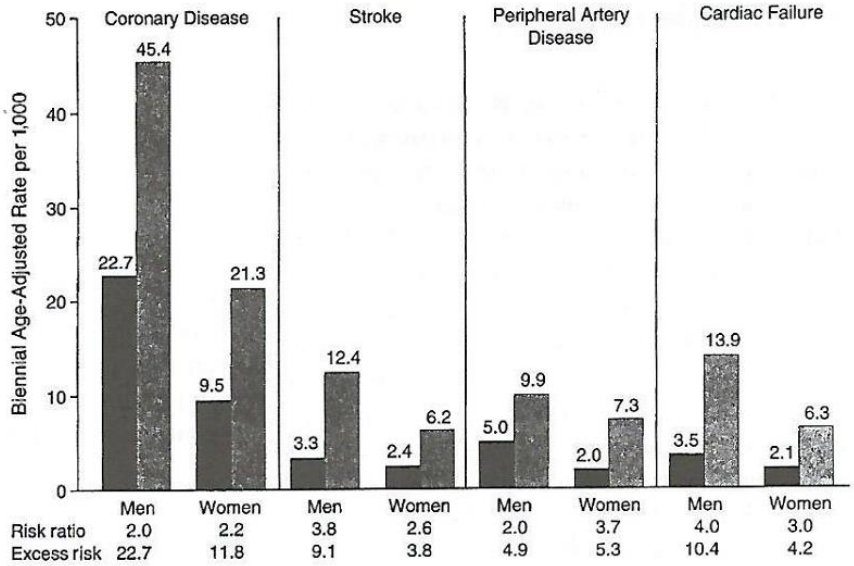


Figure 2 *- Risk of cardiovascular events by hypertensive status in subjects aged from 35 to 64 years. Coronary diseases include clinical manifestations such as MI, angina pectoris, sudden death, other coronary deaths and coronary insufficiency syndrome. Peripheral artery disease is manifested as intermittent claudication.*
Left bars in each set of columns represents normotensives and right bars represents hypertensives.
Adapted from Kaplan's Clinical Hypertension[33].

Several other studies had been made, pointed repeatedly hypertension as one of the most important and independent risk factors for the onset of several diseases such as coronary heart disease (CHD), myocardial infarction (MI), stroke and chronic kidney disease (CKD), often leading patients to invasive and costly interventions such as coronary artery bypass surgery, carotid artery surgery, dialysis, etc.[34-36].
For that reason, WHO considers hypertension a major public health problem, with serious consequences, not only for patients but also for health care systems[37, 38].

Cardiovascular disease accounts for approximately 17 million deaths a year, nearly one third of the total, and of these, complications of hypertension account for 9.4 million deaths

worldwide every year. HTA is pointed as responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke[38] and is pointed as a major risk factor for increased mortality and morbidity rates[39].

As WHO, DGS consider hypertension a major risk factor for cardiovascular diseases. In last analysis of "Programa Nacional para as Doenças Cérebro-Cardiovasculares" of 2014[12] , DGS point circulatory system diseases as leading cause of death in Portugal, corresponding to 30,4% of deaths that occur in 2012. In 2013 ischemic stroke accounted for about 20000 episodes and 250000 days of hospitalization, and myocardial infarction accounted for about 13000 episodes and 175000 days of hospitalization. In the same year were performed 13897 percutaneous coronary angioplasties and 2575 coronary artery bypass surgery[12].

Economically speaking, hypertension presents a considerable burden to National Health System (NHS), not only respecting to antihypertensive medication, the therapeutic subgroup with higher charges for NHS, corresponding to 19% of drug costs (247072850€ in 2013)[40], but also concerning to expenses associated with the emergency room due to cardiovascular complications, hospitalization and needed medical procedures.

Justification and objectives of this Thesis

Justification and objectives of this Thesis

As seen previously, hypertension is one of the most prevalent diseases of this century, responsible for high morbidity and mortality rates and for high costs to the health care system. Therefore, numerous research has been undertaken in this field in order to develop strategies targeted to prevent and improve treatment of this disease. However, blood pressure goals are still far from being achieved.

Determine the factors that influence the control of blood pressure is a major challenge. Understanding what lead a treated hypertensive patient to fail his blood pressure control targets, comprehend modifiable variables, how they can be detected and controlled, can be an important contribution to enable the design of more appropriate and more effective intervention strategies for hypertension control.

Objectives

The overall objective of this work is the identification of objective and measurable factors associated with the risk of non-control of blood pressure of hypertensive patients under pharmacological antihypertensive treatment.

In order to develop and achieve the initial purpose, the following specific objectives were outlined:

- Identification of published evidence regarding risk factors for blood pressure uncontrolled in patients under pharmacological antihypertensive therapy.
- To assess heterogeneity associated with the use of 8-item Morisky Medication Adherence Scale (MMAS-8), the most used instrument to assess patient's self-report adherence to medication.
- To develop and validate the European-Portuguese cross-cultural adaptation of the 8-Items Morisky Medication Adherence Scale in a Portuguese sample.
- To develop a short version of Maastricht Utrecht Adherence in Hypertension Questionnaire (MUAH), an instrument originally developed to assess the reasons for poor adherence to antihypertensive medication.

- To assess the influence of different administration methodologies in the application of adherence questionnaires and in their results.
- To develop and validate the Portuguese adaptation of the Hypertension Knowledge Test questionnaire (HKT).

Factors associated with non-control of blood pressure in hypertensive patients under pharmacological antihypertensive treatment – a systematic review and meta-analysis

Factors associated with non-control of blood pressure in hypertensive patients under pharmacological antihypertensive treatment - a systematic review and meta-analysis

Introduction

As previously mentioned, hypertension is far from being a disease under control. Despite the amount of research done in this field, blood pressure goals are still far from being achieved, with almost half of hypertensive population with BP levels above the target goals. The lack of awareness and adequate treatment has been pointed as major causes for this rates and, for several years, efforts have been done to improve diagnose of hypertension and develop more effective treatments. Several guidelines were developed and many randomized control trials were done in order to improve physicians' knowledge about the disease and tools available to treat it. Indeed, if we analyse the evolution of control rates over the years, we can see a gradual improvement of blood pressure values, but not enough.

Several factors have already been addressed as major influences in the progress of hypertension, such as unhealthy diet, particularly excessive salt intake, tobacco, harmful use of alcohol, physical inactivity, diabetes, obesity, age, race and gender. Also physician-related factors such as knowledge and time spending with patients seem to have influence hypertension development. It is not clear if these factors, considered major causes for hypertension are the same causes for uncontrolled hypertension in treated patients.

Understanding factors that contribute to poor blood pressure control in patients under pharmacological treatment, addressing modifiable risk factors and reduce exposure them, identify patients profiles with increased risk of uncontrolled BP and set up a closer follow up of them, can prevent uncontrolled hypertension and its complications as well as decrease cardiovascular disease incidence.

Objective

Several studies have been developed so far to evaluate the influence of several variables in blood pressure control. Our aim was to perform a systematic review and meta-analysis of these studies to synthetize the evidence about risk factors associated with uncontrolled blood pressure, in patients under pharmacological antihypertensive treatment.

Methods

Search strategy and study selection

A literature review was conducted in order to identify all studies that used multivariable logistic regression models to identify predictive factors of not achieving adequate BP control in patients under pharmacological antihypertensive treatment. A computerized search was performed using Medline (PubMed), Scielo and Scopus in January 2015. Studies were identified by the following search terms:
(((Hypertension[MH] OR "Blood Pressure"[MH] OR "Antihypertensive Agents"[MH]) AND ("Drug Resistance"[MH] OR "Treatment Failure"[MH])) OR ("uncontrolled hypertension" OR "uncontrolled blood pressure" OR "uncontrolled BP")) AND ("Regression Analysis"[MH] OR "Multivariate Analysis"[MH] OR "Risk Factors"[MH] OR "Predictive Value of Tests"[MH] OR predict*)

Two independent investigators (A.C.C., F.F-L.) screened the studies based initially on their title and abstract to identify irrelevant records. The same two researchers appraised the full text articles, to exclude studies using the following exclusion criteria:

(i) articles neither available at any of the research team University libraries nor provided by the authors after request;

(ii) articles not written in Roman characters;

(iii) articles that don't use multivariate logistic regression to evaluate baseline values of variables;

(iv) articles that include non-treated patients in multivariate logistic regression;

(v) articles that don't provide Odds Ratio (OR) values with a Confidence Interval of 95%;

(vi) articles with inconsistencies in Odds ratio analysis, and

(vii) articles with hypertension resistance patients that included patients with controlled blood pressure under 4 or more antihypertensive drugs in the control group (uncontrolled patients).

Multiple reports of the same study were aggregated as one study.

Data extraction

Data were extracted by the same two independent researchers and relevant information from all included studies was gathered using a pre-designed data extraction form. The following information was extracted:

1. Data referent to study eligibility;
2. Methodology used to collect data;
3. Characteristics of patients surveyed;
4. Definition of controlled blood pressure;
5. Inclusion criteria in both case and control group;
6. Independent variables analyzed, and
7. Odds ratio resultant from multivariate logistic regression, as well as confidence interval.

Only baseline data were included, for both test group and control group, when existed.

Data analysis

Data reported in included studies were used for 12 different meta-analysis, evaluating the influence in blood pressure control of age, gender, smoking habits, health insurance, family history of hypertension, adherence to therapy, BMI and diabetes. The effect size and the Confidence Interval at 95% (95% CI) from individual studies were calculated and pooled using a random-effects model, which takes into account variability among studies rather than chance. The heterogeneity was assessed using the inconsistency index (i-square). Values of i-square near 25% were considered to show low heterogeneity, values close to 50% denoted moderate heterogeneity, and those over 75% were considered to show substantial heterogeneity[41].

All statistical analyses were performed using the Comprehensive Meta-Analysis Version 2.0 software (CMA 2.0; Biostat Inc., Englewood, NJ, USA).

Results

A total of 2905 articles resulted from the search, excluding 2699 in the screening phase and 152 in the full-text phase, resulting in 53 articles (corresponding to 51 studies) included for qualitative extraction and 42 articles (corresponding to 40 studies) for meta-analyses (Figure 3).

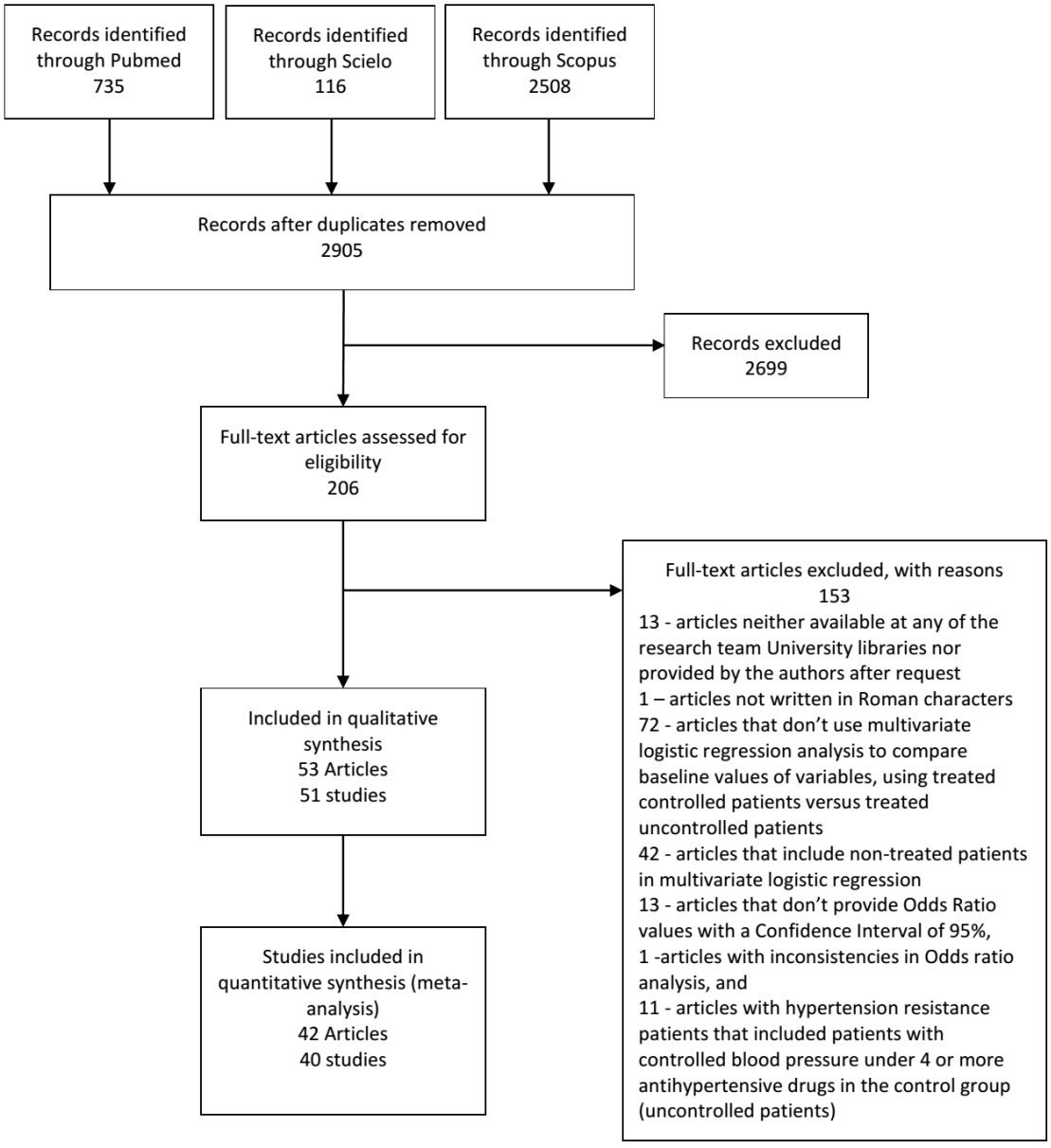


Figure 3 *- PRISMA flow diagram.*

The selection include studies with data collected from 1988 and that took place in a total of 21 different countries.

Globally, 73 different independent variables were analysed trough the 53 selected studies. A total of 12 meta-analysis were possible, evaluating 8 different independent variables. In order to ease data analysis independent variables were grouped in categories, as shown in Table 2.1.

Table 2.1 - Categorization of independent variables analysed in this systematic review

Category	**Variables**
Demographic data	Age, Gender, Race, Education, Socioeconomic status, Marital status, Urban vs rural
Health lifestyle	Physical exercise, Stress, Sedentary lifestyle, Sodium intake, Calcium intake, Magnesium intake, Potassium intake
Abuse substances	Smoking habits, Alcohol consumption, Illicit drug use
Health system	Health insurance, Number of healthcare visits, Therapy intensification, Primary care physician, Physician's age, Physician's degree of motivation
Family history	Family history of HTA, Family history of CVD
Hypertension	Grade of HTA, Years of HTA, Office DBP, Office SBP, Ofice PP, Heart rate
Antihypertensive therapy	Number of antiHTA, Type of antiHTA, Treatment cost, Number of daily doses
Attitudes and behaviours	Adherence, Knowledge, Time from last BP measurement, Patient's concerns about having the disease
Obesity	BMI, Waist/hip ratio, Waist circumference
Cardiovascular disease	LVH, MI, History CVD, Metabolic syndrome, Framingham Score, Congestive Heart Failure, Angina, Coronary artery disease, Taking antiplatelets
Diabetes	Diabetes, Insulin resistance, Fasting glucose intolerance
Dyslipidaemia	Total cholesterol, HDL, Triglycerides, Dyslipidaemia, Taking statins
Kidney diseases	CKD, Microalbuminuria, Serum creatinine
Other comorbidities	Sleep- related breathing disorders, Stroke, Arthritis, Depression, Presence of comorbidities, Number of drugs taken, Taking nonsteroidal anti-inflammatories, Frailty, Hospitalization, Cognitive mini-examination
Polymorphisms	Inducible nitric oxide synthase haplotype

Demographic Data

Age

A total of 24 studies evaluated age influence in BP control, being 10 of them possible to meta-analyse (Table 2.2).

Table 2.2 - Individual assessment of each study regarding suitability for inclusion in adherence meta-analysis.

Study	Justification
Grote (2000)[42]	**Appropriate for meta-analysis**
Lloyd-Jones (2000)[43]	OR stratified by SBP control and DBP control
Degli Esposti (2004)[44]	**Appropriate for meta-analysis**
Isaza (2004)[45]	OR for factors associated with blood pressure control
King (2006)[46]	**Appropriate for meta-analysis**
Ostchega (2008)[47]	Age treated as categorical variable
Gus (2008)[48]	**Appropriate for meta-analysis**
Ham (2011)[49]	OR for factors associated with blood pressure control
Durant (2010)[50]	**Appropriate for meta-analysis**
Koizumi (2013)[51]	**Appropriate for meta-analysis**
Olomu (2013)[52]	OR for factors associated with blood pressure control
Elperin (2014)[53]	**Appropriate for meta-analysis**
Rodolfo (2009)[54]	Age treated as categorical variable
Balijepalli (2014)[55]	Age treated as categorical variable
Chen (2003)[56]	Age treated as categorical variable
Consoli (2010)[57]	Age treated as categorical variable
Cortez-Dias (2013)[58]	**Appropriate for meta-analysis**
Egan (2011)[59]	**Appropriate for meta-analysis**
Gonçalves (2007)[60]	**Appropriate for meta-analysis**
Jackson (2002)[61]	Don't present CI values
Mutua (2014)[62]	OR for factors ass[63]ociated with blood pressure control
Ono (2004)[64]	OR for factors associated with blood pressure control
Tonstad (2004)[65]	Stratified OR by gender
Triolo (2004)[63]	Age treated as categorical variable

Regarding the studies that couldn't be included in meta-analysis, 6 obtained non statistical significant results[45, 52, 54, 56, 61, 64] and the other 8 studies conclude that age is a risk factor for uncontrolled hypertension (Table 2.3).

Table 2.3 - Multivariate logistic regression results of studies not included in meta-analysis.

Study	OR for uncontrol risk	Reference group	Test group	OR	lower CI	upper CI
Ostchega (2008)[47]	Yes	40-59 years	20-39 years	0.73	0.43	1.25
			60-79 years	1.69	1.31	2.17
			≥ 80 years	3.56	2.42	5.25
Ham (2011)[49]	No	Continous variable		0.97	0.95	0.98
Balijepalli (2014)[55]	Yes	≤ 50 years	> 50 years	1.52	1.40	1.65
Consoli (2010)[57]	Yes	< 65 years	≥ 65 years	1.37	1.06	1.76
Mutua (2014)[62]	No	Continous variable		0.64	0.43	0.96
Triolo (2004)[63]	Yes	< 65 years	≥ 65 years	3.64	1.99	6.66
Tonstad (2004)[65]	Yes	Men aged 40-45 years	Men 60 years	1.90	1.10	3.00
			Women 60 years	2.70	1.60	4.50
			Men 75 years	2.30	1.40	3.80
			Women 75 years	5.60	3.30	9.50

Lloyd-Jones *et al.* (2000)[43] analysed influence of age in control of SBP and DBP separately, concluding that, patients with age above 75 years have 4.34 times more risk of having uncontrolled SBP than patients with less than 60 years (OR=4.34; 95% CI 3.10-6.09). Otherwise, regarding DBP, no statistical significant results were obtained (OR=0.61; 95% CI 0.37-1.03).

Tonstad *et al.* (2004)[65] assessed the impact of age in both genders separately, concluding that in both, the risk for uncontrolled blood pressure rises with age, but women had 2 times higher risk than men to uncontrolled BP in all age groups.

In meta-analysis, no statistical significant results were obtained, with a pooled effect size of 1.029 (95% CI 0.986-1.074) (Figure 4), and heterogeneity assessed by i-square of 97%.

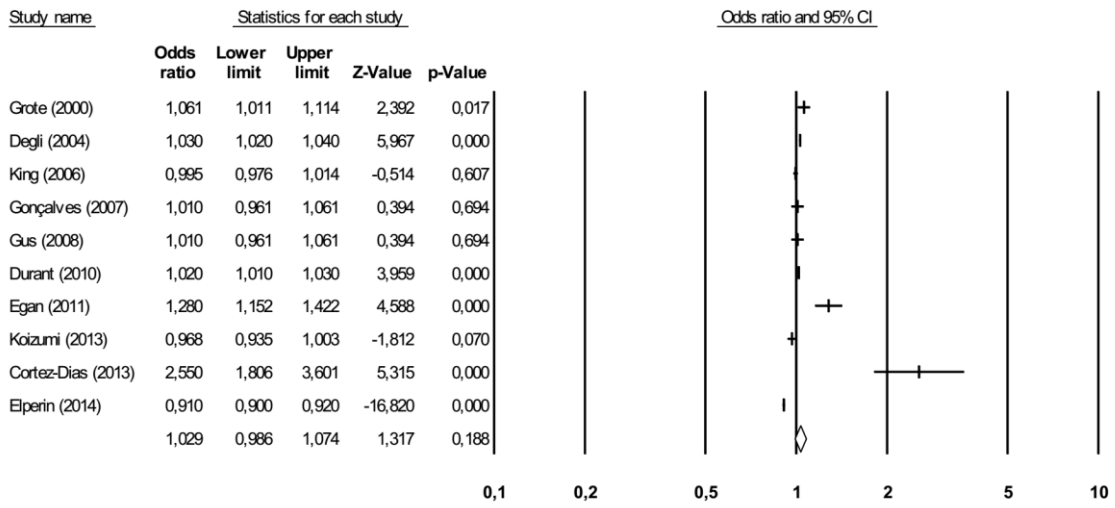


Figure 4 *- Meta-analysis of age influence in blood pressure control.*

Urban vs rural

Durant *et al.* (2010)[50] and King *et al.* (2006)[46] evaluate likelihood of having uncontrolled BP according to residence area. While the first didn't obtain statistical significant results (OR=1.090; 95% CI 0.880-1.350), King *et al.* found that living in rural areas decreases the risk of high blood pressure (OR=0.297; 95% CI 0.160-0.546).

Education level

The influence of patient's level of education in BP control was assessed by 4 studies[47, 50, 65, 66]. In all of them, this variable has a no significant impact in BP control. Due to differences in categorizing levels of education (Table 2.4), meta-analysis was impossible.

Marital status

Although 7 studies[53, 54, 56, 66-69] evaluated this variable, due to differences in marital status classification when addressing the reference group, no meta-analysis was possible. Of them, only 3[53, 67, 69] obtain statistical significance in multivariate logistic regression analysis but directionality of results are different (Table 2.5). In Elperin *et al.* (2014)[53] and Inciardi *et al.* (2003)[69] studies not married or unpartnered patients had higher risk of having BP out of control, but in Morgado *et al.* (2010)[67] the married patients are the ones in higher risk. As so, no conclusion is possible towards marital status.

Table 2.4 - Multivariate logistic regression results of studies assessing education level as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Ostchega (2008)[47]	Yes	More than high school	Less than high school	1.09	0.78	1.53
			High school	0.98	0.76	1.27
Durant (2010)[50]	Yes	> 8th grade	≤ 8th grade	1.09	0.86	1.40
Gee (2012)[66]	Yes	Post secondary graduate	Less than high school	1.20	0.70	2.00
			High school	0.90	0.40	1.90
Tonstad (2004)[65]	Yes	Men with < 13 years	Men with ≥ 13 years	1.20	0.90	1.70
			Women with ≥ 13 years	0.80	0.60	1.10

Table 2.5 - Multivariate logistic regression results of studies assessing marital status as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Morgado (2010)[67]	**Yes**	**Not married**	**Married**	**5.30**	**1.70**	**16.40**
Gee (2012)[66]	Yes	Married	Not married	1.30	0.80	2.20
Elperin (2014)[53]	**Yes**	**With partner**	**Unpartnered**	**1.15**	**1.14**	**1.17**
Rodolfo (2009)[54]	Yes	Married	Cohabiting	0.80	0.40	1.60
			Single	0.90	0.50	1.70
			Widowed	0.60	0.30	1.20
Banegas (2002)[68]	No	With partner	Unpartnered	1.10	x	X
Chen (2003)[56]	Yes	Married/Cohabiting	Single	0.89	0.47	1.67
			Widowed	0.84	0.42	1.65
			Divorced/separated	0.83	0.46	1.52
Inciardi (2003)[69]	**Yes**	**Married**	**Not married**	**1.86**	**1.09**	**3.16**

Race

The impact of race on blood pressure control was assessed by 9 studies. The diversity of races considered as reference group among several studies hindered the realization of meta-analysis (Table 2.6).

Table 2.6 - Multivariate logistic regression results of studies assessing race as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
King (2006)[46]	Yes	White	Black	0.75	0.43	1.33
Ostchega (2008)[47]	**Yes**	**Non-Hispanic white**	Mexican American	1.22	0.85	1.76
			Non-Hispanic black	**1.40**	**1.10**	**1.79**
Durant (2010)[50]	**Yes**	**White**	**Black**	**1.56**	**1.31**	**1.86**
Redmond (2011)[70]	**Yes**	**Non-Hispanic white**	Mexican American	1.08	0.80	1.45
			Non-Hispanic black	**1.90**	**1.57**	**2.31**
Delgado (2012)[71]	**No**	**Non-Hispanic white**	**African american**	**0.81**	**0.70**	**0.93**
Olomu (2013)[52]	No	Other	White	1.18	x	x
Elperin (2014)[53]	**Yes**	**Other**	**Asian /pacific islander**	**0.89**	**0.87**	**0.91**
		Other	Multiple races	0.98	0.84	1.14
		Other	Native american	0.99	0.85	1.15
		Other	**Hispanic**	**1.03**	**1.01**	**1.05**
		Other	**African american**	**1.18**	**1.16**	**1.20**
Egan (2011)[59]	Yes	Other	Black	1.38	0.94	2.03
		Other	Hispanic	1.08	0.82	1.41
Romanelli (2011)[72]	**No**	**White**	**Black**	**0.68**	**0.62**	**0.75**
			Hispanic	**0.80**	**0.74**	**0.86**
			Other	**0.81**	**0.70**	**0.94**

Globally, statistical significant results were obtained when evaluating the likelihood uncontrolled hypertension among black race, regardless of comparing groups, with odds ratios indicating that black patients have an increased risk of poor blood pressure control[47, 50, 53, 70, 71] (Table 2.6). In Romanelli *et al.* (2011)[72], OR were stratified by presence of diabetes and blacks remain significantly less likely to have their BP controlled with treatment within the nondiabetic cohort (OR 0.73; 95% CI 0.66 to 0.83; p <0.001) and in diabetic cohort (OR 0.71; 95% CI 0.59 to 0.84; p< 0.001).

Elperin *et al.* (2014)[53] also found that Hispanic patients had higher uncontrolled BP risk than other races and, inversely, Asian /pacific islander patients have lower risk of uncontrolled BP.

Gender

A total of 17 studies evaluated gender as predictor of poor blood pressure control and 10 were include in meta-analysis (Table 2.7).

Table 2.7 - Individual assessment of each study regarding suitability for inclusion in adherence meta-analysis.

Study	Justification
Lloyd-Jones (2000)[43]	**Appropriate for meta-analysis**
King (2006)[46]	**Appropriate for meta-analysis**
Ostchega (2008)[47]	Different reference group
Gus (2008)[48]	**Appropriate for meta-analysis**
Ham (2011)[49]	OR for factors associated with blood pressure control
Durant (2010)[50]	**Appropriate for meta-analysis**
Zhang (2011)[73]	OR for factors associated with blood pressure control
de la Sierra (2013)[74]	Different reference group
Koizumi (2013)[51]	Different reference group
Olomu (2013)[52]	OR for factors associated with blood pressure control
Elperin (2014) [53]	**Appropriate for meta-analysis**
Rodolfo (2009)[54]	**Appropriate for meta-analysis**
Balijepalli (2014)[55]	**Appropriate for meta-analysis**
Chen (2003)[56]	**Appropriate for meta-analysis**
Egan (2011)[59]	**Appropriate for meta-analysis**
Gonçalves (2007)[60]	**Appropriate for meta-analysis**
Ono (2004)[64]	OR for factors associated with blood pressure control

Regarding the studies that couldn't be included in meta-analysis, in Ostchega *et al.* (2008)[47], Zhang *et al.* (2011)[73] and De la Sierra *et al.* (2013)[74] studies, female had higher risk of having uncontrolled blood pressure, while opposite results were obtained by Olomu *et al.* (2013)[52], in whose results females had an increase likelihood of having good BP levels (Table 2.8).

Table 2.8 - Multivariate logistic regression results of studies not included in meta-analysis.						
Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Lloyd-Jones (2000)[43]	**Yes**	**Female**	**Male**	**1.75**	**1.16**	**2.63**
King (2006)[46]	**Yes**	**Female**	**Male**	**2.04**	**1.17**	**3.55**
Ostchega (2008)[47]	**Yes**	**Male**	**Female**	**1.29**	**1.01**	**1.64**
Gus (2008)[48]	Yes	Female	Male	1.63	0.70	3.80
Ham (2011)[49]	No	Male	Female	1.48	0.99	2.21
Durant (2010)[50]	**Yes**	**Female**	**Male**	**1.65**	**1.38**	**1.97**
Zhang (2011)[73]	No	Male	Female	0.22	X	x

In meta-analysis, a pooled effect size of 1.447 was obtained (95% CI 1.194-1.754) (Figure 5), indicating male gender as predictor of uncontrolled hypertension (heterogeneity assessed by i-square =91%).

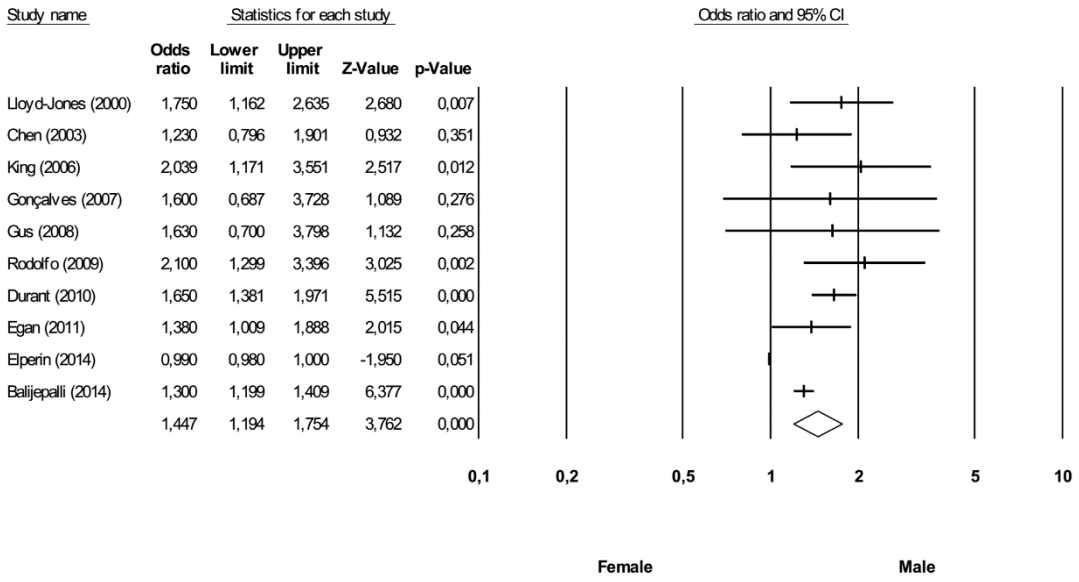


Figure 5 *- Meta-analysis of gender influence in blood pressure control.*

Socioeconomic status

Of the 4 studies that addressed this variable, only 2 obtained statistical significant results. Ostchega *et al.* (2008)[47] found that patients with lower incomes have increased likelihood of having uncontrolled hypertension, while on the other hand, Inciardi *et al.* (2003)[69]

results show that increasing income is a risk factor for uncontrolled BP. Has the income categories used in all studies were different no meta-analysis was possible (Table 2.9).

Health Lifestyle

Physical exercise

The impact of physical activity in blood pressure control was evaluated in 7 studies, 2 of them[49, 68] evaluate the likelihood of having blood pressure control according to the level of physical activity, while the others evaluate the impact of exercise in uncontrolled BP risk (Table 2.10). Only 3 have statistical significant results, in Ham *et al.* (2011)[49] and Salifu *et al.* (2005)[75] studies, low levels of physical activity increases the risk of BP uncontrolled, but in Gee *et al.* (2012)[66] opposite results were obtained. Once levels of physical exercise considered in reference group and in test group were different across studies, no meta-analysis of this variable was possible.

Sedentary lifestyle

Sedentary lifestyle was approached by 2 studies. Bøg-Hansen *et al.* (2003)[76] performed a multivariate logistic regression considering not only SBP and DBP separately, but also evaluating both genders independently. In his study, sedentary lifestyle has no statistical significant impact in both SBP or DBP control in women (OR=1.2; 95% CI 0.41-3.58 and OR=0.8; 95% CI 0.42-1.50, respectively). Regarding men, sedentary lifestyle represents a 2.3 higher risk of having SBP uncontrolled, but no statistical significant impact in DBP control (OR=12.3; 95% CI 1.07-5.09 and OR=1.0; 95% CI 0.71-1.33, respectively).

Consoli *et al.* (2010)[57] results show that likelihood of having uncontrolled hypertension is 1,54 higher in sedentary patients (OR=1.54; 95% CI 1.10-2.17).

Table 2.9 - Multivariate logistic regression results of studies assessing socioeconomic status as independent variable regarding uncontrolled hypertension.						
Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Ostchega (2008)[47]	**Yes**	**≥ 4 in Poverty income ratio (PIR)**	**< 1 PIR**	**1.68**	**1.19**	**2.37**
			1 - <2 PIR	1.18	0.81	1.73
			2 - <4 PIR	1.05	0.81	1.37
Durant (2010)[50]	Yes	> $75000	< $20000	1.34	0.97	1.85
			$20000 - $34999	1.24	0.93	1.65
			$35000 - $74000	1.22	0.93	1.59
Gee (2012)[66]	Yes	≥ $80000	$50000 - $79999	0.60	0.30	1.10
			$30000 - $49999	1.20	0.50	2.70
			$00000 - $29000	1.60	0.80	3.00
Inciardi (2003)[69]	**Yes**	**Continous variable**		**1.30**	**1.03**	**1.65**

Table 2.10 - Multivariate logistic regression results of studies assessing physical exercise as independent variable regarding uncontrolled hypertension.						
Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Ham (2011)[49]	**No**	**≥ 4 days/week**	**≤ 3 days/week**	**0.60**	**0.38**	**0.94**
Durant (2010)[50]	Yes	≥ 1 days/week	0 days/week	0.95	0.80	1.12
Gee (2012)[66]	**Yes**	**≥ 120 min/week**	**30-119 min/week**	**0.30**	**0.10**	**0.70**
			0-29 min/week	0.60	0.30	1.30
Banegas (2002)[68]	No	No	Yes	0.96	x	x
Salifu (2005)[75]	**Yes**	**Regular exercise**	**Lack of regular exercise**	**2.26**	**1.16**	**4.37**
Tonstad (2004)[65]	Yes	Low phisical activity in men	Moderate/High (men)	1.00	0.60	1.50
			Moderate/High (women)	1.20	0.80	1.70

Stress

Stress influence in blood pressure control was evaluated by Ham *et al.* (2011)[49], who used hardly ever presence of stress as reference group. He conclude that patients exposed to moderate or severe levels of stress were less likely to have their BP under control (OR=0.58; 95% CI 0.37-0.89 and OR=0.56; 95% CI 0.35-0.67 to moderator and severe levels of stress, respectively).

Sodium intake

A total of 4 studies evaluated the impact of sodium intake in blood pressure control. Goverwa *et al.* (2014)[77] and Mesli *et al.* (2014)[78] multivariate logistic regression analysis show that having no kind of dietary salt restriction increases the risk of uncontrolled hypertension (Table 2.11). The other two studies obtained no statistical significant results.

Table 2.11 - Multivariate logistic regression results of studies assessing sodium intake as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Rodolfo (2009)[54]	Yes	Dietary salt restriction	No dietary salt restriction	0.60	0.20	1.30
Goverwa (2014)[77]	**Yes**	**No adding salt to food at the table**	**Adding salt to food at the table**	**2.77**	**1.41**	**5.43**
Mesli (2014)[78]	**Yes**	**Dietary salt restriction**	**No dietary salt restriction**	**2.71**	**1.42**	**5.18**
Schroder (2002)[79]	Yes	Intake of ≥ 2400 mg/d sodium	Intake of < 2400 mg/d sodium	0.56	0.22	1.39

Calcium, Magnesium and Potassium intake

Schroder *et al.* (2002)[79] had studied the relationship of certain amounts of calcium, magnesium and potassium intake with uncontrolled blood pressure. The multivariate logistic regression performed show no statistical significant correlations between this variables and hypertension control (OR=0.57; 95% CI 0.27-1.19 for calcium intake, OR=0.59; 95% CI 0.38-1.47 for magnesium intake, and OR=0.75; 95% CI 0.25-1.41 for potassium intake).

Abuse substances

Smoking habits

A total of 14 studies addressed the relationship between smoking habits and blood pressure control. Of them, only 4 could be included in a meta-analysis (Table 2.12).

Table 2.12 - Individual assessment of each study regarding suitability for inclusion in smoking meta-analysis.

Study	Justification
McNagny (1997)[80]	Stratified OR by compliance rates
Ostchega (2008)[47]	Different reference group
Ham (2011)[49]	OR for factors associated with blood pressure control
Durant (2010)[50]	**Appropriate for meta-analysis**
Zhang (2011)[73]	Different reference group
Gee (2012)[66]	**Appropriate for meta-analysis**
de la Sierra (2012)[74]	Different reference group
Olomu (2013)[52]	OR for factors associated with blood pressure control
Balijepalli (2014)[55]	**Appropriate for meta-analysis**
Banegas (2002)[68]	OR for factors associated with blood pressure control
Bøg-Hansen (2003)[76]	Stratified OR by gender and catherogies of BP
Chen (2003)[56]	**Appropriate for meta-analysis**
Jackson (2002)[61]	Don't present CI values
Tonstad (2004)[65]	Stratified OR by gender

Regarding studies that weren't include in meta-analysis, only in 4 statistical significant results were obtained. Ostchega *et al.* (2008)[47] and de la Sierra *et al.* (2012)[74] obtained opposite results and in Zhang *et al.* (2011)[73] study, patients who smoke more than 20 cigarettes per day have less probabilities of having blood pressure under control (Table 2.13). McNagny *et al.* (1997)[80] assessed adjusted odds ratios of uncontrolled hypertension by smoking status, stratified by compliance, considering former smokers as the reference group. In noncompliant group, no statistical significant results were obtained (OR=1.3; 95% CI 0.4-4.2 and OR=1.7; 95% CI 0.5-5.6 to never and current smoker, respectively). Regarding compliant group, a significant association was found, with current smokers having 14,4 times more likelihood of having uncontrolled hypertension than former smokers (OR=14.4; 95% CI 3.3-63.3). In their study, among compliant patients, never-smokers were also more likely to have severe uncontrolled HTN than were former smokers (OR=5.7; 95% CI 1.5-21.7).

Table 2.13 - Multivariate logistic regression results of studies not included in meta-analysis.						
Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Ostchega (2008)[47]	**Yes**	**Current smoker**	**Never smoker**	**1.59**	**1.15**	**2.19**
			Former smoker	1.36	0.90	2.07
Ham (2011)[49]	No	Non smoker	Current smoker	1.29	0.80	2.09
Zhang (2011)[73]	**No**	**<20 cigaretttes/day**	**>20 cigaretttes/day**	**0.11**	**p=0.02**	
de la Sierra (2012)[74]	**Yes**	**Non smoker**	**Current smoker**	**1.78**	**1.36**	**2.34**
Olomu (2013)[52]	No	Non smoker	Current smoker	0.56	p>0.05	
Banegas (2002)[68]	No	Never smoker	Current smoker	1.07	p>0.05	
Bøg-Hansen (2003)[76]	Yes	Non smoker	Current smoker	p>0.05		
Jackson (2002)[61]	Yes	Non smoker	Current smoker	0.68	p>0.05	
Tonstad (2004)[65]	Yes	Non smoker	Current smoker	p>0.05		

Two different meta-analysis were performed, both with never smokers as reference group. One to evaluate association between current smoker status and poor blood pressure control and another to evaluate the impact of former smoker status in uncontrolled hypertension.

In first meta-analysis, current smokers versus never smokers, no statistical significant results were obtained (pooled effect size 1.064; 95% CI 0.762-1.486 and heterogeneity assessed by i-square= 80%) (Figure 6)

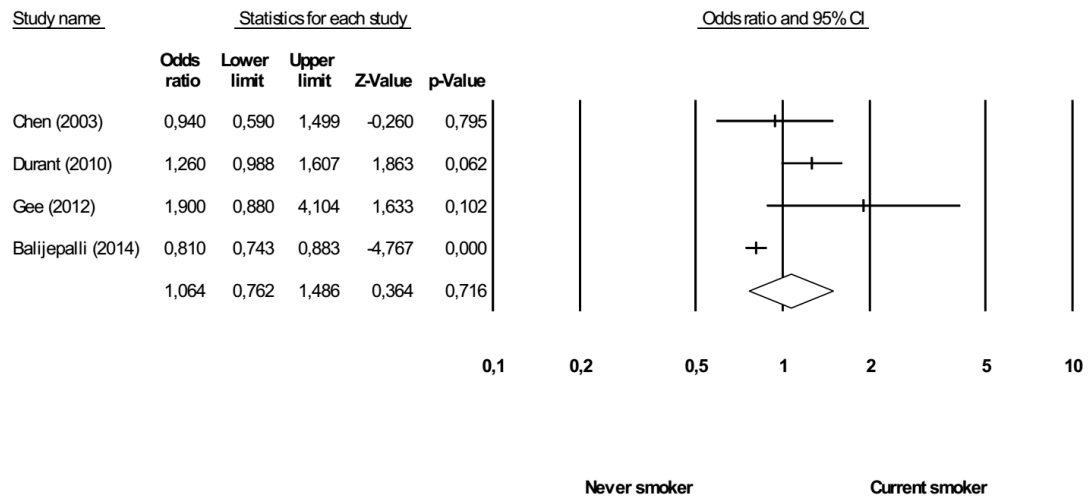


Figure 6 *- Meta-analysis of current smokers influence in blood pressure control.*

In second meta-analysis, former smokers seems to have less risk of uncontrolled hypertension that never smokers, with a pooled effect size 0.847 (95% CI 0.794-0.904) and heterogeneity assessed by i-square of 0%) (Figure 7).

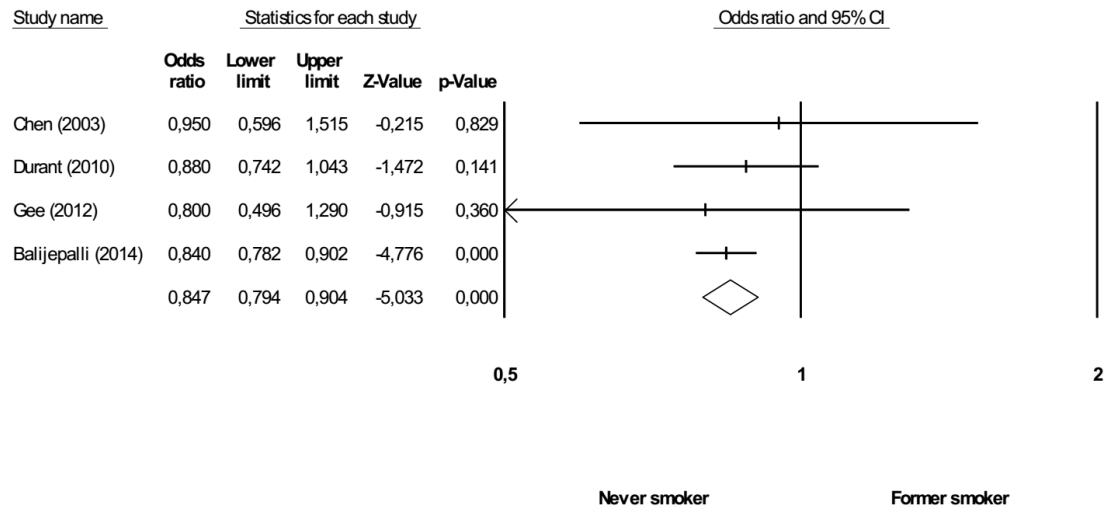


Figure 7 - *Meta-analysis of former smokers influence in blood pressure control.*

Alcohol consumption

Of the 9 studies found that assess alcohol consumption impact on BP control, only one, Consoli *et al.* (2010)[57], present statistical significant results, with the consumption of four glasses or more of alcohol per day increasing the likelihood of uncontrolled hypertension in 2.17 times in relation to patients that drink less than four glasses of alcohol per day. Taking into account the variety of reference groups used in logistic regression, no meta-analysis of this variable was possible (Table 2.14).

Illicit drug use

Only one study, Shea *et al.* (1992a)[81], evaluate association between the illicit use of drugs and lack of control of blood pressure, having however obtained no statistical significant results (OR=1.3, 95% CI 0.5-3.6).

Table 2.14 - Multivariate logistic regression results of studies assessing alcohol consumption as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Shea (1992a)[81]	Yes	no alcohol problems	alcohol problems	2.20	0.80	6.30
Ham (2011)[49]	No	no heavy alcohol drinking	≤ Monthly heavy alcohol drinking	0.60	0.36	1.00
			≥ Weekly heavy alcohol drinking	0.92	0.52	1.61
Durant (2010)[50]	Yes	moderate or heavy alcohol use	No alcohol use	1.43	0.85	2.38
Gee (2012)[66]	Yes	0-1 drink/day	≥2 drinks/day	0.80	0.30	2.00
Banegas (2002)[68]	No	Teetotal	Current	1.04	p>0.05	
Bøg-Hansen (2003)[76]	Yes	High alcohol consumption in men	Moderate alcohol consumption in men	a	A	a
		High alcohol consumption in women	Moderate alcohol consumption in women	a	A	a
Chen (2003)[56]	Yes	0 units/week	1 - <10 units/week	0.71	0.43	1.17
			10 - <21 units/week	0.89	0.50	1.60
			≥21 units/week	0.67	0.38	1.19
Consoli (2010)[57]	**Yes**	**≤ 4 glasses/day**	**≥ 4 glasses/day**	**2.17**	**1.18**	**3.99**
Tonstad (2004)[65]	Yes	zero-once weekly in men	≥2 times/week in men	1.20	0.80	1.60
			≥2 times/week in women	1.00	0.70	1.50

a) In Bøg-Hansen (2003) study, OR of uncontrolled were calculated separately to SBP and to DBP and both genders were evaluated independently. In none of situations statistical significant results were obtained.

Health system

Health insurance

A total of 6 studies approached this variable, however only 3 could be meta-analysed (Table 2.15). Of studies excluded from meta-analysis, none presented statistical significant results (Table 2.16).

Table 2.15 - Individual assessment of each study regarding suitability for inclusion in health insurance meta-analysis.

Study	Justification
Shea (1992a)[81]	**Appropriate for meta-analysis**
Ostchega (2008)[47]	**Appropriate for meta-analysis**
Durant (2010)[50]	Diferent reference group
Olomu (2013)[52]	OR for factors associated with blood pressure control
Egan (2011)[59]	Diferent reference group
Inciardi (2003)[69]	**Appropriate for meta-analysis**

Table 2.16 - Multivariate logistic regression results of studies not included in meta-analysis.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Durant (2010)[50]	Yes	Don't have health insurance	Have health insurance	1.03	0.72	1.46
Olomu (2013)[52]	No	Others	Medicaid/Medicare	1.22	p > 0.05	
Egan (2011)[59]	Yes	Don't have health insurance	Have health insurance	0.80	0.45	1.45

The results obtained in meta-analysis have low heterogeneity (i-square=0%) and are indicative that patients without health insurance have 1.7 times higher risk of uncontrolled hypertension (pooled effect size 1.703; 95% CI 1.242-2.335) (Figure 8).

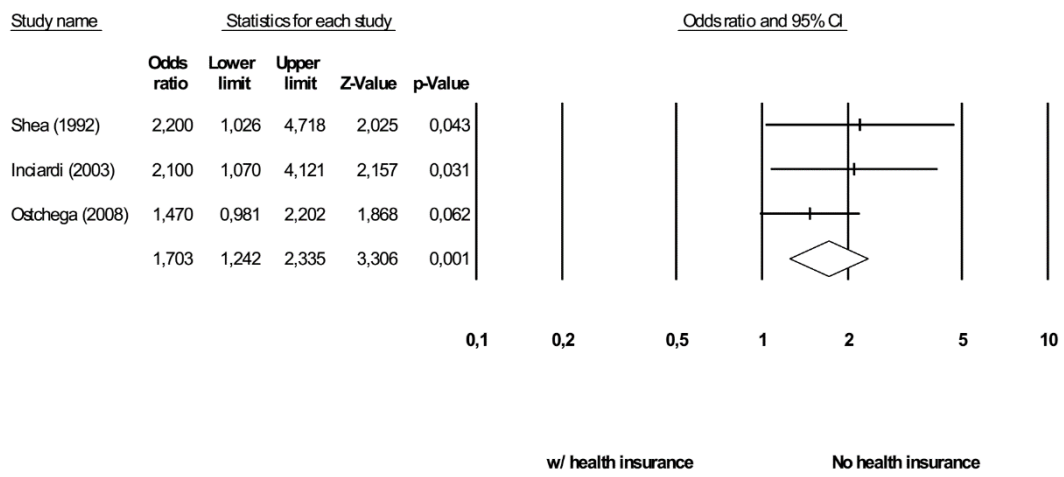


Figure 8 *- Meta-analysis of health insurance influence in blood pressure control.*

Number of healthcare visits

Four studies evaluated the influence of number of healthcare visits in the control of blood pressure, two considering this variable as continuous and two establishing different cut-points, reasons that prevent meta-analysis performing (Table 2.17). Only Ostchega *et al.* (2008)[47] had statistical significant results, with patients reporting 2-3 healthcare visits in the last year being more likely to have uncontrolled blood pressure, when compared with patients reporting 10 or more healthcare visits.

Table 2.17 - Multivariate logistic regression results of studies assessing number of healthcare visits as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
King (2006)[46]	Yes	Continous variable		0.98	0.92	1.05
Ostchega (2008)[47]	**Yes**	**≥10**	0 – 1	1.25	0.76	2.07
			2 a 3	**1.42**	**1.04**	**1.95**
			4 a 9	1.02	0.77	1.35
Olomu (2013)[52]	No	Continous variable		1.04	p=0.29	
Banegas (2002)[68]	No	> 1	≤ 1	0.80	p>0.05	

Therapy intensification

Ho *et al.* (2008)[82] studied therapy intensification importance in blood pressure control. Defined as a dosage increase for any drug or an increase in the total number of antihypertensive medications between the first and last 6 months of follow-up (being that a single substitution of drug class was not counted as intensification), therapy intensification was significantly associated with having uncontrolled BP (OR=1.31; 95% CI 1.01-1.7).

Primary care physician

Having a primary care physician was approached by Shea *et al.* (1992a)[81]. In his multivariate logistic regression, the absence of a primary care physician increases in 4.4 times de risk of uncontrolled hypertension (OR=4.4; 95% CI 2.2-8.9).

Physician's age

Degli Esposti *et al*. (2004)[44] evaluate physician's age as predictor of not achieving adequate blood pressure control. Treating this variable as continuous, statistical significant results were obtained, being every year age increment in physician's age responsible for 1,06 more times of chances of having uncontrolled BP (OR=1.06; 95% CI 1.03-1.09).

Physician's degree of motivation

The impact on blood pressure control of physician's degree of motivation was assessed by Consoli *et al.* (2010)[57]. Calculating Odds Ratio considering this as an ordinal variable, for one degree of less motivation, the risk of high blood pressure increases 1.10 times (OR=1.10; 95% CI 1.01-1.20).

Family history

Family history of HTA

Three studies evaluate family history of hypertension as a predictor of blood pressure uncontrolled[47, 53, 63], and all were included in a meta-analysis. High heterogeneity was obtained (i-square=60%) and no statistical significant pool effect size was found (Figure 9).

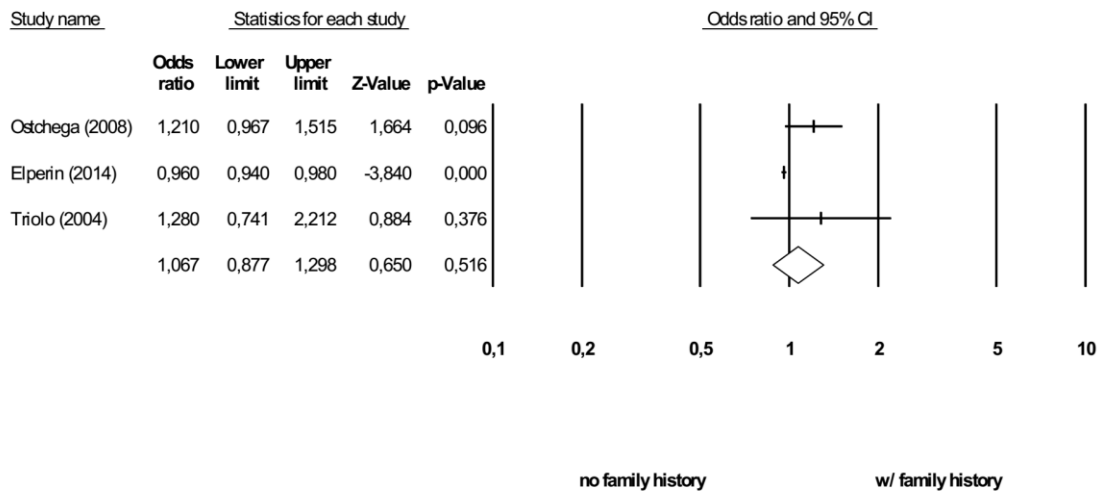


Figure 9 *- Meta-analysis of family history of hypertension influence in blood pressure control.*

Family history of CVD

Banegas *et al.* (2002)[68] and Jackson *et al.* (2002)[61] evaluate the impact of family history of cardiovascular disease in hypertension control. While Banegas *et al.* (2002)[68] doesn't obtain statistical significant results, Jackson *et al.* (2002)[61] claims that familiar history of CVD is a negative predictor of uncontrolled blood pressure (OR=0.567; p=0.014).

Hypertension

Grade of HTA

Rodolfo *et al.* (2009)[54] studied the influence of grade of hypertension in the control of blood pressure, considering pre-hypertension the reference group. After multivariate logistic regression, no statistical significance was obtained in the association of BP control and hypertension grade 1 (OR=1.1; 95% CI 0.6-2.1), but hypertension grade 2 or 3 represents a 3.8 higher risk of being an uncontrolled hypertensive patient (OR=3.8; 95% CI 1.3-11.0).

Years of HTA

Gonçalves *et al.* (2007)[60] approached the effect of hypertension duration in years in blood pressure control. They obtained no statistical significant results (OR=0.96; 95% CI 0.91-1.02).

Office SBP, Office DBP and Office PP

De Marco *et al.* (2012)[83] evaluate office systolic blood pressure as initial predictor of follow-up uncontrolled blood pressure. After multivariate logistic regression SBP confirmed to be independently associated with BP uncontrolled, with patients with higher SBP having 1.12 higher risk of uncontrolled hypertension (OR=1.12; 95% CI 1.10-1.15).

Regarding to office diastolic blood pressure and office pulse pressure, variable assessed by Ono *et al.* (2004)[64], no statistical significance was obtained (OR=0.77; 95% CI 0.58-1.03 to office DBP and OR=1.16; 95% CI 0.90-1.48 to office PP).

Heart rate

Izzo *et al.* (2011)[84] evaluate influence of heart rate in blood pressure uncontrolled. According to his results, an increasing of heart rate of 5 beats/minute correspond to an increase of 1.04 times of having uncontrolled hypertension (OR=1.04; 95% CI 1.01-1.07).

Antihypertensive therapy

Number of antihypertensive drugs

Regarding the number of antihypertensive drugs (antiHTA) taken, 8 studies approached this variable. Of them 6 have statistical significant results, however, while in 3 studies multidrug therapy was beneficial to hypertension control, in the other 3 studies multidrug therapy was a predictor for blood pressure uncontrolled. Unfortunately, as the reference group varies between studies, no meta-analysis was possible (Table 2.18).

Table 2.18 - Multivariate logistic regression results of studies assessing number of antihypertensive drugs taken as independent variable regarding uncontrolled hypertension.						
Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Zhang (2011)[73]	**No**	**Monotherapy**	**Multidrug therapy**	**43.08**	**p=0**	
Gee (2012)[66]	Yes	Monotherapy	2 antiHta drugs	0.70	0.50	1.10
			≥ 3 antiHta drugs	1.40	0.90	2.30
Elperin (2014)[53]	**Yes**	**Continous variable**		**1.37**	**1.33**	**1.41**
Isaza (2004)[45]	**No**	**Monotherapy**	**Multidrug therapy**	**1.57**	**1.05**	**2.30**
Consoli (2010)[57]	**Yes**	**< 3 antiHta drugs**	**≥ 3 antiHta drugs**	**1.81**	**1.21**	**2.71**
De Marco (2012)[83]	**Yes**	**Continous variable**		**1.20**	**1.13**	**1.27**
Mutua (2014)[62]	**No**	**< 3 antiHta drugs**	**≥ 3 antiHta drugs**	**0.41**	**0.26**	**0.64**
Ono (2004)[64]	No	Multidrug therapy	Monotherapy	3.77	0.27	51.90

Type of antiHTA

Nine studies evaluate the impact of different antihypertensive treatment on blood pressure control. Due to differences between the antihypertensive considered as independent variable no meta-analysis was possible (Table 2.19).

Analysing multivariate logistic regressions analysis of the included studies according to the antihypertensive therapeutic class:

- Renin–angiotensin system inhibitor (RAS-I) – Izzo *et al.* (2011)[84], Elperin *et al.* (2014)[53] and Egan *et al.* (2011)[59] studied the influence of taking angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) in blood pressure control, concluding that RAS-I were associated with lower risk of uncontrolled BP (OR=0.83; 95% CI 0.71-0.96; OR=0.85; 95% CI 0.82-0.88 and OR=0.59; 95% CI 0.42-0.84, respectively).
- Diuretics:

- Potassium sparing diuretics – According to Elperin *et al.* (2014)[53] and Oikawa *et al.* (2006)[85], potassium sparing diuretics were associated with lower risk of uncontrolled BP (OR=0.68; 95% CI 0.62-0.73 and OR=0.27; 95% CI 0.11-0.72, respectively).
- Loop diuretic – Elperin *et al.* (2014)[53] concluded that taking loop diuretics is associated with lower risk of uncontrolled BP (OR=0.75; 95% CI 0.71-0.79).

- Thiazide – Elperin *et al.* (2014)[53] and Egan *et al.* (2011)[59] concluded that thiazides were associated with lower risk of uncontrolled BP (OR=0.76; 95% CI 0.73-0.79 and OR=0.66; 95% CI 0.49-0.89, respectively).

- Calcium channel blockers (CCB) – opposite results were obtained, not only in the analysis of global CCB influence in BP by Mutua *et al.* (2014)[62] and Salifu *et al.* (2005)[75], but also in separately evaluation of dihydropyridine CCB and non-dihydropyridine CCB by Elperin *et al.* (2014)[53] and Egan *et al.* (2011)[59] (Table 2.19), which hindered any conclusions.
- Adrenergic blockers – Elperin *et al.* (2014)[53] assessed the impact of adrenergic blockers in BP control performing separate multivariate logistic regressions analysis to α-blockers, β-blockers and α-β-blockers. All demonstrate to be associated with lower risk of uncontrolled BP (OR=0.73; 95% CI 0.68-0.78; OR=0.85; 95% CI 0.81-0.89, and OR=0.74; 95% CI 0.68-0.81, respectively).

Table 2.19 - Multivariate logistic regression results of studies assessing type of antiHTA as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Izzo (2011)[84]	**Yes**	**No IECA ou ARA**	**IECA ou ARA**	**0.83**	**0.71**	**0.96**
Olomu (2013)[52]	No	No β-blockers	β-blockers	1.27	p=0.44	
		No IECA ou ARA	IECA ou ARA	0.63	p=0.11	
		No Diuretics	Diuretics	0.69	p=0.23	
		No CCB	CCB	0.55	p=0.15	
Elperin (2014)[53]	**Yes**	**No Potassium sparing diuretic**	**Potassium sparing diuretic**	**0.68**	**0.62**	**0.73**
		No α-blocker	**α-blocker**	**0.73**	**0.68**	**0.78**
		No Aldosterone antagonist	**Aldosterone antagonist**	**0.73**	**0.67**	**0.80**
		No α-β-blocker	**α-β-blocker**	**0.74**	**0.68**	**0.81**
		No Loop diuretic	**Loop diuretic**	**0.75**	**0.71**	**0.79**
		No Thiazide	**Thiazide**	**0.76**	**0.73**	**0.79**
		No Non-dihydropyridine CCB	**Non-dihydropyridine CCB**	**0.79**	**0.72**	**0.86**
		No β-blockers	**β-blockers**	**0.85**	**0.81**	**0.89**
		No IECA ou ARA	**IECA ou ARA**	**0.85**	**0.82**	**0.88**
		No Dihydropyridine CCB	**Dihydropyridine CCB**	**1.17**	**1.12**	**1.22**
		No Sympatholytic	**Sympatholytic**	**1.19**	**1.09**	**1.30**
		No Vasodilator	**Vasodilator**	**1.27**	**1.18**	**1.36**

Table 2.19 - Multivariate logistic regression results of studies assessing type of antiHTA as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Rodolfo (2009)[54]	Yes	No IECA	IECA monotheray	1.50	0.80	2.70
			IECA multitherapy	1.80	x	X
Egan (2011)[59]	Yes	**No IECA ou ARA**	**IECA ou ARA**	**0.59**	**0.42**	**0.84**
		No α-β-blocker or β-blocker-	α-β-blocker or β-blocker-	0.79	0.54	1.17
		No Dihydropyridine CCB	**Dihydropyridine CCB**	**0.59**	**0.38**	**0.90**
		No Non-dihydropyridine CCB	**Non-dihydropyridine CCB**	**1.97**	**1.08**	**3.58**
		No Thiazide	**Thiazide**	**0.66**	**0.49**	**0.89**
Inciardi (2003)[69]	Yes	No IECA + diuretic	IECA + diuretic	0.38	0.19	0.75
		No diuretic alone	diuretic alone	0.75	0.38	1.48
Mutua (2014)[62]	**No**	**No CCB**	**CCB**	**2.10**	**1.40**	**3.30**
Oikawa (2006)[85]	**Yes**	**No Potassium sparing diuretic**	**Potassium sparing diuretic**	**0.27**	**0.11**	**0.72**
Salifu (2005)[75]	**Yes**	**No CCB**	**CCB**	**2.30**	**1.22**	**4.32**

Treatment cost

Zhang *et al.* (2011)[73] performed a multivariable logistic regression having concluded that higher treatment cost were beneficial to hypertension control (OR=1.09, p=0.009).

Number of daily doses

Consoli *et al.* (2010)[57] evaluate the effect of the number of daily doses in blood pressure control, having conclude that patients with antihypertensive medication divided into two or three daily doses have 1.49 times higher risk of uncontrolled BP than patients with only one daily dose (OR=1.49; 95% CI 1.10–2.01).

Patient's attitudes and behaviours

Adherence

The impact of adherence in blood pressure control was assessed by 8 studies, 6 of them could be include in a meta-analysis (Table 2.20).

Table 2.20 - Individual assessment of each study regarding suitability for inclusion in adherence meta-analysis.

Study	Justification
Shea (1992a)[81]	**Appropriate for meta-analysis**
Durant (2010)[50]	**Appropriate for meta-analysis**
Schmitt (2010)[86]	**Appropriate for meta-analysis**
Morgado (2010)[67]	**Appropriate for meta-analysis**
Goverwa (2014)[77]	Different reference group
Ho (2008)[82]	**Appropriate for meta-analysis**
Okuno (2002)	OR for factors associated with blood pressure control
Salifu (2005)[75]	**Appropriate for meta-analysis**

Regarding the 2 studies excluded from meta-analysis, Goverwa *et al.* (2014)[77] treated adherence as an factor associated BP control, concluding that being compliant with the drug treatment regimen decreases the risk of uncontrolled hypertension (OR=0.34; 95% CI 0.16-0.72). Okuno *et al.* (2002)[87] calculated odds ratio for achieving the target BP in treated hypertensives, concluding that good compliance is a predictor of good blood

pressure control, although no statistical significant results were obtained (OR=1.13; 95% CI 0.49-2.64).

In meta-analysis, a pooled effect size of 1.705 was obtained (95% CI 1.335-2.177)(Figure 10), indicating adherence as predictor of uncontrolled hypertension, (heterogeneity assessed by i-square =81%).

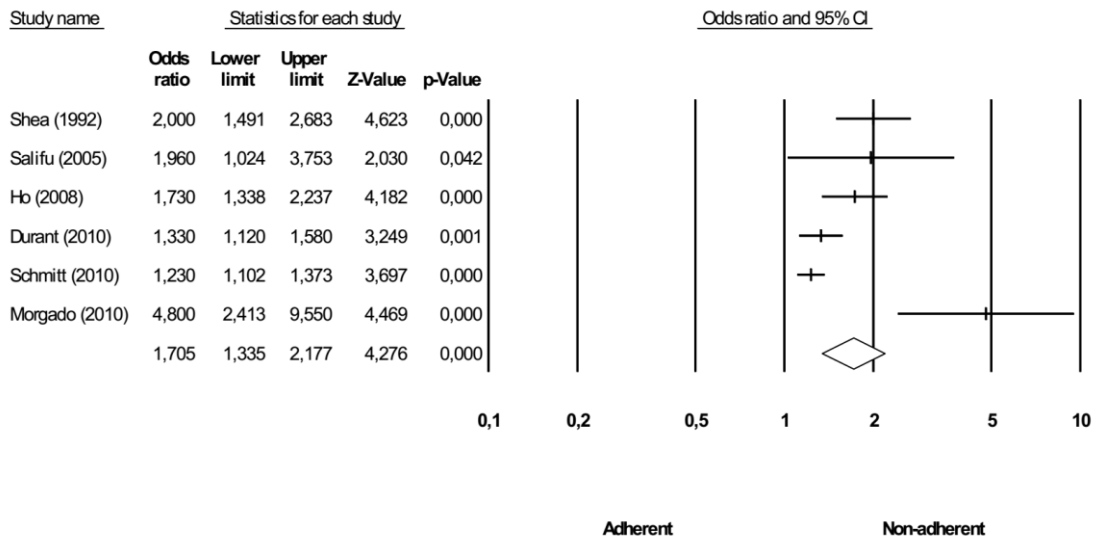


Figure 10 *- Meta-analysis of adherence influence in blood pressure control.*

Knowledge

Zhang *et al.* (2011)[73] evaluate the association between blood pressure control and patient's understanding of the danger of hypertension, concluding that higher the understanding, the better the hypertension control (OR=61.4, p=0). Same conclusions were achieved by Goverwa *et al.* (2014)[77], whose results show that having received health education on hypertension is an independent factor associated with uncontrolled hypertension (OR=0.49; 95% CI 0.25-0.97), as well as having a high perception of the risk associated to developing complications resulting from hypertension (OR=0.40; 95% CI 0.20-0.84).

Time from last BP measurement

Ostchega *et al*. (2008)[47] assessed the impact of routinely measure BP. He evaluate whether persons who had not had a BP measurement within the past 6 months were more likely to be uncontrolled compared with persons who had BP measured in the last 6 months, but no statistical significant results were found (OR=1.62; 95% CI 0.91–2.88).

Patient's concerns about having the disease

Consoli *et al*. (2010)[57] evaluate if patient more concerned about having hypertension had more risk of having uncontrolled blood pressure. According to the results of his study, more worrying about hypertension or hypertension more often experienced as a foreign body, as declared by the patient represents a 1.49 times higher risk of having uncontrolled BP (OR=1.49; 95% CI 1.17–1.90).

Obesity

BMI

A total of 23 studies evaluate the impact of body mass index in blood pressure control. Of them, 13 could be include in 4 different meta-analysis (Table 2.21), one with studies that treat BMI as continuous variable and three with studies that treat BMI as a categorical variable using as comparison groups BMI < 25 Kg/m^2 versus BMI between 25-29.9 Kg/m^2, other with studies using as comparison groups BMI < 25 Kg/m^2 versus BMI ≥ 30 Kg/m^2 and another using as comparison groups BMI < 30 Kg/m^2 versus BMI ≥ 30 Kg/m^2.

Regarding studies that weren't include in meta-analysis, 4 calculated OR for factors associated with blood pressure control[49, 52, 64, 68]. Olomu *et al.* (2013)[52] and Banegas *et al.* (2012)[68] did not obtain statistical significant results (OR=0.99, p> 0.05 and OR=1.11, p> 0.05, respectively). Ono *et al.* (2004)[64] treated BMI as continuous variable, concluding that higher the BMI, lower the likelihood of having blood pressure under control (OR=0.49; 95% CI 0.27-0.88). Ham *et al.* (2011)[49] compare patients with BMI < 25 Kg/m^2 with patients with BMI between 25-29.9 Kg/m^2, being the last ones less likely to have good BP levels (OR=0.44; 95% CI 0.20-0.95). Making the same comparison, using patients with BMI > 30 Kg/m^2, no statistical significant results were obtained (OR=0.77; 95% CI 0.55-1.07).

Lloyd-Jones *et al.* (2000)[43] calculated OR separately for SBP and DBP. In both BMI > 30 Kg/m^2 is a predictor of poor BP control, being the risk of uncontrolled DBP almost 2 times higher than uncontrolled SBP in this patients (OR=2.63; 95% CI 1.45-4.78 for DBP and OR=1.49; 95% CI 1.08-2.06 for SBP).

Tonstad *et al.* (2004)[65] evaluated both genders separately, in women no statistical significant results were obtained (OR=1.0; 95% CI 0.7-1.4), but men with BMI > 25 Kg/m^2 have 1.5 times higher risk of uncontrolled hypertension than men with lower BMI (OR=1.5; 95% CI 1.1-2.2).

Bøg-Hansen *et al.* (2003)[76] performed a multivariate logistic regression separately to SBP and to DBP and both genders were evaluated independently. In men no statistical significant association with BMI > 30 Kg/m^2 was found neither with SBP nor with DBP (OR=1.5; 95% CI 0.77-3.07 and OR=1.2; 95% CI 0.93-1.61 respectively). In women, no statistical significant association was found regarding isolated SBP (OR=1.2; 95% CI 0.71-1.88), but hypertensive women with BMI > 30 Kg/m^2 have 1.5 times more likelihood of having uncontrolled DBP (OR=1.5; 95% CI 1.14-1.91).

Chen *et al.* (2003)[56] used BMI ≤ 21 Kg/m^2 as reference group, but didn't obtain statistical significant results.

Table 2.21 - Individual assessment of each study regarding suitability for inclusion in BMI meta-analysis.	
Study	Justification
Grote (2000)[42]	**Appropriate for meta-analysis**
Lloyd-Jones(2000)[43]	Stratified OR by categories of BP
Ostchega (2008)[47]	Eliminated to avoid patients duplication (NHANES population as Egan (2011))
Gus (2008)[48]	**Appropriate for meta-analysis**
Ham (2011)[49]	OR for factors associated with blood pressure control
Durant (2010)[50]	**Appropriate for meta-analysis**
Izzo (2011)[84]	**Appropriate for meta-analysis**
Gee (2012)[66]	**Appropriate for meta-analysis**
de la Sierra (2013)[74]	**Appropriate for meta-analysis**
Olomu (2013)[52]	OR for factors associated with blood pressure control
Banegas (2002)[68]	OR for factors associated with blood pressure control
Bøg-Hansen (2003)[76]	Stratified OR by gender and catherogies of BP
Chen (2003) [56]	Different reference group
Consoli (2010)[57]	**Appropriate for meta-analysis**
Cortez-Dias (2013)[58]	Inconsistency in results
De Marco (2012)[83]	**Appropriate for meta-analysis**
Egan (2011)[59]	**Appropriate for meta-analysis**
Gonçalves (2007)[60]	**Appropriate for meta-analysis**
Goverwa (2014)[77]	**Appropriate for meta-analysis**
Ono (2004)[64]	OR for factors associated with blood pressure control
Panoulas (2007)[88]	**Appropriate for meta-analysis**
Tonstad (2004)[65]	Stratified OR by gender
Van Der Niepen (2010)[89]	**Appropriate for meta-analysis**

Regarding meta-analysis, first studies that treated BMI as continuous variable were analysed (Figure 11). A pool effect size of 1.048 was obtained (95% CI 1.028-1.070) indicating that higher the BMI, higher the risk of having uncontrolled hypertension (although heterogeneity assessed by i-square was 60%).

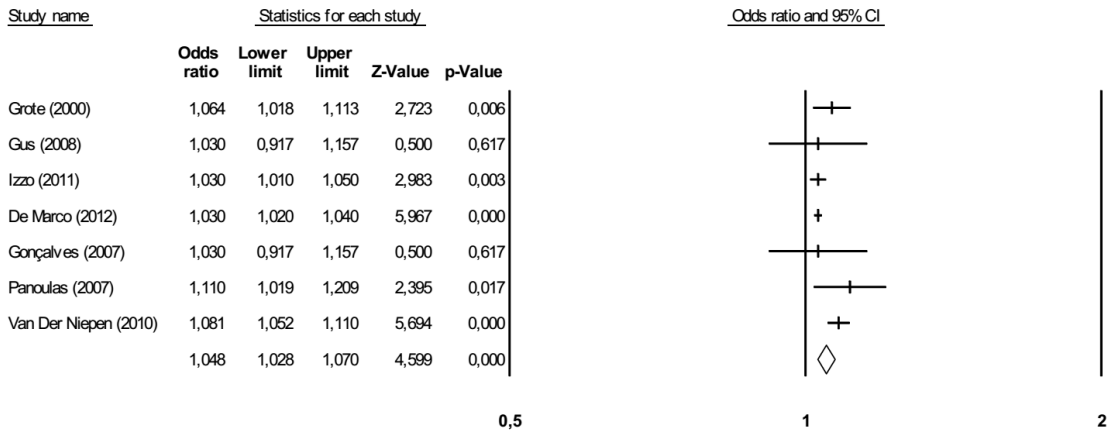


Figure 11 *- Meta-analysis of BMI, as continuous variable, influence in blood pressure control.*

After, three meta-analysis were performed considering different BMI cut-offs values. Considering BMI <25Kg/m^2 versus BMI between 25-29.9 Kg/m^2, no statistical significant results were obtained (pool effect size=1.205; 95% CI 0.834-1.743) (Figure 12) and high levels of heterogeneity were found (i-square=75%).

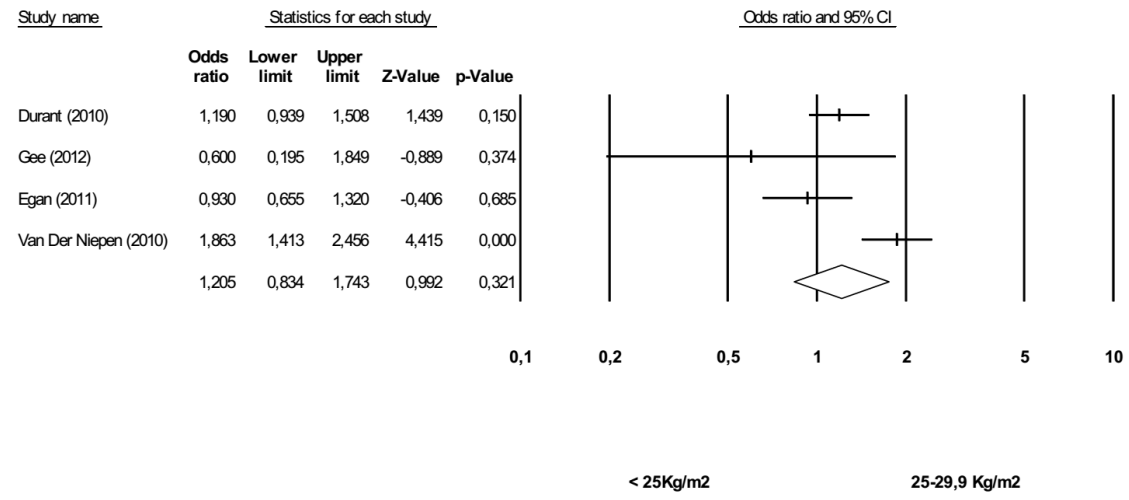


Figure 12 *- Meta-analysis of BMI levels between 25-29.9 Kg/m^2 influence in blood pressure control.*

Similar results were obtained when comparing BMI <25Kg/m^2 versus BMI ≥ 30 Kg/m^2, (pool effect size=1.310; 95% CI 0.711-2.416 and i-square=91%) (Figure 13).

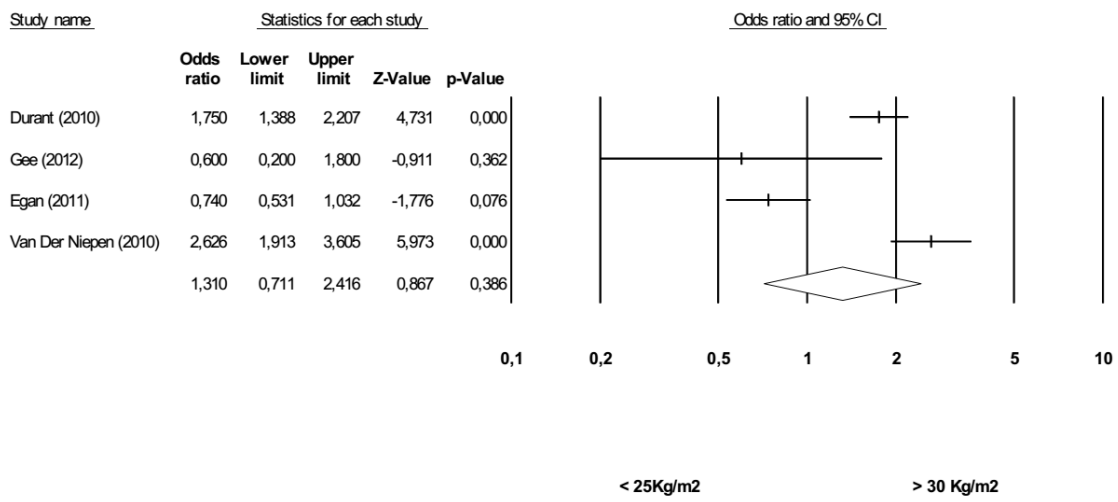


Figure 13 *- Meta-analysis of BMI levels higher than 30 Kg/m2 influence in blood pressure control.*

When evaluating BMI <30Kg/m^2 versus BMI ≥ 30 Kg/m^2, significant association was found (Figure 14), with a pool effect size of 1.437 (95% CI 1.053-1.961) and low levels of heterogeneity (i-square=53%).

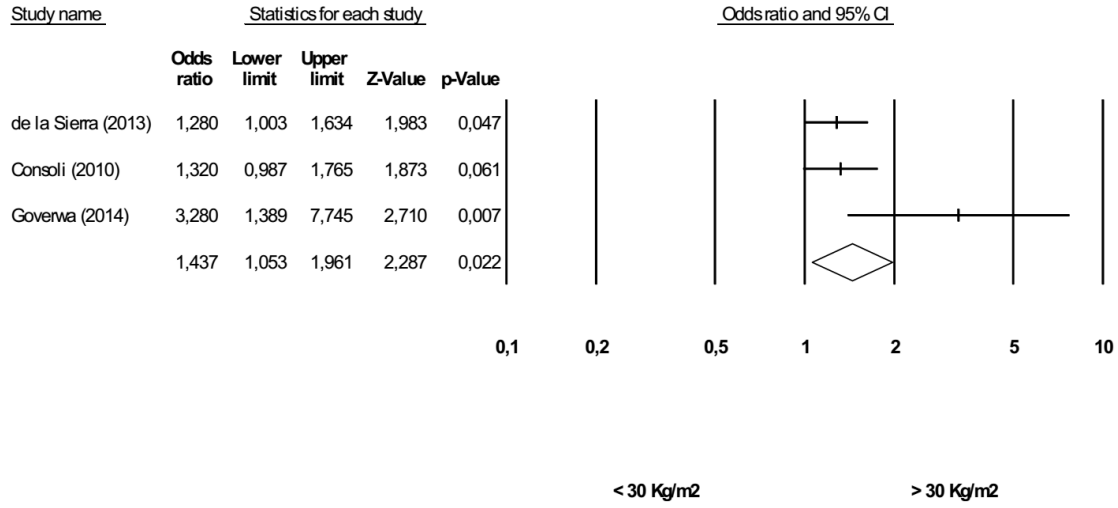


Figure 14 *- Meta-analysis of BMI levels higher than 30 Kg/m2 influence in blood pressure control.*

Waist/hip ratio

Bøg-Hansen *et al.* (2003)[76] performed a multivariable logistic regression to analyse impact of waist/hip ratio in blood pressure control. He performed different analysis according to patient gender and to categories of blood pressure control. In men, having a waist/hip ratio above 0.90/0.85 is a variable with no impact nor statistical significance in both isolated uncontrolled SBP (OR=1.0; 95% CI 0.51–2.04) and in uncontrolled DBP (OR=1.0; 95% CI 0.74-1.35). In women that have a waist/hip ratio above 0.90/0.85, no difference exists in isolated uncontrolled SBP (OR=0.9; 95% CI 0.49–1.50), but the likelihood of having uncontrolled DBP is 1.7 times higher than in women with a waist/hip ratio below 0.90/0.85 (OR=1.7; 95% CI 1.27–2.22).

Waist circumference

3 studies evaluate the association between waist circumference and BP control[55, 58, 89]. Balijepalli *et al.* (2014)[55] and Van Der Niepen *et al.* (2010)[89] treated waist circumference as categorical variable, considering as test group patients with high waist circumference (>102 cm in men; >88 cm in women). In both studies, having a waist circumference above 102 cm in men or above 88 cm in women is associated with a higher risk of having uncontrolled BP (Table 2.22). Cortez-Dias *et al.* (2013)[58] treated waist circumference as a continuous variable and similar to previous studies, higher waist circumference, higher the risk of uncontrolled hypertension.

Table 2.22 - Multivariate logistic regression results of studies assessing waist circumference as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Balijepalli (2014)[55]	**Yes**	**low/normal waist circumference**	**high waist circumference (>102 cm in men; >88 cm in women)**	**1.55**	**1.45**	**1.65**
Cortez-Dias (2013)[58]	**Yes**	**Continous variable**		**1.01**	**1.01**	**1.02**
Van Der Niepen (2010)[89]	**Yes**	**low/normal waist circumference**	**high waist circumference (>102 cm in men; >88 cm in women)**	**1.90**	**1.51**	**2.40**

Cardiovascular Disease

Left Ventricular Hypertrophy

5 studies evaluate the impact of left ventricular hypertrophy in blood pressure control. Multivariate logistic regression of all show that having LVH is a predictor of uncontrolled hypertension (Table 2.23). As one study calculated OR for determinants of hypertension control[64], one doesn't present confidence interval values[61] and one calculated OR only for isolated uncontrolled SBP[43], no meta-analysis was possible.

Table 2.23 - Multivariate logistic regression results of studies assessing left ventricular hypertrophy as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Lloyd-Jones (2000)[43]*	**Yes**	**No**	**Yes**	**1.63**	**1.04**	**2.54**
Izzo (2011)[84]	**Yes**	**No**	**Yes**	**1.05**	**1.01**	**1.09**
de la Sierra (2013)[74]	**Yes**	**No**	**Yes**	**1.86**	**1.46**	**2.36**
Jackson (2002)[61]	Yes	No	Yes	0.99	p>0.05	
Ono (2004)[64]	**No**	**No**	**Yes**	**0.47**	**0.28**	**0.79**

*In Lloyd-Jones (2000) study, OR was calculated only for uncontrolled SBP.

Myocardial Infarction

Degli Esposti *et al.* (2004)[44] evaluated prior admission for myocardial infarction has predictor of not achieving adequate blood pressure control. In his results, the presence of MI previous admissions decreases the risk of uncontrolled hypertension (OR=0.47; 95% CI 0.28–0.79).

History of Cardiovascular Disease

The influence of patients history of cardiovascular disease in blood pressure control was evaluated in 4 studies[55, 68, 76, 88]. Opposite results were obtained. In Panoulas *et al.* (2007)[88] and in Banegas *et al.* (2002)[68] the presence of CVD was a predictor of uncontrolled blood pressure, although in Banegas *et al.* (2002) the results were not statistically significant (Table 2.24). In Balijepalli *et al.* (2014)[55] history of CVD decreases the risk of poor BP control, same results than those obtained by Bøg-Hansen *et al.*

(2003)[76]. They performed a multivariate logistic regression separately to SBP and to DBP and both genders were evaluated independently. According to results, in both men and women, the risk of isolated uncontrolled SBP decreases in patients with history of cardiovascular disease (in men, OR=0.40; 95% CI 0.22-0.90 and in women OR=0.50; 95% CI 0.32-0.93), the same association was found regarding uncontrolled DBP, although in women results were not statistically significant (in men, OR=0.50; 95% CI 0.29-0.98 and in women OR=0.50; 95% CI 0.27-1.05).

Ostchega *et al.* (2008)[47] evaluated if the number of reported cardiovascular diseases could influence BP control. Considering not having cardiovascular diseases has reference group, he performed multivariate logistic regression to analyse the impact of having 1, 2 and 3 or more CVD. No significant results were obtained.

Once one study calculated OR for determinants of hypertension control[68] , another present stratified OR[76] and another categorize number of CVD[47], no meta-analysis was possible.

Table 2.24 - Multivariate logistic regression results of studies assessing history of CVD as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Balijepalli (2014)[55]	**Yes**	**No CVD history**	**CVD history**	**0.81**	**0.76**	**0.87**
Banegas (2002)[68]	No	No CVD history	CVD history	0.86	p>0.05	
Bøg-Hansen (2003)[76]	Yes	No CVD history	CVD history	a	a	a
Panoulas (2007)[88]	**Yes**	**No CVD history**	**CVD history**	**4.01**	**1.27**	**12.69**
Ostchega (2008)[47]	Yes	**No CVD history**	1 CVD	1.28	0.96	1.70
			2 CVD	0.99	0.64	1.55
			3 or more CVD	1.06	0.65	1.73

a) In Bøg-Hansen (2003) study, OR of uncontrolled were calculated separately to SBP and to DBP and both genders were evaluated independently.

Metabolic Syndrome

Cortez-Dias *et al.* (2013)[58] evaluated risk associated with metabolic syndrome, concluding that patients with metabolic syndrome have 1.15 times more likelihood of having uncontrolled BP than patients without this comorbidity (OR=1.15; 95% CI 1.01–1.30).

Framingham Score

Egan *et al.* (2011)[59] calculated OR for independent relationship between Framingham risk score and uncontrolled hypertension, concluding that patients with FRS higher than 10% have more than 2 times risk of uncontrolled hypertension than patients with FRS below 10% (FRS 10%-20% - OR=2.42; 95% CI 1.57-3.73 and FRS >20% - OR=2.64; 95% CI 1.78-3.91).

Congestive Heart Failure

Jackson *et al.* (2002)[61] calculated odds ratios for determinants of hypertension control and found that congestive heart failure is a negative predictor of uncontrolled hypertension (OR=0.44, p= 0.0453).

Angina

Jackson *et al.* (2002)[61] evaluated the influence of presence of angina in blood pressure control, but no significant results were obtained (OR=1.131, p>0.05).

Coronary Artery Disease

The impact of coronary artery disease in hypertension control was evaluated by two studies. Triolo *et al.* (2004)[63] found that patients with coronary artery disease have lower risk of uncontrolled blood pressure (OR=0.35; 95% CI 0.17-0.72). Otherwise, in Jackson *et al.* (2002)[61] study, this was a positive predictor of uncontrolled BP, although with no statistical significance (OR=1.458, p>0.05).

Taking antiplatelet drugs

Tonstad *et al.* (2004)[65] evaluated the influence of being treated with acetylsalicylic acid in blood pressure control. He performed independent analyses according to patients gender and in both no significant results were obtained (in men OR=1.1; 95% CI 0.7-1.6 and in women OR=1.0; 95% CI 0.7-1.5).

Diabetes

Diabetes

13 studies approached diabetes as a predictor of uncontrolled hypertension. Of these 8 could be include in a meta-analysis (Table 2.25).

Table 2.25 - Individual assessment of each study regarding suitability for inclusion in adherence meta-analysis.

Study	Justification
Degli Esposti (2004)[44]	**Appropriate for meta-analysis**
Ostchega (2008)[47]	**Appropriate for meta-analysis**
Rodriguez-Roca (2009)[90]	**Appropriate for meta-analysis**
Morgado (2010)[67]	**Appropriate for meta-analysis**
Izzo (2011)[84]	**Appropriate for meta-analysis**
Balijepalli (2014)[55]	**Appropriate for meta-analysis**
Banegas (2002)[68]	OR for factors associated with blood pressure control
Bøg-Hansen (2003)[76]	Stratified OR by gender and catherogies of BP
Jackson (2002)[61]	Don't present CI values
Mutua (2014)[62]	OR for factors associated with blood pressure control
Ono (2004)[64]	OR for factors associated with blood pressure control
Triolo (2004)[63]	**Appropriate for meta-analysis**
Van Der Niepen (2010)[89]	**Appropriate for meta-analysis**

Regarding studies that weren't include in meta-analysis, 3 calculated OR for factors associated with blood pressure control [62, 64, 68]. Banegas *et al.* (2002)[68] and Ono *et al.* (2004)[64] did not obtain statistical significant results (OR=0.86, p>0.05 and OR=1.99; 95% CI 0.16-25.3, respectively). In Mutua *et al.* (2014)[62] study, the presence of diabetes decreases the likelihood of having blood pressure under control (OR=0.54; 95% CI 0.36-0.81).

Jackson (2002)[61] found presence of diabetes as a significant predictor of uncontrolled blood pressure (OR=2.92, p<0.001).

In Bøg-Hansen *et al.* (2003)[76] study, where OR were calculated separately for each gender and evaluated independently isolated SBP and DBP, regarding isolated SBP no statistical significant association was found neither in men, nor in women (OR=1.5; 95% CI 0.80-2.86 and OR=1.4; 95% CI 0.80-2.39, respectively). Concerning DBP, in both genders, the

presence of diabetes is a predictor of uncontrolled DBP (OR=2.3; 95% CI 1.34-4.09 in men and OR=3.3; 95% CI 1.85-5.72 in women).

In meta-analysis a pool effect size of 3.187 was obtained (95% CI 1.852-5.484, i-square=96%) indicating Diabetes as a strong predictor of uncontrolled hypertension (Figure 15).

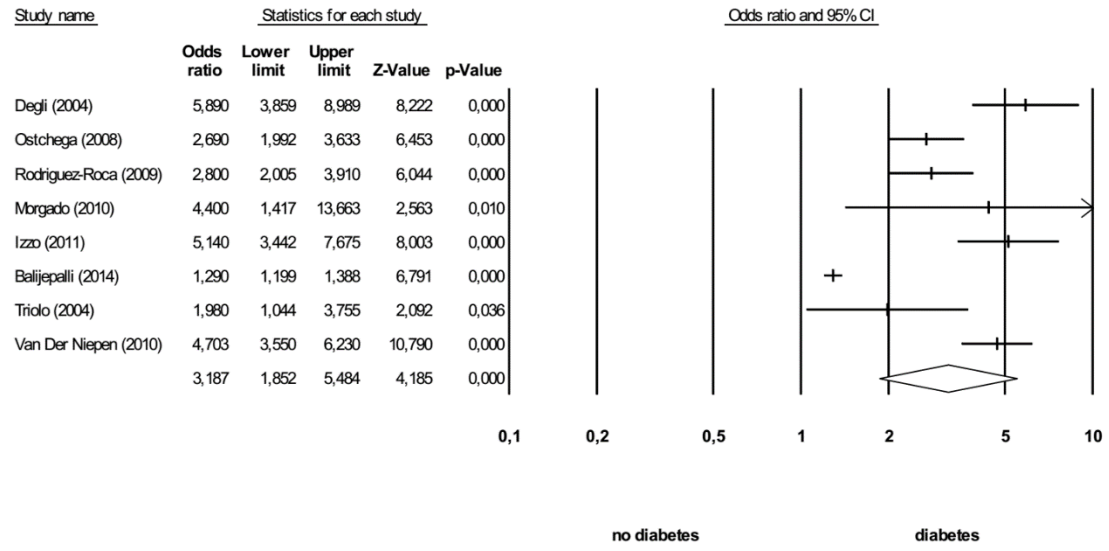


Figure 15 *- Meta-analysis of diabetes influence in blood pressure control.*

Insulin resistance

Bøg-Hansen *et al.* (2003)[76] try to establish associations between high cardiovascular disease risk factor levels and categories of blood pressure control. When evaluating the impact of Insulin resistance calculated by HOMA (homeostasis model assessment, where insulin resistance = fasting insulin (μ U/ml) x fasting glucose (mmol/l) x 22.5 $^{-1}$), in both genders no impact is caused in isolated uncontrolled SBP by insulin resistance above 3.2 (in men OR=1.20; 95% CI 0.62-2.39, and in women OR=1.0; 95% CI 0.56-1.66). Regarding to uncontrolled DBP, same results were obtained in men's category (OR=1.1; 95% CI 0.84–1.49) but in women's category, insulin resistance above 3.2 seems to be predictor of uncontrolled DBP (OR=1.4; 95% CI 1.07–1.89).

Fasting glucose intolerance

This variable was approached by two studies. Cortez-Dias *et al.* (2013)[58] analysed association between impaired fasting glucose and uncontrolled BP, finding that patients with fasting glucose values above 110 mg/dl have 1.25 times more risk of uncontrolled BP (OR=1.25; 95% CI 1.02–1.53).

Bøg-Hansen *et al.* (2003)[76] used different cut-off to categorize this variable and considered values of fasting glucose above 5.5 mmol/l (which are equivalent to 100mg/dl)). In male patients, fasting glucose > 5.5 mmol/L is a predictor of isolated uncontrolled SBP (OR= 1.9; 95% CI 1.03–3.54), but in women no statistical significant results were obtained (OR=1.1; 95% CI 0.71–1.72). Regarding to DBP, in male patients no statistical significant results were obtained (OR=1.2; 95% CI 0.95–1.56), but in women, fasting glucose > 5.5 mmol/L seems to be associated with DBP uncontrolled (OR=1.4; 95% CI 1.08–1.79).

Dyslipidaemia

Dyslipidaemia

In 3 studies that assess the impact of dyslipidaemia in BP control none obtained statistical significant results (Table 2.26).

Table 2.26 - Multivariate logistic regression results of studies assessing dyslipidaemia as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Koizumi (2013)[51]	Yes	Without dyslipidaemia	With dyslipidaemia	0.71	0.49	1.04
Consoli (2010)[57]	Yes	Without dyslipidaemia	With dyslipidaemia	1.25	0.98	1.60
Jackson (2002)[61]	Yes	Without dyslipidaemia	With dyslipidaemia	1.00	not significant	

Total cholesterol

Influence of total cholesterol on blood pressure control was evaluated by 6 studies. Since they used different cut-offs to categorize this variable no meta-analysis was possible (Table 2.27). 3 Studies present convergent results, in de la Sierra *et al.* (2013)[74], Balijepalli *et al.* (2014)[55] and in Salifu *et al.* (2005)[75] high levels of total cholesterol were predictors for uncontrolled hypertension. Although Banegas *et al.* (2002)[68] and Triolo *et al.* (2004)[63]

present similar OR, no statistical significant results were obtained. Bøg-Hansen *et al.* (2003)[76] who calculated OR separately to SBP and to DBP and to both genders nor in isolated SBP (in men OR= 1.2; 95% CI 0.63–2.38 and in women OR= 1.1; 95% CI 0.72–1.70) nor in DBP (in men OR= 1.2; 95% CI 0.89–1.54 and in women OR= 1.0; 95% CI 0.77–1.28) obtained statistical significance.

Table 2.27 - Multivariate logistic regression results of studies assessing total cholesterol as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
de la Sierra (2013)[74]	**Yes**	**< 200 mg/dL**	**≥ 200 mg/dL**	**1.50**	**1.19**	**1.90**
Balijepalli (2014)[55]	**Yes**	**< 200 mg/dL**	**≥ 200 mg/dL**	**1.24**	**1.16**	**1.33**
Banegas (2002)[68]	No	Normal	High	1.05	not significant	
Bøg-Hansen (2003)[76]	Yes	< 6.5 mmol/L (250 mg/dl)	≥ 6.5 mmol/L (250 mg/dl)	a	a	a
Salifu (2005)[75]	**Yes**	**< 240 mg/dL**	**≥ 240 mg/dL**	**3.10**	**1.36**	**7.00**
Triolo (2004)[63]	Yes	< 220 mg/dL	≥ 220 mg/dL	1.08	0.66	1.78

a) In Bøg-Hansen (2003) study, OR of uncontrolled were calculated separately to SBP and to DBP and both genders were evaluated independently.

High Density Lipoprotein (HDL)

The predictive value of HDL towards blood pressure control was evaluated by 5 studies. Since they used different cut-offs to categorize this variable no meta-analysis was possible (Table 2.28). Of them, only Cortez-Dias *et al.* (2013)[58], the only one that treated HDL as continuous variable, obtained statistical significant results, although OR remain very close to number 1.

Table 2.28 - Multivariate logistic regression results of studies assessing HDL as independent variable regarding uncontrolled hypertension.

Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Lloyd-Jones (2000)[43]*	Yes	≥ 1.2 mmol/L	0.9-1.2 mmol/L	0.73*	0.47*	1.15*
			< 0.9 mmol/L	0.49*	0.28*	0.85*
Rodolfo (2009)[54]	Yes	≥ 50 mg/dL	< 50 mg/dL	1.70	0.80	3.50
Balijepalli (2014)[55]	Yes	HDL ≥ 40 mg/dl in men and ≥ 50 mg/dl in women	HDL < 40 mg/dl in men and < 50 mg/dl in women	0.96	0.88	1.03
Bøg-Hansen (2003)[76]	Yes	≥ 0.9/1.0 mmol/L	< 0.9/1.0 mmol/L	a	a	a
Cortez-Dias (2013)[58]	**Yes**	**Continous variable**		**1.01**	**1.00**	**1.01**

a) In Bøg-Hansen (2003) study, OR of uncontrolled were calculated separately to SBP and to DBP and both genders were evaluated independently; *In Lloyd-Jones (2000) study, OR was calculated only for uncontrolled DBP.

Triglycerides

5 studies assessed the influence of triglycerides in BP control. Since they used different cut-offs to categorize this variable no meta-analysis was possible (Table 2.29). Cortez-Dias *et al.* (2013)[58] et De Marco *et al.* (2012)[83] treated this variable as continuous and in both, higher triglycerides, higher the risk of uncontrolled hypertension. Similar results were obtained by de la Sierra *et al.* (2013)[74] and by Balijepalli *et al.* (2014)[55], who treated triglycerides as a categorical variable establishing the cut-off of 150mg/dl. Bøg-Hansen *et al.* (2003)[76] who calculated OR separately to SBP and to DBP and to both genders, used a similar cut-off (1,7 mmol/L which is equivalent to 150mg/dl), but didn't obtain statistical significance regarding association between triglycerides and isolated uncontrolled SBP neither in men nor in women (in men OR=1.5; 95% CI 0.81–2.62 and in women OR=1.3; 95% CI 0.82–2.02). Regarding to DBP, in male patients no statistical significant results were obtained (OR=1.1; 95% CI 0.88–1.44), but in women, triglycerides > 150mg/dl seems to be a risk factor for uncontrolled DBP (OR=1.4; 95% CI 1.10–1.84).

Table 2.29 - Multivariate logistic regression results of studies assessing Triglycerides as independent variable regarding uncontrolled hypertension.						
Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
de la Sierra (2013)[74]	**Yes**	**< 150 mg/dL**	**≥ 150 mg/dL**	**1.63**	**1.28**	**2.07**
Balijepalli (2014)[55]	**Yes**	**< 150 mg/dL**	**≥ 150 mg/dL**	**1.11**	**1.04**	**1.19**
Bøg-Hansen (2003)[76]	Yes	< 1.7 mmol/L (150 mg/dl)	≥ 1.7 mmol/L (150 mg/dl)	a	a	a
Cortez-Dias (2013)[58]	**Yes**	**Continous variable**		**1.00**	**1.00**	**1.00**
De Marco (2012)[83]	**Yes**	**Continous variable**		**1.12**	**1.04**	**1.21**
a) In Bøg-Hansen (2003) study, OR of uncontrolled were calculated separately to SBP and to DBP and both genders were evaluated independently.						

Taking statins

Two studies evaluated the association between taking lipid-lowering medications and uncontrolled hypertension. Balijepalli *et al.* (2014)[55] found that patients takin lipid-lowering medications have a lower risk of uncontrolled BP (OR=0.85; 95% CI 0.79–0.92). Tonstad *et al.* (2004) [65] evaluated both genders separately and in both men and women same association was found (in men OR=0.6; 95% CI 0.5-0.9 and in women OR=0.7; 95% CI 0.5-1.0).

Kidney diseases

Chronic Kidney Disease

Egan *et al.* (2011)[59] and Triolo *et al.* (2004)[63] evaluated the independent relationship between the presence of chronic kidney disease with uncontrolled hypertension. Altough pointing that CKD could increase the risk of uncontrolled BP, Egan *et al.* results were not statistically significant (OR=1.12; 95% CI 0.81-1.55). Triolo *et al.* analysed both CKD with and without proteinuria (above 1g/24hours), in both evaluations this comorbidity seems to be a predictor of poor blood pressure control with risk of uncontrolled BP being 3.79 times higher in patients with CKD and this odds increases to 6.39 times if patient have proteinuria (OR=3.79; 95% CI 1.01-14.20 and OR=6.39; 95% CI 2.27-18.00, respectively).

Microalbuminuria

Bøg-Hansen *et al.* (2003)[76] evaluated the association between microalbuminuria levels of at least 20 mg/l in first morning urine and hypertension control. In men this relationship have no statistical significance neither for isolated SBP nor for DBP (OR=1.3; 95% CI 0.67-2.36 and OR=1.2; 95% CI 0.66-2.05, respectively). In women, no statistical significance was obtained regarding isolated SBP, but women with microalbuminuria have 3.2 times more risk of having uncontrolled BP (OR=1.4; 95% CI 0.67-2.59 and OR=3.2; 95% CI 1.68-6.22).

Serum creatinine

Salifu *et al.* (2005)[75] analysed the influence of serum creatinine in BP control. They performed a multivariate logistic regression testing this relationship for every 0.4mg/dl rise in serum creatinine above 1mg/dl, and found an increased risk, but results did not achieved statistical significance (OR=1.50; 95% CI 0.98-2.31).

Other comorbidities

Depression

Almas *et al.* (2014)[91] used Hospital Anxiety and Depression Scale (HADS) as tool for assessing psychological distress in patients and nonclinical groups to determine the association between depressive disorders and uncontrolled hypertension. After performing a multiple logistic regression, depression was significantly associated with uncontrolled BP, having patients with depression 1.94 times more risk of uncontrolled hypertension than patients without this comorbidity (OR=1.94; 95% CI 1.3-2.8).

Sleep- related breathing disorders

Association between sleep-related breathing disorders and blood pressure control were approached by 3 studies. As they used different tool to assess the presence of sleep disorders, no meta-analysis was possible (Table 2.30).

Table 2.30 - Multivariate logistic regression results of studies assessing sleep-related breathing disorders as independent variable regarding uncontrolled hypertension.						
Study	OR for uncontrol risk	reference group	test group	OR	lower CI	upper CI
Grote (2000)[42]	**Yes**	**RDI as continous variable**		**1.02**	**1.01**	**1.03**
Gonçalves (2007)[60]	**Yes**	**AHI<10 episodes/h**	**AHI≥10 episodes/h**	**4.80**	**2.00**	**11.70**
Gus (2008)[48]	**Yes**	Epworth <10	Epworth >10	1.00	0.91	1.10
		Low risk in Berlin Questionnaire	**High risk in Berlin Questionnaire**	**4.10**	**1.80**	**9.31**

Grote *et al.* (2000)[42] assessed if sleep-related breathing disorders were related to reduced blood pressure control through respiratory disturbance index (RDI). Multiple logistic regression analysis model shows that in patients younger than 50 years, each RDI unit, increased the probability of having uncontrolled hypertension by approximately 2%, but in patients over 50 years this relationship isn't significant.

Gonçalves *et al.* (2007)[60] investigated if there is an association between obstructive sleep apnea syndrome (OSAS) and uncontrolled hypertension. They performed a multiple logistic regression analysis considering apnea-hypopnea index (AHI) higher than 10 episodes per hour as independent variable. According to the results, patients with OSAS (AHI≥10 episodes/h) have a 4.8 times more likelihood of having uncontrolled BP than patients without this comorbidity.

Gus *et al.* (2008)[48] investigate the association between sleep disorders and BP control through Epworth sleepiness scale (ESS) and the Berlin Questionnaire. ESS had no statistical significant result, but Berlin Questionnaire was strongly and independently associated with uncontrolled hypertension.

Stroke

Koizumi *et al.* (2013)[51] and Jackson *et al.* (2002)[61] evaluated the impact of past history of stroke on blood pressure control. In none of studies significant associations were found (OR= 0.604; 95% CI 0.274–1.331 and OR=0.58, p>005, respectively).

Arthritis

Inciardi *et al.* (2003)[69] examine the association of uncontrolled hypertension with presence of arthritis, attributing 2.46 times higher risk of poor BP control in patients with this comorbidity (OR=2.46; 95% CI 1.22-4.97)

Presence of comorbidities

King *et al.* (2006)[46] and Ham *et al.* (2011)[49] evaluated the likelihood of having uncontrolled blood pressure in patients with comorbidities. The first didn't found no statistical significant results (OR=0.876; 95% CI 0.494-1.551) but according to Ham, patients with comorbidities have 1.62 times more chance of having controlled BP than patients without comorbidities (OR=1.62; 95% CI 1.15-2.29).

Number of drugs taken

The influence of number of medications taken by patients was investigated by 3 studies. Degli Esposti *et al.* (2004)[44] determine that an increasing number of other medications currently being taken by the patient is a significant factor that reduced the risk of uncontrolled BP (OR=0.80; 95% CI 0.73-0.88). Olomu *et al.* (2013)[52] and King *et al.* (2006)[46] found no statistical significant results (OR=1.01, p=0.99 and OR=0.99; 95% CI 0.905-1.084, respectively).

Taking nonsteroidal anti-inflammatories

Gee *et al.* (2012)[66] assessed the impact of the use of nonsteroidal anti-inflammatory drug in blood pressure control. No statistical significant results were obtained (OR=1.1; 95% CI 0.6-2.2).

Hospitalization

Olomu *et al.* (2013)[52] approached the impact of emergency department or hospitalization in blood pressure control, but found no statistical significant results (OR=0.91, p=0 .37).

Cognitive mini-examination

Banegas *et al.* (2002)[68] studied the influence of cognitive performance in risk of uncontrolled hypertension, but no statistical significant results were obtained (OR=1.18, p>0.05).

Frailty

Koizumi *et al.* (2013)[51] examined the relationship between hypertension status and Basic Checklist for Frailty (BCF) categories in elderly: impaired oral function, difficulty eating hard food, impaired instrumental activities of daily living (IADL) status and ability to manage bank account. In multivariate logistic regression impaired IADL status and ability to manage bank account were not statistical significant factors (OR=1.169; 95% CI 0.984-1.389 and OR=1.695; 95% CI 0.937-3.067, respectively), but patients with impaired oral function have 1.236 times more likelihood of having uncontrolled blood pressure (OR=1.236; 95% CI 1.003-1.523) as well as patients with difficulty eating hard food, that have 1.690 times more risk of uncontrolled hypertension (OR=1.690; 95% CI 1.121-2.548).

Polymorphisms

Inducible nitric oxide synthase haplotype

Oliveira-Paula *et al.* (2013)[92] assessed whether three functional inducible nitric oxide synthases (iNOS) genetic polymorphisms or iNOS haplotypes are associated with hypertension uncontrolled. No significant associations between iNOS genotypes and poor BP control were found.

Discussion

This systematic review evaluate a total of 73 different independent variables possibly correlated with poor BP control in treated hypertensive patients. Only 12 meta-analysis were possible, evaluating 8 different independent variables. The reduce number of meta-analysis performed was due, in 48 cases, to the reduce number of articles that approached the variable and, in 17 situations, due to differences in variable categorization.

Taking into account that variables such as sodium intake, total cholesterol and sleep- related breathing disorders, which actually are pointed as major uncontrolled blood pressure factors and are studied in several investigations, could not be meta-analysed due to a lack of standardization in variable treatment and classification, is easy to understand that the evaluation of minor factors, such as number of health care visits, number of antihypertensive drugs taken and type of antihypertensive treatment, was compromised.

The standardization in outcome reports in clinical trials had been already approached by several authors, who defend that the selection of appropriate outcomes or domains is crucial when designing clinical trials in order to compare directly the effects of different interventions in ways that minimize bias[93-95]. A potential solution is an agreed standardized set of outcomes known as a core outcome set (COS) to be measured in all studies for a specific condition. Defined as a standardised set of outcomes which should be measured and reported, as a minimum, in all effectiveness trials for a specific health area, COS allow results of studies to be compared, contrasted and combined as appropriate, as well as ensuring that all trials contribute usable information.

Alongside with this outcome report inconsistency, outcome switching is another bias source, when the results of an analysis are used to choose which outcomes will be reported, selectively un-reported results would remain un-accessible to users of the research. In Dwan *et al.* (2008)[95] systematic review for example, when comparing trial publications to protocols, 40-62% of studies had at least one primary outcome that was changed, introduced, or omitted, which prevent the perform of a meta-analysis.

In order to minimize these bias, several investigation groups were created to develop recommendations for reporting outcomes, as CONSORT Group[96], and for monitoring clinical trials for switched outcomes, as COMPare project[97].

Analysing the results obtained, although cannot be meta-analysed, some variables such as total cholesterol and sleep breathing disorders present the expected OR directionality, being possible predictors of poor blood pressure control, but other variables such as socioeconomic status, number of antihypertensive drugs or history of CVD present divergent results. Furthermore, some interesting variables such as therapy intensification, number of daily doses or metabolic syndrome were only approached by one single study, which prevents any conclusion regarding the risk factor they represents. Even so, among the variables that cannot be meta-analysed, 3 may be highlighted: salt consumption, left ventricular hypertrophy and the knowledge of patients regarding hypertension disease. They were approached, with statistical significant results, by more than one study, being pointed as possible predictors of uncontrolled blood pressure.

Regarding the 12 meta-analysis performed 6 originate statistical significant results, pointing gender, health insurance, adherence to therapy, obesity and diabetes as variables that contribute to a poor control of blood pressure in hypertensive treated patients. However, in none, levels of heterogeneity below the recommended cut-off of 50% were obtained, which decreases the strength of the results. As so, investigation in this area is important, more studies are request in order to provide enough data to perform sensitivity analyses to determine whether the study characteristics could have influenced the results and to enable better and more robust conclusions.

Analysing our data, diabetes was the variable with the most impact in BP control of hypertensive treated patients. As comorbidity, the impact of diabetes is 3 times higher than obesity, and comparing with adherence, the effect of diabetes is 2 times higher.

Conclusions

The variables identified as having a negative influence on the control of blood pressure in patients under pharmacological antihypertensive treatment were gender, health insurance, adherence to therapy, obesity and diabetes. However, the impact of diabetes as

comorbidity is the most important, being 2 times higher than adherence to therapy and 3 times higher than obesity.

Efforts to standardizing outcomes reports are important and needed interventions to improve published data on this field, increase quality of evidence within systematic reviews performed and to allow more and better meta-analysis that can add substantial knowledge in this area. Further investigation is needed to allow more robust conclusions and to enable the categorization of risk factors according to its impact in the control of blood pressure.

Medication adherence assessed by 8-items Morisky medication adherence scale (MMAS-8): a systematic review and meta-analysis

Medication adherence assessed by 8-items Morisky medication adherence scale (MMAS-8): a systematic review and meta-analysis

Introduction

One of the main factors highlighted in our systematic review as cause for uncontrolled BP was adherence. Defined as the extent to which patients take medications as prescribed by their health care providers[98], adherence is one of the elements more closely associated with therapeutic success[99, 100]. Non-adherence has been associated not only with the lack of control of several chronic diseases as diabetes, hypertension and dyslipidaemia[101, 102], but also with the onset of complications of the diseases and the decrease of patient's quality of life[98, 101-105].

The impact of non-adherence in health care systems also must be taken into account, since it is pointed out as responsible for over 20% of hospital admissions due to preventable adverse reactions, representing unnecessary costs and having a major economic impact[106-108].

Adherence to therapy has therefore become a growing concern for the scientific community, health care professionals and health systems, and its evaluation has become an important step for the evaluation of the patient and of the effectiveness of his medication. Being a dynamic and multifactorial process, conditioned by several variables, whether clinical, social or personal, assessment of adherence to therapy has become a challenge and have been developed several approaches to determine accurately the degree of adherence of a patient to his medication.

There are currently several methods and tools able to assess adherence to therapy, but the complexity of behaviours that this concept encompasses prevented, so far, the development of a method that can be considered a "gold standard"[98, 109]. Generally we can distinguish two broad classes of methods for assessing compliance, direct measures and indirect measures, each with advantages and disadvantages that must be considered individually, depending on the evaluation of the aims of the study and the type of population to be studied (Table 3.1).

Table 3.1 - Characteristics of methods of assessment of adherence to therapy.			
		Advantages	Disadvantages
Direct measures	Directly observed therapy	Non invasive	Expensive Mobilization of human resources Requires constant return visits Impractical for routine use
	Measurement of the level of medicine or metabolite	Accurate Objective	Expensive Invasive Depends on the pharmacokinetics of the drug Affected by drug and food interactions Affected by "white-coat adherence" Not available to all drugs
	Measurement of the biologic marker		
Indirect measures	Rates of prescription refills	Inexpensive Non invasive Easy application	Only valid to assess chronic medication adherence Depends on the fidelity of the patient to the pharmacy - reliable only in hospitalar pharmacy
	Pill counts	Inexpensive Non invasive Easy application	Easily altered by the patient Affected by social desirability
	Electronic Medication Monitors (MEMS)	Precise Non invasive Easy application Tracks patterns of taking medication	Expensive Not adapted to all pharmaceutical forms Requires return visits to download data from medication vials
	Patient questionnaires, patient self-reports	Inexpensive Non invasive Easy application Quick data collection Provides data on behavioural patterns of the patient, as well as their attitudes and beliefs	Affected by phenomenon such as social desirability or response acquiescence Influenced by health literacy level of the patient

Direct methods are more expensive than the indirect methods, but also more accurate, robust and objectives. Its main disadvantages are the need of human resources, being time consuming and impractical for routine use, and its main application are clinical trials.

Indirect methods are cheaper, practical and easier to apply, allowing faster obtainment of results and in addition allowing to assess not only adherence but also patient's behavioural patterns. However they are not as accurate as direct methods, being more subject to bias as social desirability and response acquiescence.

Encompassed in indirect methods, self-report scales are simple, reliable and easy to administer approaches, being one of the most used methods in investigation and in clinical practice. Several studies have been made in order to develop a self-report tool able to assess patient's adherence as accurately and precisely as possible[110-115].

In 1986 Morisky *et al.*[116] developed the 4-Item Morisky Medication Adherence Scale (MMAS-4) to assess general adherence to prescribed medication. MMAS-4 comprised of four questions assessing reasons for non-adherence (intentional and unintentional): forgetfulness, carelessness, feeling better, and feeling worse. This instrument has been widely used in several studies and in many different countries[117-122]. In 2008, Morisky *et al*. modified MMAS-4 and supplemented it with additional items addressing the circumstances surrounding adherence behaviour, with the objective of assessing adherence in hypertensive patients, named it as 8-Item Morisky Medication Adherence Scale (MMAS-8)[115]. The scale has demonstrated high internal consistency (Cronbach's alpha = 0.83) as well as good sensitivity (93%) and specificity (53%), reasons that lead MMAS-8 to be one of the most used self-report scales worldwide in evaluation of adherence to therapy. MMAS-8 was validated to several languages, like French[123], German[124], Chinese[125], Malay[126], Turkish[127] and Persian[128], and was also validated to other medical conditions like diabetes[129], epilepsy[130] and osteoporosis[131].

The use of MMAS-8 is protected by US copyright laws and a license agreement must be obtained from Professor Morisky. Similarly, coding and scoring criteria of the MMAS-8 are trade secrets of the Owner and confidential, not having been described in the original article, being assigned upon request to the author[132].

The instrument consists in 7 dichotomous (Yes/No) items plus a five-point Likert scale item. Questions were formulated to avoid a 'yes-saying' bias and the wording of the item 5 is reversed to prevent the tendency to respond in a specific way to a series of questions regardless of their content. The last question requires standardizing the code (from 0 to

4), being assigned 1, 0.75, 0.50, 0.25 or 0 points to “Never”, “Almost never”, “Sometimes”, “Frequently” or “Always”, respectively.

Using a reliable instrument assessed may not be enough to allow global comparisons. Slight differences due to poor cross-cultural adaptations or diverse socio-cultural environment may result in undetectable differences among studies[133]. Systematic reviews and meta-analyses can provide convincing and reliable evidence relevant to many aspects of medicine and health care[134], however, these small variations may drastically increase the heterogeneity of a meta-analysis using the given instrument[135].

The MMAS-8 scoring system is not intuitive which may result in potential discrepancies in the application of the instrument. Additionally, the effects of using MMAS-8 in culturally different environments have not been sufficiently evaluated.

Objectives

The aim of this study was to assess heterogeneity associated with the use of MMAS-8 by means of a systematic review and meta-analysis of studies that use this instrument to evaluate medication adherence.

Methods

Search strategy and study selection

A literature review was conducted in order to identify all studies that have used the MMAS-8. A computerized search was performed using Medline (PubMed), Scielo and Scopus in January 2015. Studies were identified by the following search terms:

- Pubmed: "mmas-8" OR (8 AND item* AND "medication adherence scale");
- Scielo: mmas-8 OR ("medication adherence scale" AND 8), and
- Scopus: mmas-8 OR ("medication adherence scale" AND item* AND 8).

A manual search appraising the reference lists of included articles complemented the electronic search. Any kind of study design was eligible for the analysis. Conference proceedings and studies where expert opinion was used to determine medication adherence were excluded.

Two independent investigators (A.C.C., F.F-L.) screened the studies based initially on their title and abstract to identify irrelevant records. The same two researchers appraised the full text articles, to exclude studies using the following exclusion criteria:

(i) Studies not reporting results obtained with the use of 8-Items Morisky Medication Adherence Scale;
(ii) Non-original research articles;
(iii) Articles not written in Roman characters, and
(iv) Articles neither available at any of the research team University libraries nor provided by the authors after request.

When more than one article reported results from one study, the one containing biggest population was considered.

Data extraction

Data were extracted by the same two independent researchers and results were collected into a table, containing data referent to study eligibility, characteristics of patients surveyed, data reporting the way used in the application of MMAS-8 or the scoring system, and the results obtained with MMAS-8. For longitudinal studies or experimental studies only baseline data were included, while in studies with control groups, baseline data of each group were collected.

Data analysis

Data reported in included studies were used for three different analyses: mean score and standard deviation of the MMAS-8, number of patients scoring over 6 (medium and high adherent), and number of patients scoring 8 (high adherent). The effect size and the Confidence Interval at 95% (95% CI) from individual studies were calculated and pooled using a random-effects model, which takes into account variability among studies rather than chance.

The heterogeneity was assessed using the inconsistency index (i-square). Values of i-square near 25% were considered to show low heterogeneity, values close to 50% denoted moderate heterogeneity, and those over 75% were considered to show substantial

heterogeneity[41]. Sensitivity analyses were performed to determine whether the study characteristics could have influenced the results. For this, the studies were grouped based on the following characteristics: existence of copyright solicitation, presence of Donald E. Morisky or any other authors of the article creating the MMAS-8 [115] as co-author of the included study, type of the study (application or a validation study), previous validation (or not) of the 8-MMAS version used, presence of a description of the scoring system in the article, study design, remuneration for patients reported, type of application of the questionnaire (self-report filling or administered), professional who apply the questionnaire, the setting where the data collection occurred, and country. Subgroup analyses were also made considering patient characteristics like age, type of condition, and exclusion criteria reported (i.e. patients older than 65 years, patients younger than 55 year, patients with cognitive impairment).

All statistical analyses were performed using the Comprehensive Meta-Analysis Version 2.0 software (CMA 2.0; Biostat Inc., Englewood, NJ, USA).

Results

A total of 93 articles were identified in literature searches. After two exclusion phases, 73 articles, correspondent to 65 studies, were included in qualitative analyses, with 62 articles (57 studies) containing data that allowed the inclusion in a meta-analysis (Figure 16).

The studies took place in a total of 24 different countries, with 4 multicenter studies[136-139]. Study designs comprised 3 longitudinal studies[136, 140, 141], 3 interventional non-controlled studies[142-144], 1 interventional controlled studies[145], and 58 cross-sectional studies.

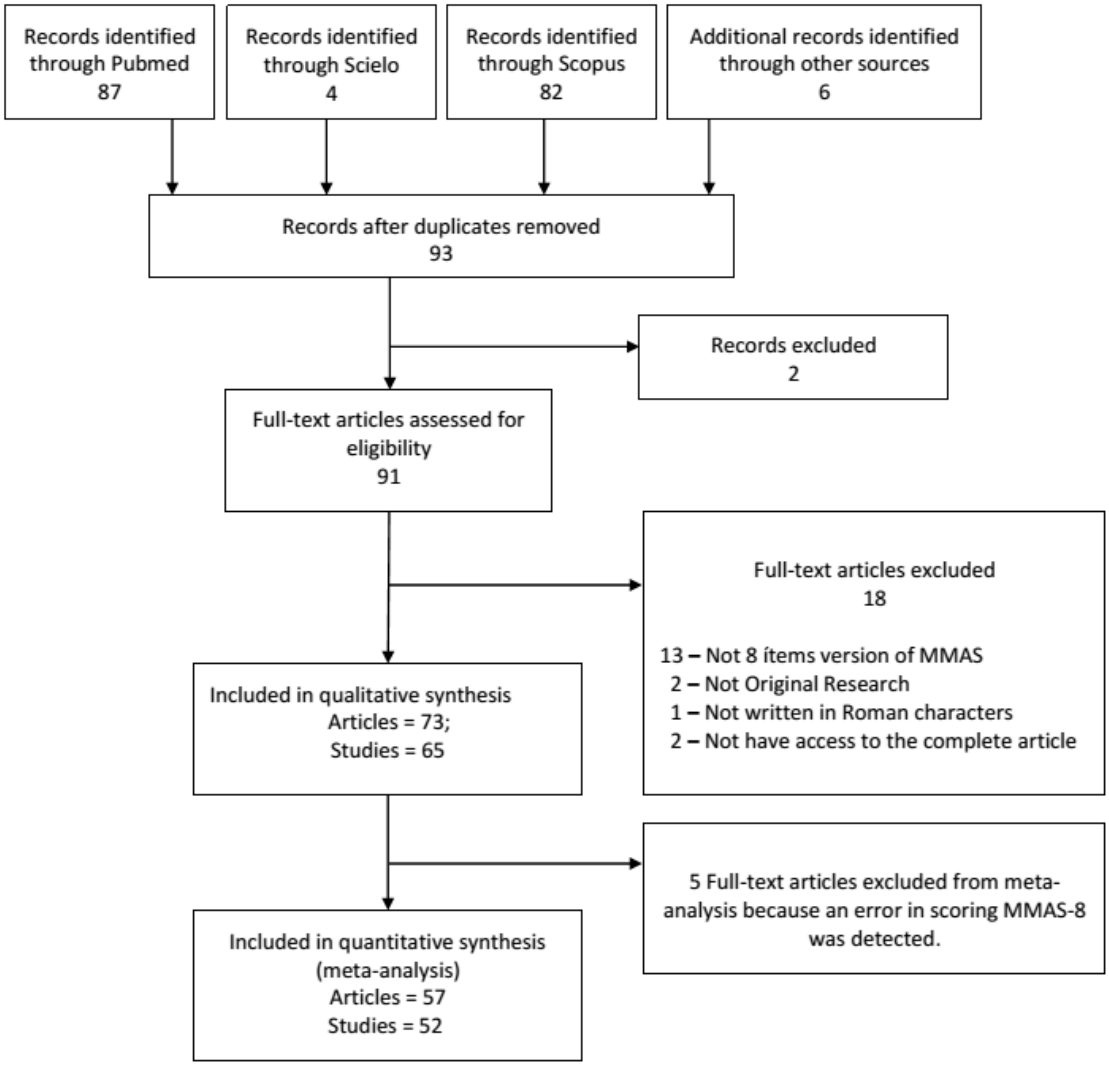


Figure 16 *- PRISMA Flow Diagram.*

Regarding the setting where MMAS-8 was applied, in 10 studies data were collected remotely using interviews by phone or by mail[129, 131, 138, 139, 146-151], 4 studies took place in community pharmacies[145, 152-154], 4 in ambulatory settings[124, 143, 155, 156], and 47 in hospitals or institutionalized clinics. Concerning the surveying method, 10 studies do not refer how MMAS-8 was administered, 34 studies MMAS-8 was a self-administered, and in 21 studies data were obtained by interviewers (1 was a physician, in 2 a pharmacist, 2 a nurse, 11 a researcher, in 3 medicine or pharmacy students, and in 2 studies the interviewer was not identified).

Of 65 studies included, 19 were validation studies and 46 used the MMAS-8 to assess medication adherence in different populations. A summary of studies found reporting validation of MMAS-8 is presented in Table 3.2 and a summary of studies found reporting the use of MMAS-8 to evaluate adherence to medication is presented in Table 3.3.

Three of the validation studies presented incomplete statistical reporting, with no estimation of internal consistency through Cronbach's alpha calculation[157-159]. Only 21 of the 46 studies using MMAS-8 to evaluate adherence mentioned using a previously validated version of the MMAS-8 (including the MMAS-8 original version).

MMAS-8 was used to evaluate medication adherence in 20 different medical conditions: hypertension (n=17), diabetes (n=14), cardiovascular disease (n=5), inflammatory bowel diseases (n=5), psychiatric diseases (n=5), asthma (n=2), epilepsy (n=2), osteoporosis (n=2), cancer (n=2) and human immunodeficiency virus (n=1).

Any of the authors from the MMAS-8 conception team also appeared in 22 of the 65 studies included. Of the remaining 43 studies, only 22 reported having requested permission to the Morisky team, and subsequently having access to the scoring instructions. Nine studies completely explain the scoring system, using three studies an incorrect system. Other five studies provide some information about the scoring system, not sufficient to identify the accuracy. Only 12 studies reported having inverted the score of question 5. Inconsistencies in the description of the scoring were found in one study[152].

Table 3.2 - Summary of studies reporting validation of MMAS-8.					
Author (year)	**Copyright**	**Author participation**	**Validation (language/population)**	**Statistical Analysis**	**Results**
Arnet (2015)[124]	Yes	Yes	German version (adults with prescriptions for aspirin and/or clopidogrel)	Internal consistency - Cronbach's α test and item-to-total correlations Construct validity - exploratory factor analysis, principal component analysis (PCA), followed by varimax rotation Convergent validity - non-parametric Spearman's rho test (BMQ-Specific and electronic punch cards)	Internal consistency - Cronbach's α=0.31 and item-to-total correlations ranged from −0.015 to +0.530 Construct validity - four components were retained Convergent validity - The MMAS-8D scores were significantly correlated with the Necessity (r=0.31, P < 0.01) and the Concerns sub-scores of the BMQ (r=−0.16, P < 0.05)
Hacihasanoglu Asilar (2014)[127]	Yes	Yes	Turkish version (Hypertension)	Construct validity - Factor analysis. Internal consistency - Cronbach's α test and item-total correlation	Internal consistency - Cronbach's α = 0.79 and item-total correlation of the scale ranged between 0.30 and 0.62
DiBonaventura (2014)[129]	No	No	English version (Type 2 diabetes)	Construct validity - exploratory factor analysis (using principal axis factoring with a varimax rotation) Internal consistency - Cronbach's α, inter-item correlations, item-total correlations and Item response theory (IRT) analyses Convergent validity - HbA1c	Construct validity - one factor be retained (eigenvalue =1.80) Internal consistency - Cronbach's α=0.68, IRT analyses were then undertaken, and revealed that a two-parameter model was a significantly better fit than a one-parameter model based on both a lower Akaike

Table 3.2 - Summary of studies reporting validation of MMAS-8.

Author (year)	Copyright	Author participation	Validation (language/population)	Statistical Analysis	Results
					information criterion (AIC) (6844.79 versus 6965.94) and a significant likelihood-ratio test ($\chi 2[7]=135.15$, P=0.05) Convergent validity - each point increase in the level of nonadherence was associated with a 0.21 increase in HbA1c (B=0.212, P<0.05)
Yan (2014)[125]	Yes	Yes	Mandarin version (MI patients)	Internal consistency - Cronbach's α and the corrected item-to-total correlations test–retest reliability - intra-class correlation coefficient at a 4-week interval Construct validity - testing the relationship between the C-MMAS-8 and the other three measures, which conceptually related to medication adherence: three subscales (treatment control, personal control and coherence) of the revised illness perception questionnaire	Internal consistency - Cronbach's α=0.77 and the corrected item-to-total correlations ranged from 0.14 to 0.64 test–retest reliability - ICC=0.77 Construct validity - The score of the C-MMAS-8 was positively correlated with the scores of the treatment control subscale (r=0.32, P < 0.01), personal control subscale (r=0.47, P < 0.01) and illness coherence subscale (r=0.44, P < 0.01)

Table 3.2 - Summary of studies reporting validation of MMAS-8.					
Author (year)	**Copyright**	**Author participation**	**Validation (language/population)**	**Statistical Analysis**	**Results**
Reynolds (2014)[150]	Yes	Yes	Osteoporosis-Specific Morisky Medication Adherence Scale (long-term users of bisphosphonates)	Internal consistency - Cronbach's α coefficient and Item-Total Correlation Coefficient Test–retest reliability - Intraclass Correlation Coefficient Convergent validity - Spearman's correlation between OS-MMAS-8 scores and MPR and the domains of the other self-reported measures (BMQ, SEAMS, TSQM, GSRS, SF-12v2) with Bonferroni correction for multiple comparisons. Construct validity - confirmatory factor analysis	Internal consistency - Cronbach's α=0.74 and Item-Total Correlation Coefficient ranged from 0.32 to 0.57 Test–retest reliability - ICC=0.83 (95% CI 0.76–0.88) Convergent validity - small to moderate correlations with SEAMS (0.39), BMQ concerns (-0.20), BMQ NCD (0.21), TSQM with the exception of the side-effects domain, and GSRS scores with the exception of the constipation syndrome domain. The TSQM convenience domain had the largest correlation with OS-MMAS-8 medication adherence score (0.48). No significant correlations were found between OS-MMAS-8 and SF-12v2. Construct validity - Confirmatory factor analysis indicated that the 8-items of OS-MMAS-8 loaded on a single factor

Table 3.2 - Summary of studies reporting validation of MMAS-8.

Author (year)	Copyright	Author participation	Validation (language/population)	Statistical Analysis	Results
					Sensitivity, Specificity, and Positive Predictive Value (PPV) of OS-MMAS-8 were 81.5, 45.7, and 75.9%, respectively
Yang (2014)[130]	No	No	Chinese version (Epilepsy)	Internal consistency - Cronbach's α coefficient Test-retest reliability - intraclass correlation coefficient (ICC) Construct validity - factor analysis Convergent validity - Pearson's correlation with LAEP and seizure frequency	Internal consistency - Cronbach's α=0.556 Test-retest reliability - ICC=0.729 Construct validity - Three factors (eigenvalue > 1) were extracted in our study, explaining a total variance of 58.2% Convergent validity - There was a significant correlation found between adherence and seizure frequency (r=-0.708, p < 0.001), adherence and adverse effects (r=-0.484, p < 0.001)
Kim (2014)[160]	Yes	Yes	Korean version (Hypertension)	Internal consistency - Cronbach's α Test-retest reliability - Intraclass correlation (ICC) Convergent validity - using Pearson correlation coefficients between the	Internal consistency - Cronbach's α=0.56 Test-retest reliability - ICC=0.91 Convergent validity - Korean MMAS-8 was positively associated with the

Table 3.2 - Summary of studies reporting validation of MMAS-8.					
Author (year)	**Copyright**	**Author participation**	**Validation (language/population)**	**Statistical Analysis**	**Results**
				MMAS-8 and the previous 4-item Morisky, Green, and Levine scale Construct validity - Confirmatory factor analysis (CFA) and exploratory factor analysis (EFA)	original 4-item Morisky-Green and Levine scale (r=0.92; P < 0.01) Construct validity - CFA for the 1-factor model of the MMAS-8 showed a poor fit on the fit indices (RMSEA=0.087, TLI=0.825, and CFI=0.875). EFA showed 3 factors with eigenvalues greater than 1, which explained 58.5% of the total variance
Shin (2013)[158]	Yes	No	Korean version (rural older adults with hypertension)	Reliability - Kuder–Richardson alpha coefficient and Item–total correlations Construct validity - Exploratory factor analysis with a principal component extraction Convergent validity - Spearman's correlation coefficient with 4-item measure of adherence	Reliability - Kuder–Richardson alpha coefficient=0.71 and Item–total correlations ranged between 0.245–0.553 Construct validity - EFA showed two factors with eigenvalues >1.0, accounting for 52.22% of the variance Convergent validity - MMAS-K was positively correlated with the 4-item MMAS (r=0.874, P < 0.001)

Table 3.2 - Summary of studies reporting validation of MMAS-8.

Author (year)	Copyright	Author participation	Validation (language/population)	Statistical Analysis	Results
Oliveira-Filho (2014)[161]	Yes	Yes	Brazilian-Portuguese version (Hypertension)	Internal consistency - Cronbach's α Test–retest reliability - Pearson's correlation coefficient Known-groups validity - Chi square and t tests, assuming that patients with poor lower adherence scores also report poor BP control	Internal consistency - Cronbach's α=0.682 Test–retest reliability - Spearman's rank correlation coefficient of 0.928 (P< 0.001) Known-groups validity
Lee (2013b)[162]	Yes	Yes	Korean version (Type 2 Diabetes)	Internal consistency - Cronbach's α with corrected item-total correlations Test-retest reliability - intraclass correlation ICC Convergent validity - Pearson's correlation coefficient to assess the association between the MMAS-8 and the MMAS-4 Known-groups validity - association of the MMAS-8 categories (high, medium, and low adherence) and HbA1c levels	Internal consistency - Cronbach's α=0.66 and item-total correlations ranged between 0.230 and 0.658 Test-retest reliability - ICC=0.79 Convergent validity - MMAS-8 was positively associated (r=0.88; P<0.01) with MMAS-4. Known-groups validity - Poor glycaemic control (HbA1c >7%) was twice as prevalent in the low-adherence group (MMAS-8 score<6) compared with the high-adherence group

Table 3.2 - Summary of studies reporting validation of MMAS-8.					
Author (year)	**Copyright**	**Author participation**	**Validation (language/population)**	**Statistical Analysis**	**Results**
				Construct validity - Both confirmatory factor analysis (CFA) and explanatory factor analysis (EFA)	Construct validity - CFA – GFI=0.82, RMSEA=0.17, NFI=0.47, TLI=0.44, RFI=0.47 and CFI=0.49 EFA showed three factors with eigenvalues >1, which explained 62.4% of the total variance
Fabbrini (2013)[157]	Yes	Yes	Italian version (linguistic validation in patients with Parkinson)		
Wang (2012)[163]	Yes	No	patients taking warfarin specific MMAS (Chinese and English version)	Internal consistency - Cronbach's α. Criterion-related validity - correlation of scale scores and medication refill adherence (MRA) values Construct validity - Confirmatory factor analysis	Internal consistency - Cronbach's α=0.56 Criterion-related validity - The scale scores were significantly correlated with the MRA values (rs=0.17; p=0.04) Construct validity - CFA indicated that the 8-item MMAS was unidimensional (RMSEA=0.03), and the eight items loaded well onto one factor, with factor loadings ranging from 0.20 to 0.81

Table 3.2 - Summary of studies reporting validation of MMAS-8.

Author (year)	Copyright	Author participation	Validation (language/population)	Statistical Analysis	Results
Korb-Savoldelli (2012)[123]	Yes	No	French version (Hypertension)	Internal consistency - Cronbach's α coefficient and the item-total correlations Construct validity - principal component analysis (PCA) with varimax rotation and confirmatory factor analysis Test-retest reliability - Intraclass correlation coefficient	Internal consistency - Cronbach's α=0.54 and the item-total correlations ranged from -0.05 to +0.43 Construct validity - PCA indicating that the 8-item scale was one-dimensional and Confirmatory factor analysis confirmed that the French MMAS was one dimensional but the association between item 5 and "medication adherence" (represented by the factor summarizing the variables of the questionnaire) was not significant Test-retest reliability - ICC=0.68
Reynolds (2012)[131]	Yes	Yes	Osteoporosis-Specific Morisky Medication Adherence Scale (newly prescribed daily or weekly bisphosphonate therapy)	Internal consistency - Cronbach´s α coefficient and the item total correlation coefficient Test-retest reliability - Intraclass correlation coefficient Convergent validity - Spearman correlation between OS-MMAS scores and Osteoporosis-Specific	Internal consistency - Cronbach's α=0.82 and the item total correlation coefficient ranged from 0.40 to 0.68 Test-retest reliability - ICC=0.77 Convergent validity - Convergent validity was supported by significant correlations between OS-MMAS and the SEAMS, BMQ necessity, BMQ

Table 3.2 - Summary of studies reporting validation of MMAS-8.					
Author (year)	**Copyright**	**Author participation**	**Validation (language/population)**	**Statistical Analysis**	**Results**
				BMQ, SEAMS, GSRS, TSQM and SF-12v2 Construct validity - confirmatory factor analysis	necessity-concerns differential, and TSQM scores Construct validity - Confirmatory factor analysis indicated that the 8 items of OS-MMAS loaded on a single factor
Trindade (2011)[159]	Yes	No	English (inflammatory bowel disease)	Convergent validity - logistic regression analysis between the MMAS and Pharmacy fill Nonpersistence (Continuous single interval medication availability (CSA) and mean possession ratio (MPR))	
Sakthong (2009)[164]	Yes	No	Thai version (Type 2 diabetes)	Internal consistency - Cronbach's alpha Test–retest reliability - Intraclass correlation coefficients Convergent validity - Pearson's correlation coefficients (r) between the MMAS-8, the previous 4-item Morisky scale and MA-VAS Known-groups validity – Association of MMAS-8 categories (high,	Internal consistency - Cronbach's α=0.61 Test–retest reliability - ICC=0.83 Convergent validity - MMAS-8 was positively associated with the original 3-item Morisky scale ($r=0.77$; $p < 0.01$) and MA-VAS ($r=0.57$; $p < 0.01$). Known-groups validity - a significant relationship between the MMAS-8 and

Table 3.2 - Summary of studies reporting validation of MMAS-8.					
Author (year)	**Copyright**	**Author participation**	**Validation (language/population)**	**Statistical Analysis**	**Results**
				medium, low adherence) and A1C levels Construct validity - Exploratory factor Analysis. The factor analysis was conducted by a Principal Component Analysis, followed by Varimax rotation with Kaiser normalization	blood glucose control was found (c2 = 6.7; p = 0.035) Construct validity - Exploratory factor analysis showed 3 factors with eigenvalues greater than 1, which explained 57.4% of the total variance
Morisky (2008)[115]	ORIGINAL	ORIGINAL	English version (Hypertension)	Concurrent validity - Pearson's correlation coefficient of the scale with MMAS-4 Predictive validity - Associations with blood pressure levels, knowledge, attitude, social support, stress, coping, and patient satisfaction with clinic visits Construct validity - confirmatory fac-tor analysis Internal consistency - Cronbach's alpha and item-total correlations	Concurrent validity - 8-item scale was significantly correlated with the previously validated 4-item self-reported medication-taking scale (Pearson correlation, 0.64; P<0.05) Predictive validity - A significant relationship between the adherence scale and blood pressure control (chi-square, 6.6; P<0.05) was found Construct validity - Confirmatory factor analysis indicated that the 8-item scale was unidimensional and the items loaded well on the single factor

Table 3.2 - Summary of studies reporting validation of MMAS-8.					
Author (year)	**Copyright**	**Author participation**	**Validation (language/population)**	**Statistical Analysis**	**Results**
					Internal consistency - Cronbach's α=0.83 and item-total correlations were >0.30
Al-Qazaz (2010)[126]	Yes	Yes	Malaysian version (Type 2 Diabetes)	Internal consistency - Cronbach's alpha and item to total correlation coefficient Test–retest reliability- Spearman's rank correlation Convergent validity - Spearman rank correlation between MMAS-8 scores and the scores on the four-item, original Morisky scale Known group validity - association of HbA1c levels (≥7% and <7%) and MMAS-8 categories using Chi square	Internal consistency - Cronbach's α=0.675 and item to total correlation coefficient ranged from 0.287 to 0.459 Test–retest reliability - Spearman's rank correlation coefficient of 0.816 ($p < 0.001$) Convergent validity - A positive correlation between the MMAS-8 and the four-item original MAS was found ($r = 0.792$; $p < 0.01$) Known group validity - The Chi square ($\chi 2$) test shows a significant relationship between MMAS-8 categories and HbA1c categories ($\chi 2 = 20.261$; $p \geq 0.001$)
Moharamzad (2015)[128]	Yes	Yes	Persian Version (Hypertension)	Internal consistency - Cronbach's α coefficient and item-to-total correlation coefficients	Internal consistency - Cronbach's α = 0.697 and item-to-total correlation

Table 3.2 - Summary of studies reporting validation of MMAS-8.

Author (year)	Copyright	Author participation	Validation (language/population)	Statistical Analysis	Results
				Construct validity - principal component analysis (PCA) with varimax rotation and confirmatory factor analysis Test–retest reliability - Pearson's correlation coefficient Known groups' validity - association between controlled BP (i.e., systolic BP < 140 mmHg and diastolic < 90 mmHg) and the MMAS-8 categories	coefficients range between 0.257 and 0.644 Construct validity - The PCA with varimax rotation indicated that the two component accounts for 60.6% of variance in the dataset (32.6% for the first components) Test–retest reliability - Spearman's rank correlation coefficient of 0.940 (P< 0.001) Known groups' validity - Overall score of the MMAS-8 was significantly correlated with systolic BP (r= - 0.306) and diastolic BP (r= - 0.279) with p < 0.001 for both BP measurements

3.3 - Summary of studies reporting the application of MMAS-8.								
Author (year)	**Copyright**	**Author participation**	**Report the Score**	**Inversion of item 5**	**How classificate adherence (Results)**	**Mean±SD**	**N**	**Population**
Kang (2014)[165]	Yes	No	No		>6 - good adherence (55%) 1-6 - poor adherence (45%)	6.4	2445	Hypertension
Thurston (2014)[166]	No	No	No		8 - high adherence (14%) 6–<8 - medium adherence (27.1%) <6 - low adherence (58.9%)	5.5 ±1.8	192	Type 2 Diabetes
Kekale (2014)[167]	Yes	No	No		8 - high adherence (23%) 6–<8 - medium adherence (56%) <6 - low adherence (21%)		86	Chronic myeloid leukemia
Wong (2014a)[156]	No	No	No		>6 - good adherence (9.2%) 1-6 - poor adherence (18.4%) Not on medication (72.3%)		3866	Representative sample of residents living in Henan Province, China
De Las Cuevas (2014)[168]	Yes	No	Yes	Yes	8 - high adherence (24.9%) 6–<8 - medium adherence (46.8%) <6 - low adherence (28.3%)	6.3±1.6	967	Psychiatric disorder
Wong (2014b)[169]	Yes	Yes	Yes	Yes	>6 - good adherence (67.8%) 1-6 - poor adherence (32.2%)	6.79± 1.37	565	Type 2 Diabetes

3.3 - Summary of studies reporting the application of MMAS-8.

Author (year)	Copyright	Author participation	Report the Score	Inversion of item 5	How classificate adherence (Results)	Mean±SD	N	Population
Olszanecka-Glinianowicz (2014)[141]	No	No	No		≤ 4 - Adherence (67.6%) > 4 - Non-adherence (32.4%)		6220	Asthma and COPD
Chan (2014)[145]	No	No	Yes	Yes		Control group = 5.79 Font-Enlarged label group = 5.73 Pictogram incorporated label group = 5.99	110	Type 2 Diabetes and/or Hypertension
Aljumah (2014)[170]	No	No	No				403	Major depressive disorder
Kebede (2014)[142]	No	No	No		8 - good adherence (36.3%) <8 - low adherence (63.7%)		600	HIV
Tran (2014)[139]	No	No	No		8-6 - High and moderate adherence <6 - Low adherence		610	At least one condition that had required

3.3 - Summary of studies reporting the application of MMAS-8.								
Author (year)	**Copyright**	**Author participation**	**Report the Score**	**Inversion of item 5**	**How classificate adherence (Results)**	**Mean±SD**	**N**	**Population**
								ongoing health care for at least 6 months
Moss (2014)[171]	Yes	No	No		8-6 – adherence <6 - Low adherence	6±2	106	Inflammatory Bowel Disease
Abebe (2014)[172]	No	No	No		8 - high adherence (45.9%) 6–<8 - medium adherence (28.7%) <6 - low adherence (25.4%)		391	Diabetes
Farsaei (2014)[146]	No	No	No		8 - high adherence (23.6%) 6–<8 - medium adherence (54.7%) <6 - low adherence (21.7%)		508	Diabetes with insulin therapy
Bramlage (2014)[136]	No	No	Yes	No	8 - high adherence (28.2%) 6–<8 - medium adherence (29.3%) <6 - low adherence (42.5%)	6.0 ± 2.05	10798	Hypertension
Alhewiti (2014)[173]	Yes	No	No		8-6 - High adherence (43.1%) <6 - Low adherence (56.9%)		408	Chronic diseases
Martin-Latry (2014)[174]	No	No	No		8-6 - adherence (81.6%) <6 - Low adherence (12.6%) Not assessable (5.8%)		103	Patients with high cardiovascular risk
Chiu (2014)[137]	Yes	No	No		8 - high adherence (18.9%) 6–<8 - medium adherence (34.1%) <6 - low adherence (47.0%)	5.53±2.03	1054	Asthma

3.3 - Summary of studies reporting the application of MMAS-8.

Author (year)	Copyright	Author participation	Report the Score	Inversion of item 5	How classificate adherence (Results)	Mean±SD	N	Population
Sweileh (2014a)[175]	Yes	No	No		8-6 - High adherence (43.2%) <6 - Low adherence (56.8%)		294	Type 2 Diabetes
Kretchy (2014)[176]	Yes	No	No		8 - high adherence (6.75%) 6–<8 - medium adherence (12.50%) <6 - low adherence (80.75%)		400	Hypertension
Sweileh (2014b)[177]	Yes	No	Yes	Yes	8-6 - Adherent (57.3%) <6 - Non-adherent (42.7%)		405	Type 2 Diabetes
Langley (2014)[148]	Yes	No	No		8 - high adherence 6–<8 - medium adherence <6 - low adherence		4000	Dyslipidaemia and/or Type 2 Diabetes and/or Hypothyroidism
Zyoud (2013)[178]	Yes	Yes	No		8 - high adherence (36.2%) 6–<8 - medium adherence (26.8%) <6 - low adherence (36.8%)		410	Hypertension
Lupattelli (2014)[138]	Yes	No	No		8 - high adherence 6–<8 - medium adherence <6 - low adherence		210	Chronic diseases during pregnancy
Goodhand (2013)[179]	Yes	No	Yes	Yes	8-6 - Adherent (48%) <6 - Non-adherent (52%)	(YA) 5,6±0,2 (A) 6,1±0,2	144	Inflammatory bowel disease

3.3 - Summary of studies reporting the application of MMAS-8.								
Author (year)	**Copyright**	**Author participation**	**Report the Score**	**Inversion of item 5**	**How classificate adherence (Results)**	**Mean±SD**	**N**	**Population**
Fornaro (2013)[180]	No	No	No		8 - high adherence 6–<8 - medium adherence <6 - low adherence		220	Bipolar-II acute depressed patients
Tangkiatkumjai (2013)[181]	Yes	No	No		8 - high adherence (26.6%) 6–<8 - medium adherence (47.7%) <6 - low adherence (25.7%)		421	Chronic Kidney Disease
Lee (2013c)[182]	Yes	Yes	No		8-7 - adherent (65.1%) <7 - non-adherent (32.6%)	6.7±1.4	1114	Hypertension
Lee (2013a)[143]	No	No	No		1 – Adherent 2-8 - non-adherent	1.14±1.46	86	65 years or older
Sankar (2013)[155]	Yes	No	No		8-6 - High adherence (26%) <6 - Poor adherence (74%)	4.45±1.91	346	Diabetes
Wang (2013)[183]	Yes	No	No		higher scores indicating better medication adherence (MMAS-8 score= 8 in 34.5%)	7.0±1.1	174	Patients taking warfarin
Sommers (2012)[144]	No	No	No		8 - high adherence 6–<8 - medium adherence <6 - low adherence	7.89±0.55	30	Gastrointestinal cancer
Oliveira-Filho (2012)[184]	Yes	No	Yes	Yes	8 - high adherence (19.7%) 6–<8 - medium adherence (33.2%) <6 - low adherence (47.1%)	5.8±1.8	223	Hypertension
Bailey (2012)[152]	No	No	Yes	Yes	8 - high adherence (24%)	5.6±2.1	58	Diabetes

3.3 - Summary of studies reporting the application of MMAS-8.

Author (year)	Copyright	Author participation	Report the Score	Inversion of item 5	How classificate adherence (Results)	Mean±SD	N	Population
					6–<8 - medium adherence (32%) <6 - low adherence (45%)			
Sweileh (2012)[185]	Yes	Yes	No		8 - high adherence (22.1%) 6–<8 - medium adherence (44.3%) <6 - low adherence (33.6%)	6.1±1.7	131	Schizophrenia
Wilke (2011)[151]	Yes	Yes	No		8 - high adherence (28.5%) 6–<8 - medium adherence (36.2%) <6 - low adherence (35.3%)	6.14±1.954	340	Chronic diseases
Jamous (2011)[186]	Yes	Yes	No		8 - high adherence (38.5%) 6–<8 - medium adherence (44.6%) <6 - low adherence (16.9%)	6.8±1.3	130	Type 2 Diabetes
Muntner (2011)[187]	Yes	No	No		8 - high adherence (32%) 6–<8 - medium adherence (35%) <6 - low adherence (32%)		284	Patients taking Clopidogrel
Sweileh (2011)[188]	Yes	Yes	No		8 - high adherence (36.0%) 6–<8 - medium adherence (49.3%) <6 - low adherence (14.7%)	6.9±1.3	75	Epilepsy
Gatti (2009)[153]	No	No	Yes	Yes	0-2 - high adherence (47%) >2 - low adherence (53%)		275	
Krousel-Wood (2009) [154]	Yes	Yes	No		8 - high adherence (58%) 6–<8 - medium adherence (33%)	7.4±0.9	87	Hypertension

3.3 - Summary of studies reporting the application of MMAS-8.								
Author (year)	**Copyright**	**Author participation**	**Report the Score**	**Inversion of item 5**	**How classificate adherence (Results)**	**Mean±SD**	**N**	**Population**
					<6 - low adherence (9%)			
Berni (2011)[189]	No	No	No		8-6 - High and medium adherence (60%) <6 - Low adherence (40%)		42	Hypertension
Long (2012)[149]	No	No	Yes		8 - high adherence (25.9%) 6–<8 - medium adherence (33.5%) <6 - low adherence (40.6%)	5.7±2.0	4070	Inflammatory bowel disease
Banerjee (2013)[190]	Yes	No	No		8 - high adherence (19.2%) 6–<8 - medium adherence (13.8%) <6 - low adherence (66.9%)		239	Unipolar depression
Arulmozhi (2014)[191]	Yes	No	No		8 - high adherence (49.3%) 6–<8 - medium adherence (24.7%) <6 - low adherence (26.0%)	6.6± 2.0	150	Type 2 Diabetes
Holt (2013)[192] and Islam (2008)[147]	Yes	Yes	No		8-6 - High adherence (85.8%) <6 - Low adherence (14.2%)		2194	Hypertension

Meta-analysis of the 33 studies reporting sufficient data of the mean MMAS-8 score (Figure 17) resulted in a pooled value of 6.247 (95% CI 6.053-6.442), with a very high heterogeneity (i-square = 98.8%). Meta-analysis of the proportion of medium/high adherent (score 6 or over), including 45 studies, presented a pooled proportion of 65.1% (95% CI 60.6-69.3) with an i-square = 97.3% (Figure 18). And the 38 studies included in the meta-analysis of highly adherent patients (MMAS-8 = 8) lead to in a polled mean of 27.4% (95% IC 24.4-30.6) with an i-square = 93.9% (Figure19). The subgroup analyses of the three meta-analyses could not identify any moderator variable that significantly reduced heterogeneity (Table 3.4).

	Mean	Standard error	Lower limit	Upper limit	p-Value
Morisky, 2008	6,600	0,043	6,515	6,685	0,000
Krousel-Wood, 2009	7,400	0,096	7,211	7,589	0,000
Sakthong, 2009	5,710	0,094	5,525	5,895	0,000
Al-Qazaz, 2010	6,130	0,130	5,875	6,385	0,000
Jamous, 2011	6,800	0,114	6,577	7,023	0,000
Sweileh, 2011	6,900	0,150	6,606	7,194	0,000
Wilke, 2011	6,140	0,106	5,932	6,348	0,000
Korb-Savoldelli, 2012	6,960	0,089	6,786	7,134	0,000
Long, 2012	5,700	0,031	5,639	5,761	0,000
Oliveira-Filho, 2012	5,800	0,121	5,564	6,036	0,000
Reynolds, 2012	6,400	0,155	6,096	6,704	0,000
Sommers, 2012	7,890	0,100	7,693	8,087	0,000
Sweileh, 2012	6,100	0,149	5,809	6,391	0,000
Fabbrini, 2013	6,100	0,043	6,015	6,185	0,000
Goodhand, 2013a	5,600	0,024	5,553	5,647	0,000
Goodhand, 2013b	6,100	0,023	6,054	6,146	0,000
Lee, 2013	6,700	0,042	6,618	6,782	0,000
Sankar, 2013	4,450	0,103	4,249	4,651	0,000
Shin, 2013	6,390	0,183	6,030	6,750	0,000
Wang, 2013	7,000	0,083	6,837	7,163	0,000
Arulmozhi, 2014	6,600	0,163	6,280	6,920	0,000
Chiu, 2014	5,530	0,063	5,407	5,653	0,000
De Las Cuevas, 2014	6,300	0,051	6,199	6,401	0,000
de Oliveira-Filho, 2014	5,780	0,061	5,660	5,900	0,000
Hacihasanoglu, 2014	5,000	0,164	4,678	5,322	0,000
Kim, 2014	6,600	0,072	6,458	6,742	0,000
Moss, 2014	6,000	0,194	5,619	6,381	0,000
Reynolds, 2014	6,200	0,090	6,024	6,376	0,000
Thurston, 2014	5,500	0,130	5,245	5,755	0,000
Wong, 2014	6,800	0,059	6,685	6,915	0,000
Yan, 2014	5,840	0,144	5,558	6,122	0,000
Arnet, 2015	7,500	0,096	7,313	7,687	0,000
Moharamzad, 2015	5,570	0,132	5,312	5,828	0,000
	6,247	0,099	6,053	6,442	0,000

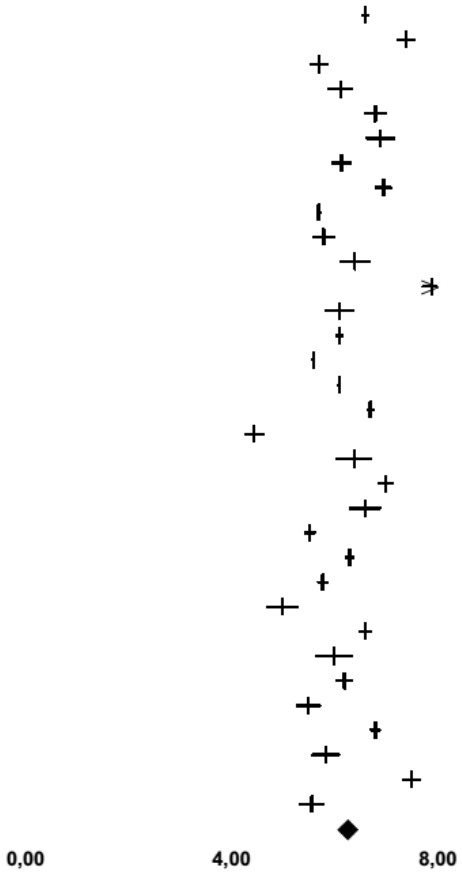


***Figure 17** - MMAS-8 mean score meta-analysis.*

	Event rate	Lower limit	Upper limit	p-Value
Islam, 2008	0,858	0,843	0,872	0,000
Morisky, 2008	0,679	0,654	0,703	0,000
Krousel-Wood, 2009	0,908	0,827	0,953	0,000
Sakthong, 2009	0,541	0,485	0,597	0,151
Al-Qazaz, 2010	0,617	0,543	0,686	0,002
Berni, 2011	0,595	0,443	0,731	0,220
Jamous, 2011	0,831	0,756	0,886	0,000
Muntner, 2011	0,676	0,619	0,728	0,000
Sweileh, 2011	0,853	0,754	0,917	0,000
Trindade, 2011	0,509	0,416	0,601	0,849
Wilke, 2011	0,647	0,595	0,696	0,000
Kane, 2012	0,660	0,581	0,731	0,000
Korb-Savoldelli, 2012	0,824	0,765	0,871	0,000
Long, 2012	0,594	0,579	0,609	0,000
Oliveira-Filho, 2012	0,529	0,464	0,594	0,384
Reynolds, 2012	0,693	0,615	0,762	0,000
Sweileh, 2012	0,664	0,579	0,740	0,000
Banerjee, 2013	0,331	0,274	0,393	0,000
Fabbrini, 2013	0,696	0,663	0,727	0,000
Fornaro, 2013	0,777	0,718	0,827	0,000
Goodhand, 2013	0,875	0,810	0,920	0,000
Lee, 2013	0,584	0,529	0,637	0,003
Sankar, 2013	0,260	0,217	0,309	0,000
Shin, 2013	0,663	0,561	0,752	0,002
Tangkiatkumjai, 2013	0,743	0,700	0,783	0,000
Zyoud, 2013	0,632	0,584	0,677	0,000
Abebe, 2014	0,747	0,701	0,787	0,000
Alhewiti, 2014	0,431	0,384	0,480	0,006
Arulmozhi, 2014	0,740	0,664	0,804	0,000
Chiu, 2014	0,526	0,495	0,556	0,096
De Las Cuevas, 2014	0,703	0,674	0,731	0,000
de Oliveira-Filho, 2014	0,533	0,501	0,564	0,046
Farsaei, 2014	0,783	0,746	0,817	0,000
Hacihasanoglu, 2014	0,413	0,346	0,483	0,016
Kekale, 2014	0,791	0,692	0,864	0,000
Kim, 2014	0,673	0,624	0,719	0,000
Kretchy, 2014	0,193	0,157	0,234	0,000
Martin-Latry, 2014	0,816	0,729	0,879	0,000
Reynolds, 2014	0,615	0,566	0,661	0,000
Sweileh, 2014a	0,432	0,376	0,489	0,020
Sweileh, 2014b	0,573	0,524	0,620	0,003
Thurston, 2014	0,411	0,344	0,482	0,015
Yang, 2014	0,793	0,707	0,858	0,000
Arnet, 2015	0,943	0,857	0,978	0,000
Moharamzad, 2015	0,460	0,392	0,529	0,258
	0,651	0,606	0,693	0,000

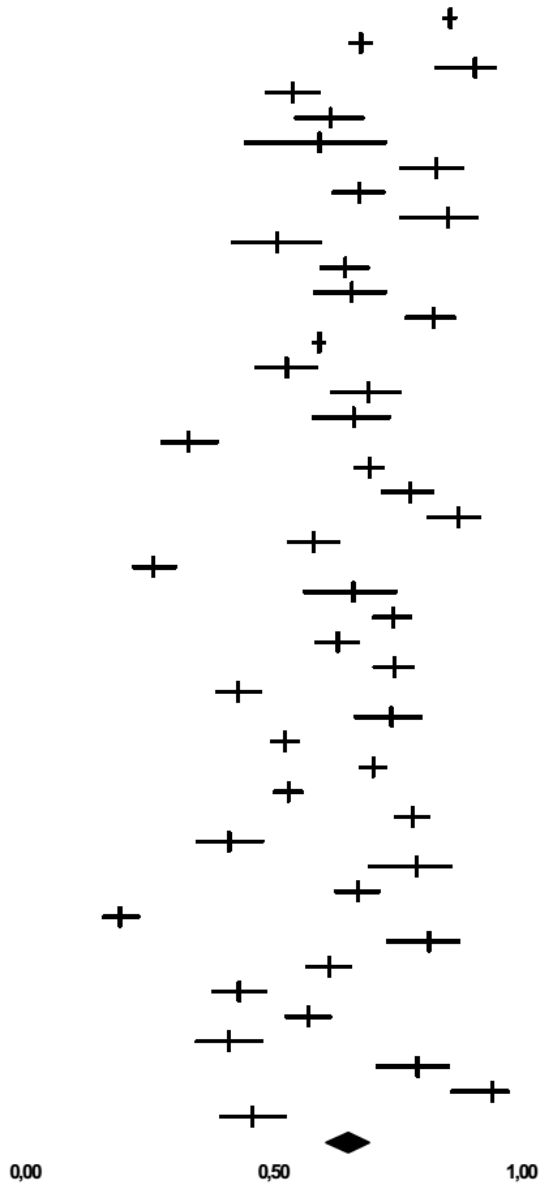


Figure 18 *- MMAS-8 medium/high adherent event rate (score 6 or over) meta-analysis.*

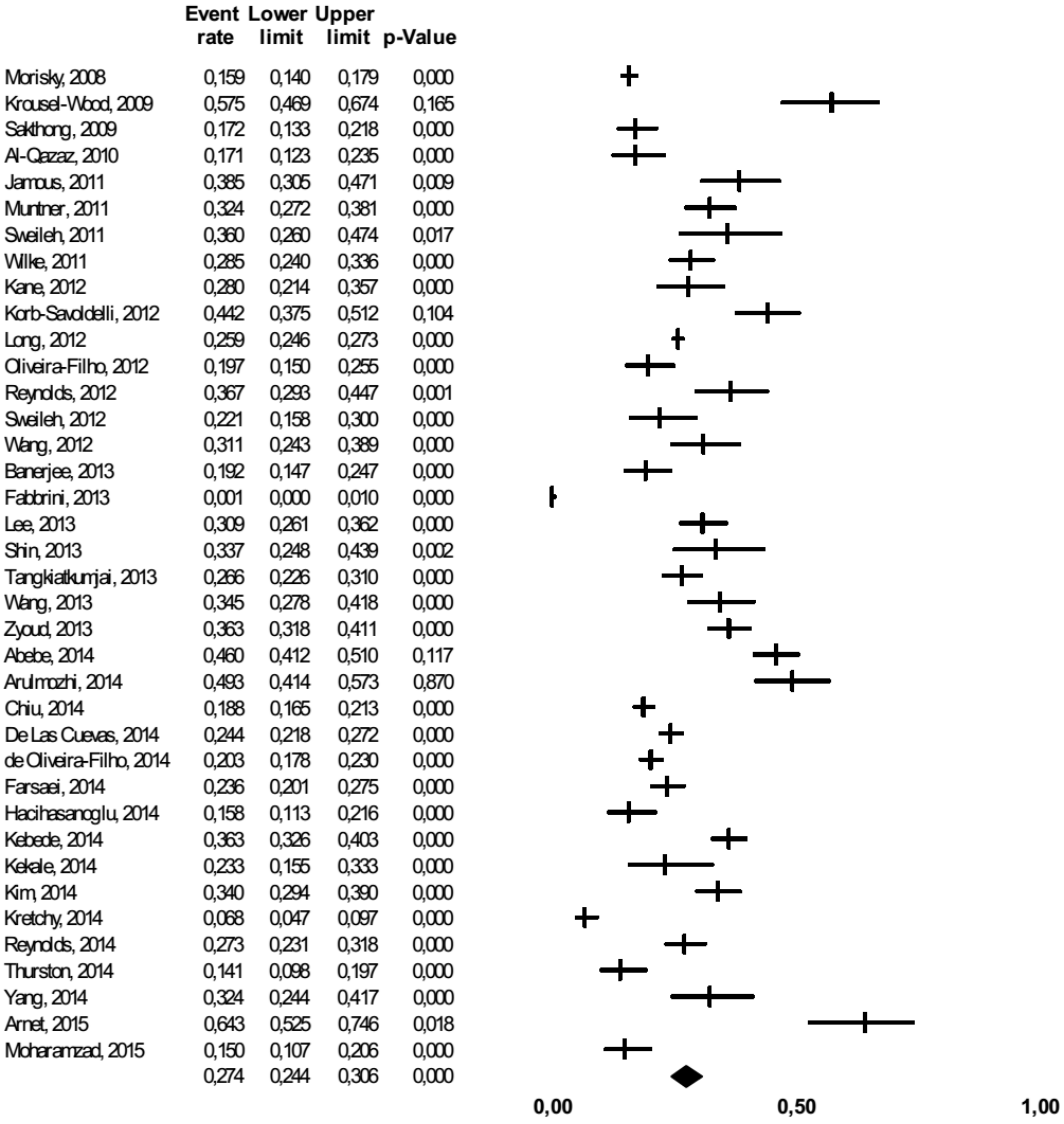


Figure 19 *- MMAS-8 highly adherent event rate (score=8) meta-analysis.*

Table 3.4 - Results of subgroup analysis of MMAS-8.									
	Mean score of subgroup analysis of MMAS-8 mean score Meta-analysis			Mean score of subgroup analysis of MMAS-8 medium-highly adherent (score 6 and over) Meta-analysis			Mean score of subgroup analysis of MMAS-8 highly adherent (score=8) Meta-analysis		
	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)
Copyright									
Yes	3	6.36 (4.95 to 7.78)	99.5	37	0.64 (0.58 to 0.69)	97.5	32	0.27 (0.23 to 0.31)	93.6
No	30	6.24 (6.04 to 6.43)	98.6	8	0.70 (0.61 to 0.78)	96.0	6	0.29 (0.22 to 0.37)	95.5
Morisky as author									
Yes	18	6.37 (6.14 to 6.60)	97.5	20	0.67 (0.61 to 0.73)	97.0	18	0.28 (0.23 to 0.34)	93.9
No	15	6.10 (5.83 to 6.37)	98.9	25	0.63 (0.57 to 0.69)	97.3	20	0.27 (0.23 to 0.31)	94.2
Study´s design									
Cross-sectional	32	6.20 (6.01 to 6.38)	98.6	43	0.64 (0.60 to 0.69)	97.4	36	0.27 (0.24 to 0.30)	93.9
Longitudinal	0	--	--	2	0.81 (0.49 to 0.95)	93.6	1	0.32 (0.27 to 0.38)	N.A.
Interventional not controlled	1	7.89 (7.69 to 8.09)	N.A.	0	--	--	1	0.36 (0.33 to 0.40)	N.A.
Interventional controlled	0	--	--	0	--	--	0	--	--
Age of patients									
< 65 years	25	6.15 (5.92 to 6.38)	98.7	28	0.63 (0.58 to 0.68)	96.1	27	0.27 (0.23 to 0.31)	93.9
≥ 65 years	7	6.67 (6.27 to 7.08)	98.1	10	0.75 (0.67 to 0.82)	95.9	7	0.35 (0.24 to 0.48)	93.0
Not reported	1	5.70 (5.64 to 5.76)	N.A.	7	0.56 (0.40 to 0.71)	98.0	4	0.18 (0.11 to 0.29)	95.4
Type of patients									
Chronic disease	28	6.17 (5.96 to 6.38)	98.8	37	0.65 (0.60 to 0.70)	97.4	30	0.28 (0.24 to 0.32)	94.7
Psychiatric disease	4	6.32 (6.08 to 6.56)	90.4	7	0.64 (0.52 to 0.74)	96.9	6	0.24 (0.17 to 0.32)	84.5
HIV	0	---	---	0	--	--	1	0.36 (0.32 to 0.40)	N.A.

Table 3.4 - Results of subgroup analysis of MMAS-8.

	Mean score of subgroup analysis of MMAS-8 mean score Meta-analysis			Mean score of subgroup analysis of MMAS-8 medium-highly adherent (score 6 and over) Meta-analysis			Mean score of subgroup analysis of MMAS-8 highly adherent (score=8) Meta-analysis		
	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)
Cancer	1	7.89 (7.69 to 8.09)	N.A.	1	0.79 (0.69 to 0.86)	N.A.	1	0.23 (0.15 to 0.33)	N.A.
Not reported	--	---	---	--	---	---	--	---	---
Score explanation									
No	25	6.20 (5.93 to 6.47)	98.6	36	0.63 (0.58 to 0.68)	97.6	32	0.27 (0.24 to 0.30)	93.9
Totally	4	6.23 (5.82 to 6.64)	99.3	5	0.76 (0.64 to 0.84)	92.5	3	0.33 (0.21 to 0.47)	93.7
Partially	4	6.55 (5.92 to 7.18)	98.8	4	0.68 (0.56 to 0.78)	93.8	3	0.12 (0.02 to 0.51)	96.9
Validation or application study									
Validation	18	6.24 (5.97 to 6.51)	99.1	29	0.65 (0.59 to 0.71)	98.0	21	0.28 (0.24 to 0.32)	94.1
Application	15	6.26 (5.99 to 6.53)	97.6	16	0.64 (0.59 to 0.69)	92.9	17	0.27 (0.22 to 0.32)	93.8
Setting									
Pharmacy	2	6.77 (5.54 to 8.01)	98.7	2	0.80 (0.44 to 0.95)	94.7	2	0.42 (0.18 to 0.70)	95.9
Hospital	26	6.25 (6.04 to 6.45)	98.6	36	0.63 (0.58 to 0.68)	96.0	31	0.25 (0.22 to 0.29)	94.2
Ambulatory	3	6.12 (4.12 to 8.11)	99.6	3	0.69 (0.28 to 0.93)	98.2	2	0.50 (0.25 to 0.75)	92.9
Remote (phone or internet)	2	5.94 (5.45 to 6.43)	96.4	4	0.73 (0.55 to 0.86)	99.3	3	0.26 (0.25 to 0.27)	0
Country									
Europe	7	6.38 (6.04 to 6.72)	99.1	10	0.77 (0.72 to 0.81)	86.1	6	0.30 (0.20 to 0.43)	94.4
North America	8	6.46 (5.92 to 7.01)	99.1	10	0.67 (0.58 to 0.76)	98.2	8	0.28 (0.22 to 0.35)	94.8
South America	2	5.78 (5.68 to 5.89)	0	2	0.53 (0.50 to 0.56)	0	2	0.20 (0.18 to 0.23)	0
Africa	0	---	---	2	0.46 (0.07 to 0.91)	99.5	3	0.25 (0.11 to 0.48)	98.4

Table 3.4 - Results of subgroup analysis of MMAS-8.									
	Mean score of subgroup analysis of MMAS-8 mean score Meta-analysis			Mean score of subgroup analysis of MMAS-8 medium-highly adherent (score 6 and over) Meta-analysis			Mean score of subgroup analysis of MMAS-8 highly adherent (score=8) Meta-analysis		
	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)
Middle East	5	6.08 (5.39 to 6.76)	96.8	10	0.62 (0.52 to 0.71)	96.1	7	0.26 90.19 to 0.33)	90.0
Asia	11	6.16 (5.73 to 6.58)	98.7	11	0.59 (0.49 to 0.68)	96.5	12	0.28 (0.23 to 0.33)	90.9
Multicentric	0	---	---	0	--	--	0	--	--
Evidence of correct scoring									
No	29	6.25 (6.01 to 6.49)	98.6	40	0.64 (0.59 to 0.68)	97.4	35	0.27 (0.24 to 0.30)	94.1
Yes	4	6.23 (5.82 to 6.64)	99.3	5	0.76 (0.64 to 0.84)	92.5	3	0.33 (0.21 to 0.47)	93.7
Self-report									
Interview	8	6.35 (5.86 to 6.85)	98.6	16	0.68 (0.59 to 0.76)	98.3	16	0.28 (0.23 to 0.34)	95.7
Self-report	20	6.37 (6.11 to 6.62)	98.4	22	0.64 (0.60 to 0.68)	94.6	19	0.28 (0.24 to 0.32)	92.4
Nor reported	5	5.61 (5.21 to 6.00)	99.0	7	0.59 (0.40 to 0.76)	97.4	3	0.20 (0.17 to 0.23)	0
Investigator									
Physician	1	6.10 (6.01 to 6.18)	N.A.	1	0.70 (0.66 to 0.73)	N.A.	1	0.00 (0.00 to 0.01)	N.A.
Pharmacist	2	5.91 (5.50 to 6.32)	85.4	2	0.57 (0.50 to 0.65)	61.5	2	0.17 (0.14 to 0.21)	0
Nurse	2	6.41 (5.31 to 7.50)	97.7	2	0.78 (0.70 to 0.85)	77.5	3	0.42 (0.35 to 0.49)	80.6
Investigator of University	21	6.28 (6.00 to 6.56)	99.0	31	0.63 (0.57 to 0.69)	96.7	24	0.26 (0.22 to 0.31)	93.0
Student	3	6.36 (5.66 to 7.05)	98.7	3	0.63 (0.52 to 0.73)	92.9	3	0.34 (0.20 to 0.52)	97.2
E-mail/telephone	4	6.09 (5.74 to 6.45)	94.6	6	0,71 (0.57 to 0.81)	98.9	5	0.27 (0.25 to 0.30)	64.9
Local of data collection									
Only one setting	14	6.66 (6.41 to 6.92)	97.1	19	0.69 (0.63 to 0.74)	94.3	17	0.31 (0.25 to 0.38)	94.8

Table 3.4 - Results of subgroup analysis of MMAS-8.

	Mean score of subgroup analysis of MMAS-8 mean score Meta-analysis			Mean score of subgroup analysis of MMAS-8 medium-highly adherent (score 6 and over) Meta-analysis			Mean score of subgroup analysis of MMAS-8 highly adherent (score=8) Meta-analysis		
	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)
More than one setting	19	5.94 (5.74 to 6.15)	98.5	26	0.62 (0.56 to 0.68)	98.0	21	0.25 (0.21 to 0.28)	93.2
One country or multicenter									
Only one country	32	6.27 (6.07 to 6.47)	98.8	44	0.65 (0.61 to 0.70)	97.3	37	0.28 (0.25 to 0.31)	93.7
Various countries (multicenter)	1	5.53 (5.41 to 5.65)	N.A.	1	0.53 (0.49 to 0.56)	N.A.	1	0.18 (0.16 to 0.21)	N.A.
MMAS-8 as unique method									
Yes	22	6.10 (5.89 to 6.31)	98.8	32	0.63 (0.58 to 0.68)	97.8	25	0.26 (0.23 to 0.30)	95.0
No	11	6.54 (6.06 to 7.01)	98.2	13	0.69 (0.62 to 0.76)	93.0	13	0.29 (0.24 to 0.36)	90.8
Excluded patients > 65 years									
Yes	2	6.50 (5.72 to 7.28)	93.0	6	0.63 (0.47 to 0.77)	96.8	4	0.27 (0.20 to 0.35)	81.2
No	31	6.23 (6.03 to 6.43)	98.8	39	0.65 (0.61 to 0.70)	97.4	34	0.27 (0.24 to 0.31)	94.4
Excluded patients < 55 years									
Yes	3	6.27 (6.13 to 6.41)	0	4	0.72 (0.53 to 0.85)	97.9	3	0.32 (0.26 to 0.38)	60.8
No	30	6.24 (6.03 to 6.44)	98.9	41	0.64 (0.60 to 0.68)	96.5	35	0.27 (0.24 to 0.30)	94.3
Excluded patients with cognitive impairment									
Yes	9	5.78 (5.24 to 6.32)	98.3	14	0.57 (0.44 to 0.69)	98.6	8	0.21 (0.17 to 0.26)	84.0
No	24	6.42 (6.20 to 6.64)	98.9	31	0.68 (0.64 to 0.72)	95.8	30	0.29 (0.26 to 0.33)	94.7
One or more language of MMAS-8									
Yes	2	6.26 (4.82 to 7.70)	99.5	1	0.53 (0.49 to 0.56)	N.A.	3	0.27 (0.17 to 0.40)	93.0

Table 3.4 - Results of subgroup analysis of MMAS-8.									
	Mean score of subgroup analysis of MMAS-8 mean score Meta-analysis			Mean score of subgroup analysis of MMAS-8 medium-highly adherent (score 6 and over) Meta-analysis			Mean score of subgroup analysis of MMAS-8 highly adherent (score=8) Meta-analysis		
	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)	N	Mean (CI 95%)	I^2 (%)
No	31	6.25 (6.05 to 6.44)	98.8	44	0.65 (0.61 to 0.70)	97.3	35	0.27 (0.24 to 0.31)	94.0
Patient remunerated									
Yes	2	6.26 (6.08 to 6.44)	19.6	2	0.65 (0.57 to 0.72)	65.3	2	0.31 (0.23 to 0.41)	78.2
No	31	6.24 (6.04 to 6.45)	98.9	43	0.65 (0.60 to 0.69)	97.4	36	0.27 (0.24 to 0.30)	94.2
Version validated									
No	9	6.06 (5.61 to 6.52)	98.1	19	0.65 (0.58 to 0.72)	96.6	14	0.29 (0.24 to 0.35)	93.7
Yes	9	6.41 (6.03 to 6.79)	99.4	10	0.66 (0.52 to 0.77)	99.0	7	0.25 (0.18 to 0.33)	95.0
Validation	15	6.26 (5.99 to 6.53)	97.6	16	0.64 (0.59 to 0.69)	92.9	17	0.27 (0.22 to 0.32)	93.8
Translation									
No	2	6.35 (5.90 to 6.80)	82.1	6	0.73 (0.67 to 0.78)	80.6	5	0.36 (0.27 to 0.46)	94.2
Yes	9	6.11 (5.68 to 6.53)	98.5	13	0.61 (0.52 to 0.69)	96.9	11	0.25 (0.20 to 0.31)	90.2
Validation	22	6.29 (6.05 to 6.54)	99.0	26	0.65 (0.59 to 0.71)	97.7	22	0.26 (0.23 to 0.31)	94.1
MAPI									
No	31	6.31 (6.11 to 6.51)	98.8	42	0.67 (0.62 to 0.71)	97.3	36	0.28 (0.25 to 0.31)	94.0
Yes	2	5.29 (4.73 to 5.85)	86.4	3	0.43 (0.40 to 0.47)	0	2	0.15 (0.12 to 0.19)	0

Discussion

In only seven years, MMAS-8 is being widely used as the gold standard instrument to assess medication non-adherence. Although MMAS-8 has demonstrated being a highly reliable instrument, we found important heterogeneity among the results of the studies using this instrument to assess non-adherence. Heterogeneity, when measured with the i-square, expresses the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies[193]. Our results show that more than 95% of the variations identified in the MMAS-8 scores are due to variation among the studies. These variations may be associated with different populations, differences in the intervention performed, or with differences in measuring methods. However, we used only MMAS-8 values from cross-sectional studies or at baseline, which eliminates the potential influence of differences in the intervention.

Despite the commonly recognized goal of meta-analyses is to obtain a global index to measure the magnitude of an effect, this quantitative evidence gathering technique is also used to identify whether the studies are homogeneous and to find the moderator variables associated with the heterogeneity among these studies[194]. To identify the potential causes of heterogeneity sensitivity analysis and subgroup analysis should be performed using moderator variables[195].

Being MMAS-8 a questionnaire, one could expect that the mode of administration would influence on the results[196]. The knowledge and expertise of the authors on the scoring system could also be a source of heterogeneity. In our analysis, despite having used moderator variables related to the study characteristics, as well as those related to population characteristics, we could not identify any variable that substantially reduced the heterogeneity in any of the subgroups.

High heterogeneity was presented as a weakness in healthcare professional interventions[197] and specifically when aiming to reduce non-adherence[198]. Presenting a high heterogeneity already in baseline implies that researchers would never be able to identify the potential causes of the heterogeneity that may appear in a meta-analysis of intervention studies. In order to identify causes of heterogeneity and increase the value of

the MMAS-8, further investigations should use this instrument in highly homogeneous populations, with strict application procedures.

Conclusions

The 8-Item Morisky Medication Adherence Scale (MMAS-8) is being accepted as the gold-standard to assess medication non-adherence. Despite the demonstrated reliability and internal consistency, a meta-analysis of cross-sectional studies and baseline values of longitudinal or interventional studies identified a high heterogeneity. Subgroup analyses with moderator variables (patient characteristics and study or scoring characteristics) could not reduce the heterogeneity.

Cross-cultural adaptation of 8-item Morisky Medication Adherence Scale

Cross-cultural adaptation of 8-item Morisky Medication Adherence Scale

Introduction

As mentioned in the previous chapter, one of the possible causes for MMAS-8 high heterogeneity may be validation problems regarding psychometric properties and cross-cultural adaptation of MMAS-8 to other languages.

As any measurement process, questionnaires are subject to a certain amount of error that may affect their precision and accuracy. So, before its application, and to ensure questionnaire quality, is necessary to undertake a validation process, meaning it's necessary to evaluate if the questionnaire meets a number of requirements that ensure its validity, reliability and sensitivity to change, a set of characteristics named psychometric properties[199]. Two dimensions must be assessed, validity and reliability.

Validity is the questionnaire ability to measure the desired concept, in MMAS-8 particularly, the ability to measure adherence to medication. Comprises three distinct concepts:

- Content validity: evaluates if the items on a questionnaire are related and representative of the construct being measured, in this case adherence to medication;
- Criterion validity: evaluates if the questionnaire is measuring what it claims to measure, in this case, if the final result can categorize correctly a patient as adherent. To evaluate this, concurrent and convergent validity are assessed, and the results of the questionnaire being tested are compared, respectively, with other adherence measures or with other measures known to be related to adherence, as for example knowledge of the disease, and
- Factorial validity: evaluates questionnaire structure, its dimensions and subscales. Through factorial analysis, questionnaire structure is assessed and items organization in subscales is evaluated.

Reliability is the questionnaire ability to produce the same results, under the same conditions, in different occasions. It is related to the degree of independence of the results obtained in relation to accidental circumstances that occurs in the application of the questionnaire. Two parameters are evaluated to assess reliability:

- Internal consistency: items that measure the same concept should generate homogeneous answers related to each other. Through Cronbach's alpha, homogeneity of content is evaluated, and
- Test-retest reliability: is related to the reproducibility of the questionnaire. A questionnaire applied on two different occasions, to the same patient, with the same conditions, must obtain the same results.

Despite MMAS-8 being validated to more than 20 languages and to several other diseases than hypertension, in some validation studies, internal consistency of MMAS-8 is lower than the expected, and some authors, like Arnet *et al.* (2015)[124], Kim *et al.* (2014)[160] and Sakthong *et al.* (2009)[164] proposed a multidimensional model instead of the accepted unidimensional one. Considering adherence a dynamic concept, that encompasses complex behaviours, this seems to be a valid hypothesis.
If we consider that adherence can be affected by several factors and is primarily classified as intentional (that is conditioned by beliefs, attitudes and expectations that influence patients' motivation to begin and persist with the treatment regimen) or unintentional (that is conditioned by the capacity and resource limitations that prevent patients from implementing their decisions to follow treatment recommendations and involves individual and environment constraints)[200], after analysing theoretical content of MMAS-8 items, a bidimensional model seems to be an interesting approach.

Actually there is no validated version of MMAS-8 to European-Portuguese. In 2014, Oliveira-Filho *et al.*[161] developed a Brazilian-Portuguese version, however due to important idiomatic differences between Brazilian-Portuguese and European-Portuguese, the application of the Brazilian-Portuguese version to Portuguese population is not recommended.

In Portugal, hypertensive patients adherence to therapy can be assessed through one previously validated instrument, Medida de Adesão aos Tratamentos [Measure Treatment Adherence] (MAT)[201]. MAT was developed in 2001 and consists in a 7 item questionnaire based on MMAS-4[116] and Shea *et al.* (1992b)[202]. Being an instrument with a good internal consistency (Cronbach's alpha=0.74), it became a reference in assessment of adherence in Portugal, being used in several studies[203-206]. However, as a Portuguese instrument, used only in this country, it presents a problem when we try to compare the results with similar studies made in other countries, hindering the cross-sectional and longitudinal comparability of Portuguese studies with others.
Being the MMAS-8 considered a gold standard questionnaire to assess patient's adherence to medication worldwide, it is the ideal instrument to use if we want to ensure comparability between studies.

Objectives

The main objective of this study was to develop and validate the European-Portuguese adaptation of the 8-Items Morisky Medication Adherence Scale in a Portuguese sample, namely to examine the factorial structure of MMAS-8 with a confirmatory analysis and to estimate its convergent and concurrent validities.

Methods

This was a cross-sectional study. To obtain a diverse sample of hypertensive patients, data were collected in 9 community pharmacies in the central region of Portugal (urban and rural) and in the Hospital Infante D. Pedro, EPE in Aveiro.

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra (Registration number CE_105.2013). The study aims and procedures were explained to all potentially eligible patients and inclusion was validated after written informed consent was signed by the patient.

Permission to use MMAS-8 was requested to the author and a license contract and a copyright agreement was signed.

8-item Morisky Medication Adherence Scale

The instrument consists in 7 dichotomous items and a five-point Likert scale. Questions were formulated to avoid a "yes-saying" bias, so in the first 7 questions, one point is assigned to each "no" answer, except in item 5 which is reversed to prevent the tendency to respond in a specific way to a series of questions regardless of their content. In the last question is necessary to standardize the code (0–4) and score is obtained dividing by four. Patients are classified, according to the score obtained, as Low adherent (score<6), Medium adherent (score 6- <8) and High adherent (score=8).

Translation and cross-cultural adaptation of MMAS-8

A process of translation and back-translation according to international guidelines was performed[207, 208]. The original questionnaire was submitted to 3 bilingual translators, who were aware of the goals of the study and developed three independent translations of the original items to Portuguese. The three versions were compared in order to generate a consensual version. The reverse translation, from Portuguese to English, was carried out by another bilingual translator who was not involved in developing the initial version and who did not know the objectives and concepts of the study. This new English version was compared to the original version and occasional discrepancies were corrected. Finally a cross-culturally adapted version was obtained through a consensus meeting, attended by 2 experts in pharmacology and 1 expert in Portuguese language, after semantic, idiomatic, cultural and conceptual equivalence evaluation.

A pilot test was performed in a Portuguese population (n=20) to ensure patient understanding and eventual doubts and difficulties in the use of the questionnaire. After small adjustments based on proposed changes, we obtained the final Portuguese version of the questionnaire. The patients who participated in this face-validity phase were not included in the following phases of study.

Medida de Adesão aos Tratamentos

The MAT[201] is a Portuguese validated questionnaire developed to assess patients' adherence to medication. It consists of 7 items scaled according to a six point Likert scale, ranging from "always" (1) to "never" (6). The level of adherence is obtained by summing up the values of each item and then dividing by the total number of items. Higher scores are indicative of greater level of adherence. The classification of patients as adherent or non-adherent is made according scores near the median values.

Hypertension Knowledge Test

The Hypertension Knowledge Test (HKT)[209] is a 21 items questionnaire developed to assess patient's knowledge about hypertension, its causes and treatment and ways to prevent and control high blood pressure. It is divided into two parts, 12 true or false questions and 9 multiple choice questions. The knowledge level is calculated by assigning one point to each correct answer, obtaining a total score ranging from 0 to 21. The higher the score obtained, the greater the patient knowledge about hypertension.

Data collection

Data collection took place between March 2014 and September 2015. Inclusion criteria were patients older than 18 years and taking at least one antihypertensive drug. All patients who met the inclusion criteria, attending to participating pharmacies and hospital in the study were invited to participate. The interview was made by a trained pharmacist in a private office, where data on personal and family history were collected and the MMAS-8, MAT and HKT instruments were administered.

Statistical Analysis

In order to examine the factor structure of the Portuguese version of the MMAS-8, a confirmatory factor analysis (CFA) using AMOS, version 20.0 (IBM, AMOS development Corporation, Meadville, PA,USA) was performed. Models were estimated using the maximum likelihood method. Model fit was assessed using the chi-square goodness-of-fit statistic the comparative fit index (CFI) the standardised root-mean-square residual (SRMR) and the root mean square error of approximation (RMSEA). Model fit is considered very good when the CFI is above 0.95, the SRMR is below 0.10 and the RMSEA is below 0.5[210].

Whenever a model did not fit the data well, alternative models were also tested. The development of competing models was based on theoretical considerations and analysis of the data and two models were tested, one included all the 8 items of the MMAS-8 loading on one global factor, overall adherence to antihypertensive medication and another model with two subscales correlated between them, one subscale concerning to unintentional non-adherence behaviours with items 1, 2, 4, 5 and 8 and another subscale concerning to intentional non-adherence behaviours with items 3, 6 and 7. Internal consistency of the MMAS-8 was examined via Cronbach's alpha. Convergent validity was assessed by evaluating the association between MMAS-8 and MAT and concurrent validity was assessed by evaluating the association between MMAS-8 and HKT.

Results

Study participants

A sample of 472 patients were enrolled in the study, with a mean age of 68.18±10.56 years, being 243 (51.5%) female. The average time since hypertension diagnose was 10.92±8.51 years, with maximum disease duration of 50 years. In the study sample, 255 (54%) had dyslipidemia, 133 (28%) had diabetes, 127 (27%) had heart disease and 40 (8%) already had a stroke. Using Morisky *et al*. (2008)[5] dichotomous cut-offs to classify patients as adherent (score≥6) or non-adherent (score<6), characteristics of patients according to adherence levels are presented in Table 4.1.

Table 4.1 - Characteristics of patients according to adherence levels.				
	Non-adherent patients - MMAS-8 score<6 (n=132)	Adherent Patients - MMAS-8 score ≥6 (n=340)	t	p
Age	66.44±11.22	68.86±10.22	-2.25	**0.025**
Sex (male)	71 (53.8%)	172 (50.6%)	0.39	0.54
Average time with hypertension	9.46±7.07	11.48±8.96	-2.59	**0.010**
Family history	52 (39.4%)	141 (41.5%)	0.17	0.75
Diabetes	35 (26.5)	98 (28.8%)	0.25	0.65
Dyslipideamia	66 (50%)	189 (55.6%)	0.64	0.47
Stroke	10 (7.6%)	30 (8.8%)	0.19	0.72
Mean MAT	5.47±0.38	5.85±0.20	-10.97	**<0.001**
Mean HKT*	14.79±2.78	15.56±2.71	-2.12	**0.035**
*Due to missing answers HKT values were calculated to a sample of 80 patients non-adherent (MMAS-8 score<6) and 217 adherent patients (MMAS-8 score ≥6).				

The mean MMAS-8 score obtained for was 6.74±1.39. Using the recommended cut-offs, 132 (28%), 181 (38.3%) and 159 (33.7%) of patients were in the low, medium and high adherence groups, respectively. Table 4.1 describes the answers obtained.

The mean score obtained for MAT was 5.74±0.31 and the mean score obtained for HKT was 15.35±2.79.

Table 4.2 – Distribuition of responses to MMAS-8 items.		
Item	Patients responses	Entry (n= 472) n (%)
Às vezes esquece-se de tomar os seus comprimidos para a pressão arterial?	Não	317 (67.2%)
Nas duas últimas semanas, houve algum dia em que não tomou os seus medicamentos para a pressão arterial?	Não	379 (80.3%)
Já alguma vez parou de tomar a sua medicação ou diminuiu a dose, sem avisar o seu médico, porque se sentia pior quando os tomava?	Não	418 (88.6%)
Quando viaja ou não está em casa, às vezes esquece-se de levar consigo os seus medicamentos?	Não	404 (85.6%)
Ontem tomou os seus medicamentos para a hipertensão arterial?	Sim	434 (91.9%)
Quando sente que a sua pressão arterial está controlada, por vezes deixa de tomar os seus medicamentos?	Não	446 (94.5%)
Já alguma vez se sentiu incomodado por seguir corretamente o seu esquema de tratamento para a pressão arterial?	Não	390 (82.6%)
Com que frequência tem dificuldade em lembrar-se de tomar todos os seus medicamentos para a pressão arterial?	Nunca	228 (48.3%)
	Quase nuca	189 (40%)
	Às vezes	44 (9.3%)
	Frequentemente	10 (2.1%)
	Sempre	1 (0.2%)

Confirmatory factor analysis

The first CFA model (Model 1) included all the 8 items of the MMAS-8 loading on one global factor, overall adherence to antihypertensive medication. The model revealed a poor fit to the data, with, with chi-square (20)=132.13, p<0.001; the CFI=0.81; RMSEA=0.11 [90% Confidence interval: 0.09; 0.13] and the SRMR=0.07. The analysis of modifications indices and the evaluation of each item phrasing suggested that the introduction of error correlations, between items 2 and 5 and between items 6 and 7 would improve model fit and were included in the model. Final model presented a very good fit, with chi-square (18)=48.465, p<0.001; the CFI=0.95; RMSEA=0.06 [90% Confidence interval: 0.04; 0.08] and the SRMR=0.04.

A second model (model 2) was tested, examining the fit of the theoretical model of two subscales correlated between them, subscale 1 with items concerning to unintentional non-

adherence behaviors and subscale 2 with items concerning to intentional non-adherence behaviors, to the data. The same error covariances of model 1 were introduced in this model. Final model presented a very good fit, with chi-square (17) = 45.90, p<0.001; the CFI=0.95; RMSEA=0.06 [90% Confidence interval: 0.04; 0.08] and the SRMR=0.04.

Chi-square difference between the two models revealed that model fit for both models was not statistical significant $\Delta \chi$ 2= 1.6, p =0.206).

Internal consistency

Cronbach´s alpha score for all items of a global scale was 0.60 and the removal of any item would not affect alpha significantly. The item total correlation coefficient for the 8 items ranged from 0.11 to 0.64.

Considering the multidimensional model tested, Cronbach´s alpha was 0.65 for unintentional non-adherence behaviours and 0.31 for intentional non-adherence behaviours. The item total correlation coefficient for the unintentional non-adherence behaviours ranged from 0.26 to 0.62, and for intentional non-adherence behaviours ranged from 0.10 to 0.24 (Table 4.3).

Table 4.3 - Confirmatory Factor Analysis of MMAS-8.

Item	Unidimensional Model		Multidimensional Model			
	ITC	Factor loading	ITC		Factor loading	
			Subscale 1	Subscale 2	Subscale 1	Subscale 2
Às vezes esquece-se de tomar os seus comprimidos para a pressão arterial?	0.45	0.72	0.51	-	0.73	-
Nas duas últimas semanas, houve algum dia em que não tomou os seus medicamentos para a pressão arterial?	0.44	0.52	0.53	-	0.53	-
Já alguma vez parou de tomar a sua medicação ou diminuiu a dose, sem avisar o seu médico, porque se sentia pior quando os tomava?	0.11	0.17	-	0.10	-	0.21
Quando viaja ou não está em casa, às vezes esquece-se de levar consigo os seus medicamentos?	0.26	0.29	0.26	-	0.29	-
Ontem tomou os seus medicamentos para a hipertensão arterial?	0.27	0.22	0.29	-	0.22	-
Quando sente que a sua pressão arterial está controlada, por vezes deixa de tomar os seus medicamentos?	0.30	0.29	-	0.24	-	0.52
Já alguma vez se sentiu incomodado por seguir corretamente o seu esquema de tratamento para a pressão arterial?	0.17	0.19	-	0.21	-	0.42
Com que frequência tem dificuldade em lembrar-se de tomar todos os seus medicamentos para a pressão arterial?	0.64	0.89	0.62	-	0.88	-

Unidimensional model has a Cronbach's α= 0.60; In multidimensional model, subscale 1 has a Cronbach´s α= 0.65 and subscale 2 has a Cronbach´s α=0.31; ITC - Item Total Correlation Coefficient.

Convergent validity

Convergent validity was estimated by correlating the MMAS-8 score with MAT, another measure assessing the same construct. The MMAS-8 was highly and significantly correlated with MAT (0.67, $p<0.001$), confirming that both instruments are assessing correlated constructs.

Concurrent validity

Concurrent validity was estimated by correlating the MMAS-8 score with the HKT score, assuming that patients with more knowledge about hypertension will be more adherent to hypertensive medication. The MMAS-8 was significantly correlated with HKT (0.14, $p=0.014$).Using the cut off score suggested by Morisky[115], we divided the group of participants in adherent (MMAS-8 score ≥6) and non-adherent (MMAS-8 score <6) and compared the knowledge about hypertension between these groups Results showed that there are significant differences between the two groups ($t(295) = 2.123$, $p=0.035$. Adherent participants had more knowledge on hypertension than the non-adherent (15.56±2.77 and 14.79±2.78, respectively).

Discussion

In this study, we validated a Portuguese version of MMAS-8 in a sample of hypertensive patients, as it was for the original version. We obtained a version with a low internal consistency with a Cronbach's alpha of 0.60, considerably lower than the original version (α =0.83)[115]. We found values of alpha below 0.65 in other MMAS-8 validations, independently of using hypertensive patients, as in French (α =0.54)[123] and Korean (α =0.56)[160] validations, or patients with other pathologies like patients with chronic antiplatelet treatment, in a German validation (α =0.31)[124], epilepsy, in a Chinese validation (α =0.56)[130] and diabetes, in a Thai validation (α =0.61)[164]. In these studies authors suggested that low internal consistency levels were due to multidimensionality of the scale, rather than to its inconsistency. For example, Arnet *et al.* (2015)[124] , after performing an exploratory factor analysis, defend that MMAS-8 has four dimensions and Kim *et al.* (2014)[160] identify three dimensions of the scale.

After analysing theoretical content of each item, and considering that adherence can be primarily classified as intentional or unintentional, we decided to perform a CFA to test two different models: Model 1, which included all the 8 items of the MMAS-8 loading on one global factor and Model 2, with two correlated subscales, one concerning to unintentional non-adherence behaviours and another concerning to intentional non-adherence behaviours. In both hypothesis we obtained a very good fit to the data with no statistical differences between them, meaning that both models can be use in adherence assessment. In both models, internal consistency was low (in unidimensional model α =0.60 and in multidimensional model α =0.65 for subscale 1 and α =0.31 for subscale 2) which can be explained by theoretical content of items. MMAS-8 is a scale with items that aim to identify reasons for non-adherence. According to Voils *et al.* (2011)[211], two fundamental measurement issues related to self-report adherence measures exists, causal indicators and effect indicators. Reasons for non-adherence are classified as causal indicators, which by definition may not be highly intercorrelated. In fact, knowing that adherence can be affected by a multiplicity of factors, from factors related to the patient, to socioeconomic factors, health related factors, etc.[212], low correlation levels between each factor may be expected. As so, the use of statistics with Cronbach's alpha are inappropriate for these indicators, as high internal consistency depends upon high inter-item correlation, being required the use supplementary information to evaluate multiple-item measures of this scale.

Portuguese version of MMAS-8 was capable of distinguish adherent from non-adherent patients in a sample of hypertensive patients with equal clinical characteristics, as well as it correlated in a statistically significant way with MAT, proving its convergent validity. As in the original validation[115], where Morisky *et al.*, found that knowledge of hypertension was significantly associated with medication adherence, in testing convergent validity of our version with a hypertension knowledge measure, the HKT questionnaire, not only MMAS-8 was significantly correlated with HKT, but also adherent participants had more knowledge on hypertension than the non-adherent.

Conclusion

We obtained a Portuguese version of the 8 item Morisky Medication Adherence Scale, a unidimensional scale with an acceptable internal consistency and good convergent and concurrent validity, which can be used either in research or in clinical practice.

Being MMAS-8 considered a gold standard questionnaire to assess patients adherence to medication worldwide, after validating the Portuguese version, a potential standard exists to assess Portuguese patient's adherence to medication, which will allow the cross-sectional and longitudinal comparability of Portuguese studies with international studies.

Developing a Maastricht Utrecht Adherence in Hypertension questionnaire short version: MUAH-16

Developing a Maastricht Utrecht Adherence in Hypertension questionnaire short version: MUAH-16

Introduction

As mentioned in previous chapters, adherence is one of the most responsible factor for therapeutic success in hypertension and effective measures of adherence are needed and several methods have been developed to assess patient's adherence to medication. By classifying patients as non-adherents, development of strategies to improve adherence and consequently improve the outcomes become a priority to researchers.

In the last decades, several interventions to enhance adherence with antihypertensive medication have been performed with ambiguous results. In Schroeder *et al.* (2004)[213] systematic review, some motivational strategies and complex interventions appear promising, but still lack of evidence. In Haynes *et al.* (2008)[214] systematic review, effects from simple interventions were inconsistent from study to study with less than half of studies showing benefits. Same conclusions were obtained by Nieuwlaat *et al.* (2014)[198], who defends that current methods of improving medication adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized.

This lack of evidence may happen due to the absence of individual tailoring of interventions. Adherence is a complex concept that includes several dimensions that interact with each other and affect the patient and his adherence to the recommendations on the treatment made by his health care provider. Primarily, non-adherence can be classified as intentional or unintentional[200, 215]. Intentional non-adherence is conditioned by patient's will, who consciously does not take medication as prescribed. It is affected by patient's beliefs, attitudes and expectations and is influenced by patients' motivation to begin and persist with the treatment regimen. Unintentional non-adherence is conditioned by the capacity and resource limitations that prevent patients from implementing their decisions to follow treatment recommendations and involves individual and environment constraints.

In 2003, WHO identified factors that influence patient's adherence behaviour[101]. Five dimensions were highlighted as the main intervention areas regarding the improvement of patient's adherence to therapy (Figure 20).

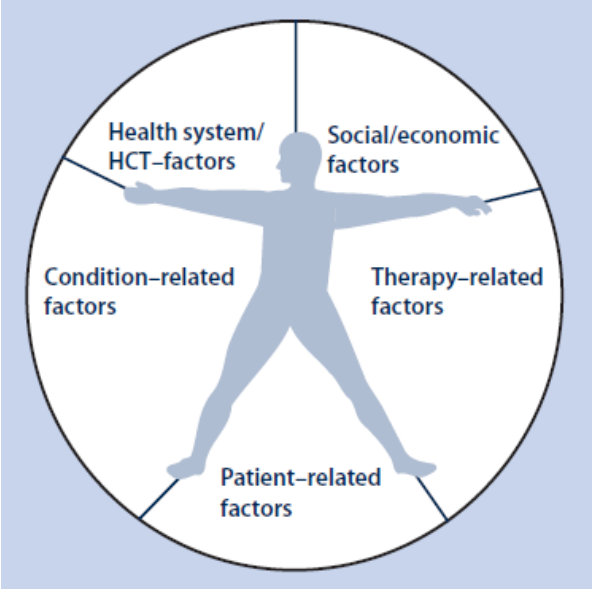


Figure 20 *- Dimensions of adherence. Adapted from World Health Organization, Adherence to long-term therapies - Evidence for action. 2003 [100].*

- Patient-related factors – that englobes, not only forgetfulness and misunderstanding instructions about how to take the medications, but also the patient knowledge and skill in managing the disease symptoms and treatment. In this dimension, beliefs about medication should also be include;
- Social/economic factors – that comprise the socioeconomic status of the patient, as well as the costs of medication, distance from treatment setting and family support;
- Health system-related factors – that involves the quality of the relationship between patient and health professionals as well as physician knowledge and motivation, implementation of guidelines and therapeutic intensification;
- Therapy-related factors – related to complexity of treatment regimen, not only associated with monotherapy or polymedication but also the number of daily doses and the presence or absence of adverse effects of treatment, and
- Condition-related factors – associated with the duration and symptomatology of the disease.

As so, if instead of just classifying the patient as adherent or not, the reasons for non-adherence were also understood, the designing of intervention to improve adherence could be more targeted and optimized and so, more successful.

Among the several self-report instruments designed to assess adherence to medication, the Maastricht Utrecht Adherence in Hypertension Questionnaire (MUAH)[216] provides valuable information about the reasons for poor adherence, being a possible tool to assess barriers of non-adherence to antihypertensive medication. The MUAH, developed in 2006, it's a patient-oriented questionnaire that address cognitive and behavioural factors for the assessment of adherence problems that hamper intake of medication in patients who are prescribed with antihypertensive drugs. MUAH measures 4 adherence-related dimensions such as positive attitude towards health care and medication, lack of discipline, aversion towards medication and active coping with health problems, having a good internal consistency in each scale (Cronbach's alpha of 0.75, 0.80, 0.63 and 0.76 respectively).
However, probably due to the comparison of different adherence assessment methods and difficulties in the methodological implementation of them, data on convergent validity is difficult to interpret, with results below expectations, mainly with no statistical significance in the association between sum scores of the 4 scales of MUAH and electronic monitoring nor with pharmacy records. Also, the MUAH presents a high number of items, which difficult its use in clinical practice and does not have a global score, disabling patient's adherence classification. A shorter and version of MUAH, that assess the same adherence dimensions and allows obtaining an overall score, enabling classifying not only the causes of non-adherence but also adherence level itself, would be an added value to improve MUAH applicability.

Objectives

The objectives of this study were to develop a short version of MUAH (MUAH-16) and compare its construct validity and factorial structure with a confirmatory factor analysis (CFA) between the original and the short version, as well as estimate its convergent validity.

Methods

This cross-sectional study was approved by the Ethics committee of the Faculty of Medicine of the University of Coimbra (Registration number CE_105.2013). The study aims and procedures were explained to all potentially eligible patients and inclusion was validated after written informed consent was signed by the patient.

Maastricht Utrecht Adherence in Hypertension Questionnaire

The MUAH[216] is a 25 item questionnaire scaled according to a seven point Likert scale ranging from "totally disagree" (1) to "totally agree"(7). The questions are grouped in 4 factors: Factor I: positive attitude towards health care and medication, Factor II: lack of discipline, Factor III: aversion towards medication and Factor IV: active coping with health problems. After obtain permission from the authors, a process of translation and back-translation of MUAH to Portuguese was performed according to international guidelines[207, 208].

8-item Morisky Medication Adherence Scale

The MMAS-8[115] consists in 7 dichotomous items and a five-point Likert scale. Questions were formulated to avoid a "yes-saying" bias, so in the first 7 questions, one point is assigned to each "no" answer, except in item 5 which is reversed to prevent the tendency to respond in a specific way to a series of questions regardless of their content. In the last question is necessary to standardize the code (0–4) and score is obtained dividing by four. Patients are classified, according to the score obtained, as Low adherent (score<6), Medium adherent (score 6 - <8) and High adherent (score=8).

Measure Treatment Adherence [Medida de Adesão aos Tratamentos] (MAT)

The Measure Treatment Adherence (MAT)[201] consists of 7 items scaled according to a six point Likert scale, ranging from "always" to "never". The level of adherence is obtained by adding the values of each item and then dividing by the total number of items. Higher scores mean greater level of adherence. The classification of patients as adherent or non-adherent is made according scores near the median values.

Data collection

Questionnaires were administrated between March 2014 and September 2015 in 7 community pharmacies in the central region of Portugal (urban and rural) and in the Hospital Infante D. Pedro, EPE in Aveiro.

All patients who attending to participating pharmacies in the study, who were older than 18 years and taking at least one antihypertensive drug were invited to participate.

Data on personal and family history were also collected, as well as MMAS-8 and MAT instruments were administered.

Statistical analysis

Data were analysed using IBM SPSS, version 20.0 (IBM Corporation, Armonk, NY, USA) and IBM AMOS, version 20.0 (IBM Corporation, Meadville, PA, USA).

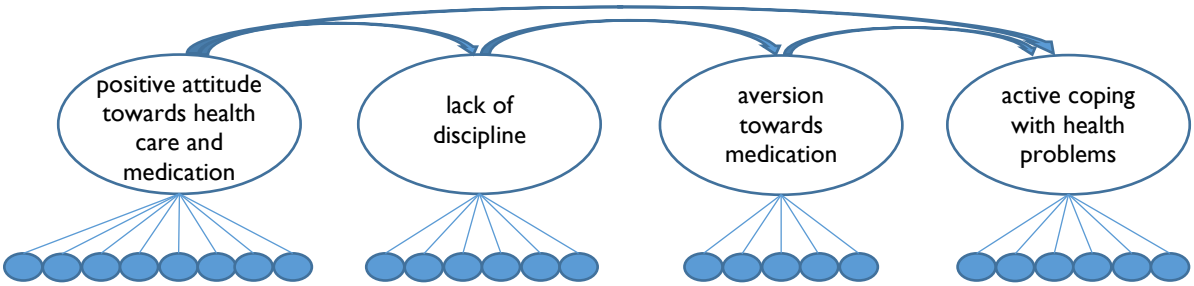
Missing values were low level (< 2%) and were replaced by the mean of the score of the item factor of each subject.

The development of the short version of the MUAH was based upon statistical and theoretical decisions.

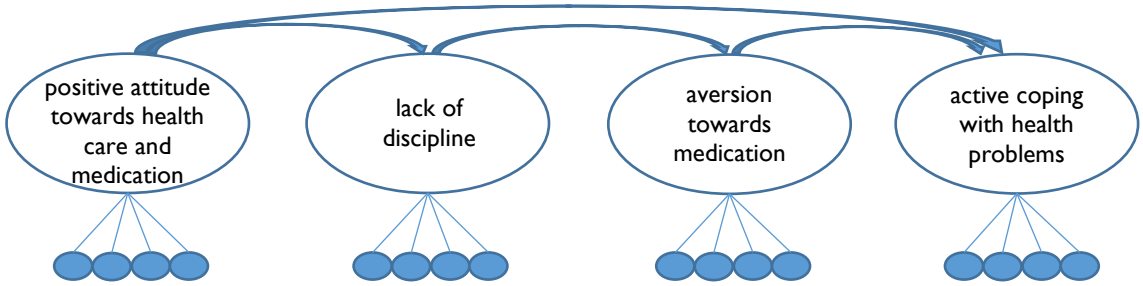
The conceptual organization of the MUAH, consisting of 4 factors, was maintained. The reduction of the items was based on the elimination of items that had weaker contribution to the factor where they belonged. Therefore, we examined the factor loadings of each item in its subscale by conducting an exploratory factor analysis for each subscale extracting just one factor. The analysis of the factor loadings and the discussion on the theoretical importance of each item substantiate the decision of which items should be kept.

The original version of the MUAH (Model 1) was then compared with the final short version of the MUAH (Model 2) using the confirmatory factor analysis procedure. Finally, we compared the short version of the MUAH with all factors correlated (Model 2a) with the short version of the MUAH where the four subscales contribute to a higher order factor, a global factor of adherence (Model 2b) Figure 21.

Model 1 – MUAH original version



Model 2a – MUAH-16



Model 2a – MUAH-16

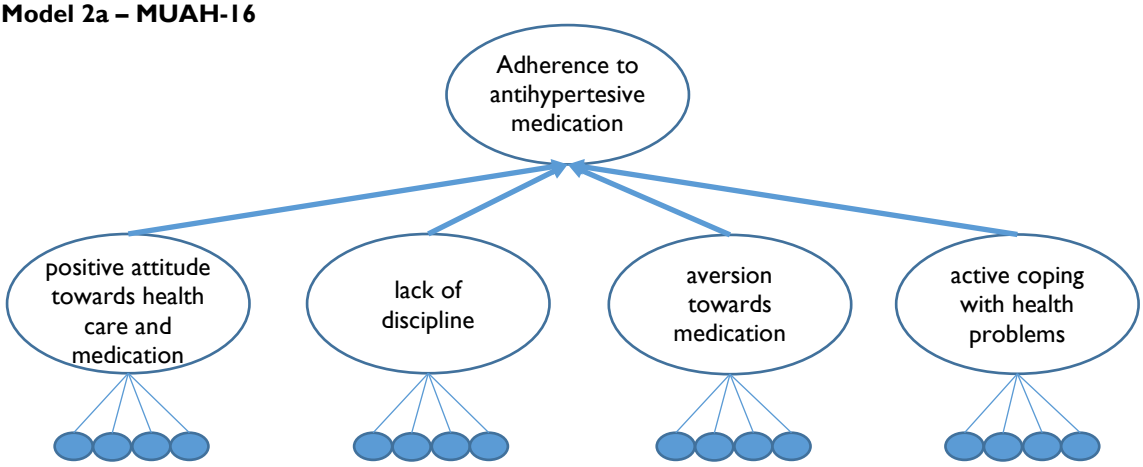


Figure 21 *- Models of MUAH tested in Confirmatory Factor Analysis.*

Results

A sample of 423 patients participated in the study, with a mean age of 68.16±10.53, being 225(53.2%) female.

Development of the short version of the MUAH

To develop the short version of the MUAH we examined the loadings of all items in each subscale. These results are reported in Table 5.1.

The four items that had higher loadings in their respective subscale were maintained. In the Subscale I: positive attitude towards health care and medication, 4 factors clearly had a better contribution to the subscale (items 3, 5, 7 and 35), all of them with loadings higher than 0.20. Regarding the subscale II: lack of discipline, all items had adequate loadings. However, to increase consistency between the items, we chose to maintain the items that contributed to the subscale in the same direction, that is, items 23, 24, 26 and 36.

For the subscale III: aversion towards medication, the same criteria was followed, that is, we retained the items that influenced the final subscale score in the same direction (items 9, 13, 14 and 16). Finally, the subscale IV: active coping with health problems, the four items with the highest loadings were retained, that is, items 20, 21, 22 and 39. The item 39 had a loading below the recommended cut off (0.16), but after examining its content, we decided that it would be an important item in that subscale and decided to maintain it in the short version.

Table 5.1 - Factor loadings of original version of MUAH.				
	Factor loadings			
Item	1	2	3	4
Subscale 1: positive attitude towards health care and medication				
3_I feel better taking medication every day	0.42	-	-	-
5_If I take my medication every day, I feel confident that my blood pressure is under control	0.59	-	-	-
7_The pros of taking medication weight up against the cons	0.50	-	-	-
32_The information that GP gave me about taking my medication was satisfactory	0.24	-	-	-
33_The information the pharmacy gave me about taking my medication was satisfactory	0.17	-	-	-
34_ I do not worry too much about my blood pressure if I take my medication every day	0.19	-	-	-
35_I think I contribute to the improvement of my blood pressure when I take my medication every day	0.43	-	-	-
43_When I worry too much about my health, I will try to find something to take my mind off it	0.03	-	-	-
Subscale 2: lack of discipline				
18_I have persons in my surroundings that help me to take my medication	-	-0.33	-	-
23_It happens that I am not sure whether I have taken my tablets	-	0.26	-	-
24_I have a busy life; that is why I sometimes forget to take my medication	-	0.44	-	-
25_I tend to forget my medication because I am not aware of having a high blood pressure	-	-0.59	-	-
26_During holidays or weekends I sometimes forget to take my medication	-	0.29	-	-
36_I find it hard to stick to my daily regimen of medication taking	-	0.45	-	-
Subscale 3: aversion towards medication				
9_When my blood pressure is under control during my medical checkups, I want to take less medication	-	-	0.69	-
11_I prefer homeopathic medication to lower my blood pressure	-	-	0.59	-
13_I dislike taking medication every day	-	-	0.49	-
14_I am afraid of side effects	-	-	0.35	-
16_I think it is not healthy for your body to take medication every da	-	-	-0.28	-
Subscale 4: active coping with health problems				
20_I take special care to do enough exercise to reduce the risk of getting cardiovascular diseases	-	-	-	0.86
21_I eat less fat in order to avoid cardiovascular diseases	-	-	-	0.85
22_I eat less salt in order to avoid cardiovascular diseases	-	-	-	0.23
37_When I intend to live a healthy life, I almost always succeed on doing this	-	-	-	0.16
39_I gather information about possibilities to solve health problems	-	-	-	0.12
40_I am goal-oriented when solving health problems	-	-	-	0.08

The final version of the MUAH had 16 items, divided by 4 subscales, with 2 of them (subscales I and IV) assessing positive factors affecting adherence to hypertensive medication and two of the them (subscales II and III) assessing negative factors towards adherence. As such, the theoretical structure of the questionnaire was maintained similar to the original version.

Comparison between the original and short version of the MUAH

We compared both versions using confirmatory factorial analysis. The original version of the MUAH was identified as Model 1 and the short version of the MUAH as Model 2.

Model 1 had a poor fit to the data (χ 2269 = 663.41, p<0.001, CFI=0.695, RMSEA=0.06). Model 2 had a very good fit to the data (χ 2100 = 171.07, p<0.001, CFI=0.92, RMSEA=0.04. The comparison of the chi-square of both models ($\Delta\chi$ 2169=492.34; p<0.001) revelled that Model 1 and Model 2 were significantly different, with Model 2 reporting a better fit to the data.

Comparison of the model fit for the MUAH-16 with correlated factors (Model 2a) and with MUAH-16 with a higher order factor (Model 2b)

Considering the importance of a global score of adherence, we compared the fit of the model of the short version of the MUAH considering that all factors were correlated (Model 2a) and that a higher order factor, a global score of adherence, accounted for the variance of the four subscales (Model 2b) (Figure 21). Chi square difference of the model ($\Delta\chi$ 22=4.06; p=0.067) revealed that the fit of both models were not statistically different. All other fit indices were also equivalent (Table 5.2). Therefore, both models have a good fit to the data.

Table 5.2 - Comparison of the model fit for the MUAH-16 with correlated factors (Model 2a) and with MUAH-16 with a higher order factor (Model 2b).		
	Model 2a	Model 2b
X^2	167.01	171.07
Degrees of freedom	98 p<0.001	100 p<0.001
CFI	92	92
RMSEA (CI)	0.41 (0.30-0.51)	0.41 (0.30-0.51)
SRMR	0.05	0.05

Internal consistency

Internal consistency measured by Cronbach's alpha for all items of a global scale was 0.64 and the item total correlation coefficient for the 16 items ranged from 0.08 to 0.39. Considering the four subscales, Cronbach's alpha was 0.53, 0.36, 0.59 and 0.51 for subscales I, II, III and IV respectively.

Convergent validity

Global mean score of MUAH-16 was 5.49±0.82. Regarding other adherence questionnaires administered, mean MMAS-8 score was 6.36±1.61 and mean MAT score was 5.74±0.33. Concerning convergent validity, estimated by correlating both global score and the four subscales of MUAH-16 with MMAS-8 and MAT, two other measures of adherence to medication, both global score and all the subscales of MUAH-16 correlated positively and significantly with the MMAS-8 and the MAT scores (Table 5.3).

Table 5.3 - Correlation between MUAH-16 and MMAS-8 and MAT.		
	MMAS-8	MAT
Subscale 1: positive attitude towards health care and medication	0.28*	0.23*
Subscale 2: lack of discipline	0.44*	0.40*
Subscale 3: aversion towards medication	0.32*	0.32*
Subscale 4: active coping with health problems	0.12	0.10
Global MUAH-16 score	0.45*	0.41*
*p<0.001 and in the other values p<0.05.		

Discussion

In relation with other questionnaires that assess adherence to medication, the original MUAH version has the advantage of evaluate and categorize different adherence dimensions, allowing a better understanding of patient's behaviors and consequently, lead to the design of more targeted interventions with more successful results. However, the original version was too extensive to be used in clinical practice. After performing an exploratory factor analysis together with theoretical decisions, we obtained a short version of MUAH with 16 items, maintaining the original conceptual organization in 4 subscales.

The MUAH-16 presents lower internal consistency than the original version[216] (respectively for subscales I, II, III and IV, Cronbach's alpha of 0.53, 0.36, 0.59 and 0.51, instead of 0.75, 0.8, 0.63 and 0.76 obtained in the original version), a limitation we were expecting due to the reduction of the number of items for each subscale. When evaluating internal consistency of an instrument through Cronbach's alpha, several limitations must be taken into account, specially, the impact of test length in the value of alpha obtained. If the test is too short, the value of alpha is reduced, which doesn't mean that the instrument is worthless to use[217-219]. In fact, in short scales, measures of unidimensionality, as factor analysis, are equally important to Cronbach's alpha on homogeneity assessment of the instrument. Indeed, internal consistency is necessary, but not sufficient condition for measuring homogeneity in a sample of test items[217]. As so, by reducing the number of items of each subscale to four, a reduction of alpha values was expected, nevertheless, the evaluation of confirmatory factor analysis to both models tested, show that the short

version has a better fit to the data than the original version, better representing each adherence dimension evaluated.

The original version of MUAH does not provide a global score. The higher the score obtained in each subscale the higher the positive attitudes towards health care and medication, the lack of discipline, the aversion towards medication and the active coping with health problems, respectively[216]. The authors found a correlation between adherence and subscale II (lack of discipline)and between adherence and subscale I (positive attitude towards health care and medication) – higher score in subscale II higher probability of being poor adherent, otherwise, patients with a higher score on subscale I had a significantly lower probability of being poor adherent. In order to obtain a global score of adherence we hypothesized a model in which subscales I and IV contribute positively to adherence (example: "I feel better taking medication every day"), and subscales II and III are negatively associated with adherence (example: "I find it hard to stick to my daily regimen of medication taking"). As so, in statistical analysis, the score obtained in subscales II and III was inversed, being items 9, 13, 14, 16, 23, 24, 26 and 36 scoring inversely: "totally disagree" (7) to "totally agree" (1). After comparing the fit of the model of MUAH-16 considering that all factors were correlated, with the fit of the model of MUAH-16 with a global score of adherence, chi square difference of the model revealed that the fit of both models were not statistically different and that all other fit indices were also equivalent. Thus both models have a good fit to the data and we can assess patient's adherence with this instrument.
This fact was also supported by convergent validity analysis, in which MUAH-16 global score of adherence was correlated with MMAS-8 and MAT, two other adherence instruments.

Conclusions

The short version of MUAH measures adherence-related dimensions and global adherence to antihypertensive medication. It can be easily applied in the clinical setting, giving health professionals more extended information about the patient's reasons for poor adherence and allowing the development of more targeted interventions in order to improve adherence to antihypertensive medication.

Impact of mode of administration of adherence questionnaires in the results obtained

Impact of mode of administration of adherence questionnaires in the results obtained

Introduction

As said before, the evaluation of patients using questionnaires is a common exercise in clinical practice. Because they are non-expensive and easy to administer instruments, which enable rapid gathering of information and easy interpretation of results, they become an important method for analysis and evaluation of several parameters associated with health, beliefs and attitudes of patients.

The method of collecting patient-reported data, or mode of administration (MOA), is receiving increasing attention in both research and clinical contexts, with several studies focusing on assessing the different effects on the accuracy and quality of the data obtained according to MOA used, as well as assessing the bias associated with MOA regarding results interpretation[220-226].

Primarily we can define two types of MOA, self-administered, in which questions are answered personally by the patient, and interviewer-administered, were the interviewer reads questions to the patient and records his responses[227]. These main MOAs can be further divided into sub-categories, each with different advantages and associated bias (Table 6.1).

Table 6.1 - Summary of potential biases by mode of questionnaire administration.

Potencial for	Face-to-face interviews	Telephone interviews	Self-administered, postal	Self-administered, electronic
More complete population coverage for sampling	High	Low	High	Low
Survey response	High	Low	Medium-Low	Low
Item response/completion of questionnaire	High	Low	Low	Low
Recall bias	Low	Low	High	High
Social desirability bias	High	High	Low	Low
'Yes-saying' bias	High	High	Low	Low
Interviewer bias	High	High	-	-

Adapted from Bowling *et al.* (2005)[196].

Therefore, one of the first decisions to make when designing a survey, is the selection of the MOA that will be used. That decision depends on two essential questions, the available resources to develop the research and the adaptation of the characteristics of each method to the objectives and to the target population of the research[196, 226, 227]. While on one hand, the interviewer-administered method adds significant costs in implementing the survey because the need of investigators to ask and record the answers, on the other hand, the self-report methods are less likely to be affected by phenomenon such as social desirability or response acquiescence, but they present a larger number of item non-response as well as they are dependent on the degree of literacy of patients. So, when designing the survey, the researchers decide which MOA is more effective to the characteristics of the population included in the study to enhance and optimize the results.

Adherence to therapy is one of the concepts most evaluated through the use of questionnaires. Being essential in therapeutic success and in the evaluation of therapeutic efficiency, adherence has become a priority to physicians, other health professionals and for investigators[101, 102].

When assessing adherence to therapy, particular characteristics of the population must be taken into account. Since, in most cases, this concept evaluates patients who takes drugs chronically, typically it evaluates older population, known to have lower levels of health literacy[206, 228]. Defined as an individual's capacity to access, understand and use basic health information and services in order to make appropriate health decisions[229], health literacy has a rapid decline after 55 years of age, having adults over the age of 65 years lowest levels of health literacy when compared with younger age groups[228, 230]. This means that older people will have more difficulties in understanding and completing the questionnaires, thus, the interviewer-administrated methodology may seem more attractive in assessing adherence to therapy of chronic patients.

Objectives

Being interviewer-administrated methodology highly influenced by social desirability or response acquiescence, our aim was to assess the impact of this MOA in the application of an adherence questionnaire and evaluate its influence in results and interpretation of data when compared with a self-report administration methodology.

Methods

To evaluate the differences between interview and self-report applications, and after request permission to the author, we used Medida de Adesão aos Tratamentos [Measure Treatment Adherence] (MAT)[201] that assess adherence to antihypertensive therapy of hypertensive patients.

Data collection

Data were collected in 7 community pharmacies in the central region of Portugal (urban and rural), between March 2014 and September 2015. All patients older than 18 years and taking at least one antihypertensive drug who met the inclusion criteria, attending to participating pharmacies in the study were invited to participate. In the first phase of data collection, the questionnaire was applied in the form of interview, to a sample of 299 patients. The interview was made by a trained pharmacist in a private office, where data on personal and family history were collected as well as MAT was administered.
In the second phase of data collection, due to the requirement of the MOA, the ability to read was added as inclusion criteria. The questionnaire was applied in a self-report way, to a sample of 126 patients. The filling was made in a private office, where data on personal and family history were collected and MAT was administered.

This was a cross-sectional study approved by the Ethics committee of the Faculty of Medicine of the University of Coimbra (Registration number CE_105.2013). The study aims and procedures were explained to all eligible patients and inclusion was validated after written informed consent was signed by the patient.

Medida de Adesão aos Tratamentos [Measure Treatment Adherence]

The MAT[201] was developed in 2001 and consists of 7 items, scaled according to a six point Likert scale, ranging from "always" to "never". The level of adherence is obtained by adding the values of each item and then dividing by the total number of items. Higher scores mean greater level of adherence. The classification of patients as adherent or non-adherent is made according scores near the median values.

The instrument has a good internal consistency, with a Cronbach's alpha of 0.74, and presents good concurrent validity when compared with pill counting, with correlation coefficient of 0.48[201].

Statistical analysis

To compare the self-report with the interview version of the MAT, we first tested the fit of the original model to the data using confirmatory analytic procedures in AMOS (Version 20.0, IBM Corporation, Meadville, PA). Models were estimated using the Maximum likelihood method. Overall model fit was tested with the chi-square statistic and other goodness of fit indices: the comparative fit index (CFI), and the standardized root mean square residual (SRMR), following the recommendation of Hu & Bentler (1998)[231] of using a two-index presentation strategy. Values above 0.90 or 0.95 on the CFI, are considered good or very good fit, respectively. Values up to 0.08 in the SRMR are considered good.

To examine measurement and structural invariance across MOA, we followed Vanderberg and Lance recommendations[232]. First, we examined configural invariance, where the same factor structure was tested simultaneously for both groups, with no equality constrains imposed on any of the parameters. The fit of this model served as the baseline model to which the more restrictive models were compared. Second, we examined measurement invariance, significant chi-square changes indicate non-invariance of the models.

Finally, we also inspected and compared both groups for values of skewness, kurtosis and extreme values.

Results

A sample of 425 patients participated in the study, with a mean age of 68.21±10.56 years, being 226 (53.2%) female. General adherence level was good, with a global MAT mean score of 7.74±0.33. Demographic details of the sample for both MOAs are presented in Table 6.2.

Table 6.2 - Demographic characteristics of participants.

	Interviewer administered MOA (n =299)	Self-report MOA (n =126)	t/χ^2	p
Mean Age	68.32±10.75	67.94±10.16	0.35	0.730
Sex (% female)	53.5	52.4	0.05	0.832
Average time since hypertension diagnose	10.63±8.48	11.00±8.47	-0.41	0.679
Diabetes (%Yes)	27.8	23.8	0.71	0.471
Dyslipidemia (%Yes)	53.2	52.4	0.02	0.915
Stroke(%Yes)	8.7	5.6	1.220	0.325
Heart disease (%Yes)	25.8	27.8	0.19	0.718
Family history of hypertension (%Yes)	39.8	45.2	1.081	0.332
MAT mean score	5.78±0.28	5.65±0.42	3.26	0.001

Confirmatory factor analysis

The model revealed a poor fit to the data, with, with chi-square (14) = 144.12, $p<0.001$; the CFI=0.81and the SRMR=0.8.

The analysis of the modification indices revealed that the introduction of error covariances would increase model fit. We analysed the content of the items and introduced error covariances between items 1 and 2; 3 and 4; 1 and 6; 5 and 7. The final model revealed a very good fit to the data, with, with chi-square (10) = 16.86, p=0.078; the CFI=0.99and the SRMR=0.02.The following analyses of the models for determining invariance was based on this model.

Testing invariance of MAT across MOA

To test the measurement invariance of the MAT across MOA, we first proceeded with a confirmatory factor analysis on each sample separately. The results are presented in Table 6.3.

Table 6.3 - Fit indices for Confirmatory factor analysis between the samples, separately.

Model	χ 2	df	p	CFI	SRMR
Self-report	12.34	10	0.263	0.99	0.04
Interview	25.81	10	0.004	0.92	0.04

Df: Degrees of freedom; CFI: Comparative Fit Index; TLI Tucker Lewis Index; SRMR = standardized root mean square residual.

We then performed the analysis of invariance, examining the difference between the configural and the constrained model. Results of the configural model, where no equality constraints were included, confirmed a good fit to the model ($\chi^2(2)=38.2$, $p=0.008$; CFI=0.98; RMSEA=0.05 [90% CI: 0.02; 0.07]; SRMR=0.04). We proceeded with estimating invariance in factor loadings, by constraining them to equality. The results are suggestive of non-invariance, as the chi-square difference between this model and the configural model is significant ($\Delta\chi^2(6)=15.50$, $p=0.17$).

Analysis of item endorsement

To evaluate differences in item endorsement between the MOA samples, we evaluated item's distribution shape (kurtosis) and asymmetry (skewness) (Table 6.4). We also analyzed the frequency of extreme answers (Figure 22). In the interview administration, we obtained lower values of Skewness and higher levels of Kurtosis, meaning that distribution of answers in this MOA tend to be less symmetrical.

Table 6.4 - Shape of the distribution of answers according to MOA.				
Items	Kurtosis		Skewness	
	Interview	Self-report	Interview	Self-report
1) Alguma vez se esqueceu de tomar os medicamentos para a sua doença?	0.08	3.89	-1.01	-1.33
2) Alguma vez foi descuidado com as horas da toma dos medicamentos para a sua doença?	1.61	6.92	-1.62	-1.96
3) Alguma vez deixou de tomar os medicamentos para a sua doença por se ter sentido melhor?	21.39	6.28	-4.56	-2.53
4) Alguma vez deixou de tomar os medicamentos para a sua doença, por sua iniciativa, após se ter sentido pior?	17.85	7.32	-4.11	-2.79
5) Alguma vez tomou mais um ou vários comprimidos para a sua doença, por sua iniciativa, após se ter sentido pior?	96.30	13.89	-9.88	-3.67
6) Alguma vez interrompeu a terapêutica para a sua doença por ter deixado acabar os medicamentos?	3.07	0.80	-1.81	-1.34
7) Alguma vez deixou de tomar os medicamentos para a sua doença por alguma outra razão que não seja a indicação do médico?	72.61	20.93	-8.45	-4.45

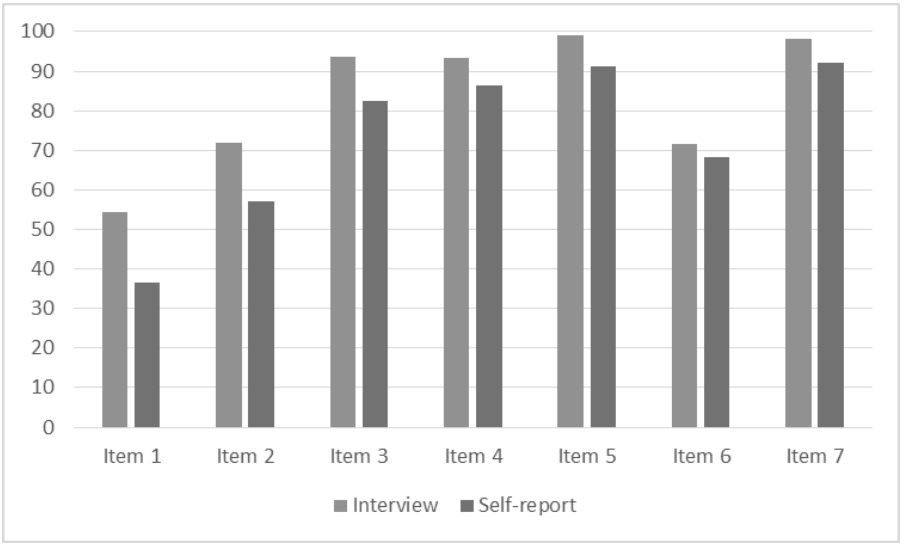


***Figure 22** - Percentage of patients answering "Never".*

Discussion

In this study, MAT is confirmed to be a good instrument to assess hypertensive patient's adherence to antihypertensive medication. We performed a confirmatory factor analysis and, after correlate items conceptually associated, a very good fit to the data was obtained, not only in the global model, but also in both methodologies of application, meaning that in both MOAs, MAT represents adherence to antihypertensive medication. However, caution is needed in interpreting the results once adherence levels obtained by the two MOAs are different. In the interview administration, we obtained lower values of Skewness and higher levels of Kurtosis, meaning that distribution of answers in this MOA tend to be less symmetrical, making it difficult to distinguish non-adherent patients based on their answers. These data are converging with those obtained in the analysis of frequency distribution of answers, with a mean 9.7% higher tendency to answer "never" in the interview administration methodology.
If we consider the scoring system of MAT, where the 7 items are scaled according to a six point Likert scale, ranging from "always"=1 to "never"=6, and considering that the level of adherence is obtained by adding the values of each item and then dividing by 7, in the interview, there is a tendency to overestimate adherence.

This can be justify because interview methodology is more influenced than self-report by phenomenon such as social desirability or response acquiescence[221, 227, 233]. This fact is defended by Bowling *et al.* (2005)[196] in their narrative review of the literature on the effects of mode of questionnaire administration on data quality. As interviews involves social interaction with another person, they can lead to respondents taking social norms into account when responding, resulting in social desirability bias and leading to over-report of desirable behaviours, as adherence to medication. Furthermore, not only respondents may systematically alter questionnaire responses in the direction they perceive to be desired by the investigator, as, when all the questions evaluating the same issue are negative statements, patients tend to answer "No" to all questions, regardless of the content, a phenomenon known as "No-saying"[234, 235]. These phenomenon potentially induce an increase number of answers "Never", which will lead to an increase in the final score of MAT, meaning, higher values of adherence, which is consistent with Leggett *et al.*

(2016)[236] conclusions that report the tendency to overestimating adherence in questionnaires evaluation.

This is a major and important bias that may influence the results of the questionnaires, and that must be taken into account when choosing the tool to assess adherence to therapy, along with the psychometric properties of the instrument.

This is also a potential bias that must be taken into account in meta-analysing adherence data. High heterogeneity was presented as a weakness in healthcare professional interventions[197] and specifically when aiming to reduce non-adherence[198]. Is known that the use of different methodologies to assess adherence increases heterogeneity of meta-analysis[237], but there is a lack of information regarding heterogeneity induced by the use of different application methodologies in self-report administration, being necessary to develop research in this direction.

As so, despite interview-administered questionnaires seams more attractive to be used in elderly population, self-report administration is more recommended. In patients with low levels of health literacy, which can compromise the results of self-report, the use of a multi-method approach that combines feasible self-reporting and reasonable objective measures, as recommended by WHO[101] seems to be more accurate.

Limitations of the study

A potential limitation of our study was the fact that we applied the questionnaire in different populations in the interview administered way and in the self-report administration. Other studies with the same objective applied the same instrument with different methodologies in the same population, with an interval between 14 days to one month[1, 2, 5, 26]. As adherence questionnaires are short, and the wash out time is reduce, we chose to use different populations in other to avoid the risk of contamination of the results, having the caution to ensure comparability between populations (Table 6.2).

Conclusions

Adherence to medication is essential in therapeutic success and its evaluation become a priority. Commonly assessed through questionnaires application, the methodology used to collect information depends on several factors, being the interview the more attractive method due to low literacy levels of the typically studied population. However, caution is needed when interpreting results due to higher prevalence of social desirability or response acquiescence in interview methodology, when compared to self-report administration, which may lead to overestimated adherence levels. As so, self-report administration must be preferred in questionnaires application that assess adherence to therapy. When investigators intend to include patients with low literacy levels, interview administration may be considered, although the bias of this choice must be taken into account in the results, and preferably an additional adherence evaluation method should be concomitantly used to minimize this bias.

Cross-cultural adaptation of Hypertension Knowledge Test into Portuguese

Cross-cultural adaptation of Hypertension Knowledge Test into Portuguese

Introduction

According to the systematic review performed, several variables were identified as having a negative influence on the control of blood pressure in patients under pharmacological antihypertensive treatment, being the impact of diabetes as comorbidity is the most important, immediately followed by adherence to therapy.

When studying adherence to therapy, another concept often appears associated, patient's knowledge about their disease. The level of knowledge on hypertension (i.e. risk factors and therapeutic targets, factors affecting hypertension control, like diet, physical activity and drugs therapy) has been associated with medication adherence and subsequently with blood pressure control[238]. In fact, patient's knowledge about the disease has been highlighted as one of the most important patient-related factors[239] responsible for poor control of blood pressure. Patients who have been educated about the importance of treatment become more involved with their therapy[240, 241]. The lack of knowledge of appropriate systolic blood pressure was identified as a risk factor for poor blood pressure control[239, 242, 243]. And such patients may have been less likely to take their medication, adopt healthy lifestyle changes, or see their physician if their blood pressure was outside the ideal range[239, 242, 243].

Although, in our previous systematic review about factors associated with non-control of blood pressure in hypertensive patients under pharmacological antihypertensive treatment, no meta-analysis was possible regarding this variable, the selected studies pointed in the same direction, in Zhang *et al*. (2011)[73], higher patient's understanding of the danger of hypertension, the better the hypertension control and according to Goverwa *et al*. (2014)[77], patients with lower risk of uncontrolled blood pressure are the ones that had received health education on hypertension and that had a high perception of the risk for developing complications due to hypertension. Thus, patient's knowledge about hypertension is a potential target to develop interventions to improve BP control.

While many studies have evaluated patient awareness of hypertension[8, 10, 66, 244-247], critical elements of BP knowledge have not been adequately assessed. The development of instruments that can properly assess knowledge is an important contribution to design effective intervention strategies for the control of blood pressure. Several instruments have been used to evaluate patient's knowledge about hypertension[248-250], however validated instruments reporting their internal consistency and reliability are scarce. The Hypertension Knowledge Test (HKT)[209] was initially created to assess the level of knowledge about hypertension in Korean-American patients. HKT items were developed from National HBP Education Program, the National Heart, Lung, and Blood Institute (Check Your High Blood Pressure (IQ)), a literature review and a community input. The HKT is an easy-to-use questionnaire covering several items related to the disease as the etiology, diagnosis, treatment and prevention methods. The HKT has demonstrated good internal consistency (α=0.70) and shown to be a sensitive and reliable instrument[209].

Although in Portugal some studies evaluated the degree of knowledge of hypertensive patients regarding their disease and the relationship between their knowledge and blood pressure control[67, 251], no validated instrument for assessing the knowledge about hypertension in Portuguese hypertensive population exists.

Objectives

Thus, the main objective of this study was to develop and validate the Portuguese adaptation of the Hypertension Knowledge Test questionnaire in a Portuguese sample, namely to examine the factorial structure of the HKT with a confirmatory analysis and to estimate it's convergent and construct validities.

Methods

This was a cross-sectional study. To obtain a diverse hypertensive population, data were collected in 7 community pharmacies in the central region of Portugal (urban and rural) and in the Hospital Infante D. Pedro, EPE in Aveiro.

The study was approved by the Ethics committee of the Faculty of Medicine of the University of Coimbra (Registration number CE_105.2013). The study aims and procedures were explained to all potentially eligible patients and inclusion was validated after written informed consent was signed by the patient.

Hypertension Knowledge Test

The Hypertension Knowledge Test is a questionnaire with 21 items and it was developed to assess patient's knowledge about hypertension, its causes and treatment and ways to prevent and control high blood pressure. It is divided into two parts, 12 true or false questions and 9 multiple choice questions. The knowledge level is calculated by assigning one point to each correct answer, obtaining a total score ranging from 0 to 21.

Translation and cross-cultural adaptation of the HKT

A process of translation and back-translation according to international guidelines was performed[207, 208]. After obtaining author's permission, the original questionnaire was submitted to 3 bilingual translators, who knew the goals and concepts of the study, who create 3 independent Portuguese translations. The three versions were compared in order to generate a consensus version. The reverse translation, from Portuguese to English, was carried out by another bilingual translator who was not involved in developing the initial version and who did not know the objectives and concepts of the study. This new English version was compared to the original version and occasional discrepancies were corrected. Finally a cross-culturally adapted version was obtained through a consensus meeting, attended by 2 experts in pharmacology and 1 expert in Portuguese language, after semantic, idiomatic, cultural and conceptual equivalence evaluation.

A pilot test was performed in a Portuguese population (n=20) to ensure patient understanding and eventual doubts and difficulties in the use of the questionnaire. After

small adjustments based on changes proposed, we obtained the final Portuguese version of the questionnaire. The patients who participated in this face-validity phase were not further included in the study.

Instruments used to assess HKT validity

Batalla Test

Originally, Batalla was developed to assess patient knowledge regarding hypertension. It consists in 3 questions: "Is Hypertension a disease for life?", "Hypertension can be controlled with diet and/or medication?", and "Name 2 or more organs affected by increased blood pressure". The patient was classified as having a good knowledge when correctly answered all questions[248, 249].

Strelec Test

Strelec is an instrument developed to assess patients consciousness regarding hypertension and its treatment[250]. It consists of 10 true-false questions. One point was attributed to each correct answer and the final score was calculated by summing the points obtained. Higher scores mean greater level of consciousness regarding hypertension.

Medida de Adesão aos Tratamentos

The Medida de Adesão aos Tratamentos [Measure Treatment Adherence] (MAT)[201] is a questionnaire developed to assess patients' adherence to medication. It consists of 7 items scaled according to a six point Likert scale, ranging from "always" (1) to "never" (6). The level of adherence is obtained by adding the values of each item and then dividing by the total number of items. Higher scores mean greater level of adherence. The classification of patients as adherent or non-adherent is made according scores near the median values.

Data collection

Data collection took place between March and August 2014, and the Portuguese version of the HKT was applied to a sample of, at least 300 patients. Inclusion criteria were patients older than 18 years and taking at least one antihypertensive drug. All patients who met the inclusion criteria, attending to participating pharmacies and hospital in the study were

invited to participate. The interview was made by a trained pharmacist in a private office, where data on personal and family history were collected and the HKT, MAT, Strelec, and the Batalla instruments were administered. Due to the use of interview method, all participants' answers were coded and therefore there were no missing values.

Statistical Analysis

In order to examine the factor structure of the Portuguese version of the HKT, a confirmatory factor analysis (CFA) using MPlus 6 was performed[252]. Model was estimated using the maximum likelihood (MLMV) method, which provides robust standard errors and robust chi-square in case of deviation from normality adjusting for mean and variance[252].

According to Kline *et al.* (2008)[210], samples above 300 participants are considered large and consequently adequate to use analysis such as the CFA. To evaluate overall model fit, we used the chi-square goodness-of-fit statistic, where non-significant values indicate good fit of the model to the data. In addition, it is recommended that other fit indices can be used to ascertain model fit[210], namely the comparative fit index (CFI), the standardised root-mean-square residual (SRMR) and the root mean square error of approximation (RMSEA). Model fit is considered adequate or good when the CFI is above 0.90 or 0.95, the SRMR is below 0.10 and the RMSEA is below 0.10 or 0.08[210]. The report of the combination of these fit indices has been recommended for a better analysis on the model fit[253].

Whenever a model did not fit the data well, the model was inspected for respicification and alternative models were also tested. The development of competing models was based on theoretical considerations and analysis of the data. Finally, the internal consistency of the HKT was estimated using the Cronbach's alpha.

Results

Study participants

Of the 304 patients enrolled in the study, the mean age was 68.12±10.83 years and 162 (53.3%) were female. The average time since hypertension diagnose was 11.13±8.65 years,

with maximum disease duration of 50 years. In the study sample, 171 (56.3%) had dyslipidemia, 91 (29.9%) had diabetes, 89 (27.6%) had heart disease and 28 (9.2%) already had a stroke. Of the 162 women enrolled 13 (4.3%) had history of hypertension during pregnancy. The adherence mean score obtained for MAT was 5.78±0.27.

The mean score obtained for HKT was 15.33±2.79. Table 7.1 summarizes the proportion of correct responses to each item. Table 7.2 describes the frequencies of answers of the multiple choice questions.

Confirmatory factor analysis

The first CFA model included all the 21 items of the HKT loading on one global factor, Overall Knowledge of Hypertension. The model revealed a poor fit to the data, with, with χ^2 (189) = 226.68, p=0.03; the CFI=0.78; RMSEA=0.03 [90% Confidence interval: 0.01; 0.4] and the SRMR = 0.05. The analysis of modifications indices and the evaluation of each item phrasing suggested that the introduction of error correlations (between items 8 and 11, items 13 and 15 and items 16 and 19) would improve model fit and were included in the model. Final model presented an adequate fit, with χ^2 (182)=200.12, p=0.23; the CFI=0.92; RMSEA=0.02 [90% Confidence interval: 0.00; 0.03] and the SRMR=0.05, indicating that the construct being tested, knowledge on Hypertension, is unidimensional.

Table 7.1 - Proportion of correct answers on the Hypertension Knowledge Test (n=304).

Item	Response format	Correct answer	
		n	%
Q1. Se a sua mãe ou pai tiverem hipertensão o seu risco de tornar-se hipertenso é maior?	T/F	225	74
Q2. Jovens adultos não têm hipertensão?	T/F	279	91.8
Q3. A hipertensão tem sempre sintomas?	T/F	170	55.9
Q4. A hipertensão não põe a vida em risco?	T/F	298	98
Q5. A pressão arterial é alta quando é igual ou superior a 140/90mmHg?	T/F	257	84.5
Q6. Se tiver peso a mais tem um risco 2 a 6 vezes maior de desenvolver hipertensão?	T/F	298	98
Q7. Exercício físico regular pode ajudar a reduzir a pressão arterial?	T/F	258	84.9
Q8. Os portugueses consomem 2 a 3 vezes mais sal ou sódio do que necessitam?	T/F	286	94.1
Q9. Beber bebidas alcoólicas reduz a pressão arterial?	T/F	205	67.4
Q10. A hipertensão é um problema apenas dos homens?	T/F	303	99.7
Q11. Hipertensão na gravidez é um problema temporário e não necessita de acompanhamento após o parto?	T/F	219	72
Q12. A pressão arterial diminui com o tempo frio?	T/F	121	39.8
Q13. A hipertensão prejudica o seu organismo ao longo do tempo por:	MC	102	33.6
Q14. Porque é que a Hipertensão é chamada um "assassino silencioso"?	MC	292	96.1
Q15. Uma pessoa é diagnosticada com hipertensão se tiver:	MC	99	32.6
Q16. Uma boa pressão arterial é:	MC	297	97.7
Q17. Qual das seguintes afirmações é verdadeira sobre os medicamentos para a hipertensão:	MC	95	31.3
Q18. Qual das seguintes afirmações é falsa sobre os medicamentos para a hipertensão:	MC	145	47.7
Q19. Todos os seguintes problemas de saúde podem ser provocados pela hipertensão, exceto:	MC	216	71.1
Q20. Todas as seguintes afirmações são alterações que pode fazer na sua dieta para reduzir a sua pressão arterial, exceto:	MC	392	96.1
Q21. Todas as seguintes alterações do estilo de vida podem ajudar a baixar a sua pressão arterial, exceto:	MC	204	67.1

Abbreviation: MC=multiple choice; T/F=true or false.

Table 7.2 - Frequencies of answers of multiple choices questions.		
	n	%
Q13. A hipertensão prejudica o seu organismo ao longo do tempo por:		
Fazer com que tenha diabetes	33	10.9
Fazer com que ganhe peso	6	2
Danificar os seus vasos sanguíneos	102	33.6
Deixá-lo nervoso	114	37.5
Q14. Porque é que a Hipertensão é chamada um "assassino silencioso"?		
O risco de morrer de hipertensão é baixo	0	0
Quando não há dor nem se sente doente é porque se está bem	7	2.3
Pode não ter sintomas e pode por a vida em risco	293	96.4
Q15. Uma pessoa é diagnosticada com hipertensão se tiver:		
Muitas dores de cabeça que persistem há mais de 6 meses	72	23.7
Um familiar com hipertensão	4	1.3
Stress e pressão constantes	92	30.3
Pressão arterial elevada em 3 ocasiões diferentes	99	32.6
Q16. Uma boa pressão arterial é:		
Menos de 90/50 mmHg	0	0
Menos que 140/90 mmHg	297	97.7
145/110 mmHg	5	1.6
180/100 mmHg	0	0
Q17. Qual das seguintes afirmações é verdadeira sobre os medicamentos para a hipertensão:		
Há muitos tipos de medicamentos para a Hipertensão	95	31.1
Deve ser tomada uma medicação extra quando a pressão arterial está alta	147	48.4
Os medicamentos não devem ser tomados se se beber álcool	42	13.8
Todos os medicamentos causam impotência sexual	0	0
Q18. Qual das seguintes afirmações é falsa sobre os medicamentos para a hipertensão:		
Tomar os medicamentos para a Hipertensão durante muito tempo pode prejudicar o seu organism	145	47.7
A partir do momento em que começa a tomar medicação tem de continuar a tomá-la a vida toda	113	37.2
Mesmo que se sinta bem tem de tomar a medicação como o prescrito	20	6.6
Quando sente que a dose dos medicamentos deve ser alterada, deve falar primeiro com o seu médico	0	0
Q19. Todos os seguintes problemas de saúde podem ser provocados pela hipertensão, exceto:		
Ataque cardiac	7	2.3
Artrite	215	70.7
AVC	22	7.2
Insuficiência Renal	43	14.1

Q20. Todas as seguintes afirmações são alterações que pode fazer na sua dieta para reduzir a sua pressão arterial, exceto:		
Comer frango assado em vez de frito	6	2
Parar de comer batatas fritas	1	0.3
Evitar adicionar sal de mesa à comida	3	1
Comer fast-food ou fritos	291	95.7
Q21. Todas as seguintes alterações do estilo de vida podem ajudar a baixar a sua pressão arterial, exceto:		
Levantar 50Kg	210	69.1
Andar vigorosamente 30 minutos 3 vezes por semana	21	6.9
Beber menos do que 2 bebidas alcoólicas por dia	48	15.8
Parar de fumar	7	2.3

Internal consistency and validity

HKT internal consistency was assessed with Cronbach's alpha. Cronbach's alpha score for all items was 0.65 and the removal of any item would not affect alpha significantly. Values of the alphas if item deleted and the item total correlations are reported in Table 7.3.

Table 7.3 - Internal consistency reliability of the Hypertension Knowledge Test

Item	Item-total correlation coefficient	Cronbach's alfa if item deleted
Q1. Se a sua mãe ou pai tiverem hipertensão o seu risco de tornar-se hipertenso é maior?	0.30	0.63
Q2. Jovens adultos não têm hipertensão?	0.03	0.66
Q3. A hipertensão tem sempre sintomas?	0.03	0.67
Q4. A hipertensão não põe a vida em risco?	0.13	0.65
Q5. A pressão arterial é alta quando é igual ou superior a 140/90mmHg?	0.24	0.64
Q6. Se tiver peso a mais tem um risco 2 a 6 vezes maior de desenvolver hipertensão?	0.20	0.65
Q7. Exercício físico regular pode ajudar a reduzir a pressão arterial?	0.25	0.64
Q8. Os portugueses consomem 2 a 3 vezes mais sal ou sódio do que necessitam?	0.30	0.64
Q9. Beber bebidas alcoólicas reduz a pressão arterial?	0.33	0.63
Q10. A hipertensão é um problema apenas dos homens?	-0.10	0.63
Q11. Hipertensão na gravidez é um problema temporário e não necessita de acompanhamento após o parto?	0.34	0.65

Q12. A pressão arterial diminui com o tempo frio?	0.18	0.62
Q13. A hipertensão prejudica o seu organismo ao longo do tempo por:	0.39	0.65
Q14. Porque é que a Hipertensão é chamada um "assassino silencioso"?	0.10	0.63
Q15. Uma pessoa é diagnosticada com hipertensão se tiver:	0.31	0.65
Q16. Uma boa pressão arterial é:	0.23	0.64
Q17. Qual das seguintes afirmações é verdadeira sobre os medicamentos para a hipertensão:	0.28	0.63
Q18. Qual das seguintes afirmações é falsa sobre os medicamentos para a hipertensão:	0.33	0.64
Q19. Todos os seguintes problemas de saúde podem ser provocados pela hipertensão, exceto:	0.26	0.65
Q20. Todas as seguintes afirmações são alterações que pode fazer na sua dieta para reduzir a sua pressão arterial, exceto:	0.05	0.62
Q21. Todas as seguintes alterações do estilo de vida podem ajudar a baixar a sua pressão arterial, exceto:	0.40	0.63

Convergent validity was estimated by correlating the final score of the HKT with other measures assessing the same construct, knowledge on hypertension. The HKT was moderately and significantly correlated with Batalla (0.32, $p<0.001$) and Strelec scores (0.31, $p<0.001$), confirming that both instruments are assessing correlated constructs.

Construct validity was estimated by examining differences on adherence based on knowledge on hypertension, assessed by the HKT scores. Based on the median (15), groups were formed: scores below de mean were considered lower knowledge and scores above the mean were considered high knowledge. Participants with lower knowledge (<15) had a mean MAT score of 5.74±0.33 and those with higher knowledge (≥15) had a mean score of 5.81±0.22 ($t = -2.29$, $p=0.04$).

Discussion

Our study aimed to examine the factorial structure and validity of the Portuguese version of the HKT. To our knowledge, this is the first study using confirmatory analysis procedures to examine the factor structure of the HKT, confirming the measurement model of the

instrument and the unidimensional theoretical structure of the instrument[210], indicating that all the items are contributing to the assessment of knowledge on hypertension.

The original validation was made managing the questionnaire to two distinct samples, in study 1 to middle-aged hypertensive (mean age=51.9±5.7 years) and in study 2 to elderly hypertensive (mean age=70.9±5.5 years)[209]. The results were presented in separate for each study and for the total sample. If we compare our Cronbach's alpha (α=0.65) to the one obtained in the total sample of the original validation (α=0.70), our was inferior. Still, if we make the comparison with the alpha obtained in study 2 (α=0.62), which has a population mean age more similar with ours, we obtained a higher alpha.

Even though we obtained a Cronbach's alpha <0.70, it still enough to consider that Portuguese version of HKT presents an acceptable internal consistency.

One possible explanation for a Cronbach's alpha slightly below the recommended value may be the existence of some uncorrelated items. Regarding item total correlation in Portuguese version, values of item total correlation range between -0.1 and 0.40, having 6 items (Q2, Q3, Q4, Q10, Q14 and Q20) which did not meet the cutoff of 0.15[254], (more than the obtained in the study 2 of the original validation, with values ranging between 0.11-0.32, where two items, Q3 and Q6, did not meet that cutoff). The fact that these items do not contribute much to the final score may be due largely to the high percentage of correct answers that they present. This can be explained by the characteristics of the population surveyed, since we applied the instrument to hypertensive patients under treatment, with good levels of adherence. Once removal of any item would not affect alpha significantly, the removal of this items could cause this questionnaire ceased being valid for application in other contexts, particularly in a less informed population.

Analyzing the answers obtained in multiple choice questions, Q13, Q15, Q17 and Q18 were the ones which caused more doubts in the patients, with less than 50% of correct answers. In Q17 ("Which of the following statements is true about HBP medications?") about 48% of patients responded that "It should be taken an extra medication when blood pressure is high." One possible reason for these results is that the question could be misinterpreted, confounding taking an extra dose of medication and taking other medication. Thus, in future applications of HKT Portuguese version, it may be useful to consider an alternative wording for this question, for example, by replacing the expression "medicação extra" for "medicação adicional".

The difficulties in accurately answer to items 13, 15 and 18 may be explained by the low level of health literacy that the Portuguese population presents[206]. These results are similar to those obtained by Williams *et al.* (1998)[255] where patients with poor literacy skills were less likely to answer correctly to knowledge questions. Health literacy is independently related to disease knowledge[256], and there are several studies showing that patients with lower literacy levels have lower levels of knowledge about their disease[255, 257-259]. In fact, Portuguese population health literacy is low. In Salgado *et al.*(2013), in measuring health literacy with Newest Vital Sign, 95% of the Portuguese respondents scored in the three lowest possible scores, indicating a notable floor effect[206].

According to literature, health literacy is inversely associated with age[255, 260, 261], patients with marginal and inadequate literacy are older than patients with adequate literacy, meaning that older patients should have worse knowledge about their disease. However, in the HKT original validation study, Han *et al.* (2011)[209] showed that knowledge about hypertension increases with age and with time of disease. Same results were obtained by Hyre *et al.*(2007)[262], where patients diagnosed with hypertension for ten or more years ago were more likely to have a better understanding of the importance of medication-taking behaviors and their effects on long-term health. This findings suggest that personal experience with hypertension and cardiovascular disease, rather than basic knowledge, may lead to improved adherence behavior. Thus, when developing strategies to improve blood pressure control, particular characteristics of knowledge about hypertension must be taken into account, requiring the utilization of specific validated instruments.

Final score of the HKT was correlated with other measures assessing the same construct, Batalla and Strelec. The HKT was moderately and significantly correlated with both instruments, showing that the construct assessed is correlated but not exactly the same. In fact, HKT allows to evaluate knowledge about hypertension, not only related to symptoms and diagnosis of the disease, but also related to ways to prevent and control high blood pressure, antihypertensive medications, and harmful effects of hypertension over time. These multifaceted characteristics are an added value that enable obtaining more complete and specific information about the patient's knowledge about this condition.

Limitations of the study

A potential limitation of our study was the questionnaire application mode used. We used interviewer-administration method, which may lead to some biases reported in the literature[221, 222, 225]. However we considered the interview the best method to allow the inclusion of patients with very low literacy, either pure literacy or functional literacy, since we want that the validated instrument can be applied in every type of population, regardless of their degree of literacy.

Conclusions

We obtained a Portuguese version of the Hypertension Knowledge Test with an acceptable internal consistency, discriminatory capacity, and predictive power regarding adherence, which can be used either in research or in clinical practice.

After validating the HKT, a potential standard exists which could avoid the practice of using non-validated questionnaires in Portugal. This will allow the cross-sectional and longitudinal comparability of studies. With this questionnaire, not only clinicians and researchers, but also health policy decision makers, can assess the gaps in patients' knowledge about hypertension, and consequently develop educational activities.

Future research is warranted to assess if knowledge evaluated by the Portuguese version of HKT can be associated with process variables, such as adherence or outcome variables, as blood pressure control.

Concluding remarks

Concluding remarks

Hypertension is one of the world's most prevalent diseases and its management is a timely topic and one of interest world-wide. Research teams around the world try to understand the mechanisms that lead to the onset of this disease, understand the factors that influence it, and try to develop more effective drugs and with fewer side effects. In order to increase the blood pressure control and reduce associated cardiovascular mortality, several interventions have been carried out by different entities aiming to improve the diagnosis and treatment of this disease. However, about half of Portuguese hypertensive patients remains with blood pressure values higher than the therapeutic goals.

So what lead two different treated patients to respond differently to drug therapy? Is there any factor associated with uncontrolled blood pressure despite pharmacological treatment? In this research we tried to answer to these question, we aimed to identify objective and measurable factors, associated with risk of poor control of blood pressure in hypertensive patients under pharmacological therapy.

Our first systematic review demonstrated that few meta-analysis were possible and in 73 different independent variables identified, only eight were amenable to meta-analyse. The fact that different research teams use different core outcome sets and that the same outcome was reported differently across studies were the major causes of this difficulty. Indeed, in variables such as salt intake, total cholesterol, triglycerides and alcohol consumption, being treated as categorical variable, with different cut-offs, hindered the possibility of meta-analysis and making it difficult to obtain the best evidence available for clinical practice. Additionally, high levels of heterogeneity were obtained in meta-analysis performed, which doesn't allow drawing robust conclusions from those results. As so, more homogeneous investigation is needed and the use of standard methodologies in the same type of research is a warranty of results comparability, which is essential in systematic reviews. Nevertheless, gender, health insurance, adherence to therapy, obesity and diabetes were identified as having a negative influence on the control of blood pressure in patients under pharmacological antihypertensive treatment. The impact of diabetes as comorbidity is the most important, being 2 times higher than adherence to therapy and 3 times higher than obesity.

One of the major modifiable factors that stands out in our research was adherence to medication. Our results are in line with other studies that demonstrate the importance of adherence to antihypertensive treatment.

In Portugal, although increasing importance has been assigned to adherence, few robust investigation exists. We could only identify 3 published studies that aimed to assess patient's adherence to medication[203, 205, 206]. The only validated instrument to assess antihypertensive medication adherence before our work was the Medida de Adesão ao Tratamento (MAT)[201], developed in 2001 by an ISCTE research team. MAT is a questionnaire with good internal consistency but has the disadvantage of being a national instrument, which prevents cross comparisons with studies from other countries. To ensure the homogeneity of methods we seek in the literature which would be the best instrument to use. In fact, no gold standard concerning adherence questionnaires exists, but one clearly stands out, the 8-items Morisky Medication Adherence Scale (MMAS-8)[115]. Being currently translated and validated to more than 20 different languages, MMAS-8 is the most used questionnaire worldwide to assess adherence to medication. Nevertheless, using a reliable instrument assessed may not be enough to allow global comparisons. The MMAS-8 scoring system is not intuitive which may result in potential discrepancies in the application of the instrument. Additionally, the effects of using MMAS-8 in culturally different environments have not been sufficiently evaluated. Therefore, we performed a systematic review and meta-analysis to assess heterogeneity associated with the use of MMAS-8, finding that, despite the demonstrated reliability and internal consistency, the use of this instrument is associated to high heterogeneity. No subgroup analyses with moderator variables (patient characteristics and study or scoring characteristics) could reduce this heterogeneity. As so, further studies should be undertaken with the most homogenous population possible, in order to evaluate if this heterogeneity is due to the instrument itself or to external variables. We cannot ignore that, by being so easy to use, MMAS-8 was apply in very different samples, with very different conditions.

We hypothesize that one of the possible causes for MMAS-8 high heterogeneity may be validation problems regarding psychometric properties and cross-cultural adaptation of MMAS-8 to other languages. Once again, being the use of MMAS-8 protected by US

copyright, translation and cross-cultural validation of the instrument may be affected. As so, and considering that in Portugal no worldwide used instrument is validated so far, we develop and validate the European-Portuguese adaptation of the 8-Items Morisky Medication Adherence Scale in a Portuguese sample. Namely we intend to examine the factorial structure of MMAS-8 with a confirmatory analysis and to estimate its convergent and concurrent validities.

We obtained a Portuguese version of the 8-item Morisky Medication Adherence Scale, a unidimensional scale with an acceptable internal consistency and good convergent and concurrent validity. As in other validations[124, 160, 164], internal consistency wasn't perfect, but confirmatory factor analysis shows that this instrument has a good fit to the data, representing well adherence to antihypertensive medication. With this Portuguese version of MMAS-8, now a potential standard exists to assess Portuguese patient's adherence to medication, which will allow the cross-sectional and longitudinal comparability of Portuguese studies with international studies.

Our objective when validating these kind of instruments to Portuguese was, not only be able to measure adherence, but also be able to obtain valuable data to design more effective intervention strategies. So, as important as having the best instrument to assess adherence, is designing the right intervention to improve it. Indeed several pharmaceutical interventions have been performed, unfortunately with results below expectations and still lack of evidence of benefits associated to them. One of possible cause for this lack of evidence may be the absence of individual tailoring of interventions. Adherence is a complex concept that includes several dimensions that interact with each other and affect patient and his adherence. Understanding reasons for poor adherence and consequently individualizing interventions may be a possible way of improving adherence more effectively.

In Portugal no validated instrument capable of assess barriers of non-adherence to antihypertensive medication exists. We research in published literature the existent tools available and, among the several self-report instruments, the Maastricht Utrecht Adherence in Hypertension Questionnaire (MUAH)[216] provides valuable information about the reasons for poor adherence, being a possible tool to assess barriers of non-adherence to

antihypertensive medication. Being a patient-oriented questionnaire that address cognitive and behavioural factors for the assessment of adherence problems, MUAH measures 4 adherence-related dimensions such as positive attitude towards health care and medication, lack of discipline, aversion towards medication and active coping with health problems. Thus, we decided to translate it and validate it to Portuguese.

While evaluating the questionnaire psychometric properties some difficulties in the methodological implementation arise and the lack of a global score that allows adherence classification appears as one major gap in this instrument. Therefore, we developed a short version of MUAH (MUAH-16) and compare its construct validity and factorial structure with a confirmatory factor analysis (CFA) between the original and the short version, as well as estimate its convergent validity. The version of MUAH we developed, with less items evaluating each dimension and with a global score of adherence has good psychometric properties and it can be easily applied in the clinical setting, giving health professionals more extended information about the patient's reasons for poor adherence.

We hypothesized that the methodology used in questionnaires application may influence the results obtained. Our data was collected in community pharmacies and our samples had mean ages above 65 years, corresponding mainly to an older population, known to have lower levels of health literacy and more difficulties in understanding and completing the questionnaires. As so, interviewer-administrated methodology seamed more attractive to questionnaires application. Knowing that this methodology is highly influenced by social desirability and response acquiescence[221, 227, 233], we aimed to assess the differences between interviewer-administered and self-administered methodologies in the application of an adherence questionnaire, using MAT, a Likert scale questionnaire, as instrument to evaluate adherence. Indeed, CFA shows that both interview and self-report methodologies represents well adherence to therapy, although results of the self-report data are indicative of better fit. In the interview administered, we obtained lower values of skewness and higher levels of kurtosis, meaning that distribution of answers in interview tend to be less symmetrical, making it difficult to distinguish non-adherent patients based on their answers. Also, patients under interview-administration presented 9.7% higher chance to answer "never" (the most favourable answer). So, although interview is the most attractive method to evaluate populations with low literacy levels, caution is needed when interpreting results

due to higher prevalence of social desirability or response acquiescence in this methodology, when compared to self-report administration, which may lead to overestimated adherence levels. Thus, self-report administration must be preferred in questionnaires application that assess adherence to therapy.

Proceeding with the analysis of the first systematic review results, in addition to medication adherence, other variable stood out. Being an important contributor to blood pressure control, and also a growing area of intervention in community pharmacies, the knowledge of patients regarding hypertension disease was one of the focuses of our research. Despite the importance assigned to this variable, a lack of research on this field remains. Although it has been recognized that interventions in order to improve knowledge of hypertension contribute to an improvement in blood pressure control, validated instruments, that properly assess knowledge, and consecutively allow the design of more targeted interventions, are scarce. The Hypertension Knowledge Test (HKT)[209] is an easy-to-use questionnaire covering several items related to the disease as the etiology, diagnosis, treatment and prevention methods, and has demonstrated good psychometric properties, namely internal consistency. As so, we proposed to develop and validate the Portuguese adaptation of the Hypertension Knowledge Test questionnaire in a Portuguese population, examine its factorial structure with a confirmatory factor analysis and to estimate it's convergent and construct validities. We obtained a Portuguese version of HKT with an acceptable internal consistency, discriminatory capacity, and predictive power regarding adherence. Now a potential standard exists which could avoid the practice of using non-validated questionnaires in Portugal. This will allow the cross-sectional and longitudinal comparability of studies and, not only clinicians and researchers, but also health policy decision makers, can assess the gaps in patients' knowledge about hypertension, and consequently develop educational activities.

With these validations, was possible to bridge the existent gap in Portugal for the assessment of factors that contributes most to hypertensive therapy success. Contributing with fully validated questionnaires, not only to assess adherence to antihypertensive therapy, but also to understand the causes of non-adherence and the patient's knowledge of their disease, our work represents a step forward in the attempt to develop more effective strategies to control hypertension in Portugal.

Our overall goal was to identify the impact of different variables in poor blood pressure control in hypertensive patients under pharmacological treatment and develop an instrument that allow systematic patients classification according to their risk of having uncontrolled blood pressure. This way, patients could be treated differentially according to their needs, and human and material resources could be used more efficiently. Adjusting the frequency of visits to the health professional and the frequency of diagnose and monitoring exams to each patient, a more rational use of health care system resources would be assured and consequently economic and health gains would be obtained.

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Appendices

Appendix 1: Medical College of Coimbra University Ethics Committee Approval

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FMUC FACULDADE DE MEDICINA
UNIVERSIDADE DE COIMBRA

COMISSÃO DE ÉTICA DA FMUC

Of. Refª **101-CE-2013**
Data 16 / 12 **/2013**

C/C aos Exmos. Senhores
Investigadores e co-investigadores

Exmo Senhor
Prof. Doutor Joaquim Neto Murta
Director da Faculdade de Medicina de
Universidade de Coimbra

Assunto: Pedido de parecer à Comissão de Ética - Projecto de Investigação autónomo (refª CE-105/2013).

Investigador(a) Principal: Isabel Vitória Neves de Figueiredo Santos Pereira (FFUC), Fernando Fernández-Llimos, Ana Cristina Gaspar Cabral, Maria Margarida Coutinho de Seabra Castel-Branco Caetano e Maria Margarida Duarte Ramos Caramona.

Titulo do Projecto: *"Adaptação transcultural para português de inquéritos de adesão à terapêutica e conhecimento sobre hipertensão".*

A Comissão de Ética da Faculdade de Medicina, após análise do projecto de investigação supra identificado, decidiu emitir o parecer que a seguir se transcreve: ***"Parecer Favorável".***

Queira aceitar os meus melhores cumprimentos.

O Presidente,

Prof. Doutor João Manuel Pedroso de Lima

GC

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Appendix 2: Hospital Infante D. Pedro de Aveiro Ethics Committee Approval

CENTRO HOSPITALAR DO BAIXO VOUGA, E.P.E. / AVEIRO

Avenida Artur Ravara – 3814-501 AVEIRO
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sec-adm@chbv.min-saude.pt

Ex.ma Senhora
Prof. Maria Margarida Caramona
Responsável Grupo Farmacologia
Faculdade de Farmácia da
Universidade de Coimbra
Pólo Ciências Saúde-Azinhaga Santa Comba
3000-548 COIMBRA

S/ Ref.ª	S/ Comunicação de	N/ Ref.ª	Aveiro,
		063580	2015-08-05

ASSUNTO: Pedido de autorização para a realização de trabalho – Dra. Ana Cabral.

Na sequência do V/ofício de 25 de novembro de 2013, para a realização de um trabalho intitulado "**Avaliação do Risco de Não Controlo da Pressão Arterial em Doentes sob Terapêutica**", a realizar pela Dra. Ana Cabral, informa-se que foi autorizado pela Direção Clínica e que não foi solicitado o parecer da Comissão de Ética por não se terem encontrado dúvidas dessa natureza, procedimento conforme com a legislação em vigor á data do pedido e da realização do inquérito.

Com os melhores cumprimentos.

O Diretor Clínico

(Dr. Paulo Ferreira)

Na resposta indicar o número e as referências deste documento. Em cada ofício tratar só de um assunto.

GM.

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