CRANFIELD UNIVERSITY

Margarida de Fátima Neto Espírito Santo

EVALUATION OF HEALTH OUTCOMES ASSOCIATED WITH MEDICATION IN SOUTHERN PORTUGAL USING A NOVEL APPROACH FOR **MED**ICATION **RE**VIEW: *ReMeD* STUDY

Cranfield Biotechnology Centre, SATM
Doctor of Philosophy

PhD
Academic Year: 2010 - 2016

Supervisor: Dr J.D. Newman
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This thesis is submitted in partial fulfilment of the requirements for the degree of PhD

ABSTRACT

Currently, a large portion of the world's population uses medication on a regular basis and uses health services frequently, mainly due to the increase of longevity and the growing number of chronic diseases (CD).

Consequently, a correct medication management is needed in order to improve the responsible use of medicines and health outcomes. Portugal shows a high prevalence of CD such as hypertension, obesity, dyslipidaemia and diabetes. Moreover, the Algarve region presents some shortcomings in accessibility to healthcare.

Therefore, this research project arises with the main aim of establishing a methodology to analyse the outcomes of the process of medication use (MU) through medication review (MR) , in a clinical practice setting in Southern Portugal (AEDMADA clinic), applied in the ReMeD study. Patient´s data was collected individually and then systematically analysed considering the humanistic, economic and clinical outcomes.

A questionnaire (SAHL-S&E) was previously adapted for the Portuguese language aimimg to identify subjects with low health literacy (HL), which was then used during the MR.

The ReMeD study was conducted in 118 patients, mainly ≥65 years, hypertense, diabetic, dyslipidemic and presenting a very high cardiovascular risk.

Humanistic outcomes showed 25.4% of patients having low medication knowledge, 43.2% with low HL and about 25% being non-adherent to medication.

Economic outcomes revealed that most patients were polymedicated (73.8%) and monitored by 2-3 Physicians, and about 15% suffering hospitalization in the last year.

Negative clinical outcomes (NCO) were identified in 99.2% of patients, and 74.6% presented risks of developing NCO.

As a whole, the ReMeD methodology seems appropriate to identify situations from the process of MU, useful to outline new strategies aimed to improve patient's MU and the empowerment for disease management. Applying this novel approach enables the conduction of MR in a clinical setting, allowing to pinpoint modifiable situations, contributing to improve health outcomes.

Keywords:

Clinical outcomes, medication, medication management, outcomes, pharmaceutical care.

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Knowing is not enough; we must apply. Willing is not enough; we must do.

Goethe

Thus, this project resulted from the contribution of several people and entities.

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Nobody cares how much you know, until they know how much you care.

T. Roosevelt

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LIST OF ABBREVIATIONS

ADE	Adverse drug event
ADR	Adverse drug reaction
AED	Atherosclerotic disease
AGE	Advanced glycated end-products
ASHP	American Society of Hospital Pharmacists
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
CD	Chronic Diseases
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CMR	Clinical medication review Comprehensive medication review
COPD	Chronic obstructive pulmonary disease
CRF	Chronic renal failure
CVD	Cardiovascular disease
DALYS	Disability-adjusted life years
DBP	Diastolic blood pressure
DDD	Defined daily dose
DL	Dyslipidemia
DM	Diabetes mellitus
DRP	Drug-related problem
DTP	Drug therapy problem
ESC	European Society of Cardiology
EUR	Euro
FFA	Free fatty acids
FS	Food supplements
Glut-4	Glucose transporter 4
GP	General practitioner
HbA1c	Glycated haemoglobin

HDL-C	High-density lipoprotein cholesterol
HL	Health literacy
HMR	Home medicines review
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Haynes-Sackett test
HT	Hypertension
ICC	Intraclass correlation coefficient
LDL-C	Low-density lipoprotein cholesterol
LIMM	Lund integrated medicines management
MACE	Major adverse cardiovascular event
MAI	Medication appropriateness index
MAP	Medication-related action plan
MAT	Measure Treatment Adherence
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MK	Medication knowledge
MPP	Medication related problem
MR	Medication review
MTA	Medicines therapy assessment
MTM	Medication therapy management
MTR	Medication therapy review
MU	Medication use
MUFA	Monounsaturated fatty acids
MUR	Medicines use review
NCO	Negative clinical outcome
NHS	National Health System
NMS	New medicine service
NO	Nitric oxide
NOM	Negative outcome associated with medication
NSAID	Nonsteroidal anti-inflammatory drug
OAD	Oral antidiabetic drug
OTC	Over-the-counter medicine

PAI-1	Plasminogen activator inhibitor-1
PAR	Population attributable risk
PCNE	Pharmaceutical Care Network Europe
PDC	Proportion of days covered
PI3K	Phosphatidylinositide 3-kinase
PIDT	Potentially inappropriate drug therapy
PIM	Potentially inappropriate medication
PKC	Protein kinase C
PMK	Patient medication knowledge
PPAR	Peroxisome proliferator-activated receptor
PPAR γ	Peroxisome proliferator-activated receptor gamma
PUFA	Polyunsaturated fatty acids
RAGE	AGE receptor
RCT	Randomized controlled trial
RMMR	Residential management medication review
ROS	Reactive oxygen species
RR	Relative risk
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
SmPC	Summary of product characteristics
SR-B	Scavenger receptor B
TC	Total cholesterol
TIA	Transient ischemic attack
tPA	Tissue plasminogen activator
TRP	Treatment related problem
USA	United States of America
WC	Waist circumference
WHO	World Health Organization

1 INTRODUCTION

The increasing number of lived years per subject involved a rise in the amount of the chronic diseases suffered, many starting at a young age, and presenting a long duration. (1) These clinical situations usually require the use of long-term therapeutic schemes, leading to the emergence of new pharmacological therapies and other approaches to improve patient´s health and quality of life. New and more therapeutic alternatives have emerged in recent decades, as a result of the research carried out by the pharmaceutical industry and research groups in several clinical areas.

However, the increment in the variety and duration of the use of medicines cannot happen inconsequently, leading to an increased risk of adverse drug reactions, especially in those patients who are under polymedication (2), and comprising a growth in the healthcare costs.

Therefore, as a consequence of the needs triggered by the increase of patient´s lifespan, health services also present a high rate of utilization, with an increasing difficulty in responding to the population´s needs. Unfortunately, the accessibility to the Portuguese healthcare is not yet at the level of other European countries, presenting inequality for the various population groups and in the various regions of the country. (3)

Health professionals are often called upon to contribute effectively to the improvement in the rational use of health services and to the provision of effective services aiming to enhance the subject´s health outcomes.

Therefore, the Pharmacist has a central role to be developed in the provision of services related to the use of medicines, contributing with his extensive knowledge and expertise in the area of pharmacotherapy management, targeting the improvement of patient´s health outcomes. (4)

Pharmaceutical services, despite their general diversity and variety of approaches, are directed towards the provision of patient-centered services. (5) These services have added great value when provided within a multidisciplinary team of professionals, including Pharmacists in liaison with other professionals,

such as medication review and pharmacotherapy follow-up, particularly when developed in primary healthcare units. (6)

There are several countries where the medication review service is already implemented as an integrated service within the health system, contributing to the improvement of patient´s health outcomes, with benefits for the reduction of costs associated with patient´s health and quality of life. (7)

The medication review service is not formally integrated in the healthcare services provided in Portugal, although it is a potential opportunity to improve patient´s health outcomes, and for professionals such as Pharmacists, allowing the extension of services available to the population within healthcare units and contributing to improved health outcomes. It is therefore important to develop further research in order to help better understand how this medication review service could be implemented in Portugal.

Considering the current scenario described above, the main aim of this research is to establish a methodology to analyse outcomes in the process of medication use through medication review, in a clinical setting.

Therefore, the hypothesis of this study is that a specific methodology applied in the medication review will be feasible and useful for the identification of specific situations, contributing to an improvement of patient's health outcomes.

To test this hypothesis, there were specific goals: 1) the adaptation to the Portuguese language of the “Short Assessment of Health Literacy - Spanish and English (SAHL-S&E)”; and 2) the clinical patient evaluation, characterization of pharmacotherapeutic profile, analysis of medication review outcomes, identification of predictive factors for clinical outcomes associated to medication review, and analysis of eligibility criteria for medication review programs available in Australia, Canada and England, developed as the **ReMeD** study.

A literature review is enclosed in the Introduction chapter, including a revision about the state of healthcare in Portugal (health outcomes, health system and medicines use), the concept of pharmaceutical care, and which services are

provided in this scope, as the medication review service. Beside, the tools identified by other authors to perform this same activity in other countries, such as medication adherence evaluation, medication knowledge evaluation, disease knowledge evaluation and identification of inappropriate medication, were also approached within this literature review.

Health literacy (HL), as it might influence the capacity of the patients to manage their own medication and have an impact in health outcomes (8), was also included in the literature review. The tools used to assess HL were identified and the SAHL-S&E was then selected to be adapted to the Portuguese language, since it was previously recognized to be appropriate to identify subjects with low degree of health literacy. The resulting tool from this adaptation was used in the medication review activity held in the ReMeD study.

The Results chapter is presented in two separate sub-chapters; the first one is related to the adaptation of the SAHL-S&E questionnaire to the Portuguese language; and the second to the results obtained in the ReMeD study.

1.1 Healthcare in Portugal

1.1.1 Health Outcomes

In the last two (2) decades an increase in longevity has been observed in the Portuguese population, both at birth and at 65 years. (9)

This increase in longevity is followed by a greater number of the pathologies suffered by the Portuguese subjects.

Currently, in Portugal, the main causes of morbidity, disability and premature death are circulatory system diseases (30%), malignant tumors (24%), respiratory diseases (12%), and endocrine, nutritional and metabolic diseases (5%). (9)

Regarding circulatory system diseases, the most common is ischemic heart disease, whose most relevant clinical manifestation is acute myocardial

infarction, and cerebrovascular disease, including ischemic stroke. However a positive outcome was observed in recent years in the mortality by acute myocardial infarction, which decreased 18.23% between 2009-2013 (10) The analysis from the burden of disease in Portugal identified the cerebrovascular and ischemic heart diseases, as well as diabetes, as the main causes of DALYS (disability-adjusted life years), with a most pronounced burden in the last decade (death and disabilities combined). (11) The risk factors identified associated to these causes, in descending order were: dietary, high systolic blood pressure, tobacco, high body mass index, high fasting plasma glucose, alcohol and drug use, high total cholesterol, occupational risks, low glomerular filtration rate and low physical activity. (9)

Consequently, the inclusion of high-risk individuals, regarding intervention in the management of risk factors for cardiovascular diseases, is a major priority (Table 1). (12)

Table 1: Priority patients regarding cardiovascular diseases (CVDs).

Priority patients for CVDs	Established CVD
	Diabetes *mellitus*
	Renal disease (moderate to severe)
	High level of individual risk factors
	High SCORE risk

Legend: CVD – Cardiovascular Disease; SCORE - Systematic Coronary Risk Evaluation.

[Adapted from (12)*]*

Several risk factors have been identified as the main contributors to increase this risk for CVDs, some that can be treated and changed, others that cannot be modified. (Table 2).

Table 2: Major risk factors for cardiovascular diseases (CVDs).

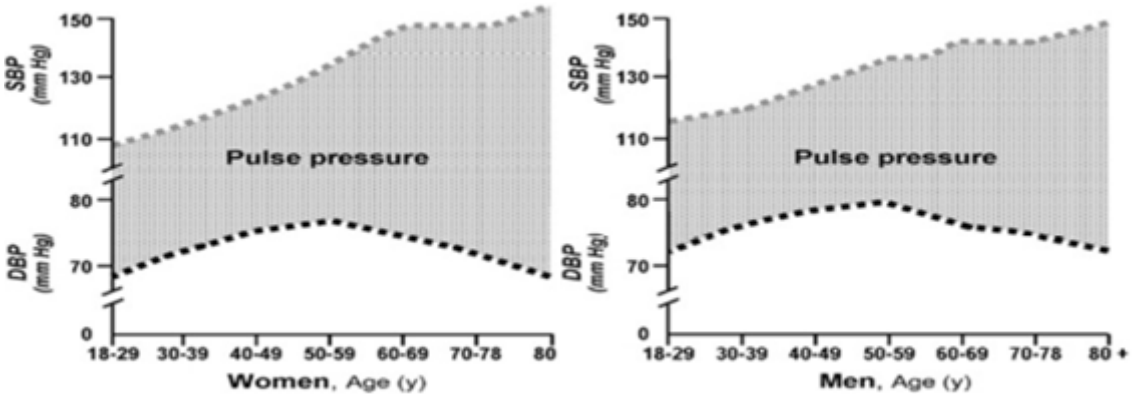
***Major* risk factors**	Non-modifiable	Age
		Familiar prevalence of early-onset CVD (before 55 years in men and 65 years in women)
	Modifiable	Systolic blood pressure
		Diabetes
		BMI > 25 kg/m^2
		Smoking habits
		Diet

Legend: CVD – Cardiovascular Disease; BMI - Body mass index.

[Adapted from (12)*]*

Arterial hypertension (HT) is highly prevalent in most Western countries populations, and was already identified not only as one of the major risk factors for cardiovascular diseases (CVDs), but also as a very serious public health problem worldwide, being responsible for about half of the deaths from heart disease and stroke. (13)

Blood pressure (BP) is a physiologic parameter that will vary with subjects´ age, presenting higher values with the increase of the subject´s age, mostly in elderly subjects (Figure 1). (14)



Legend: DBP – diastolic blood pressure; SBP – systolic blood pressure; Y - years. (14)

Figure 1: Changes in blood pressure values according to subjects´ age.

In Portugal, the results of a population study obtained in 2003/04 indicated that the prevalence of hypertension (HT) was 42.1%, from which only 39.0% were treated patients and 11.2% had controlled BP values. (15)

Another Portuguese study (VALSIM) held in primary care setting (2006/07), showed a prevalence of HT adjusted for gender, age and region size of 42.6% (16). Regarding the group of diabetic hypertensive patients, 78.4% were being treated with antihypertensive drugs, but only 9.3% had controlled blood pressure (17).

More recently, the PHYSA study, a Portuguese population-based cross-sectional survey (2011/2012), which enrolled a stratified sample (for age and sex) of subjects from 18-90 years old, was developed to find out the prevalence, awareness, treatment and control of hypertension and the 24-h sodium excretion (24h-UNa). (18) This study included the assessment of blood pressure at two moments (visit 1 and 2), and at the first visit, the prevalence of hypertension was of 42.2%. Among hypertensive patients, about three quarters (74.9%) were being treated and 42.5% had their BP values under control (BP<140/90 mmHg). The value for 24h- UNa (urine sodium concentration) was greater in patients with diagnosis of hypertension , when compared to normotensive individuals (185.4±64.8 *vs.* 177.8±64.5 mmol/day; $p<0.02$), concluding that the daily intake of salt (10.7 grams) was almost double the WHO recommendation (19), which should be less than 5 grams. (18)

It is noteworthy that the Algarve region presented the lowest rate of control of hypertension in the national territory (18.4% for men and 21.8% for women), according to the results of a Portuguese report regarding cerebrovascular diseases (2015). (9)

Dyslipidemia is another *major* risk factor associated with cardiovascular disease, and the effectiveness of the treatment is closely related to a significant reduction of cardiovascular risk. (12)

The results from a Portuguese study including a sample of patients treated with statins, indicated that the majority of patient´s values for LDL-C (62.9%) and

total cholesterol (68%) were not in the range of the recommended values by the European Society of Cardiology. (20)
Diabetes *mellitus* (DM) is also a *major* risk factor for CVD and the most common cause of kidney failure in the Western world. (12)

The prevalence of diabetes in the Portuguese population was 12.9% (20 - 79 years) in 2012, which corresponded to an estimation of 1 million individuals with diabetes. A strong direct correlation between the increase in the prevalence of diabetes and the aging of individuals was found. (21)

The first prevalence study performed in Portugal by Gardete-Correia *et al*. (2010), found 43.6% undiagnosed diabetic patients (population between 20 and 79 years old) and about 90% of diabetic patients being overweight or obese. (22)

Although in the last five years a significant decrease has arisen in the number of potential life years lost (YLL) for Diabetes *mellitus* (DM) in Portugal (-15%), in 2012 this disease still accounted for approximately seven YLL per death from diabetes in the population under 70 years of age. In addition, the number of patients discharged from the hospital associated with DM diagnosis has significantly increased throughout the same period (increased 78.5% between 2003 and 2012). (21)

Nevertheless, between 2005 and 2013, there has been a decrease of 1.6% in the number of new cases of DM in Portugal. According to the 2014 report, DM has an overall prevalence of 13.1%, in which 7.4% of the patients were diagnosed and 5.7% weren´t. (23)

In the same report, about 20% of diabetic patients followed in the Portuguese National Health Service had a value for HbA1c >8%, 66.2% had a LDL-C value <100 mg/dL (although this prevalence was only 8.1% in 2012), 37.7% had a blood pressure value <130/80 mmHg, and 67.7% had a value for blood pressure <140/90 mmHg. (23)

In diabetic patients, a number of microvascular and macrovascular complications may arise, and the risk of complications increases with increased

hyperglycaemia (Figure 2). (24) While microvascular complications may be associated with previous hyperglycaemia, a less pronounced association has been verified for macrovascular complications. Nevertheless, relative to macrovascular complications such as myocardial infarction, it has been established that the risk decreases 14% for each 1% of reduction on the mean value of HbA1c. (25)

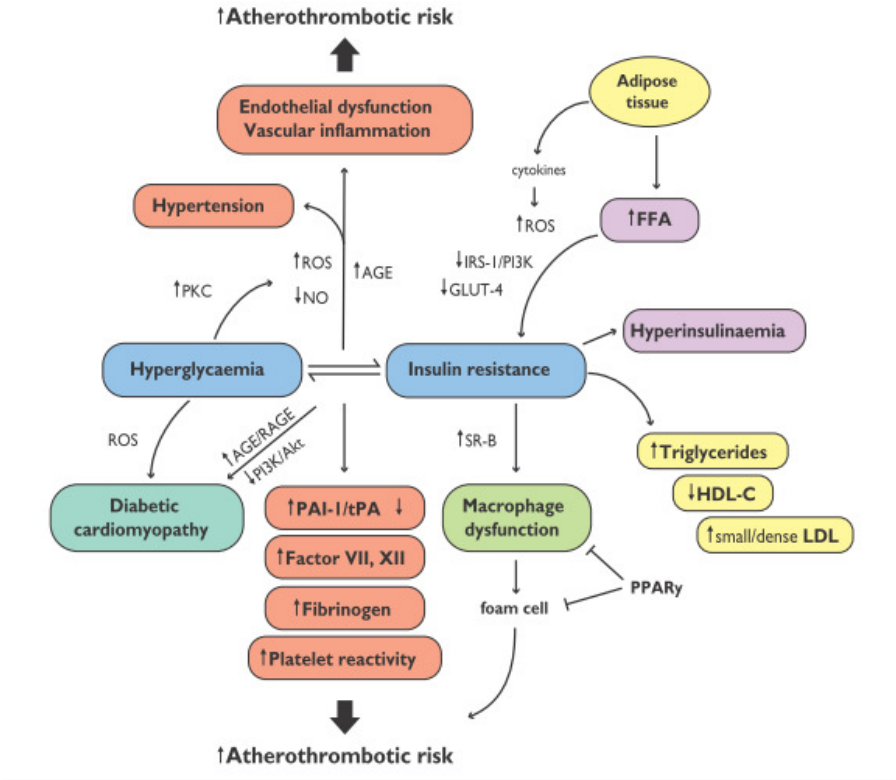


Figure 2: Diabetes complications pathways.

Legend: AGE - advanced glycated end-products; FFA - free fatty acids; GLUT- 4 - glucose transporter 4; HDL-C - high-density lipoprotein cholesterol; LDL - low-density lipoprotein; NO - nitric oxide; PAI-1 - plasminogen activator inhibitor-1; PKC - protein kinase C; PPARγ - peroxisome proliferator-activated receptor γ; PI3K - phosphatidylinositide 3-kinase; RAGE - AGE receptor; ROS - reactive oxygen species; SR-B - scavenger receptor B; tPA - tissue plasminogen activator. (24)

Adults who have both diabetes and hypertension have increased risk for kidney disease (evaluated through albumin excretion and/or impaired glomerular filtration rate - GFR) and atherogenic risk factors including dyslipidaemia, hyperuricaemia, elevated fibrinogen and left ventricular hypertrophy (24).

Moreover, different studies have demonstrated that an increase in body weight can lead to an increase of harmful effects on cardiovascular health, being obesity also marked as a major risk factor for CVDs. (12,26)

Smoking habits have been widely identified as a key factor for the increased risk for CVDs. (12,26) Interestingly, this fact has been reflected in the policies of several countries including Portugal, where measures that discourage tobacco use have been implemented in the last decade. (27,28)

The use of tobacco products has been related to CVDs such as fatal myocardial infarction and stroke. (29)

Also in another population-based case-control study in young people with incident acute myocardial infarction cases, a dose–effect response was present, and the odds favouring myocardial infarction reached an eight-fold increase for those that smoked more than 25 cigarettes per day compared to those who never smoked. (30)

The Portuguese National Health Survey (2014) identified a prevalence of smoking habits in about 20% of the Portuguese population (≥15 years or above), where from those 16.8% smoked daily. An increased consumption in male subjects (27.8%) was observed, compared to female (13.2%). (31)

Physical activity can improve modifiable metabolic risk factors, such as high-density lipoprotein cholesterol (HDL-C), total cholesterol, obesity, hypertension, and glucose metabolism and control, promoting a decrease in the risk of CVDs. (12,32) (32)

A Portuguese report about physical activity published in 2011 described a positive correlation in the amount of minutes per day of sedentary activity with individual´s age, verifying an average of 602±115 minutes per day for male and 580±112 for female older subjects. Only 9% of Portuguese subjects indicated to practice physical exercise regularly (at least 5 days a week) and 36% reported not to practice any kind of physical exercise. (33)

A protective effect for CVD mortality in healthy individuals can be reached through physical activity, which can be observed in subjects with isolated or in clusters risk factors, and those who have ≥ 1 metabolic risk factor may benefit from significant decreases in CVD mortality risk by practicing a light or moderate/vigorous activity (≥ 3 times/week). (34)

Improving global cardiovascular risk requires in most cases a multifactorial approach. For that reason, the National Program for Cardiovascular Diseases and the National Health Plan 2020 included as goals the global reduction of cardiovascular mortality, the reduction of early mortality and finally, the reduction of the global burden of disease and morbidity. (9,10)

1.1.2 Health System

The health of the Portuguese citizens is covered mainly by a public system (National Health System – NHS). There are some private healthcare providers in the health market, and some of those private institutions may have agreements with the NHS for the provision of health services.

The Portuguese NHS arose in 1979, whereby the Portuguese State guarantees the right to health protection for all Portuguese citizens, regardless of their economic situation. (35) The Portuguese State assumes the responsibility of defining and coordinating the Portuguese health policy.

The legislation that consolidates the bases of the Portuguese NHS was published in 1990, which included the rights and duties of the users of public health services. (36)

Two levels of care arose in the NHS: The primary health care includes health promotion, disease prevention and outpatient care, while the secondary/differentiated health care is related to hospital care, hospitalization, and specialized outpatient care. (35,36)

Over the last years, with the increase in longevity and in the number of chronic diseases, there has been a greater demand for health services in general.

Hence, several reforms have been placed with the aim of improving the accessibility of citizens to health services, since the existing services seem to be insufficient to meet the needs of the entire Portuguese population. (37)

Consequently, a number of private groups have emerged in the Portuguese healthcare market over the last decade in order to provide such health-related needs. (38)

In addition, some public-private partnerships by the Portuguese government were established, with the aim to fill the existing gaps in the response to the needs of the Portuguese patients.

Despite their original definition, primary health care centers are more centred in the treatment of diseases than in the primary level of health promotion. Human, material and physical resources are not sufficient for the services demanded by the Portuguese population. This situation worsened with the recent economic crisis, which has forced Portugal to strong fiscal restraint measures since 2010. Consequently, a decrease in health expenses has been registered since 2010, on a % above the average of the OCDE countries. (39)

To make matters worse, a decrease in the number of doctors per 100,000 inhabitants in primary health care was also verified in recent decades. (40)

The referral process of patients for specialized health care is slow and has some limitations, as well as its waiting list, which has been increasing in recent years. (41)

Recently, users from Portuguese primary health care units who participated in a satisfaction survey regarding these units and the services provided, scored as the weakest point the information provided for the procedures performed in hospital setting. (42)

Portuguese citizens often utilize private healthcare, particularly searching for specialized care. The use of these private healthcare may be fully borne by patients or reimbursed by patient´s private health insurance.

Accessibility to health care is variable according to the geographical area within the country. Areas with the lowest population density, where the inhabitants are older, are the places where accessibility is more limited. (41)

In the Portuguese territory we can find variations along the different regions in the absolute number of General Practitioners, and the ratio of General Practitioners per 100,000 inhabitants. In addition, the specialized care distribution is not uniform throughout the national territory. (41)

The region of Algarve together with Alentejo, both in the south of Portugal, presented the lowest concentration of medical specialists (41), as well as a lower average of medical consultations, when compared to the national average. (43)

Considering the health care provided to diabetic patients within the Portuguese National Health System (NHS) in primary care units, the Algarve region presented the lowest coverage rate of provided consultations (59.1%, 72.8% for Portugal). (44) It is important to note that a growth in the incidence rate of diabetes is expected to happen in the coming years (2016-2024) in Portugal. (45)

1.1.3 Medicines Use

In Portugal, it is the Ministry of Health that establishes the level of reimbursement for each medicine placed in the outpatient market. After this decision, the co-payment is decided according to 4 levels (A-90%, B-69%, C-37% and D-15%), according to several criteria such as the therapeutic indications of the medicine, its use, the entities that prescribe it, and with the levels of consumption for patients suffering from certain pathologies. (46)

The so-called special co-payment of medicines is provided for two types of situations, depending on the beneficiaries themselves or on the pathologies or special groups of users. For medicines integrated in the group A an increase of 5% in co-payment is added and in medicines from Group B, C and D an

increase of 15% is added for pensioners with low incomes (i.e, < 14 times the minimum monthly guaranteed payment). (46)

The co-payment attributed to the Portuguese citizens has been increasing during the last years, which may have been influencing their decision of purchasing or not the drugs prescribed, and consequently affecting their adherence to treatment and therefore, the expected health outcomes. (41)

Since 2010, in the context of reducing health expenses, the Portuguese Government has also implemented actions to decrease expenses with prescribed drugs, particularly costs at outpatient level. In the period between January and April 2016 the amount spent on medicines by the National Health Service was about EUR 400 million (about 52 million packages), 0.5% higher than the same period the previous year (2015). (47) The pharmacotherapeutic groups that represented a greater expense were "other antidiabetics" and "agents acting on the renin-angiotensin system", corresponding to the following drugs: metformin-vildagliptin, metformin-sitagliptina, rivaroxaban, fluticasone-salmeterol, glargine insulin, rosuvastatina, quetiapine, dabigatran, olmesartan medoxomil- hydrochlorothiazide and sitagliptin (Table 3). (47)

Table 3: Portuguese National Health System charges with drugs (Jan-April 2016).

Pharmacotherapeutic Group	Expenses by NHS (€)	Expenses (%)
Other oral antidiabetics	59.775.937	15.1
Agents acting on the renin-angiotensin system	33.719.830	8.5
Antithrombotic agents	28.422.782	7.2
Antipsycothics	22.792.090	5.8
Insulins	21.748.380	5.5
Antidyslipidemic agents	20.540.691	5.2
Antiepileptics and Anticonvulsants	15.168.894	3.8
Selective beta-2 adrenoreceptor agonists	13.454.942	3.4
Antidepressants	10.767.132	2.7
Others (Group 3.4.6)	10.621.660	2.7
Others Groups	159.133.824	40.2
Total	396.146.162	100.0

Legend: Group 3.4.6 - Cardiovascular System, Others; NHS – National Health System.

[Adapted from (47)*]*

Considering the number of packages dispensed, the 10 (ten) pharmacotherapeutic groups with higher dispensing number were those including mainly drugs acting in the cardiovascular system, central nervous system and in the alimentary tract and metabolism (Table 4). (47)

Table 4: Portuguese National Health System market analysis of number of medicines packages (Jan-April 2016).

Pharmacotherapeutic Group	Number of packages	%
Agents acting on the renin-angiotensin system	4.727.202	9.0
Antidyslipidemic agents	3.738.277	7.1
Anxiolytics sedatives and hypnotic	3.594.048	6.9
Other oral antidiabetics	3.025.944	5.8
Antidepressants	2.596.343	5.0
Gastric acid modifiers	2.429.463	4.6
Antithrombotic agents	2.306.187	4.4
Analgesics and antipyretics	1.646.894	3.1
Diuretics	1.439.842	2.7
Antiepileptics and Anticonvulsants	1.328.071	2.5
Other Groups	25.542.171	48.8
Total	52.374.442	100.0

[Adapted from (47)*]*

Throughout the year 2014, about 27.82 million of antihypertensive medicines, 10.62 million of antidyslipidemic medicines and 6.77 million of anticoagulants and antithrombotic (number of packages) were consumed in Portugal. About half of expenses on drugs of the cardiovascular group was within antihypertensive drugs (53.05%), and a quarter within antidyslipidemic dugs (26.69%). (9)

After the legislation change on the ownership of Pharmacy in 2007 (48), some medicines were also allowed to be dispensed in other stores, although exclusively the ones not subject to medical prescription (the so-called over the counter medicines - OTCs). In 2015, the most frequently dispensed drugs in

these stores were: paracetamol (14%), ibuprofen (5%), diclofenac (5%), chlorpheniramine/paracetamol (4%) and saccharomyces *boulardii* (4%). (49)

In January 2016, the Portuguese National Health System (NHS) showed a deficit of €259 million, being pharmaceutical products (medicines), products dispensed in Pharmacies, resources of diagnosis and complementary therapies, and public-private partnerships and capital expenditures, the items that were identified contributing to this great increase in expenses. (50)

Among the European countries, Portugal appears with one of the highest consumption of medicines, although the health outcomes are not better than those observed in other countries which present lower consumption and consequently lower costs. (51)

Besides direct expenses with medication, there are also indirect expenses. These can be attributed to the costs associated with adverse drug reactions (ADRs), including costs related to hospital admissions and other health care associated costs. (52)

Data from several prospective studies conducted in the USA, showed that ADRs are responsible for 15% of hospital admissions. (53) In Europe, a median rate of 3.5% was found for hospitalizations caused by ADRs, and 10.1% for ADRs during hospitalization. (54)

A Portuguese study, which analysed ADRs occurred in hospitals at Lisbon area, found an incidence of 11.1% for ADRs, being more than 50% avoidable. (55)

Another Portuguese study held in subjects visiting the urgency at Faro´s Hospital found that a negative result of pharmacotherapy was the cause of the visit in 53% of the subjects. (56)

Mortality can be a parameter associated to the use of medicines. In a tertiary Spanish hospital, about 10% of deaths were suspected of having been caused by drugs and in about 8% of deaths, drugs were suspected to have contributed. (57)

Also patient´s morbidity appears to be related with medicine´s use. In a study conducted in a Spanish tertiary care hospital, Pedrós *et al.* (2014) identified that only 4.2% of urgent hospitalizations were caused by ADRs, but that about 92 % of cases were predictable. (58)

ADRs may arise as a cause of hospital admission but also during hospitalization, and in that period the incidence of ADRs appears to be increased. (59)

Morbidity associated to drugs is also increased in patients with chronic conditions, such as the increase of hospitalizations induced by ADRs in patients with polypharmacy, particularly in elderly patients. (60,61) Considering this fact concerning the elderly population, Nair *et al.* (2016) already validated a score aimed to predict ADRs related hospitalization in subjects 65 years and older. (62)

The preventable drug-related morbidity has been pointed as a main cause of hospital admissions, leading to resource consumption and increased health costs. (52,63) In Portugal it was estimated that 43,000 patients are hospitalized unnecessarily every year. (63)

Prevention of drug-related morbidities is a complex process, and implies a multifactorial approach, either with intervention both at the organizational level and at the patient level. (64,65)

The additional costs for a longer length of stay attributed to ADRs in a group of American community hospitals were of $3.000 dollars on average and also an increment of 3.1 days in the length of hospitalization was achieved. (66)

In order to contribute to subject´s health care, it is necessary to include in the health system an activity that can contribute to medication management, and this could be the responsibility of the Pharmacist. Medication review can be a great contribution to the improvement of the responsible use of the medicines and may contribute to an optimization of the resources spent on health, particularly in the context of the pharmacological treatment.

1.2 Pharmaceutical Care

In recent decades, the pharmaceutical profession has evolved to be more patient-oriented. (67,68) The concept of "Pharmaceutical Care" appeared in the United States of America, being first presented by Mikeal *et al.* in 1975, and defined as "*the care that a given patient requires and receives which assures safe and rational drug usage*". (69)

Latter, Brodie *et al*. introduced a new definition targeted to the patient, adding the identification of patient needs related to pharmacotherapy, and the provision of the necessary service before, during and after the treatment. (70)

In 1990, Hepler & Strand published what was a milestone in the concept of Pharmaceutical Care, defining it as "*the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life*". A new role was identified for the Pharmacist, including collaboration with the patient and other health professionals in the implementation and monitoring of the therapeutic plan, becoming aware of these professionals' responsibility in morbidity and mortality related to drugs. The following outcomes were expected: identifying potential and actual drug related problems (DRPs); resolving actual DRPs; and preventing potential DRPs. (71)

Also the American Society of Hospital Pharmacists (ASHP), published in 1993 its position on the concept of Pharmaceutical Care, defining it very similarly to Hepler & Strand. (72)

In that same year (1993), the International Pharmaceutical Federation (FIP) signed a document dedicated to Pharmaceutical Care enhancing the awareness for the importance of the Pharmacist role. The document showed the need for the Pharmacist's integration in multi-professional health teams and to develop standard operation procedures for developing programs in this area, which included identification and monitoring of therapeutic outcomes, evaluation and assessment of drug related problems. The Pharmacist was assigned with an important role, not only in the individual patient but also within the community. (4)

In 1994, a group of European researchers devoted to the subject, founded the Pharmaceutical Care Network Europe (PCNE), a network dedicated to the development of Pharmaceutical Care in the daily practice, aiming to contribute to the development of improved pharmaceuticals based practice. (73)

The book “Pharmaceutical Care Practice”, published by Cipolle, Strand and Morley in 1998, focused increasingly on the patient. (74) A second edition was published in 2004, further enhancing the Pharmacist's role in optimizing pharmacotherapy (resulting from medical prescription and others) in order to improve outcomes and patient quality of life by integrating a multidisciplinary team. (75) In the third edition (2012), the authors added to the previous definition “*the goal of achieving positive outcomes for the patient's health*”. (76)

In 1999, a group of Spanish researchers introduced the concept of “*Atención Farmacéutica*”, the corresponding process to Pharmaceutical Care raised by Strand *et al*., having the goal of "*achieving appropriate, effective and safe pharmacotherapy for all patients*”, that included not only the content of the Pharmaceutic Care, but also the analysis of two modalities of Pharmaceutic Care: global and at-risk-group. (77,78)

In 2001, the Spanish Department of Pharmacy and Health Products published a document with the concepts regarding Pharmaceutical Care, called Pharmaceutical Attention and defined as “*active participation of the pharmacist in the assistance of the patient through the dispensation and monitoring of pharmacotherapeutic treatment in co-operation with doctors and other health service staff, in order to achieve results that improve the patients quality of life*”. A set of clinical activities were included in this concept: the indication of drugs that do not require a prescription, disease prevention, health education, pharmacovigilance, personalized pharmacotherapeutic monitoring and all others that are related to the rational use of drugs. According to their definition, the pharmacotherapeutic monitoring should include “*the detection, prevention and solution of Adverse Drug Reactions (ADR)*”. (79)

In 2013, the Pharmaceutical Care Network Europe (PCNE) together with other Pharmacists experts in Pharmaceutical Care from several European countries,

USA and Australia, established Pharmaceutical Care as "*the pharmacist's contribution to the care of individuals in order to optimize medicines use and improve health outcomes*". (80)

1.2.1 Pharmaceutical Services

Pharmaceutical Services have been defined as "*those relating to drug therapy including pharmaceutical care services, medication management services, clinical services and cognitive pharmaceutical services*". (81)

Some authors defend that clinical pharmacy include two main service´s areas: services to monitor and identify risk factors in the process of medicine´s use (dispensing of drugs, preventable morbidity indicators, medication review) and services to act reactively (pharmacotherapy follow-up and disease management). (5)

Nevertheless, the terminology used at the level of the pharmaceutical services it's not consensual, becoming therefore important to define the content and the definitions used in each research project and considered in the services provided. (82)

The inclusion of the Pharmacist within the primary care team or in the community pharmacy has been recommended in the referral-consultation process, as an asset in the process of medicine´s use by the patients. (83)

The assessment of Pharmacist´s Interventions (PI) on the results of published studies is not performed consistently and comprehensively in several fields, being the clinical domain the most reported and more systematically used. (84) Other scopes such as humanistic, economic, and process-related aspects are often omitted, incomplete, or ambiguous in most tools. (84)

A systematic review conducted by Aguiar *et al*. (2016) identified a positive effect of the Pharmacist interventions in the accomplishment of type 2 diabetic patients to achieve glycemic control, namely on the HbA1c target value,

verifying a greater homogeneity between randomized controlled trials (RCTs) conducted in the United States with a baseline value for HbA1c of 9%. (85)

Some studies showed a positive impact on adherence, clinical and humanistic outcomes, while health care utilization and costs were less assessed (n=15, 23.4%). (86) Other studies didn´t achieved a statistical significant improvement from the Pharmaceutical Care, as shown in the results of the RESPECT trial, considering no significant changes reached in the appropriateness of prescribing or quality of life in older patients included in this trial. (87)

In Portugal, the studies carried out within the Pharmaceutical Care scope are still few and these services are not carried out systematically. In addition, the partnership with health institutions and other health professionals are still scarce and punctual. The public health system does not yet include, to date, these services in a formal and contractual model. (6)

Nevertheless, a couple of studies have been already carried out in this area, both in private and public health´s institutions, and performed within academic research projects. (6)

An intervention study was conducted in type 2 diabetes patients in a Portuguese primary health care center, to evaluate the impact of a medication follow-up program on clinical and humanistic outcomes. (88)

A prospective randomised controlled trial, developed in a Portuguese secondary care hypertension/dyslipidemia outpatient clinic in the university teaching hospital of Cova da Beira Hospital Centre, showed a positive impact of the pharmaceutical care program, finding a significant improvement in blood pressure control (for systolic blood pressure: -6.8 mmHg, p=0.006; for diastolic blood pressure: -2.9 mmHg, p=0.020) and medication adherence (74.5% *vs.* 57.6%, p=0.012) in patients treated with antihypertensive agents. (89)

Published in 2010, a study was performed with the main goal of exploring the acceptability to users of pharmaceutical care provided in Portuguese community pharmacies. The results evidenced a trusting and collaborative relationship where the Pharmacist was seen as a health care provider, despite the fact that

patients were not able to identify clear expectations about the service, neither in terms of the Pharmacist's role or their expected outcomes. (90)

The American College of Clinical Pharmacy defined "Clinical Pharmacy" as "*that area of pharmacy concerned with the science and practice of rational medication use*", and is inserted within the philosophy of Pharmaceutical Care. The clinical Pharmacist is recognized as an expert in the therapeutic use of medications and to provide therapeutic evaluations and recommendations. (91)

In 2010 a research group presented a broad hierarchical model for Cognitive Pharmaceutical Services including the following sections: medicines information; compliance, adherence and/or concordance; disease screening; disease prevention; clinical intervention or identification and resolving drug related problems; medication use reviews; medication management/medication therapy management (which includes home medication reviews, residential care home medication reviews and medication reviews with follow up); disease state management for chronic conditions; participation in therapeutic decisions with medical practitioners (in clinical setting and/or in the pharmacy); and prescribing (supplement or independent). (92)

A systematic search for systematic reviews, following the recommendations of the Cochrane Collaboration, identified eight categories of clinical services: patient counselling, risk factors prevention and control, adherence/compliance, medication review, pharmacotherapy follow-up, medication reconciliation, information to Physicians or the health care team and prescription of new treatments. (93)

Despite the different nomenclatures and definitions of clinical pharmaceutical services, the main goal lies in improving the medicine´s use process and clinical, humanistic, and economic outcomes.

1.3 Medication review

A single and worldwide definition for medication review (MR) does not exist. For different countries, depending on their health care policies and professional operating, MR could involve different inclusion criteria, procedures and also outcomes.

However, several countries such as Australia, Canada, New Zealand, United Kingdom and United States of America have developed and implemented medication review systematically under the Pharmaceutical Care programs. (94)

1.3.1 Pharmaceutical Care Network Europe (PCNE)

In Europe, the PCNE group has discussed and presented for the first time in Leuven (2012) a definition and levels of pharmacist-led medication review. During the following PCNE meetings this matter was being addressed and some changes were made, as a result of the evidence provided by research groups from several countries [Berlin (2013), Malta (2014) and Mechelen (2015)]. In 2012, PCNE published a definition for MR that includes "*an evaluation of a patient's medicines with the aim of optimizing the outcomes of medicine therapy*", that involve "*identifying the risks, detecting medication-related problems and suggesting solutions*". (95)

The latest PCNE definition of medication review (2016) describes MR as "*a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes*", including "*detecting drug related problems and recommending interventions*". Prescribed medicines (including devices) and products over-the-counter (OTC´s) or obtained in other locations are all included in "patient´s medicines", and "optimising" refers to effectiveness, quality of life, efficiency and safety, in order to improve clinical, economic and humanistic outcomes relative to the previous parameters. Identification of drug-related problems (DRPs) is expected (actual or potential), as well the recommended interventions (although follow-up is not included). (96)

Pharmaceutical Care Network Europe considers actually four (4) types of MR, as described in Table 5.

Table 5: Types of Medication review (MR) according PCNE.

MR Type	Sources of information	Possible Outputs
Type 1 Simple	Medication history	Drug interactions Some side-effects Unusual dosages and adherence issues
Type 2a Intermediate	Medication history Patient interview	Drug interactions Some side-effects Unusual dosages Adherence issues Drug-food interactions Effectiveness issues Side effects Problems with OTC
Type 2b Intermediate	Medication history Patient interview Clinical data	Drug interactions Some side-effects Unusual dosages Adherence issues Drug-food interactions Effectiveness issues Indication without a drug Drugs without indication
Type 3 Advanced	Medication history Patient interview Clinical data	Drug interactions Some side-effects Unusual dosages Adherence issues Drug-food interactions Effectiveness issues Side effects Problems with OTC Indication without a drug Drugs without indication Dosage issues

Legend: MR - Medication Review; OTC - Over-the-counter medicines; PCNE – Pharmaceutical Care network Europe.

[Adapted from (80,96)*]*

According to a cross-sectional European wide online survey (2014), about 64% of the 25 European countries indicated having at least one type of medication review procedure in their country, but a low rate of type III clinical medication

reviews was achieved, being established in only 6 countries (Croatia, Denmark, Finland, Netherlands, Spain and Sweden). (97)

1.3.2 United States of America

The Medicare Modernization Act (MMA), in the United States America (2003), was created to help the Medicare beneficiaries to afford the increasing cost of prescription drugs, and the use of "Medication Therapy Management (MTM)" programs were developed to contribute to an appropriate and cost-effective drug use among beneficiaries, targeted to patients with multiple chronic diseases taking multiple medications. (98)

In 2004, a group of American Associations assembled and reached the definition of Medication Therapy Management (MTM) services as being "*a distinct service or group of services that optimize therapeutic outcomes for individual patients*", which was not focused on individual medicines. (99)

Later, in 2008, a new version included a set of services that should be provided according to the individual needs of patients (Table 6). (99)

Table 6: Medication Therapy Management (MTM) services.

MTM Services
▪ Performing or obtaining necessary assessments of the patient's health status ▪ Formulating a medication treatment plan ▪ Selecting, initiating, modifying, or administering medication therapy ▪ Monitoring and evaluating the patient's response to therapy, including safety and effectiveness ▪ Performing a comprehensive medication review to identify, resolve, and prevent medication-related problems, including adverse drug events ▪ Documenting the care delivered and communicating essential information to the patient's other primary care providers ▪ Providing verbal education and training designed to enhance patient understanding and appropriate use of his/her medications ▪ Providing information, support services, and resources designed to enhance patient adherence with his/her therapeutic regimens ▪ Coordinating and integrating MTM services within the broader health care management services being provided to the patient
Legend: MTM – Medication Therapy Management.

[Adapted from (99)*]*

Some MTM services were included in health services of the public sector (Medicaid and Medicare Part D plans) that adopted a comprehensive medication therapy review service (MTR), as well in the private sector (insured groups, managed care populations, self-insured employers, and self- paying individual patients). These MTM services should be provided by Pharmacists, in collaboration with the patient, the Physician and other health professionals. Five core elements were included in the MTM services in the pharmacy practice: Medication therapy review (MTR), Personal medication record (PMR), Medication-related action plan (MAP), Intervention and/or referral, and Documentation and follow-up. (99)

The MTM has been pointed as a positive contribution to medication appropriateness or drug therapy regimens, although these benefits were not always converted into improvements in health or costs, leaving the recommendation for the future determination of which points of MTM that really contribute to health outcomes. (100) In this review, 44 studies were analysed, including 21 trials and 4 non-randomized controlled studies, where 28 had a medium, low, or mixed risk of bias. MTM services were considered effective for adults with one or more chronic diseases who were taking prescription medications regarding intermediate outcomes (such as biometric and laboratory measures, drug therapy problems identified, drug therapy problems resolved, medication adherence, goals of therapy met, and patient engagement in medication management), patient-centered outcomes (such as disease-specific morbidity, disease-specific or all-cause mortality, adverse drug events, health-related quality of life, activities of daily living, patient satisfaction with health care, work or school absenteeism, and patient and caregiver participation in medical care and decision making), and resource utilization (such as prescription drug costs, other health care costs, and health care utilization). (100)

Effectively, MTM comprises a set of distinct services. One is Medication Therapy Review (MTR) that comprises conducting a “Comprehensive Medication Review (CMR)”, by a Pharmacist. This review should include a

structured analysis based on the patient as a whole. Previous to the CMR, patient´s consent must be obtained, then a "Personal Medication Record" and a "Medication List" should be achieved. Then, a copy should be delivered to the patient to be shared with the Physician or caregiver and to maintain a current record of medication, respectively. During interview, Medication Related Problems (MRP´s) should be identified (including adherence), and a "Medication-related Action Plan (MAP)" should be developed in order to solve problems or to prevent its occurrence. After MTR a referral to other healthcare professionals may be required. The frequency of this service is a CMR per year, and the eligibility criteria are described in Table 7. The need for a MTM can be identified either by a Pharmacist, Physician or other healthcare professionals. (99,101)

Table 7: Eligibility criteria for Medication Therapy Management (MTM).

Eligibility Criteria	▪ Patient has experienced a transition of care, and his or her regimen has changed ▪ Patient is receiving care from more than one prescriber ▪ Patient is taking five or more chronic medications (including prescription and non-prescription medications, herbal products, and other dietary supplements) ▪ Patient has at least one chronic disease or chronic health condition (e.g., heart failure, diabetes, hypertension, hyperlipidaemia, asthma, osteoporosis, depression, osteoarthritis, chronic obstructive pulmonary disease) ▪ Patient has laboratory values outside the normal range that could be caused by or may be improved with medication therapy ▪ Patient has demonstrated non-adherence (including underuse and overuse) to a medication regimen ▪ Patient has limited health literacy or cultural differences and therefore requires special communication strategies to optimize care ▪ Patient wants or needs to reduce out-of-pocket medication costs ▪ Patient has experienced a loss of or significant change in health plan benefit or insurance coverage ▪ Patient has recently experienced an adverse event (medication- or non–medication-related) while receiving care ▪ Patient is taking high-risk medication(s), including narrow therapeutic index drugs (e.g., warfarin, phenytoin, methotrexate) ▪ Patient self-identifies and presents with perceived need for MTM services *Additional targeted MTRs for new or ongoing medication-related problems, or further significant changes in patient´s health status or conditions*

[Adapted from (99,101)*]*

In 2013, the most common MTM activities/services reported by providers included: creation of a personal medication record/list (63%), providing an intervention/recommendation to prescriber (59%) and conducting a CMR (58%). (102)

1.3.3 Australia

The Pharmaceutical Society of Australia recognizes two types of MR: basic and comprehensive, wherein the first is the process that occurs during the dispensing of drugs at the pharmacy counter, and the second is a structured and collaborative service provided by Pharmacists and General Medical Practitioners (GPs). (103)

Since July 2015, four types of services are included in the Community Pharmacy Programmes in the scope of "Medication Management Programmes" which aims to "*support quality use of medicines services that are designed to reduce adverse medicine events and associated hospital admissions or medical presentations*": Clinical Interventions, Home Medicines Reviews (HMR), Residential Management Medication Reviews (RMMR), MedsCheck and MedsCheck Diabetes. The service referred as "Clinical Interventions" has a focus on intervention to resolve and document drug-related issues that are identified within community pharmacy. The others services have a main goal of enhancing quality use of medicines and reduce the number of adverse medicines events, and are to be held in the following locations respectively: patient´s home, aged care facilities and community pharmacies. (104)

In programmes that cover a medication review, a clinical medication review is performed, established as "*a structured and collaborative service aimed at identifying and resolving medication-related problems (MRPs)*". (105)

In the MedsCheck service, a comprehensive medication review is not completely performed as in HMR and RMMR, and only the available data at the time of consultation is considered.

The services described are performed by a registered Pharmacist or accredited Pharmacist (Table 8). (105–107)

Table 8: Description of Medication Review services available in Australia.

Service	Eligibility Criteria	Frequency	Referral
Home Medicines Review (HMR)	▪ Patient is living in a community setting; ▪ Currently taking five or more regular medicines ▪ Taking more than 12 doses of medicine per day ▪ Experiencing significant changes to their medicine regiment (in the last three months) ▪ Recently discharged from hospital ▪ Taking medicine with a narrow therapeutic index or that requires therapeutic monitoring ▪ Experiencing symptoms suggestive of an adverse medicine reaction ▪ Having difficulty managing their own medicines because of low level literacy and language skills or impaired sight ▪ Attending a number of different doctors, both General Practitioners and specialists *Att: Not available to in-patients of public or private hospitals, day hospital facilities, transition care facilities or to residents of a Government Funded Facility*	One each 24 months, except for a list of situations: ▪ Discharge from hospital after an unplanned admission in the previous four weeks; ▪ Significant change to medication regimen in the past three months; ▪ Change in medical condition or abilities (including falls, cognition, physical function); ▪ Prescription of a medicine with a narrow therapeutic index or requiring therapeutic monitoring; ▪ Presentation of symptoms suggestive of an adverse drug reaction; ▪ Sub-therapeutic response to therapy	Pharmacist; consumer or their carer; GP or other healthcare provider
Residential Medication Management Review (RMMR)	Patient is a permanent resident of: ▪ An Australian Government funded ACF, as defined by the *Aged Care Act* (1997); or a MPS facility ▪ Patient is a resident in an Australian Government funded transition care facility for more than 14 consecutive days	One each 24 months, except for the list of situations identified for HMR and: ▪ Suspected non-compliance or problems with managing medication related devices *Att: must be done within 90 days of the date of the referral to be remunerated*	Pharmacist; consumer or their carer; GP or other healthcare provider

Table 8 *(Continued)*

Service	Eligibility Criteria	Frequency	Referral
MedsCheck	▪ Living at home in a community setting ▪ Has not received a MedsCheck, Diabetes MedsCheck, Home HMR or RMMR in the previous 12 months ▪ Taking five or more prescription medicines ▪ Had a recent significant medical event (a recent event or new diagnosis that has the potential to impact on the consumer's medication adherence or knowledge of their medicine regime and may increase the risk of medication misadventure)	One each 12 months	Pharmacist; consumer or their carer; GP or other healthcare provider
MedsCheck Diabetes	▪ Living at home in a community setting ▪ Has not received a MedsCheck, Diabetes MedsCheck, HMR or RMMR in the previous 12 months ▪ Type 2 diabetes diagnosed within the past 12 months and unable to gain timely access to existing diabetes education /health services in their community ▪ Type 2 diabetes is less than ideally controlled and unable to gain timely access to existing diabetes education /health services in their community.	One each 12 months	Pharmacist; consumer or their carer; GP or other healthcare provider

Legend: ACF: Australian Conservation Foundation; DVA: Department of Veterans´ Affairs; GP – General Medical Practitioners; MPS: Medication Packaging Systems Australia Pty Ltd.

Adapted from [(105–107)*]*

All the services outputs should include a medicines list of patient´s current medication and an action plan including goals and actions agreed by the patient and any agreed follow-up with the patient's GP and/or other healthcare provider(s) (Table 9).

Table 9: Outcomes from the Medication Review services in Australia.

Service	Process	Outcomes
Home Medicines Review (HMR)	▪ Patient interview ▪ Clinical assessment ▪ Written report to the referring GP and patient´s community Pharmacy choice	Findings: ▪ Medicine use without indication ▪ Untreated indication ▪ Drug selection ▪ Sub-therapeutic dosage ▪ Over dosage ▪ Continued use of medicine for a condition that has resolved or step down therapy for a condition that is well controlled ▪ Adverse drug reactions ▪ Drug interactions (patient has a medical issue that is the result of a drug-drug, drug – disease, drug-food or drug-laboratory test interaction); ▪ Failure to receive medicine ▪ Dose/drug related issues (confusing dosage schedules, incomplete or missing directions, duplication of medicines, disposal of unwanted or expired drugs, storage issues, problems with brand substitution or duplication, dose forms, dosing interval, route of administration or timing of dosing) ▪ Patient medication management issues (continuing ceased medicine, incorrect medicine use, signs of adherence issues, swallowing difficulties, dexterity issues, confusion or misunderstanding of medicine purpose or use) ▪ Determination of correct use and suitability of, or the need for, compliance aids, therapeutic devices and appliances ▪ Identification of the need for written/verbal information and education for the consumer regarding safe and effective use of medicines, therapeutic devices, compliance aids and self-care activities, which may include CMI leaflets

Table 9 *(Continued)*

Service	Process	Outcomes
MedsCheck and MedsCheck Diabetes	▪ Patient interview ▪ Clinical assessment with available data ▪ Written report to the referring GP and patient´s community Pharmacy choice	▪ Patient´s concerns and beliefs about their medicines ▪ Medication adherence assessment ▪ Patient´s education needs including providing written information to support improved understanding and use of medicines ▪ Drug-related problems that have been identified from the information available at the time of providing the service, using DOCUMENT ▪ Provide patients education and guidance on correct use of medication/monitoring devices ▪ Discuss with patients the management of chronic condition(s) including lifestyle factors related to medicine use and self-management

Legend: CMI – Consumer medicine information; GP – General Medical Practitioners.

[Adapted from (105,107–109)*]*

1.3.4 Canada

Medication review services are available in the state of Ontario (Canada) since 2007, as a programme in the scope of Pharmaceutical Care. The MedsCheck programme was established with the aim of helping patients "*to better understand their medication therapy and to ensure their medications are taken as prescribed and that patients are getting the most benefit from their medications*" by conducting a medication review. (110,111)

Eligibility criteria for medication review programmes are not uniform all over the world, even within a country such as Canada that has implemented this service in the Ontario province, other programs are underway in other provinces with inconsistent and highly variable criteria. The eligibility criteria for MedsCheck programmes in Ontario are described in Table 10, and this

includes conducting an interview held by a Pharmacist registered in part A (Pharmacists who provide direct patient care) of the OCP (Ontario College of Pharmacists) or a registered pharmacy intern/registered pharmacy student under the direction of the Pharmacist. MedsCheck programs are accessible to Ontario´s resident with a valid Ontario Health Card, and that agree to participate voluntarily. (112)

Table 10: Description of MedsCheck programmes available in Ontario (Canada).

Program	Eligibility Criteria	Frequency	Referral
MedsCheck	▪ Taking a minimum of 3 prescription medications for a chronic condition ▪ Eligible for a MedsCheck Follow-Up (annual): ○ Discharged from the hospital within the previous 2 weeks ○ A Pharmacist's documented decision due: significant changes made to an existing medication profile or the addition of new medication ○ Documented evidence of patient non-compliance ○ Patient changed their residence and transferred their prescriptions to other pharmacy ○ A planned hospital admission	One review per year	Pharmacist, Physician or Nurse
MedsCheck for Ontarians living with Diabetes	▪ Individuals diagnosed with type 1 or type 2 diabetes and taking 1 or more medications for treating diabetes	One review per year, a follow-up review can be performed	Pharmacist, Physician or Nurse
MedsCheck at Home	▪ Individuals taking a minimum of 3 prescription medications for a chronic condition and unable to present to the community pharmacy	One review per year	Pharmacist, Physician or Nurse
MedsCheck for Long Term Home Residents(LTC)	▪ Individuals resident in a licensed long-term care home ▪ Annual: Chronic multiple conditions, multiple medications, or requiring medications with a narrow therapeutic index or requiring therapeutic drug monitoring	A quarterly medication review and an annual interdisciplinary medication review	Pharmacist, Physician or Nurse

[Adapted from (111,113–115)*]*

The Pharmacist conducting a MedsCheck will elaborate the *MedsCheck Personal Medication Record*, that should be shared with the patient, his primary care provider (Physician, Nurse), and other people as agreed with the patient, with the outcomes (Table 11). For diabetic patients under MedsCheck for Diabetes program, a *Diabetes Education Patient Take-Home Summary* must be also delivered to the primary care provider. (116)

Table 11: Outcomes from MedsCheck programs.

MedsCheck	**MedsCheck for Long Term Home Residents (LTC)**
Drug therapy problems (DTPs): ▪ Therapeutic duplication; drug may not be necessary ▪ Requires drug; needs additional drug therapy ▪ Suboptimal response to a drug; Dosage too low; Adverse drug reaction ▪ Dangerously high dose; potential overuse; abuse; Non-compliance/adherence ▪ Other DTPs requiring further assessment or consult patient´s prescriber ▪ Follow-up measures including potential dates for subsequent Pharmacist communication and/or visits ▪ Referral services that might include Heart and Stroke, Alzheimer Society, Homecare, Diabetes Education Centres, or other	**Annual:** In-depth medication review as for other programs. **Quarterly** Information including: ▪ Medication selection, dosage, hours and route of administration, duration of therapy, treatments, allergies, drug-drug and drug-food interactions ▪ Identification of DTPs that may require a more in-depth therapy analysis (annual review) and follow-up ▪ Address prescribing protocols in the best interest of patient care

[Adapted from (116) *]*

1.3.5 New Zealand

In New Zealand, several services are available in community pharmacies under the scope of "Medicines Management Services" (Table 12). (117)

The long-term conditions (LTC) service is focused on optimising the supply and use of prescribed medicines and to manage patient´s adherence, while medicines use review (MUR) is a systematic assessment, orientated to the patient´s understanding of medicines and adherence. Medicines therapy assessment (MTA) is defined as "*a systematic, patient-centred clinical assessment of all medicines currently taken by a patient, identifying, resolving and preventing medication-related problems as well as optimising the effectiveness of medication treatment*", whilst comprehensive medicines management (CMM) is a service provided by an autonomous Pharmacist integrated in a healthcare team in order to provide support and advice about patient´s medication management with complex clinical needs. (117)

Table 12: Medicines Management services available in New Zealand.

	Medicines Adherence		**Medicines Optimisation**	
	Level 1	Level 2	Level 1	Level 2
Service	Long-Term Conditions (LTC)	Medicines Use Review (MUR)	Medicines Therapy Assessment (MTA)	Comprehensive Medicines Management (CMM)
Goal	Optimise supply and use of medications	Optimise medication understanding and adherence	Optimise medication efficacy	Optimise management of prescribed medications

[Adapted from (117)*]*

Considering the two available services including a systematic assessment of all medicines used by the patients, there are specific eligibility criteria for these services (Table 13).

Table 13: New Zealand: Medicines use review (MUR) and Medicines therapy assessment (MTA) eligibility criteria and outcomes.

	Eligibility Criteria	Outcomes
Medicines Use Review (MUR)	▪ Patients living independently in the community who have one or more chronic disease states and meet one or more of the following conditions: ▪ Taking three or more medicines and/or 12+ doses per day ▪ Multiple prescribers ▪ Have had a recent admission to hospital (especially if there was a medicine change) ▪ Taking or about to commence taking medicine(s) with a high risk of adverse effects, narrow therapeutic index and/or requires therapeutic monitoring, or is suspected of being inappropriately used ▪ Have a particular medicine related problem e.g. adverse reaction, nonadherence ▪ Are non-adherent or unable to manage their medicines ▪ Have literacy or language difficulties, dexterity problems, impaired sight, or cognitive deficiencies that impact on their ability to manage medicines	▪ Medicines Information ▪ Synchronisation of al medicines prescribed to patient ▪ Reminders in order to improve adherence ▪ Adherence support ▪ Medication Management Plan to improve medicine´s adherence ▪ Dispensing services, with dispensing frequency tailored to patient´s need ▪ Detailed assessment of level of understanding of prescribed treatment and supplementing knowledge gaps as required ▪ Assessment of level of adherence to prescribed medications and reasons or behaviours behind non-adherence ▪ Action plan with the patient to address adherence issues ▪ Formal referral and report to other health professionals ▪ Removal of out of date medicines and medicines that are no longer required (with permission) ▪ Provision of health behaviour changing strategies aimed at improving lifestyle factors

Table 13 *(Continued)*

	Eligibility Criteria	Outcomes
Medicines Therapy Assessment (MTA)	▪ Patients who have <u>one or more chronic disease state</u>, <u>two or more co-morbidities</u>, and meet <u>one or more</u> of the following conditions: ▪ Taking 4 or more medicines and/or 12+ doses per day ▪ Increased risk of medicine-related problems ▪ Experiencing or are at risk of experiencing sub-optimal response to pharmacotherapy ▪ Experienced significant changes in their medicine regimen during the last 3 months ▪ Taking or about to commence taking one or more medicines with a high risk of adverse effects ▪ Have signs/symptoms of a medicine adverse effect ▪ Taking medicine(s) with a narrow therapeutic index and/or requires therapeutic monitoring, where sub-therapeutic or toxic effects are suspected	*All the outcomes from MUR, added to the following*: ▪ Assessment of the level of adherence in the context of the potential effect on clinical outcomes ▪ Assessment of clinical status based on all available information, including clinical notes ▪ Review appropriateness of therapy and compare against alternative therapy options as appropriate ▪ Review cost-effectiveness of therapy ▪ Identify and evaluate actual and potential medicine therapy problems ▪ Negotiate treatment goals and timelines for attainment of goals with both patient and medical practitioner ▪ Reporting of suspected significant adverse medicine effects ▪ Formulate and document a pharmaceutical care plan ▪ Contribute to multidisciplinary team on the formulation and documentation of a comprehensive care plan, and to assist the team in modifying the care plan based on regular assessment of the patient's status ▪ Provision of health behaviour changing strategies aimed at improving lifestyle ▪ Recommend therapeutic medicine monitoring using target concentration intervention as appropriate ▪ Provide accurate and timely medicines information to health professionals and patients

[Adapted from (117)*]*

1.3.6 United Kingdom

Medication Review was incorporated in the General Medical Services contractual requirements in 2004 (118), in community pharmacy contracts in England and Wales since 2005 as "Medicines Use Reviews" and in Scotland since 2010 as "Chronic Medication Service" (119). The service of medication review appears to be pointed as an important tool to improve medicines use, contributing to manage polypharmacy, particularly in elderly patients and also to increase medication adherence. (119)

A UK partnership, in 2002, defined Medication review (MR) as "*a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication related problems and reducing waste*". Four levels of MR were identified in this document: level 0 (Ad hoc: an unstructured opportunistic review), level 1 (prescription review: a technical review of a list of patient´s medicines), level 2 (treatment review: a review of medicines with patient´s full notes) and level 3 (clinical medication review: face-to-face review of medicines and condition with the patient). (120)

Since some services in this area such as Medicines Use Review (MUR), a service provided in the community pharmacy, didn´t accomplish the levels defined in the previous document, a new document was published in 2008. (121) Three types of MR were then identified, replacing the previous defined in 2002, which were the following: Type 1 (prescription review), Type 2 (concordance and compliance) and Type 3 (clinical medication review). Only on Type 3, the patient´s presence was mandatory and there was access to patient´s clinical notes. In this service of medication review all participants should be included in the process (patient, Physician, Pharmacist and other health professionals), and should be conducted including all prescribed medicines, OTC´s and complementary medicines. (121)

The service of “Medicines Use Review” was introduced formally in 2005, and since then some changes arouse, introducing one of the most relevant in 2011, being the addition of target groups. (122)

In 2013, the Pharmaceutical Services Negotiating Committee (PSNC), a representative of NHS Pharmacy contractors, and NHS employers have published a guidance on “Medication Use Review”, clarifying several points, and actually service works as described in the Table 14. (123–125)

Table 14: Medicines Use Review (MUR) service characterization.

Prg	Eligibility criteria	Frequency	Referral
Medicines Use Review (MUR)	▪ Patients taking at least one "High risk medicine": NSAIDs, anticoagulants (including low molecular weight heparin), antiplatelets or diuretics; ▪ Patients taking two or more medicines for respiratory disease (adrenoreceptor agonists, antimuscarinic bronchodilators, theophylline, compound bronchodilator preparations, corticosteroids, cromoglicate and related therapy, leukotriene receptor antagonists and phosphodiesterase type-44 inhibitors). ▪ Patients recently been discharged from hospital who had changes made to their medicines while they were in hospital. Ideally patients discharged from hospital will receive an MUR within four weeks of discharge but in certain circumstances the MUR can take place within eight weeks of discharge. Prescribed two or more medicines to be eligible for a post-discharge MUR ▪ Patients at risk of or diagnosed with cardiovascular disease and regularly being prescribed at least four medicines: one or more medicines for CV/CV risk conditions (Coronary heart disease, Diabetes, Atrial fibrillation, Peripheral arterial disease, Renal/chronic kidney disease, Hypertension, Thyroid disorders, Heart failure, Stroke/TIA, Lipid disorders), with a prescription of at least one medicine from Chapters 2 (cardiovascular), 6.1 (diabetes) or 6.2 (thyroid) of the BNF. To be included the MUR target group patients must also be regularly prescribed four or more medicines in total. ▪ *MUR only provided to patients who have been using the pharmacy for the dispensing of their prescriptions for the previous three months.*	No more than one consultation in 12 month period, unless: ▪ Pharmacist opinion ▪ Recently discharged from hospital.	Other health-care professionals, patients

Legend: BNF - British national formulary; CV – Cardiovascular; NSAIDs - Nonsteroidal anti-inflammatory drugs; Prg – Program; TIA - Transient ischemic attack.

[Adapted from (123–125)*]*

According to PSNC data, during the year of 2015 (January – December) about 82.51% of Pharmacies were conducting MUR, in which about 11.639 Pharmacies were submitting reimbursement claims for each of the months during this period. (126)

Last update of Pharmacy contractual framework occurred in January 2015 and included new advanced services as "New Medicine Service (NMS)" focused in the use of new medicines for the patient, including a close personalized monitoring of the patient and dispensing information about medicines (at dispensing time, four nights after and until 21-28 days after the beginning of treatment) (127); "Stoma appliance customisation service" dedicated to patients using stoma appliance, to promote a proper use and improve the duration of use; "Appliance Use Review Service" as a service of medication review performed at patient´s home. (128) The MUR service has been defined as a structured and documented process, also to allow evaluation of the effectiveness of the service (Table 15). (129,130)

Table 15: Medicines Use Review (MUR) inputs and outputs.

	Inputs	Outputs
Medicines Use Review (MUR)	Review: ▪ Effectiveness of treatment; ▪ Appropriateness of treatment based on latest evidence; ▪ Adverse drug effects; ▪ Test results, interpreting them and acting on them where required; ▪ Whether the recommendations of previous reviews have been acted upon; ▪ Recommend new treatments, e.g. aspirin or statins in CHD patients; ▪ If the Pharmacist is a prescriber they would be able to make changes to the patient's treatment as agreed with the doctor.	Medicines-related problems: ▪ Patient not using a medicine as prescribed (non-adherence) ▪ Problem with pharmaceutical form of a medicine or use of a device ▪ Patient reports need for more information about a medicine or condition ▪ Patient reports side effects or other concern about a medicine ▪ Other (free text information can be entered in the clinical record)

Legend: CHD – Coronary heart disease.

[Adapted from (129,130)*]*

MUR´s outcomes must include a plan of actions which comprises: information/advice provided, yellow card report submitted to Medicines and Healthcare Products Regulatory Agency (MHRA), patient's issues raised with the medicine needed to be considered by the GP practice or another primary health care provider.

1.3.7 Other models

A randomized controlled trial was conducted in Netherlands, with students of the Dutch School of Medicine, to validate this tool to be used to improve prescriptions in elderly patients. This study design included the use of a five steps tool (Table 16), constructed (to Dutch language) from an existing explicit method to optimize prescriptions of multiple medications (START and STOPP criteria), already validated by the respective authors. The results for the new tool were positive, with the number of correct decisions increasing and the number of harmful decisions decreasing, more in the intervention group than in the control group. (131)

Table 16: STRIP (Systematic Tool to Reduce Inappropriate Prescribing) steps.

1. Structured history of medication use
2. Structured pharmaceutical analysis
3. Decision-making for medication choice by Physician and Pharmacist
4. Definite choice by shared decision-making with the individual
5. Follow-up and monitoring

[Adapted from (131)*]*

AbuRuz *et al*. (2006) created a classification system for treatment-related problems (TRPs) with 6 (six) main categories: indication, effectiveness, safety, knowledge, adherence and miscellaneous, nine subcategories and a total of 29

treatment related problems, which included a section on the analysis of the TRPs, indicating being useful for the training of Pharmacists for detecting TRPS. Adherence assessment addresses the issue of patient´s adherence to self-care activities or non-pharmacological therapy. (132)

Bondesson *et al*. (2009) built a questionnaire to identify medication errors and assess patient´s compliance to and beliefs about medicines called "Structured Medication Questionnaire" (Table 17). (133).

Table 17: Structured medication questionnaire developed by Bondesson *et al*.

Questions/Issues	Answers/Observations
Question 1: Do you have any person helping you with drug handling at home?	If the answer was "yes", the following questions were asked.
Question 2: Who are helping you? *Question 3*: With what?	*Att: These are sequential questions*
Question 4: How do you know how and when to take your drugs?	By memory, by labels at the container, by the prescriptions, by the drug list or in another way
Question 5: What routines are used in order to remember to take your drugs?	None, together with meals, multi-dose container or in another way
Medication list	Comparison made between the medications ordered at the hospital and the medications taken at home, according to the patient
Frequency of drug´s use	Always or as needed (how many times)
Drug´s changes	Mentioned in the medical records, changes of medication to a generic drug, incorrect dosage interval but total daily dosage not changed or withdrawal of drugs with long dosage interval
Discrepancies	Classified in 4 groups: medication erroneously added, medication erroneously not ordered, ordered dose to high and ordered dose to low

[Adapted from (133)*]*

Hellström *et al*. (2011) used this questionnaire to prepare a model [Lund Integrated Medicines Management (LIMM)] including systematic medication reconciliations upon hospital admission and a medication review while in hospital. The impact of this model was validated in a prospective, controlled study with 210 patients (65 years or older), who were admitted to one of three internal medicine wards at a University Hospital in Sweden, and with the collaboration of a multi-professional team. Results showed a significant decrease in the number of inappropriate drugs in the intervention group than in the control group and a lower number of unscheduled revisits to hospital among elderly patients, related to drug use. (134)

Modig *et al*. (2016), in Sweden, used the LIMM model, conducted by a multidisciplinary team, to evaluate the quality of clinical pharmacy service in primary care using medication reviews, orientated to the clinical relevance of recommendations provided by clinical Pharmacists. At the end, a positive impact of clinical Pharmacist´s role was achieved, with benefits for elderly patients included in this study. (135)

Mast *et al*. (2015) have developed and tested a tool ("Amsterdam Tool") to be used in clinical medication reviews by community Pharmacists, containing an interview script with 5 (five) sections and 34 questions, using as source the PCNE classification of DRPs (v6.2) and a list of DRPs compiled by De Smet *et al*. (2007) and resulting from older patients with chronic diseases. The created tool was focused on the DRPs and patient´s perspective about DRPs. (136)

In the Netherlands, Kempen *et al*. (2014) made a large-scale deployment of an online CMR (Clinical Medication review) tool allowing a systematic registration of DRPs and implemented interventions achieved from CMRs in daily practice. (137)

Also in the Netherlands, Geurts *et al*. (2016) carried out a randomized controlled trial in the primary care setting, with elderly polypharmacy patients with a cardiovascular disorder, using an application (W-PCP) to establish communication between Pharmacists and General Practitioners (GP´s),

allowing both to access patient´s data. Patients included in the intervention group were forwarded to the Pharmacist to a clinical medication review, then a pharmaceutical care plan (PCP) was established by the cooperation among Pharmacist and GP with the patient´s acceptance. The expected outcomes were potential DRPs and pharmaceutical care issues (PCIs), proposed care interventions to achieve treatment goals, and implementation of interventions. All patients were followed by a period of 1 (one) year (control group received usual care, without intervention). (138)

The “WestGem-study”, conducted in Northwest Germany (2012-2015) in outpatients with an established goal of evaluating the efficacy of a comprehensive medication review. Enrolled patients were 65 years or older, with 3 or more chronic diseases (out of 2 different organ systems), at least one cardiovascular disease, using systemically 5 or more available drugs, and having a history of 1 or more visits to the General Physician during each of the past 3 quarters of the year. The Medication Appropriateness Index (MAI) was defined to assess the quality of therapy including a weighted score (1, 2 or 3) when drug related problem were detected (139) and then the scores of all items were sum mated. Patients were randomized into three clusters, each one with an intervention at a different time, beginning all at the same time as the control group. The first medication review was conducted at the first intervention time by blinded Pharmacists, using data from medical records and the results of a standardized, comprehensive patient interview. Outcomes from medication review were provided to the Physician and another medication review was performed after 6 months. (140)

The conSIGUE program, developed in 178 Spanish community pharmacies, a cluster randomized controlled trial, prosecuted with 6 (six) months of follow-up (Medication Review with follow-up – MRF) in a population of older adults (≥ 65 years) with polypharmacy (≥5 medicines per day, considering prescribing medicines and OTC´s). Three distinct areas of outcomes were analysed: clinical outcomes [Negative outcome related to medicines (NOM), Risk of negative outcome related to medicines (rNOM) and Drug related problem (DRP)],

economic outcomes (number of medicines, emergency departments visits and hospitalization) and humanistic outcomes (health-related quality of life, medication adherence, patient's medication knowledge, perception of the severity of the health problem, perception of the medication Usefulness). The methodology adopted was the Dáder method defined by the Pharmaceutical Care Research Group at the University of Granada (2005). (141,142)

Swiss community pharmacies offer a service since 2013 called "Polymedication Check" that includes an intermediate medication review (according PCNE definition), focused on adherence problems, patients' knowledge, and handling problems, including registration of all the situations, referral to a doctor if necessary and recommendations to the patient. This service is paid by the patient´s health insurance. (143)

1.3.8 Portugal

The implementation of "Pharmaceutical Care" in the daily current practice is not yet a reality in Portugal. Some research has been conducted, although there is still not a broad implementation of pharmaceutical care or the services included such as medication review.

Recent results indicated an added value of integrating Pharmacists and pharmacies in the Primary Health Care network in Portugal, including drug information services, monitoring of health status, screening for various diseases, medication review and pharmacotherapy follow-up with other providers of health care structure (6)

Alves da Costa *et al*. (2016) proposed to identify DRPs in elderly subjects institutionalized in four (4) nursing homes (in Alentejo, Lisbon and Vale do Tejo regions), considering data from medical records and using concepts of the II Consensus of Granada (DRPs classification: necessity, effectiveness and safety). (144)

Another cross-sectional study was developed in 6 (six) Portuguese nursing homes, aiming to evaluate the need for pharmaceutical care implementation in institutionalized, polymedicated elderly, accessing patient data available at the institution, applying the tool START/STOPP to identify potentially inappropriate and appropriate, and PCNE classification for DRP´s (v 6.2). (145)

A Portuguese (mainland) cross-sectional study held in nursing homes, using medication regimen complexity index (MRCI) to assess medication regimen complexity in institutionalized elderly individuals, refers this tool as an asset to be used in routine medication review as part of the Pharmacists´ intervention. (146)

Salgado *et al*. (2013) carried out a qualitative study to explore the opinions of Australian and Portuguese nephrologists towards a potential future provision of clinical pharmacy services in outpatient dialysis centers, in which Portuguese nephrologists identify concerns with professional boundaries (Physician-Pharmacist) and lack of awareness and knowledge of Pharmacist skills, while Australian nephrologists have identified medication review, medication re-conciliation, medication history update, patient and staff education, patient compliance improvement and development and implementation of anaemia protocols as potential services to be provided by Pharmacists. (147)

A transversal descriptive study in type 2 diabetic patients, users of a Portuguese community pharmacy located in Coimbra, was developed by Simões *et al*. (2012) to identify risk situations for negative clinical outcomes in the process of drug use through medication review, having achieved an average of 10.2±4.8 findings per patient. (148)

Brazinha & Fernandez-Llimos (2014) investigated barriers to implementation of advance clinical pharmacy services at the Portuguese hospitals, being Pharmacist´s mentality and predetermined attitudes identified as the main obstacles to implementation of these services. (149)

In a cross-sectional European wide online survey (2014), Portugal indicated only to be carried out in Portugal Type II adherence and compliance review in hospital setting (national level) since 2001. (97)

1.3.9 Contributions from medication review

The results of a retrospective analysis of medication reviews with two time periods (pre-integration of the practice Pharmacist and post-integration of the practice Pharmacist) showed that the integration of a Pharmacist into the general practice team was associated with an increase in the timeliness and completion rate of medication reviews and a decrease in the time to complete a MR from a median of 56 days to 20 days. (150)

Also a systematic review and meta-analysis examined the impact of fee-for-service pharmacist-led medication review on patient outcomes and quantified this according to the type of review undertaken (adherence support and clinical medication review). Their conclusion was that fee-for-service pharmacist-led medication reviews had positive benefits on patient outcomes, in which interventions including a clinical review had a significant impact on patient outcomes. (7)

The impact of medication review in mortality and hospitalization for nursing home residents did not reveal positive results, according to the results of systematic review and meta-analysis. (151)

Hohl *et al* (2015) could not reach conclusive results for the effects of medication review on patient-oriented outcomes, due to study limitations such as the variation in interventions, missing data, methodological flaws of individual studies, and it suggested that more quality randomized trials should be conducted in future. (152)

Another systematic review aimed to assess the contribution of the Pharmacist to the programs Home Medicines Review (HMR) and Residential Medication

Management Review (RMMR), in which evidence was found to support the role of Pharmacists in delivering these services. Nevertheless, further research has been recommended on the actual clinical outcomes, since for example 54 (5.6 %) recommendations were not in line with respective guidelines. (153)

Patients using automated drug-dispensing systems could benefit from a medication service, as verified by Kwint *et al*. (2011) in a pragmatic randomized controlled study conducted in primary care, with patients recruited in Dutch community pharmacies. Patients were eligible for the study when they were 65 years-old or above, taking five (5) or more different drugs, of which at least one had to be dispensed via an automated system, and were randomized to the intervention group (received a medication review at the start of the study) or waiting-list group (received a medication review after 6 months). A significant decrease of 29% in the number of DRPs after 6 months in the intervention group versus 5% in the waiting-list group was observed, wherein at baseline there were no differences between the two groups. (154)

A positive impact on the implementation of recommendations from medication review arises from the collaboration between General Practitioners (GP) and Pharmacists, as it has been showed in a systematic review performed by Kwint *et al*. (2014). (155)

A controlled trial implemented in Germany, was conducted in psychiatric inpatients, to assess the effect of pharmacist-led medication reviews on the medication safety and the resolution of Drug Related Problems (DRP), throughout a medication reconciliation at the admission time. (156) This activity was performed weekly during hospital stay, at discharge and three months after discharge, and the results sent to the Physician. The intervention was discussed between all these professionals (intervention group). The role of the Pharmacist has been reinforced as a positive contribution integrated in a multidisciplinary team in order to improve prescribing appropriateness. However, outcomes from the interventions performed in this study do not show a clear improvement on clinical outcomes. (156)

Furthermore, Clyne *et al.* (2016) identified studies with several interventions on potentially inappropriate prescribing (PIP) in community-dwelling older adults. It wasn´t clear if a positive improvement in clinical outcomes resulted from the medication review, and also an assessment of PIP prevention impact was necessary. (157)

Results from "WestGem-study" (Germany, 2012-2015), a cluster-randomized controlled study, identified the number of drugs used by patients as a significant criteria regarding patient´s selection for medication review. Elderly patients with multimorbidity, polymedication and a cardiovascular disease seem to benefit from a longitudinal care including repeated reviews conducted by a multidisciplinary team of professionals more than a single medication review. (140)

A prospective observational study was carried out in 15 nursing homes in Andalusia (Spain) during 12 months, which included resident patients 65 years and older (332 patients), and where a medication review with follow-up was conducted. Compared to the concurrent control group, in the intervention group was observed a resolution of 1.2 (average) negative clinical outcomes per patient and a significant reduction in the average number of prescribed medication. (158)

Jokanovic *et al*. (2016) identified improvements in medicines use and health outcomes as a result from clinical medication review (CMRs), in community-settings in Australia. Although the analysed outcomes were not consistent across all included studies, an improvement was achieved in this systematic review for the following outcomes: reductions in numbers of medications prescribed, hospitalizations, potentially inappropriate prescribing and costs. (159)

1.4 Drug Related Problems

The activity of MR includes the identification of Drug Related Problems (DRPs) (96), but there is no consensus for designation and classification of DRPs. Even in the designation itself, besides drug-related problems (DRP), several other terms are used in the literature, such as drug therapy problems (DTP), medicine-related problems (MRP), medication-related problems (MTP), pharmacotherapy failures, drug treatment failures, pharmacotherapy problems and treatment-related problems. (160)

A systematic research study presented by Basger *et al*. (2014) identified 20 (twenty) different types of DRPs classification systems, finding that about 75% of the studies used a modified existing classification (Table 18). (161)

Table 18: Dug-related problems classifications.

APS-Doc	Cipolle *et al*. (1998 and 2004)
Consensus of Granada (1st, 2nd, 3rd)	PROGRAM
GSASA classification	Krska *et al*.
Norwegian	PCNE (versions 4, 5, 6 or 7)
SFPC (Societe Française de Pharmacie Clinique)	Strand *et al*. (1990)
Westerlund *et al*. (1999)	Basger *et al*. (2015)

[Adapted from (161–163)*]*

Westerlund *et al*. (1999) developed a classification system to document drug-related problems (DRPs) (type and number) identified in Sweden community pharmacies, considering DRP as “a circumstance of drug therapy that may interfere with a desired therapeutic objective”. (164) This system allows the classification of DRPs by type and kind of intervention carried out by pharmacy professionals (Table 19). (165)

Table 19: DRPs classification system by Westerlund *et al*.

Types of DRPs	Types of Interventions
1. Uncertainty aim of drug 2. Underuse of medication 3. Overuse of medication 4. Other dosage problem 5. Drug duplication 6. Drug-drug interaction 7. Therapy failure 8. Side effect 9. Difficulty swallowing tablet 10. Difficulty opening container 11. Other practical problem 12. Language deficiency 13. Prescribing error 14. Other drug-related problem	No intervention Patient medication counselling Practical instruction to patient Patient referred to prescriber Prescriber informed only Prescriber asked for information Intervention approved by prescriber Intervention disapproved by prescriber Switch of drug Referral to colleague Other intervention

[Adapted from (165)*]*

This tool only documented problems identified in patient´s medicines (OTC´s included) but not potential problems, and has a focus on DRPs documentation and intervention description. The author refers some limitations for the study, such as potential issues with self-reported data, being the participants to decide the DRP classification; underestimation of DRPs during peak hours; and low rate of drug-drug interactions, probably due to lack of knowledge about all the medication used by the patients.

A decade later, Hohmann *et al*. (2009) developed a system to document and classify DRPs hierarchically in inpatient settings (APS-Doc). (166)

More recently, in 2012, a new system for classifying DRPs in the hospital setting was created with 10 main categories and 48 subcategories, resulting from a modification of PCNE classification of DRPs (v5.1) and PI-Doc (167), which proved to be suitable for use in the various parts of the medication process such as medication reconciliation and drug therapy within both non-surgical and surgical wards. (168)

A group of Australian community Pharmacists, who conducted research for a few years in the clinical intervention in community pharmacy, developed and

validated a system to classify drug-related problems in the practice of community pharmacy, called DOCUMENT, which arose as an output of the research project "PROMISe Trial". (169,170) This DRP classification system included eight (8) categories of DRPs, having each one 1-5 subcategories (Table 20), a list of actions used to investigate DRPs, recommendations to resolve DRPs (5 categories and 1-7 subcategories each), clinical significance to patient of the interventions purposed (5 levels) and the possibility of a partial acceptance of the proposed interventions by the Pharmacist also existed. (109)

Table 20: DOCUMENT - Classification of drug-related problems.

Drug selection	DRPs related to the choice of drug prescribed or taken (such as drug duplication, drug interaction, wrong drug and no apparent indication)
Over or underdose prescribed	DRPs related to the prescribed dose or schedule of the drug (such as dose too high, dose too low and incorrect schedule)
Compliance	DRPs related to the patient's medication- related behaviour (such as taking too little, taking too much, intentional drug misuse and difficulty using a dosage form)
Untreated indications	DRPs related to actual or potential conditions that require management (such as a diagnosed condition not adequately treated or preventative therapy required)
Monitoring	DRPs related to inadequate monitoring of the efficacy or adverse effects of a drug (including laboratory and non-laboratory monitoring)
Education or information	DRPs related to knowledge of the disease or its management (such as requests for drug information, confusion about therapy or disease states and demonstration of dose administration devices)
Non-clinical	DRPs related to administrative aspects of the prescription
Toxicity or adverse reaction	DRPs related to the presence of signs or symptoms which are suspected to be related to an adverse effect of the drug (such as toxicity caused by dose, drug interaction or unknown causes)

[Adapted from (109)*]*

DOCUMENT has some specific characteristics to be applied in community pharmacy, and users need training to allow a better identification of DRPs. (169) This tool was used to document DRPs within the trial and the created

software was available in the pharmacy computer system. The outcomes from previous trial did not include analysis of DRPs resulting from the use of OTC´s. (170)

In Spain, the first Consensus of Granada was published in 1999, resulting from a work group of Pharmacists who gathered in Granada in 1998, introducing a new concept in the scope of Pharmaceutical Care: "*The detection, prevention and resolution of drug-related problems*", which resulted in a new tool for professionals to use in the clinical practice for evaluating the results of patient´s pharmacotherapy, and were adopted by several health professionals. From the first Granada Consensus, the definition of Drug Therapy Problems (DTPs) was "*a health problem, related to pharmacotherapy that interferes or may interfere with the expected patient health outcomes*". (171) The second Consensus of Granada (2002) introduced significant changes in order to clarify some difficulties that had arisen in the DPRs interpretation and some doubts of use, and the concept of drug related problems (DRP) was then defined as "*health problems, understood as negative clinical outcomes, resulting from pharmacotherapy, that for different causes, either do not accomplish therapy objectives or produce undesirable effects*". Three classes of DRPs were defined and described: necessity, effectiveness and safety (Table 21). (172)

Table 21: DRPs Classification (Second Consensus of Granada).

Necessity:
DRP 1: The patient suffers from a health problem as a consequence of not receiving the medication that he needs. DTP 2: The patient suffers from a health problem as a consequence of receiving a medicine that he does not need.
Effectiveness:
DRP 3: The patient suffers from a health problem as a consequence of a non-quantitative ineffectiveness of the medication.
DRP 4: The patient suffers from a health problem as a consequence of a quantitative ineffectiveness of the medication
Safety:
DRP 5: The patient suffers from a health problem as a consequence of a non-quantitative safety problem of a medicine.
DRP 6: The patient suffers from a health problem as a consequence of a quantitative safety problem of a medicine.

[Adapted from (172)*]*

In 2004, an intercultural translation from Spanish to Portuguese language was performed by Santos *et al.* allowing the use of this DRP classification system and the respective methodology by the Portuguese Pharmacists. (173)

After the Second Consensus of Granada, some authors raised the question whether DRPs would be elements of the medication use process or would be the outcomes of this process, suggesting the abandonment of DRPs designation and the use of "Negative Clinical Outcomes". (174)

As a result of the Third Consensus of Granada (2007), DRPs were recognised as elements of process, designed as "*situations, which throughout the process of the use of medicines, cause or may cause the appearance of a* ***n****egative* ***o****utcome associated with* ***m****edication (NOM)*". NOM was defined as "*a situation in which the patient is at risk of suffering from a health problem associated with the use of medicines, generally due to the existence of one or more DRPs, which we can consider as risk factors of this NOM*". (160) NOMs were classified in three different types (Table 22). (160)

Table 22: Classification of Negative Outcomes associated with Medication (NOM), Third Consensus of Granada (2007).

Necessity	**Untreated health problem:** The patient suffers from a health problem as a consequence of not receiving the medicine that he needs. **Effect of unnecessary medicine:** The patient suffers from a health problem as a consequence of receiving the medicine that he does not need.
Effectiveness	**Non-quantitative ineffectiveness:** The patient suffers from a health problem associated with of a non-quantitative ineffectiveness of the medication. **Quantitative ineffectiveness:** The patient suffers from a health problem associated with of a quantitative ineffectiveness of the medication.
Safety	**Non-quantitative safety problem:** The patient suffers from a health problem associated with a non-quantitative safety problem of the medication. **Quantitative safety problem:** The patient suffers from a health problem associated with a quantitative safety problem of the medication.

[Adapted from (160)*]*

Furthermore, in the Third Consensus of Granada a list of DRPs was identified, although not being exclusive but being adaptable according to the needs in clinical practice (Table 23). (160)

Table 23: List of drug-related problems (Third Consensus of Granada).

- Wrongly administered drug
- Personal characteristics
- Unsuitable storage
- Contraindication
- Inappropriate dose, dosage schedule and/or duration
- Duplicity
- Dispensing errors
- Prescription errors
- Non-compliance
- Interactions
- Other health problems that affect the treatment
- Probability of adverse effects
- Health problem insufficiently treated
- Others

[Adapted from (160)*]*

The methodology used in the Granada´s group is directed to the identification of negative outcomes associated with medication (NOM), with the analysis focused on the drug and thus directing only to the pharmacological treatment. In clinical practice, the management of some health problems favours the use of non-pharmacological measures, i.e., this methodology does not allow to identify a NOM in these cases.

Furthermore, Granada´s classification of DRPs focuses more on the classification of negative outcome associated with medication (NOM) rather in health outcomes, which in some cases may lead to doubts in the classification without any added value for the improvement of health outcomes.

PCNE has also been reaching some classification´s system of “Drug-related problems” over the last decade, wherein version 1.0 included 6 domains for

"Problems" (23 sub-categories), 6 categories of "DRPs" (34 sub-categories) and 5 levels for "Intervention" (12 sub-categories). (175)

Over the years, ten (10) further versions of classification of DRPs have been published, being the most recent released in July 2016 (v7.0). (176)

The previous version (v6.2) has been widely used for several authors since 2010, and DRPs were classified according to the nature, prevalence and incidence, considering four (4) primary domains for Problems, eight (8) primary domains for Causes, five (5) primary domains for Interventions and four (4) primary domains for Outcome of Intervention. (177)

The main changes between PCNE classifications of DRPs v6.2 and v7.0 were the following: the problem section was reduced to 3 domains ("treatment costs" has been moved); a sequence prescribing-dispensing-use was adopted for causes; an intervention level was introduced ("Acceptance" section); and the name of last section was changed to "Status of the DRP" instead of "Outcome of intervention (Table 24). (176–178)

Table 24: PCNE DRPs classification (v6.2 and v7.0)

v6.2		v7.0	
Domain		Domain	
Problems		Problems	
P1 P2 P3 P4	Treatment effectiveness Adverse reactions **Treatment costs** Others	P1 P2 P3	Treatment effectiveness Adverse reactions Other
Causes		Causes	
C1 C2 C3 C4 C5 C6 C7 C8	Drug selection Drug form Dose selection Treatment duration Drug use/administration process **Logistics** Patient Other	C1 C2 C3 C4 C5 C6 C7 C8	Drug selection Drug form Dose selection Treatment duration **Dispensing** Drug use/ process Patient related Other

Table 24 *(Continued)*

v6.2		v7.0	
Domain		Domain	
Planned Interventions		Interventions	
I0 I1 I2 I3 I4	No intervention At prescriber level At patient (or carer) level At drug level Other	I0 I1 I2 I3 I4	No intervention At prescriber level At patient level At drug level Other
		Intervention Acceptance	
		A1 **A2** **A3**	**Intervention accepted** **Intervention not accepted** **Other**
Outcome of Intervention		**Status of DRP**	
O0 O1 O2 O3	Outcome intervention unknown Problem totally solved Problem partially solved Problem not solved	O0 O1 O2 O3	Problem status unknown Problem solved Problem partially solved Problem not solved
The main changes between the two versions are marked in bold.			

[Adapted from (176–178)*]*

The PCNE classification for DRPs, uses an approach per drug/medicine, however to conduct a patient-centred approach focused on clinical conditions/health problems some situations may not be included in this approach. For example, if the patient has an untreated clinical condition, this issue would not be included in this approach. Considering the hierarchical character of the classification of DRP from PCNE, in situations where there is no identified DRP there is no possibility to identify circumstances of risk for the occurrence of DRPs (eg, medicine taken in the wrong time), unless the Pharmacist has a very systematic approach on identifying all potential DRPs. The allocation of specific causes to DRPs identified in the classification of DRPs from PCNE becomes difficult to determine, in practice, due to the plurality of causes that can lead to a DRP, since some could have a non-pharmacological origin. As an example, if a diabetic patient treated with various oral antidiabetic drugs, has an uncontrolled glycemic profile, which are the drugs that are going

to be assigned as ineffective? Can the origin of this uncontrolled glycemic profile be other than a pharmacological cause?. Moreover, in this classification system there are some issues related to the drug such as the patient's knowledge of medication or relative to the procedure´s monitoring of the disease to be undertaken by patient, that are not covered.

In 2015, the GSASA system was prepared by Maes *et al*., being validated using inpatients against the PCNE classification system (v6.2), and containing 5 categories of problems and 41 subcategories: detected problem (5 subcategories), type of problem (2 subcategories), cause of intervention (18 subcategories), intervention (11 subcategories), and outcome of intervention. (162) Two subcategories were added to problems: “Untreated conditions” and “Patient dissatisfaction” relative to the PCNE classification (v6.2). Also all problems were classified as “Manifest” or “Potential”, and in the intervention domain a subdomain “Report to pharmacovigilance centre” was added. (162)

Horvat & Kos (2016) have translated, validated and upgraded the PCNE classification of DRPs (v6.2) to be used in Slovenian community pharmacies. The main changes to the original version were the following: potential problem was added as a subdomain of problem´s domain; the cause´s domain was changed to “risk factors”, and subdomain was organized in prescribing, dispensing and use of drugs; and the intervention´s level were organized according to communication and agreement with the prescriber. (179)

Basger *et al*. (2015) constructed a system for classification of DRPs by aggregating seven (7) systems already used, hence resulting in an extensive classification system that includes nine (9) categories of causes of DRPs, 33 subcategories and 58 sub-subcategories. (163)

The methodology for classification of DRPs is not consensual and the need for a consistent and reliable system for classifying DRPs is still a reality. (161,180)

One of the points that was reported, which seems to contribute to the identification of DRPs, was clinical knowledge of Pharmacists and training appears to have an important role to improve these skills. (181,182)

1.5 Tools for Medication Review

1.5.1 Inappropriateness of medication

The incidence of drug adverse reactions increases with the use of multiple drugs, such as in polymedicated patients. This condition is common particularly in elderly patients, who with advancing age become carriers of multiple pathologies and need to use multiple drugs simultaneously as a therapeutic approach. (183,184)

To undergo on DRPs systematic identification tools should be used in order to identify situations which can lead to the onset of drugs adverse reactions, such as tools to evaluate the adequacy of therapy and to identify risk situations for specific patient groups.

Appropriateness of pharmacological treatment has been associated with increasing number of drugs used and number of diagnoses. (185)

Several designations can be used in this scope, such as “potentially inappropriate drug therapy (PIDT)”, “potentially inappropriate medication (PIM)”, and “potentially inappropriate prescribing (PIP)”. As many as 50 terms to refer to this matter have been identified in a systematic review. (186)

Gallagher et *al*. (2008) defined “potentially inappropriate medications (PIMs)” as “*medications that have no clear evidence-based indication, carry a high risk of adverse side effects or are not cost-effective*”. (187)

The concept of potentially inappropriate may have a different significance from inadequate, since the last situation is applicable to situations depending on the patient’s clinical condition, and/or relative to a potential drug-drug interaction and pharmacological disease. Then, the first concept referred can be applied to implicit methods and the other two can be applied to explicit methods. (186)

Implicit methods are judgment based, patient specific, and consider the entire medication regimen, requiring a high level of skill from the assessor [e.g. Medication Appropriateness Index (MAI) and Hamdy questionnaire]. Explicit methods are based on a list(s) with explicit drug-oriented and/or disease-oriented criteria (e.g. Beers' lists, STOPP/START, PRISCUS, and NORGEP). (188)

A systematic review with the main goal of identify tools for measuring the appropriateness of drug therapy useful in patients with multiple chronic condition, have found two (2) implicit methods [Medication Appropriateness Index (MAI) and Hamdy questionnaire] and six (6) explicit methods (Beers criteria, IPET, STOPP/START, ACOVE, CRIME and NORGEP), although none have specificity for patients with multiple chronic conditions. Within the implicit methods only MAI having been validated in clinic environment and with elderly patients, for explicit methods Beers criteria and STOPP/START fulfilled these premises. (189)

Kaufmann *et al*. published a review including 46 assessment tools for inappropriate prescribing, implicit and explicit methods being most (36) focused on elderly patients. Considering the total of tools analysed, no one covered all aspects of inappropriate prescribing, been under-prescribing the less approached. (190)

Santos *et al*. identified in a systematic review, 27 tools to detect PIDT, about a quart (27.7%) of analysed studies using two criteria, being Beers criteria used by 82.3% of the studies in its various versions. (186)

Beers criteria was developed by the American Geriatrics Society in 1991 and was the first published criteria for potentially inappropriate medications (PIMs) identification, having first been created to detect PIMs in nursing homes. (191)

In 1997, an updated and expanded version of the Beers criteria was launched, with 35 criteria defining PIM use in elderly and respective PIMs for 15 common medical conditions, also to be used in outpatient settings (192). A third version

of the Beers criteria has been published in 2003, including 48 drugs or drug´s classes to avoid in elderly and 20 diseases/conditions and drugs to be avoided in patients with these conditions. (193)

In 2012, the American Geriatrics Society (AGS), updated the Beers criteria, including the guidelines of the Institute of Medicine standards for clinical practice, the updated list of drugs/clinical conditions, and a new table of "medications to be used with caution", among other changes. (194)

More recently, in 2015, the AGS, launched a new version, which added a list of selected drugs that should be avoided or need to have their dose adjusted based on the individual's kidney function and also drug–drug interactions documented to be associated with harms in the elderly. The purpose of this new version was to be applied to all older adults, except for those in palliative and hospice care. (195)

In 2008, Soares *et al*. provided an operationalization of the Beers criteria to the Portuguese language, being adapted to the active substances approved in Portugal. This document includes two tables, one containing the list of PIMs for older adults and the other listing the PIMs according to specific clinical conditions. (196)

The Beers criteria are still very directed to the American reality, and no newer version was operationalized into Portuguese. Moreover, the last operationalized version was not found to be widely used in the country in the clinical setting, but only on a few academic projects such as the one performed by Eiras *et al*. (2016) in a Primary Care Health Centre in Oporto. (197)

STOPP/START criteria have been validated using a Delphi consensus method by Gallagher et *al*. (2008), an Irish group of researchers, consisting a list of 65 drugs and specific conditions which prescription was potentially inappropriate in subjects being 65 years or above. (187)

Latter, in 2014, a second version of STOPP/START criteria was launched, in order to integrate sets of PIMs and Potential Prescribing Omission (PPO) that

could have serious negative impact on elderly patient´s health in a clinical setting. (198)

STOPP is a tool for detection of potentially inappropriate prescriptions in elderly, consisting in a list of drugs whose prescription is potentially inappropriate in subjects with age ≥ 65 years. START criteria is a tool to address the Physician about indicated and appropriate treatments, for subjects with age ≥ 65 years with specific diseases, whereas no contraindications exists for their use. (198)

There is still no Portuguese version available of the STOPP/START criteria.

A Medication Appropriateness Index (MAI) was developed by Hanlon *et al*. (1992), consisting of 10 criteria for each medication prescribed (indication, effectiveness, dosage, correct directions, practical directions, drug–drug interaction, drug–disease interaction, duplication, duration, expense) and then each medication is rated as appropriate, marginally appropriate, or inappropriate. The design of this instrument also aimed to be used as an indicator of quality care outcome in America. (199) In 1994, a weighting scheme was created to produce a single summated MAI score per medicine. (139)

Afterward in 2006, Spinewine *et al*. pointed out a list of suggestions that could contribute to evidence the validity and reliability of the instrument, including e.g. an update of the list of drug–disease interactions, considering allergy as a drug–disease interaction, among others. (200)

In Spain, Gavilán Moral *et al*. (2013) provided an adaptation and validation of the MAI instrument to Spanish language, with a good internal consistency value (Cronbach alpha 0.99) and high reliability. (201)

Until now the adaptation and validation of this instrument into the Portuguese reality hasn´t been performed.

EU(7)-PIM list was developed by a panel of European experts, from the German PRISCUS list of potentially inappropriate medications (PIM) and other PIM lists from the USA (Beers criteria), Canada and France. EU(7)-PIM is a list

of 275 chemical substances, in which some PIM concepts are dose-related or defined by length of use or drug regimen. There were no Portuguese experts in the preparation of this list. (202) Some authors consider the EU(7)-PIM list more suitable to be used with administrative databases or surveys, in pharmacoepidemiological applications, without any subjects' clinical information. (188)

A consensus on which tools should be used to identify inappropriate medication/drugs is not yet available, mainly because each country has a specific range of available drugs, so probably each country should create/adapt their own specific(s) tool(s). (186)

Some authors believe that PIMs criteria may be used to assess the quality of the prescription (203), even in databases and using automated electronic applications, however these are not yet ready to be used directly. These tools are not used in the same way or are applied to the patient level in all countries, and are applied to the patient level. The European Science Foundation (ESF) recommended that some work should still be performed so that they could be used globally, and in particular at the European level. (188)

The results obtained in relation to potentially inappropriate medications (PIMs) depend on the tool used, and there is still no consensus on the best tool to use. Characteristics of the health systems are different across countries and continents, and these differences can be a limitation for the creation of a global tool. (204)

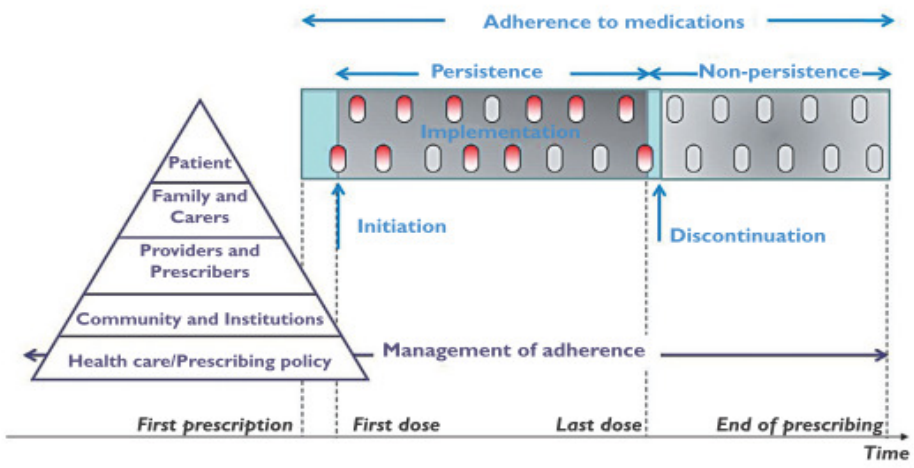
A recent Portuguese descriptive cross-sectional study was developed in four nursing homes and used several PIMs detection tools (Portuguese adaptation of Beers criteria, Beers criteria 2012, and START criteria) and START criteria (to identify potential prescribing omissions). A significant lower proportion of PIMs were detected, using the Portuguese adaptation of Beers criteria, while with the START/STOPP criteria a significant higher proportion of PIMs were identified, allowing also to detect situations such as low levels of cardiovascular risk prevention in the Portuguese elderly population. (205)

1.5.2 Medication Adherence

According to the WHO, adherence is defined as the "the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider". (206)

Several items have been addressed related to medication adherence, such as: adherence rates, causes of non-adherence, barriers, enablers to medication users, interventions to promote adherence, impact of non-adherence on health outcomes. (207)

Different terms and terminology may be used to refer to medication adherence. Within this framework, the ABC consortium held a meeting in September 2009 (Bangor University, Wales, UK), coordinating the "European consensus meeting on the taxonomy and terminology of patient compliance". The process of medication adherence was described as shown in Figure 3, and comprises three components: initiation, implementation, and discontinuation. (208)



Legend: Adherence to medication (light blue); Process of management of adherence (dark blue)

Figure 3: Illustration of the process of adherence to medication and the process of management of adherence.

[Adapted from (208)*]*

Non-adherence was identified as the following situations:

- Late or non-initiation of the prescribed treatment;
- Sub-optimal implementation of the dosing regimen;
- Early discontinuation of the treatment. (208)

Also a new designation was achieved "*Pharmionics*", which was defined as "*an adherence-related science concerned with the quantitative assessment of the three measurable components of adherence to medications (initiation, implementation, and discontinuation), and their respective contributions toward the effects of medicines*". While initiation and discontinuation are discontinuous actions, implementation is a continuous action that requires information regarding prescribed drug dosing regimen and the patient's drug dosing history. (208)

Medication adherence has been a persistent problem having a higher impact in chronic diseases. (209) For chronic diseases, medication adherence has an estimated average of only 50% for developed countries, being even lower in developing countries. (206)

Long term medication adherence has been evaluated in prospective studies, and the compliance rate showed decrease over the period of medication use. (210,211)

In the prevention of cardiovascular diseases, patients using statins for primary prevention showed to be a predictive factor for nonadherence, whereas these patients had higher probability (64%) to be more non-adherent than those who started statins on secondary prevention. (210)

Non-adherence leads to relevant complications in two different but related levels: clinical and economic outcomes. Medication non-adherence may prompt to adverse drug events (ADEs), either those could be generally responsible for poorer health outcomes and a barrier to patients further adherence. (212)

Through research conducted in this area in recent decades, adherence was described to comprise a variety of health-related behaviour's that extend beyond taking prescribed medications. (206)

Causes for non-adherence can be multiples, most of them individual with different clinical outcomes reached depending on the conditions and characteristics of patients, thus, the identification of barriers to adherence is highly relevant and the patient has a central role in this process. (213)

Research results over time has reached a list of determinants for patient´s adherence, which were grouped into the following dimensions as shown in Table 25. (206,214)

Table 25: **Dimensions for determinants of patient adherence.**

Determinants (Dimensions)	
Treatment duration	Long term *vs* short term treatment
Components	Implementation of the dosing regimen Persistence
Dimension	Socio-economic factors Health care team System-related factors Condition-related factors Therapy-related factors Patient-related factors
Direction of effect	Classification according to their effect on adherence: ▪ positive, negative, neutral, or not defined effect

[Adapted from (206,214)*]*

A systematic review including 51 other systematic reviews was carried out by Kardas *et al*. in 2013 (214), with the purpose of reviewing determinants of patient adherence resulting from research (Table 26), most of them related to

the adherence component of implementation [defined as the "*extent to which a patient's actual dosing corresponds to the prescribed dosing regimen"* (208)].

Table 26: Factors having effect on adherence.

Healthcare team and system-related factors	▪ Barriers to healthcare ▪ Drug supply ▪ Prescription by a specialist ▪ Information about drug administration ▪ Healthcare provider-patient communication and relationship ▪ Follow-up
Socio-economic factors	▪ Family support ▪ Family/Caregiver factors ▪ Social support ▪ Social stigma of disease ▪ Costs of drugs and/or treatments ▪ Prescription coverage ▪ Socioeconomic status ▪ Employment status
Patient-related factors	▪ Age ▪ Gender ▪ Marital status ▪ Education ▪ Ethnicity ▪ Housing ▪ Cognitive function ▪ Forgetfulness and reminders ▪ Knowledge ▪ Health beliefs ▪ Psychological profile ▪ Comorbidities and patient history ▪ Alcohol or substance abuse ▪ Patient related barriers to compliance (such as transportation difficulties)

[Adapted from (214)*]*

A list of causes can be addressed to medication non-adherence, and can be labelled as intentional or unintentional, when patient chooses to deviate from the treatment regimen, motivated by a rational decision-making process or the

patient (passive attitude) may be careless or forgetful about adhering to the treatment regimen, respectively. (215)

Unintentional non-adherence can be predicted by patients' medication beliefs, chronic diseases and socio-demographics, and can be a predictive signal for intentional non-adherence. (216)

Nevertheless, medication adherence rates are not always similar for patients with different illnesses. (217)

In addition, the cause for patient non-adherence cannot be attributed exclusively to the patient. (218)

Most of the methodologies used to estimate patient non-adherence systematically exclude patients who do not fill the medication order and also those who only fill the medication order once and do not refill it. Currently, there is lack of research linking medication orders to dispensing. (219)

According to Raebel *et al*. (2011), in a retrospective cohort study held at Kaiser Permanente Colorado (KPCO), including 15417 patients who were newly prescribed hypertensive, antidiabetic, or anti-hyperlipidaemia medication, the adherence rate was overestimated by 9-18% not including primary non-adherents and early non-persistent. (220)

According to a systematic review regarding the medication nonfulfillment rates and reasons, the three primary reasons identified were concerns about medications, lack of perceived need for medications, and medication affordability issues. (221)

Failure of medication regimen will have an effect on several levels: patient's quality of life, clinical results obtained, and costs to the health care system and society in general.

Poor medication adherence can be associated to less positive health outcomes such as disease-specific hospitalizations for hypertension patients (+10.9% at 2 years) and complications (+14% at 2 years), as verified by Han *et al*. (2014) in a

retrospective cohort study using the Korean National Health Insurance Claims Database, wherein all patients with hypertension, hyperlipidaemia and diabetes were identified and those who had prescribed medications for these diseases were enrolled. (86)

A study held by Rabin *et al*. (2014) on diabetic patients suggested that several interventions can lead to a decrease on the risk of early readmission, such as patient diabetes education, improving communication of discharge instructions, and increasing patient's involvement in medication reconciliation and post-discharge planning. (222)

Medication adherence has been widely studied for cardiovascular diseases since adherence can be indirectly measured by some markers regarding the control of risk factors such as blood pressure and lipid levels. (218)

In the dimension of patient related factors, literacy, patient knowledge, attitudes, and beliefs about the disease can have a negative effect on adherence (223). Furthermore belief in the necessity of medication is associated to compliance as reported by Ross *et al*. (2004). (224)

In a Cochrane review provided by Haynes *et al*. (2008) interventions performed to improve medication adherence in a long term care were complex, with the objective of achieving several adherence determinants. Despite the amount of research performed in order to demonstrate methodologies to improve drug use and health, the results haven´t been very large, and further improvements are needed to assist chronic diseases patients. (225)

Assessment of medication non-adherence can be provided using different sources, such as relevant databases, electronic health records, and pharmacy fill records. (219,226)

Measuring adherence can be achieved using various methodologies that can be classified as direct or indirect methods. Although direct methods (drug or metabolite level in urine or blood) are more accurate, they become much more expensive, being the indirect methods often used such as patient

questionnaires, patient self-reports, pill counts, rates of prescription refills, assessment of patient's clinical response, electronic medication monitors, measurement of physiologic markers, as well as patient diaries. (227)

A systematic review (Suliman *et al*., 2012) analysed the adherence barriers that were included in instruments used in 1712 citations from 5 electronic databases and described the psychometric properties of the identified surveys. The results showed that the most used instrument was the Morisky Medication Adherence Questionnaire (MAQ), in most instruments patient-related barriers were most commonly addressed, while condition, therapy, and socioeconomic barriers were underrepresented. (228)

MAQ has several positive points, being the quickest to administer, and it is the tool that has been validated in the broadest range of diseases. Self-Efficacy for appropriate Medication Use Scale (SEAMS), Brief Medication Questionnaire (BMQ), the "Hill-Bone Compliance Scale" and Medication Adherence Rating Scale (MARS) allows to self-efficacy assessment and therefore may be useful in medication management clinics, in spite of the difficulty of a global utilization since the latter scale is being directed to psychiatric populations and the prior one to hypertensive patients. (229)

The validity of self-report adherence scales must be a relevant point to be considered, and in practice, different methodologies are being used. This was analysed by Nguyen *et al*. (2014) considering an overview of 43 adherence scales. These results revealed less remark in the way as the information obtained from scales, by identifying patient-specific barriers and beliefs associated with adherence, may be a positive contribute for rational use of medication. (230)

There is no ideal methodology to assess medication adherence, so the literature refers to using multiple tools simultaneously as the most accurate way to manage this assessment, using two or more medication adherence tools in parallel. (226)

1.5.3 Medication Knowledge Assessment

Patient´s medication knowledge can be a factor contributing to patient´s medication adherence and to health outcomes as highlighted in the results of a systematic review and meta-analysis relative to patient-centred outcomes reported in studies testing interventions to increase medication adherence, being important their inclusion in medication review outcomes. (231)

Garcia-Delgado *et al*. (2009) reached a definition for patient´s medication knowledge (PMK) as "*the information acquired by the patient on medication, necessary for proper use of it that includes the therapeutic objective (indication and effectiveness), the process of use (dosage, regimen, route of administration and duration of treatment), security (adverse effects, precautions, contraindications and interactions) and conservation*". (232)

A cross-sectional study carried out in Spanish community pharmacies identified 72% of the patients with inadequate knowledge considering medication used. The lowest scores of knowledge were verified in the scope of "medication safety", respectively 12.6% for "contraindications" and 15.3% for the item "side effects". (233)

A prospective study developed in patients with inflammatory bowel disease (IBD) by Tae *et al*. (2016) showed a greater risk of relapse of IBD for non-adherent patients, and found an association of low medication knowledge with non-adherence and consequent risk of relapse. (234)

In order to asses patient´s medication knowledge some tools are available, mostly in English (235), such as the use of interviews or specific questionnaires as methodology without assessment of validity and reliability (236–239).

Garcia-Delgado *et al*. (2009) validated a questionnaire to assess patient´s medication knowledge level, including four (4) dimensions and respective determinants, having obtained a value of 0.68 for Cronbach´s alfa (Table 27). (232)

Table 27: Medication knowledge assessment: different dimensions of drug use and its determinants.

Dimension	Determinants
Therapeutic goal	Indication Effectiveness indicators
Medicines Use Process	Posology Dosing regimen Methodology of administration Duration
Security	Adverse effects Precautions Interactions Contraindications
Conservation	Conservation

[Adapted from (232)*]*

Romero-Sanchez *et al*. (2016) applied this validated questionnaire [(Garcia-Delgado et al. (2009)] in Spanish pharmacy users who went to the pharmacies getting one or more medications dispensed. The predictive factors for inadequate patient medication knowledge achieved were the unskilled workers, caregiver, and the use of more than one drug and patient´s that did not know the name of the medication. (233)

Rubio *et al*. promoted a cultural adaptation to European Portuguese language of the questionnaire previous developed by Garcia-Delgado *et al*. (2009) called "Patient Knowledge about their Medications (CPM-PT-PT)". However, the authors mentioned the need for further studies to demonstrate the equivalence of the psychometric properties (reliability and validity) of the Portuguese version, so it could be used in pharmaceutical care research projects in Portugal. (240)

Wali & Grindrod (2016) designed a protocol with semi-structured interviews to explore the major challenges in population with low health literacy regarding medication information (age >50 years, speaking English as a second language). The major barriers identified were: short time with the Pharmacist,

understanding medication information, forgetting medication information, side effects and drug interactions. (241)

1.5.4 Disease Knowledge Assessment

A lack of knowledge about disease has been reported as an important factor contributing for patient´s medication adherence, and negative health outcomes. (242)

The assessment of patient´s knowledge about disease is not a procedure performed across the board, nor there is a systematic methodology for its implementation, since each pathology has specific characteristics and the activity of disease prevention and monitoring is characteristic for each particular disease.

However, it is a common assessment procedure in chronic diseases in which the patient's behaviour, lifestyle or when managing implications in their daily life, represents a high burden in the degree of control of their disease such as in asthma (243,244), diabetes, cystic fibrosis (245,246), inflammatory bowel disease, among others.

Some tools used to assess patient´s disease knowledge are presented as a mixed evaluation of disease knowledge with medication knowledge and attitudes toward disease and medication. (247)

Kim *et al*. evaluated patient´s knowledge addressing open questions about chronic diseases regarding ways to prevent the onset of diseases and ways to detect diseases such as breast cancer, diabetes and hypertension. (248)

Some tools to access patient´s knowledge about diabetes have been developed for several groups of researchers, mostly in English such as e.g. “Brief Diabetes Knowledge Test” (thirteen multiple-choice questions) (249), that has been used for several research studies. (250) A latest version of the previous questionnaire, “Revised Diabetes Knowledge Test (RevDKT)”, allows to

evaluate the patient's general knowledge of diabetes and diabetes self-care (23 multiple-choice questions). (251)

A group of New Zealander researchers carried out a systematic review, which identified a group of questions used to assess knowledge regarding cardiovascular diseases such as stroke. (252)

Giardina *et al*. (2012) developed a longitudinal observational program to assess the relationship between cardiovascular disease knowledge, race/ethnicity, education, and body mass index (BMI). The three questions that were placed to adult women were: "*1. What is the leading cause of death among US women?; 2. What are early warning symptoms of heart attack?; 3. What are the actions to take if experiencing a heart attack?*". (253)

Arikan *et al*. (2009) validated a questionnaire to measure the knowledge level of adults about risk factors for cardiovascular diseases (CVD), which included several domains: features of cardiovascular diseases, risk factors, and the results of adopting a risk-free attitude. Nevertheless, this tool was only developed in Turkish language. (254)

Tian *et al*. (2011) developed a cross-sectional study to assess patient´s knowledge about chronic diseases (diabetes and hypertension), using a group of 12 questions, addressing basic knowledge (e.g. target values for blood pressure and glucose), risk factors for chronic diseases and daily self-care techniques. The answers were summed into a total knowledge score, being results <5 considered a low score. (255)

In a Portuguese prospective randomized trial to evaluate the Pharmacist's interventions, conducted by Morgado & Castelo-Branco (2011), patient´s knowledge about hypertension was evaluated considering target values for blood pressure and consequences of uncontrolled hypertension (at least two complications). (89)

Monitoring blood pressure is one of the recommendations provided and that can be advantageous in untreated hypertense subjects as well in treated patients

since it enables monitoring the effectiveness of pharmacological treatment and increase treatment adherence, and could be applicable to both ambulatory and home blood pressure. (12)

A low level of patient´s disease knowledge is a significant risk factor for negative outcomes in disease control such as chronic obstructive pulmonary disease (COPD). (256)

There is still no available tool to assess patient´s disease knowledge, to be used specifically in patients with diabetes, hypertension or dyslipidaemia patients, in a systematic way and that has been translated into Portuguese language.

1.5.5 Health Literacy

In 2004, a publication from the Institute of Medicine Committee on Health Literacy defined health literacy as "*the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions*". (257)

In the United States of America it has been estimated that 90 million adults have trouble understanding and acting on health care information. (257)

Patients with low literacy had fewer skills to interpret prescription medication warning labels correctly (3.4 times less). (258)

An exploratory study performed in Portugal (2009) suggested that most users of the Imaging Service of Lisbon Central Hospital did not have the literacy desirable but only minimally adequate, they felt the need to rely on other people to help read hospital flyers, and individuals who had only completed the first year of school were those who had more difficulties in reading patient information leaflet. (259)

Although in the last decade illiteracy has reduced in Portugal, according to the 2011 census, there are still about 500.000 residents aged 10 years or older who cannot read or write, i.e., unable to read and comprise written words or writing a

complete sentence. In the Algarve region, about 11% of the population is illiterate, and about 25% has only 1st full cycle. (260)

Low health literacy has been associated to higher difficulty accessing health care, following instructions from a Physician, and taking medication properly, and understanding medical information. A need has been detected concerning a more careful selection of information that is transmitted to the patient and how it is transmitted, especially by the Physician and other health professionals, including Pharmacists. (261)

A meta-analysis including 48 studies (2016) identified a positive and significant correlation between health literacy and patient adherence, in which non-adherence was more than 1.33 times higher (standardized relative risk) among individuals who had lower health literacy. (262)

Mantwill & Schulz (2015) identified, from a multiple regression analysis, “, that type 2 diabetic patients with lower health literacy levels tended to have higher medication costs. (263)

A few number of tools are available to assess health literacy, with different methodologies used, most of them having been validated to be applicable in English spoken subjects. The following tools are the ones that are available to be used: REALM (Rapid Estimate of Adult Literacy in Medicine), WRAT (Wide Range Achievement Test), TOFHLA (Test of Functional Health Literacy in Adults), NVS (Newest Vital Sign)(264), SAHLSA-50 (Short Assessment of Health Literacy for Spanish Speaking Adults). (265)

REALM tests the word recognition and pronunciation of 66-item, evaluating the vocabulary domain, but not a reading comprehension instrument, and it is expected to take about 3-4 minutes to apply this instrument (266) The REALM-R is a shorter version of REALM, including only 7-item to be applied in several research conditions. (267)

TOHFLA has been identified as a reliable indicator of patient ability to read health-related materials, including 50-item reading comprehension and 17-

item numerical (filling blank spaces of a text using words from a list), taking about 22 minutes to be applied. (268) A shorter version (S-TOFHLA) was later developed in 1999, including 4 numeracy items and 2 prose passages (12 minutes to be applied). (269)

NVS (Newest Vital Sign) is an instrument to assess health literacy base on six (6) questions about a food nutrition label, with scores from 0 to 6, been validated to be used in the United Kingdom. (270)

Salgado *et al*. evaluate the utility of this instrument as a proxy for medication adherence in community-dwelling older adults, enrolling users of 12 daycare centers in Amadora (Portugal). Nevertheless, the results showed a high prevalence of wrong answers, about 90% for all questions excluding number 5 (49.0% of wrong questions). Also no correlation was found between these results and SILS, the other instruments used to detect limited reading ability. This instrument included one question: “How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your physician or pharmacy?”, a five-point Likert-type scale [(from 1, never, to 5, always), for score lower than 2 a difficulty with reading printed health-related material was identified. (271)

SAHLSA-50 was developed from REALM, to be used in Spanish-speaking population, allowing an evaluation of subject’s comprehension of medical terms commonly used in clinical and public health settings. Includes 50 items, for which one it has a question, a key word (correct choice) and a distractor (plausible but incorrect choice), where the subject is asked to identify the correct word for the item, or the interviewer can identify the answer as “Don´t know”. (265)

The results obtained during the SAHLSA-50 validation suggested that it was a useful instrument to identify Spanish speakers with low health literacy. (265)

Interestingly, SAHLSA-50 has been already adapted and validated to Portuguese language (Brazilian) by Souza *et al*. (2014), including 18 items selected from the 50 initial from SAHLSA-50. (272)

SAHL-S&E is an instrument constructed based on the methods used for SAHLSA-50, but containing 18 items selected from REALM, having presented good reliability and results indicated that it may be useful to recognize individuals with low levels of health literacy (α >0.90), and to be used in both subjects speaking Spanish and English. (273)

Despite several studies showing the association between low health literacy and non-adherence, it appears to exist differences between low, moderate and high health literacy individuals and their non-adherent behaviour. Otini *et al*. (2014) suggested a possible U-shaped curve in the relationship between non-adherence and health literacy. This approach suggested that people with low health literacy would need a different level of intervention (self-efficacy and knowledge improvement) comparing to people with moderate levels of health literacy (that may not require intervention), while people with high health literacy may in fact be intentionally non-adherent. (274)

A new instrument has been recently validated to assess patients´ beliefs about their capability to successfully manage problematic situations related to communication with their doctor: The toll Patient's Communication Perceived Self-efficacy Scale (PCSS), can be applied to patients with inadequate or marginal health literacy. (275)

King *et al*. (2011) have reached a new definition, "pharmacotherapy literacy" as "*an individual's capacity to obtain, evaluate, calculate, and comprehend basic information about pharmacotherapy and pharmacy related services necessary to make appropriate medication-related decisions, regardless of the mode of content delivery (e.g. written, oral, visual images and symbols)*". (276)

Health Literacy may lead to negative outcomes on patient´s health, and this can occur from several ways (Figure 4). (277)

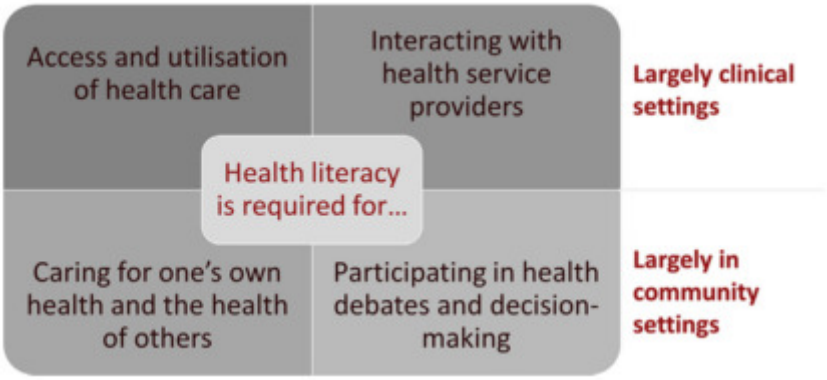


Figure 4: Health literacy and improvements in health outcomes.

Adapted from (277)

The assessment of subject´s health literacy is not mandatory for all subjects, but can be a way allowing the identification of specific needs of individuals or population groups, and to a future implementation of interventions that improve patient´s health outcomes. (277)

A low health literacy has been associated with negative health outcomes such as more hospitalizations and increased use of emergency care, lower specific medical care such as mammography screening and influenza vaccine, poorer ability to have an appropriate use of medication; and worse overall health status and higher mortality incidence among elderly subjects. (8) Also a poorer use of healthcare services appears associated with a low level of health literacy. (278)

A cross-sectional study developed in Switzerland, aimed to analyse the association between health literacy and three years of medication costs (2009–2011) in a group of patients with type 2 diabetes. It was verified a significant association ($p<0.05$) between low health literacy and higher medication costs (year 2010 and 2011). (263)

A systematic review aiming to identify Interventions to improve medication knowledge and adherence in low health literate populations, identified 37

studies assessing knowledge (of 47) and others assessing adherence (26 of 47) with a significant effect on the intended outcomes in 27 and 19 of the studies, respectively. (279)

Bandura (1977) defended a cognitive theory referring to an individual's belief in his or her ability to categorize and perform vital actions to reach for certain outcomes, considering that expectations of personal efficacy will determine future coping behaviour. (280)

Nevertheless, intervention strategies considering knowledge transfer may need to address self-efficacy among patients across all literacy levels to be successful in improving patient´s adherence. (281)

1.6 Rational and Approach - ReMeD study

The increase in the Portuguese population longevity led to a marked growth of patients presenting multiple morbidities, mainly chronic diseases. Among these chronic diseases there are several major risk factors associated with the main cause of death in Portugal, which are the circulatory diseases. (9) In addition, for diseases such as hypertension, dyslipidaemia, diabetes *mellitus*, among others, the Portuguese population presents a high prevalence and a low rate of disease control. (18,282,283)

Therefore, there has been an increase in the use of health services, reflected in an increasing number of visits to health care units during recent years. (41)

This situation, along with the economic crisis, evidenced some existing failures of the Portuguese health system in the capacity to respond effectively to the patient´s needs. This means that there is a growing need for better management of the Portuguese health resources.

Among this scenario, the number of medicines used by patients also increased. (47) This may represent not only an increase in direct medicines costs in

Portugal, but also an increase in indirect drug costs, which includes the costs associated with adverse drug reactions.

The Pharmacist, a health professional focused on patient centered care, could play an important role on patient´s health outcomes, being also an excellent opportunity to extend the services provided in the field of pharmaceutical care.

The medication review service, already available in several countries and using different methodologies, have been shown to contribute to the improvement of patient´s health outcomes in different settings such as the pharmacy, primary care units, hospitals and residential care units. In Portugal, this service has not yet been systematically implemented, so there is no systematic methodology available to be applied by the Portuguese Pharmacists.

Therefore, the aim of this thesis was to establish a methodology to analyse outcomes in the process of medication use through medication review, with the acronyms of **ReMeD study**.

The ReMeD study was developed in a clinical setting in the Southern Portugal, the “Association for the Diabetes *mellitus* study and support to diabetic patients in the Algarve” (AEDMADA) clinic located in Faro. This institution was established in 2006, with the aim of assisting diabetic patients and their families, by providing differentiated healthcare and improve patient´s health outcomes.

The methodology established to achieve the thesis objectives included three main features: patients’ clinical evaluation, patients’ medication review, and outcomes obtained from the medication review analysis.

In order to identify which patients might be more likely to benefit from this service, the predictive factors associated with negative outcomes were also identified.

A comparison of the eligibility criteria for medication review services, which have been systematically implemented in other countries (Australia, Canada and England), was performed in order to find out whether the MR methodology

used in the ReMeD study would allow similar benefits and outcomes as those obtained using other methodologies.

One of the humanistic outcomes that was considered in the methodology applied in the ReMeD study was patient´s health literacy, given the recognized relevance in patient´s health outcomes. In order to enable the signalization of patients with low health literacy, the adaptation of the questionnaire “Short Assessment of Health Literacy - Spanish and English (SAHL-S&E) to Portuguese language was performed (SAHL-PT). This was another objective defined for this thesis and was carried out prior to the implementation of the ReMeD study itself.

2 AIM AND OBJECTIVES

2.1 AIM

The main purpose of this study is to establish a methodology to analyse outcomes in the process of medication use through medication review, in a clinical setting.

2.2 OBJECTIVES

1) Adaptation to Portuguese language of the “Short Assessment of Health Literacy - Spanish and English (SAHL-S&E)” (273)
2) ReMeD study:
    a. Clinical patient evaluation:
        i. Characterization of patient´s health problems;
        ii. Characterization of biomarkers and other risk factors for cardiovascular diseases (blood pressure, lipid profile (total cholesterol, triglycerides, LDL-C, HDL-C), glycemic profile (fasting glucose, postprandial glucose and HbA1c), body mass index (BMI), smoking habits, physical exercise habits and dietary habits;
        iii. Assessment of the cardiovascular risk;
        iv. Analysis of the degree control of risk factors for cardiovascular diseases;
    b. Characterization of pharmacotherapeutic profile;
    c. Analysis of medication review outcomes:
        i. Clinical outcomes:
            1. Identification of negative clinical outcomes;
            2. Identification and characterization of drug related problems;
            3. Identification of risk situations for negative clinical outcomes;
        ii. Economic outcomes:
            1. Number of medicines;

2. Number of hospitalizations;
3. Number of Physicians following patient;
4. Rate of reimbursement of medicines.

iii. Humanistic outcomes:

1. Medication adherence assessment;
2. Patient medication knowledge;
3. Patient knowledge about disease and monitoring procedures;
4. Patient health literacy [previous adaptation of the “Short Assessment of Health Literacy - Spanish and English (SAHL-S&E)” to Portuguese language (Portugal) - SAHL-PT];
5. Help with medication;
6. Self-perceived health status;

iv. Potential interventions;

d. Identification of predictive factors for clinical outcomes associated to medication review;
e. Analysis of eligibility criteria for medication review programs available in Australia, Canada and England.

3 METHODOLOGY

3.1 Adaptation to Portuguese language of the "Short Assessment of Health Literacy - Spanish and English (SAHL-S&E)"

Study Design

Observational, descriptive, cross sectional population-based study.

Study Population

Users of the Algarve region pharmacies (8 pharmacies).

Inclusion criteria

- Patients aged 18 years and older;
- Can read and write;
- Fluent in Portuguese.

Exclusion criteria

- Patient with cognitive impairment;
- Serious vision or hearing problems.

Sample

Subjects were recruited from Faro district pharmacies (8) users in the period of 2 weeks (September 2014).

Data collection

All subjects who met inclusion criteria and accepted voluntarily to participate in this research study were enrolled in this project.

Data collection was conducted through structured interviews, by completion of a questionnaire (Appendix A).

Subject´s data were collected anonymously without identification of the subject who agreed to participate in the project.

Translation

A translation of the Spanish version of the questionnaire (273) from Spanish to Portuguese was performed, using the following procedure:

1) Translation from Spanish into Portuguese by two investigators who have expertise in the Spanish language at the University of Algarve;

2) The Portuguese version of the instruments was evaluated by two Portuguese/Spanish bilingual persons;

3) The questionnaire was translated back into Spanish by two Portuguese-Spanish independent translators, two other university professors with expertise in research.

4) Both versions were compared to the original language, confirmed checks with the translators, considered the differences, and a final version was generated.

5) The previous version of the questionnaire was applied in a pilot sample of 20 subjects who accomplished the inclusion criteria for this adaptation study, in order to identify some difficulties in the practical application of the questionnaire. In this pilot sample, there were no difficulties registered during the questionnaire application. Therefore, this version was used as the final version of the adaptation of this instrument for the Portuguese population, the SAHL-PT (Appendix B).

Application

The questionnaire included 18 medical terms to assess in Portuguese adults, the ability to read and understand common medical terms. The test application was conducted through the use of cards 10.5 x 14.8 cm (A6), each containing a medical term printed in bold at the top, and the two words associated, the keyword and the distractor, at the bottom.

The following instructions were used by the interviewer (Table 28):

Table 28: Interview instructions.

1.	Before the test, the interviewer should tell the individual being examined: "*I'll show you a card with 3 written words. First, I would like you to read a word that is on the top aloud. Then you'll read the two words below and please tell me which of the two words is related to the word from above. If you do not know the answer, please say "do not know". Do not guess.*"
2.	The first card is shown;
3.	The interviewer should tell the individual being examined: "*Now, please read the word that is on the top aloud*"
4.	The interviewer should then read the keyword and the distractor (the two words at the bottom of the card), and say: "*Which of the words is related to the word above? If you do not know the answer, please say, "I do not know.*"
5.	The interviewer can repeat the instructions until the individual examined feel comfortable with the procedure;
6.	The test continues with the remaining cards;
7.	The right answer for every test item was determined by the correct pronunciation and the association. Each correct answer corresponds to one (1) point.

The interviewer had a score table for recording the responses of subjects being examined. This registration was done without the examined subject seeing it nor being distracted by the procedure. When the test was finished, the account of the total score was performed generating the final score of the Short Assessment of Health Literacy – Portuguese (SAHL-PT) (Appendix B).

Study Variables

The maximum score that can be achieved is 18, corresponding to 1 point for each of the items included in the questionnaire.

Subjects who obtained a score equal or under 14 were considered as having “low health literacy”.

Statistical analysis

Data were analysed with IBM-SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA).

All quantitative data were analysed using descriptive statistics presented as mean, median, standard deviation, minimum and maximum. The qualitative variables were described by counts (n) and percentages (%).

Reliability was examined using Cronbach´s α test, which is one of the measures most commonly used to evaluate the internal consistency of a group of variables (items), and can be defined as the correlation expected to be derived from the scale used and other hypothetical scales of the same universe, with equal number of items that measure the same characteristic. (284) This measure indicates the extent to which the reliability of the test scores was similar in the study sample.

3.2 ReMeD Study

3.2.1 Study Design

Observational, population based, descriptive and cross-sectional study (pilot).

Study Population

This study was developed at the clinic "Association for the Diabetes *mellitus* study and support to diabetic patients in the Algarve" (AEDMADA). This association, placed in Faro, was founded in 1996, and is a non-profit charity organization with the legacy of addressing the needs of diabetic´s patients and their family. The main goals of AEDMADA are to promote early diagnosis, possible prevention and treatment to delay or prevent complications of diabetes *mellitus*. (285)

Subjects included in this research study were AEDMADA users that fulfilled the inclusion criteria described below.

Inclusion criteria

- Patients aged 18 years and older;
- Using one medicine for at least 6 months.

Exclusion criteria

- Patient with cognitive impairment.

Sample Calculation

AEDMADA has a population of active users of about 400 subjects. AEDMADA users are mainly diabetic patients, and one of the most prevalent disease in the Portuguese population is hypertension with an estimated prevalence of 42% (15). Also in the diabetic population, hypertension presents an increased prevalence (80.3%), according to a national study held in the Portuguese type 2 diabetes patients. (283) For a confidence level of 95% and a confidence interval of 5%, the calculated sample size was 117 subjects.

During the enrolment period, 126 subjects who met the inclusion criteria were included in the study. However, due to lack of complete and updated data on biomarkers for cardiovascular diseases, three (3) subjects were excluded, three (3) subjects did not bring the medication they were taking and two (2) subjects didn´t accept to participate in the study, being excluded as well.

Data collection

All subjects who met the inclusion criteria and accepted voluntarily to participate in this research study signed an informed consent prior to initiating data collection (Appendix C).

Data collection was conducted through structured interviews, which was held during a consultation in a systematic way by completion of a questionnaire (Appendix D).

Upon confirmation of the medical consultation by telephone, AEDMADA users were asked to bring with them all medications they were using (either prescribed or not by a doctor), as well as over-the-counter medicines, food supplements and natural health products.

In consultation day, subjects were led to a private room, whereas the research project was presented and respective goals. If the subjects agreed to participate they would give their written consent and the interview could be initiated.

Study Variables

Cognitive state was verified by asking the patient to identify the current year, day and day of the week.

3.2.2 Socio-demographic variables

The socio-demographic variables that were considered for patient´s characterization are described in Table 29.

Table 29: Socio-demographic variables description.

Variable	Description
Age	Full years, directly asked to the patient and confirmed by the birth date in the patient´s clinical file
Gender	Masculine or feminine
Marital status	Married/ committed, single, widower, or divorced, according to information provided by patient
Household	Alone and autonomous; alone with support; husband/wife; parents; brother; son/daughter/daughter in law/son in law/grandchildren; partner and children; institution; partner, son/daughter and grandchildren; partner, children and parents, according to information provided by patient
Qualifications	1st cycle of basic education (4th grade); 2nd cycle of basic education (junior); 3rd cycle of basic education (9 years); secondary education (12th grade); professional course/technological (Level III); higher education; cannot read or write; can read and/or write without having education degree), according to information provided by patient
Professional situation	Retired; unemployed; self-employed; employed by others; retired with activity; without professional activity, according to information provided by patient
Follow-up period (AEDMADA clinic)	Months, data obtained from the patient file

3.2.3 Variables related to patient clinical evaluation

Clinical diagnosis: Clinical profile was described using the information provided by patient, completed and confirmed with the information available in the patient´s clinical file, and was classified according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (WHO Version – 2015):

http://apps.who.int/classifications/icd10/browse/2015/en#/V.

Biomarkers and other risk factors for cardiovascular diseases: The following parameters were considered to assess cardiovascular risk: blood pressure value, glycemic profile (HbA_1c, fasting glucose, and post-prandial glucose), lipid profile (total cholesterol, triglycerides, LDL-C, HDL-C), body mass

index (BMI), smoking habits, and physical exercise, according to the reference values indicated below.

- Blood pressure (BP)

During medical consultation BP was measured, at least twice, with a minimum interval of one to two minutes between measurements, and the lowest levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were registered in the patient´s clinical file (286). Reference values adopted for SBP and DBP are described in Table 30.

Table 30: Blood pressure reference values.

Parameters	Therapeutic goal
General (286,287)	
Systolic Blood Pressure	< 140 mmHg
Diastolic Blood Pressure	< 90 mmHg
Diabetic Patients (24)	
Systolic Blood Pressure	< 140 mmHg
Diastolic Blood Pressure	< 85 mmHg
Patients with nephropathy	< 130/85 mmHg

- Glycemic profile

The parameters considered were: fasting glucose, postprandial glucose and glycated haemoglobin (HbA_{1c}). The reference values adopted for these parameters were those from the Portuguese Society of Diabetology (SPD) and the Portuguese General Direction of Health (DGS) and are described in Table 31.

The value of HbA1c was collected from the patient´s clinical file and was considered valid when obtained in a period of less than 3 months from the data collection. The values of the remaining parameters (fasting glucose and postprandial glucose) were collected in the consultation day.

The assessment of glycemic profile control was performed considering HbA1c value, analysed for each patient individually, considering their individual characteristics in accordance with applicable guidelines (Table 31).

Table 31: Reference values for glycemic profile.

Fasting glucose	Hypoglycaemia: < 70 mg/dL Normoglycaemia: 70 - 130 mg/dL (7.2 mmol/L) Hyperglycaemia: > 130 mg/dL
Postprandial glucose	Hypoglycaemia: < 70 mg/dL Normoglycaemia: 70 - 180 mg/dL (9–10 mmol/L) Hyperglycaemia: > 180 mg/dL
HbA1c	Optimal: < 6.5% General: < 6.5 - 7% Long term Diabetes *mellitus* (> 10 years), short life expectancy, comorbidities: < 7- 8%
Target values stricter for HbA1c (e.g. 6.0-6.5%) were considered for selected patients: short duration of disease, increased life expectancy without significant CVD if values can be achieved without significant hypoglycaemia or other adverse effects of treatment. *Target values less restricted (e.g. 7.5-8.0% or higher) were considered for patients with history of severe hypoglycaemia, limited life expectancy, complications in advanced stage and clinically relevant multiple morbidities and in patients where the target value is difficult to achieve in spite of intensive training in self-treatment, repeated advice and effective doses of multiple glucose lowering agents including insulin.*	

[Adapted from (288–291)*]*

- Lipid profile

The reference values adopted were those from the European Society of Cardiology / European Atherosclerosis Society (ESC/EAS) and the Portuguese General Direction of Health (DGS) for the following biochemical parameters: total cholesterol, LDL-C, HDL-C, and triglycerides, as described in Table 32.

These parameters were collected from the patient´s clinical file, and were considered valid when obtained in a period of less than 6 months from the data collection. Lipid profile analysis was performed as an individual approach, according to the applicable guidelines (Table 32).

Table 32: Lipid profile reference values.

Total Cholesterol		< 190 mg/dL
LDL-C	▪ Low cardiovascular risk (score <1%) or moderate (score 1% - 5%)	< 115 mg / dl
	▪ Asymptomatic people with high cardiovascular risk (score ≥ 5% to <10%) ▪ Family with atherogenic dyslipidemia ▪ Grade 3 hypertension (≥180 and / or ≥110 mm Hg)	< 100 mg / dl
	▪ Very high cardiovascular risk (CV clinically evident disease, type 2 diabetes or type 1 with one or more cardiovascular risk factors and/or organ- target of injury, severe chronic kidney disease [GFR <30 ml / min / 1.73 m2] or a level score ≥ 10%)	< 70 mg / dl
HDL-C		> 40 mg/dL (male) > 45 mg/dl (female)
Triglycerides		< 150 mg/dL

Legend: CV: cardiovascular; GFR: glomerular filtration rate; HDL-C – High lipoprotein cholesterol; LDL-C – Low lipoprotein cholesterol.

[Adapted from (292,293)*]*

- Body mass index

The parameter body mass index (BMI) was calculated through the formula: [(ratio of weight (kilograms) / height^2 (squared meters)], and classified according the reference values of the World Health Organization (WHO), as described in Table 33. (294)

Table 33: Body Mass Index (BMI) Classification.

BMI Classification	Kg/m²
Underweight	<18.50
Severe thinness	<16.00
Moderate thinness	16.00 - 16.99
Mild thinness	17.00 - 18.49
Normal range	18.50 – 24.99
Overweight	≥25.00
Pre-obese	25.00 – 29.99
Obese	≥30.00
Obese class I	30.00 – 34.99
Obese class II	35.00 – 39.99
Obese class III	≥40.00

[Adapted from (294)*]*

- Smoking habits

Smoking habits data were collected from information provided by the patients themselves during the interview, and were classified as: smoker, ex-smoker, non-smoker, as described in Table 34.

.

Table 34: Smoking habits characterization.

Classification	Habits
Smoker	Number of cigarettes or other similar products consumed per day.
Ex-Smoker	Quit smoking for at least one (1) year.
Non-Smoker	No smoking habits, or at least fifteen (15) years after quit smoking (after this period the cardiovascular risk is similar to someone who has never smoked, if no heart disease was developed).

- Physical exercise habits

The physical exercise habits were classified according to:

- Practice of physical exercise regularly (yes/no).
- Frequency (number of times per week).
- Duration of each session (minutes).

Cardiovascular Risk: The stratification of risk for cardiovascular diseases was achieved using the recommendations of the Portuguese General Direction of Health (DGS) and European Society of Cardiology. (24,287,295)

The cardiovascular risk of patients was classified individually in a qualitative way and was classified as “Very High Risk”, “High Risk”, “Moderate Risk” or “Low Risk”.

3.2.4 Variables related to Pharmacotherapeutic Profile

Medicines: All prescribed and consumed medicines (including over the counter medicines and food supplements) were considered at the time of the data collection and were subsequently confirmed in clinical patient process.

During the interview, patients were asked about previous situations of intolerance and / or drug allergies.

Data were collected regarding brand name medicine, drug, dosage, intakes per day, start date, prescriber, and any additional information can could be considered relevant was recorded as “observations”.

The following parameters were considered:

- Total number of medicines used by the patient [including over the counter medicines (OTCs)];
- Total number of food supplements;

Drugs were classified according ATC classification (http://www.whocc.no/atc_ddd_index/) for all medicines at 1st level (anatomical main group) and 4th level (chemical subgroup).

The information about medicines was obtained in the Summary of Products Characteristic (SmPC) available at the INFARMED site (http://app7.infarmed.pt/infomed/inicio.php) and EMA site (http://www.ema.europa.eu).

Polypharmacy was defined as patients taking 5 or more medicines.

Potential drug-drug interactions (DDI´s): were identified using online available tools: http://reference.medscape.com/drug-interactionchecker, http://www.drugs.com/drug_interactions.html and information included in the SmPC.

3.2.5 Results from Medication Review

Medication Review (MR) was performed individually for each patient presenting for each clinical, humanistic and economic outcomes. The analysis was performed by health problem, considering the diagnoses identified for each patient and also identifying clinical situations that were not being addressed.

3.2.5.1 Variables related to Humanistic Outcomes

Medication Adherence: The assessment of medication adherence was performed using two instruments: the “Measure Treatment Adherence” scale adapted from Morisky & Green and validated to Portuguese language by Delgado & Lima (Medida de Adesão aos Tratamentos - MAT) (296), and the Haynes-Sackett test (297) (Table 35).

Table 35: Medication adherence assessment instruments.

MAT: This scale measures levels of adherence to drug treatment, using seven (7) questions that use a response in a Likert scale (5 points), with a minimum value of one (1), which corresponds to "always", and a maximum of six (6), corresponding to "never". The average score of patient medication adherence was obtained by the ratio of the total values of each element and the total number of elements and can assume values between one (1) and six (6). (296)
HS: Haynes-Sackett test is a self-reported method based on asking the patient about medication adherence and is divided into two parts: the first part is not a direct question to the patient about medication use, an environment is created to an appropriate conversation and the interviewer talk to the patient about the difficulty of taking medication ("Most patients have difficulty in take all your medicines "); in the second part of the question patient is asked: "Do you have any difficulties taking yours?". When the answer is yes, considers as a non-adherent patient. When the patient's answer is no, the interviewer cannot tell the truth and then insists asking other questions: "How do you take them?" (every day, many days, some days, a few days or rarely). Patients were classified as adherent if the percentage of adherence was between 80-110%. (297,298)

Patient Medication Knowledge: The assessment of patient medication knowledge (MK) was performed during patient interview considering six parameters: *medicine´s name*, *drug´s strength*, *therapeutic indication*, *storage conditions*, *timing of administration* and/or *dosing Intervals* and *daily dose use*, as described in Table 36.

.

Table 36: Patient´s medication knowledge assessment.

Variable	Answers	Indicator
Medicine´s Name	1. Patient knows medicine´s name. 2. Patient does not know medicine´s name.	Rate (%) of medicines whose name was correctly identified
Drug´s strength	1. Knows drug´s strength 2. Does not know drug´s strength	Rate (%) of medicines whose drug´s strength was correctly identified

Table 36 *(Continued)*

Variable	Answers	Indicator
Therapeutic Indication	1. Knows the correct therapeutic indication 2. Does not know the correct therapeutic indication 3. Does not know the therapeutic indication 4. The information on the therapeutic indication is not complete	Rate (%) of medicines whose therapeutic indication was correctly identified (1 and 4)
Storage conditions	1. Correct storage 2. Incorrect storage 3. Lack of information on medication storage	Rate (%) of medicines whose storage conditions were correctly identified (1 and 3)
Timing of administration and/or dosing Intervals	1. Correct 2. Incorrect	Rate (%) of medicines whose timing administration and/or dosing intervals were correctly identified
Daily dose use	1. Correct 2. Incorrect	Rate (%) of medicines whose daily dose use was correctly identified

The score of Medication knowledge (MK) per patient was calculated as the average (in %) of the six parameters considered in the medication knowledge assessment, using the formula [(MK1+MK2+MKn)/nr total medicines] x 100.

For patients with score values below 50%, it was considered that the patient had "*low medication knowledge*".

Patient Disease Knowledge: The assessment was performed considering three domains, namely "*target value for biochemical/physiological parameters*", "*complications of uncontrolled disease*" and "*self-monitoring procedures*", as described in Table 37.

Table 37: Patient Disease knowledge assessment.

	Parameter	Answers	Assessment
Hypertension	✓ What is the target value for your BP?	✓ Correct ✓ Incorrect or ✓ Do not know	For patients with an issue identified in the evaluated parameters, a lack of knowledge will be considered
	✓ Could you please identify two possible complications for uncontrolled BP?	✓ Patients are aware of the risks of uncontrolled BP if they referred correctly at least one negative consequence for uncontrolled BP	
	✓ Did you take your BP in the last 12 months? (Yes/No) ✓ How often did you check your BP in the last 12 months? (Nr. per month)	✓ Patients who monitored regularly BP made a measurement and registration at least once a month or biweekly (299)	
Diabetes	✓ What is the target value for your blood sugar (fasting glucose and postprandial glucose)?	✓ Fasting glucose and postprandial glucose according guidelines (288–290)	For patients with an issue identified in the evaluated parameters, a lack of knowledge will be considered
	✓ Could you please identify two possible complications resulting from your uncontrolled BG?	✓ Patients are aware of the risks of uncontrolled BG if they referred correctly at least one negative consequence.	
	✓ How often in the last 7 days did you assess your BG? (number 0-7) ✓ How many days a week it was indicated to assess your BG, by your doctor, nurse or pharmacist? (number 0-7) (300)	✓ Mean±SD ✓ Mean±SD	
Dyslipidaemia	✓ What is the target values for your total BC?	✓ Total BC value according guidelines (292,293)	For patients with an issue identified in the evaluated parameters, a lack of knowledge will be considered
	✓ Could you please identify two possible complications resulting from your uncontrolled BC?	✓ Patients are aware of the risks of uncontrolled BC if they referred correctly at least one negative consequence for uncontrolled BC.	

Legend: BC - Blood cholesterol; BG - Blood glucose; BP - Blood pressure; HT - Hypertension; Nr – Number; SD – Standard deviation.

Whenever the patient had a “lack of knowledge” in one of the diseases that was included in the disease knowledge assessment, a “*lack of knowledge”* was considered.

Health literacy: According to patient interview a score was obtained for the SAHL-PT, wherein a score equal or less than 14 was considered as “low health literacy”.

Self-perceived health status: It was obtained during patient interview using the scale MOS SF-36 adapted to Portuguese language (301). A question was done to patient: “How do you consider, currently, your health?” and the patient was allowed to choose the answer between the following five (5) options: “Very poor”, “Poor”, “Fair”, “Good” or “Excellent”.

3.2.5.2 Variables related to Economic Outcomes

Medicines: All prescribed and consumed medicines (including over the counter medicines and food supplements) were considered at the time of the data collection and were subsequently confirmed in clinical patient process.

Hospitalizations: Number of times that patients were hospitalized in the last twelve (12) months and the length of hospitalization (days). This information was provided by patient during the interview and confirmed with the data from patient´s clinical file.

Physicians: During the interview, a question was held to the patient in order to analyse whether the patient was being followed by one or more Physicians and their respective medical specialty (general practice, and others specialties).

Rate of reimbursement of medicines: Described according to information provided by the patient and confirmed with the patient´s clinical file, classified as: general regime, special regime, or subsystem.

3.2.5.3 Variables related to Clinical Outcomes

Each health problem identified was analysed per individual patient. Their degree of control (effectiveness) was assessed in accordance with indicators defined in the respective clinical guidelines, considering information provided by patients, results of biochemical analysis provided by patients or available in patient´s clinical file. Drug´s safety was also analysed leading to the identification of potential adverse events reported by patients. Clinical situations that were untreated were also identified according the respective clinical guidelines, considering information provided by patients, results of biochemical analysis provided by patients or available in patient´s clinical file, but it was only considered a negative outcome when the situation was not yet identified.

Allergies and drug intolerances were recorded according patient´s information and data available in patient´s clinical file.

Negative Clinical Outcomes (NCO): The identification of negative clinical outcomes was performed with reference to various information, were classified as follows (Table 38).

Table 38: Negative Clinical Outcomes and information´s sources.

NCOs Type	Source
Disease Control	Clinical guidelines, as applicable. Treatment recommendations within the guidelines were considered appropriate, deviations were considered inappropriate.

Table 38 *(Continued)*

NCOs Type	Source
Suspected Adverse Drug Event(s)	"Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment" (302) SmPC: 4.8 Undesirable effects
Untreated Conditions	Clinical guidelines, as applicable. Treatment recommendations within the guidelines were considered appropriate, deviations were considered inappropriate.

Legend: NCO - Negative clinical outcome; SmPC – Summary of products characteristics.

Drug Related Problems (DRPs): Considered as "*an event or circumstance involving drug therapy that actually, or potentially, interferes with the desired health outcomes*" (177), identified from the information provided by patients crossed with available information in reference sources on medicinal products (Table 39). DRPs were considered as elements of the process of use of medicines. All medicines were included: prescribed medicines and over-the-counter products (OTC´s).

Table 39: Medicine´s and patient´s analysis.

	Scope	Issue	Analysis Source
Medicines	Drug selection	Therapeutic indication of medicine. Appropriateness of medication according to clinical situations, including contraindications. Potential drug-drug interaction or food-drug interaction. Duplicated drugs. Synergistic/preventive drug required.	▪ Medicine´s SmPC: ▪ 4.1 - Therapeutic indications; ▪ 4.3 – Contraindications; ▪ 4.5 - Drug interactions and other forms of interaction. ▪ Beers criteria (196)
	Drug form	Related to drug form.	▪ According to the difficulties reported by the patient.

Table 39 *(Continued)*

	Scope	Issue	Analysis Source
Medicines	Dose selection	Recommended dose Maximum dose Number of daily doses Adjustments to patients with hepatic or renal insufficiency, elderly or children, as applicable.	▪ Medicine´s SmPC: 4.2 - Posology and method of administration Clinical Guidelines
	Treatment duration	Duration of treatment and withdrawal period recommended, as applicable.	▪ Medicine´s SmPC: 4.2 - Posology and method of administration ▪ Clinical Guidelines
Patient	Medicine ´s use process	Timing of administration and/or dosing intervals. Medication adherence.	▪ Medicine´s SmPC: 4.2 - Posology and method of administration ▪ MAT scale (303) ▪ Haynes-Sackett test (297)
	Patient knowledge	Medication knowledge assessment.	▪ Assessment per medicine used.
	Other	Other issues.	

Legend: MAT – Measure Treatment Adherence; SmPC - Summary of products characteristics.

Drug related problems (DRPs) were classified considering seven (7) scopes, as described in Table 40. This classification was formulated based on the points analysed in the medication review activity, and from the adaptation of the various causes of DRP´s presented in classification of DRP´s from PCNE (v6.2) (177).

Table 40: Drug-related Problem´s (DRPs) classification.

DRP Scope	Type
Drug selection	Inappropriate drug (incl. contra-indicated)
	No indication for drug
	Inappropriate combination of drugs, or drugs and food
	Synergistic/preventive drug required and not given
	Duplicate drug

Table 40 *(Continued)*

DRP Scope	Type
Drug form	Inappropriate drug form
Dose selection	Drug dose too low
	Drug dose too high
	Dosage regimen not frequent enough
	Dosage regimen too frequent
	Dose adjustment is required (pharmacokinetics)
	Dose adjustment is required (improvement of disease state)
Treatment duration	Duration of treatment too short
	Duration of treatment too long
Drug use process	Inappropriate timing of administration and/or dosing intervals
	Drug underused (intentional non-adherence)
	Drug not used at all
	Wrong drug used
	Patient forgets to use drug (unintentional non-adherence)
Patient related	Low Medication knowledge
Other	Other DRPs

Legend: DRP – Drug-related problem; Incl. – Including.

Risk situations of NCOs: No negative clinical outcome (NCO) was identified, however problems with medication have been identified, so patient was at risk of suffering a NCO when at least one drug related problem (DRP) was identified. (142)

Planned Interventions: Intention of interventions after analysis of medication review´s outcomes. The classification of planned interventions was performed from the adaptation of "outcome of intervention" presented in the classification of DRPs from PCNE (v6.2) (177) and only the scope of the intervention was identified (Table 41).

Table 41: Planned intervention´s classification.

Planned Intervention	Description
No intervention	No intervention has been identified
At prescriber level	Intervention such as prescriptions revaluation, untreated conditions identification
At patient/carer level	Intervention at patient behaviour, medicine adherence, educational interventions
At drug level	Intervention at drug´s use such as administration time, number of units, number of doses
Other intervention	Intervention non-pharmacological, referral to other professionals (e.g. dietitian, physical exercise technician)

Eligibility criteria for medication review programs in Australia, Canada and England: The analysis of the inclusion criteria used for this service in these countries ascertains whether the study population meets these criteria. Other countries, such as the United States of America, were not included in this analysis because although they also have available this pharmaceutical service, the health system currently has significant differences from the Portuguese health system.

The eligibility criteria were analysed for the programs indicated in Table 42.

Table 42: Medication Review programs analysed.

Country	Program
Australia	Home Medication Review (HMR)
Canada	MedsCheck; MedsCheck for Ontarians living with Diabetes
England	Medicines Use Review (MUR)

3.2.6 Statistical analysis

Data were analysed with IBM-SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA) and presented as median, mean values and standard deviations (SD). Adherence to the Normal distribution was assessed using the Shapiro-Wilk test and also by analysing normal probability plots. (304)

According to the variables characteristics (normal or non-normal distribution) parametric or non-parametric procedures were used.

Comparison between groups of variables with non-normal distribution was performed using Mann-Whitney (two independent samples) or Kruskal-Wallis (k independent samples).

Group differences were analysed with a one-way analysis of variance (ANOVA), after testing for homogeneity of variance with the Bartlett's test. Pearson's correlation coefficient was used to describe the association between variables with normal distribution, Spearman´s correlation coefficient was applied for variables with non-normal distribution. Multiple comparisons were interpreted with Bonferroni's correction procedure.

In the analysis of predictive factors for negative clinical outcomes, for the independent variables that do not have a normal distribution, the logarithmic (log10) equivalent was used, in order to achieve a variable with normal distribution. Further association analyses were conducted using linear multiple regression procedures, with forward selection of predictors.

Statistical significance in all statistical tests was determined by two-tailed analysis and set at 0.05.

3.2.7 Ethical aspects

An authorization from the AEDMADA Ethics Committee was obtained for the study conduction at the clinic, and only the patients that accepted to participate

in this research and gave their written consent (Appendix C) before the start of the study were enrolled.

Patient information is confidential and each patient was identified through an identification number (enrolment number/month/year).

Furthermore, the project was submitted to Cranfield University Ethics approval (CURES), and was approved in the 22nd February 2016 (Reference: CURES/840/2016).

4 RESULTS

4.1 Adaptation of an instrument to assess health literacy to the Portuguese language

A sample of 153 subjects was used to hold the adaptation of the questionnaire purposed (SAHL-PT), including 58.2% female subjects, with a mean age of 66.7±12.3 years. Their ages ranged between 35 and 93 years, and presented a median of 69 years.

Approximately three quarters of the subjects were married (71.2%; n=109), 17.6% (n=27) were widowers, 6.5% (n=10) were divorced and 4.6% (n=7) were single.

In the analysed sample about 32.7% of subjects did not have the minimum level of education (9 years), and 20.3% (n=31) had only the 1st cycle (4 years) (Figure 5).

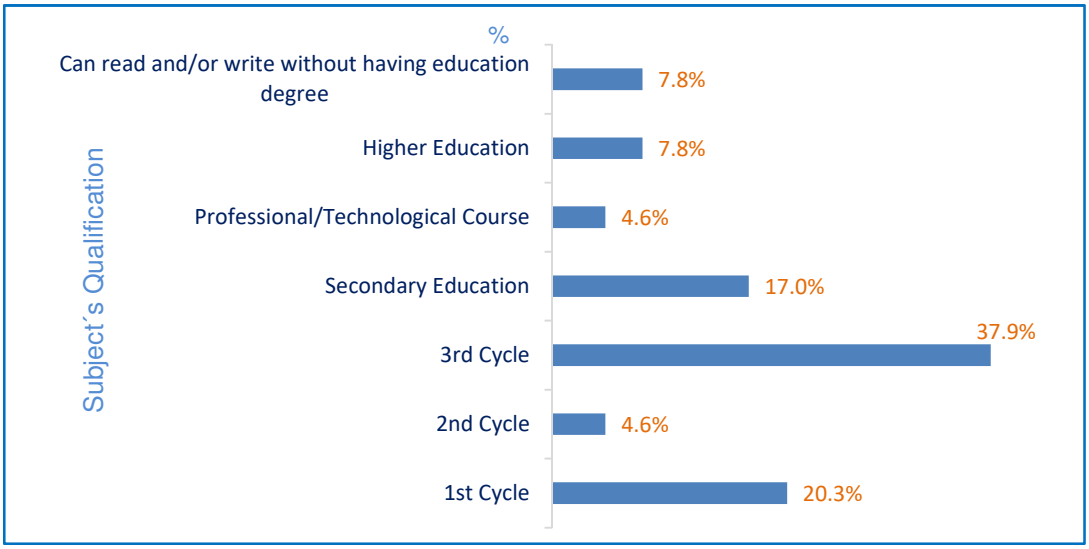


Figure 5: Characterization of subjects' qualifications.

Most subjects were 65 years or older (56.8%; n=87), were retired (58.8%; n=90), and 34.0% (n=52) had a professional activity, as described in Figure 6.

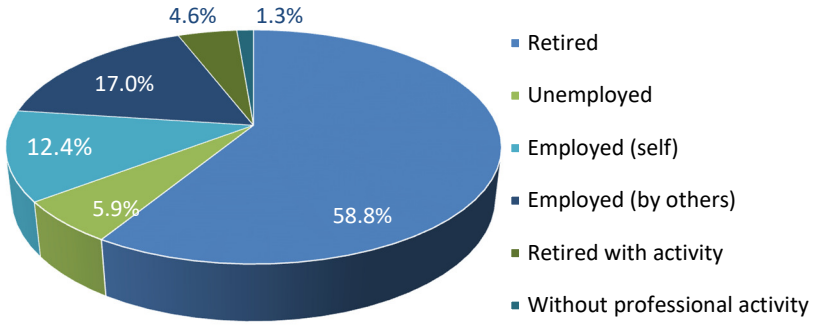


Figure 6: Characterization of subjects´ professional situation.

More than half of the individuals were living with the wife/husband (42.5%; n=65) or with partner and children (16.3%; n=25), and 31.4% (n=48) were living alone (Figure 7).

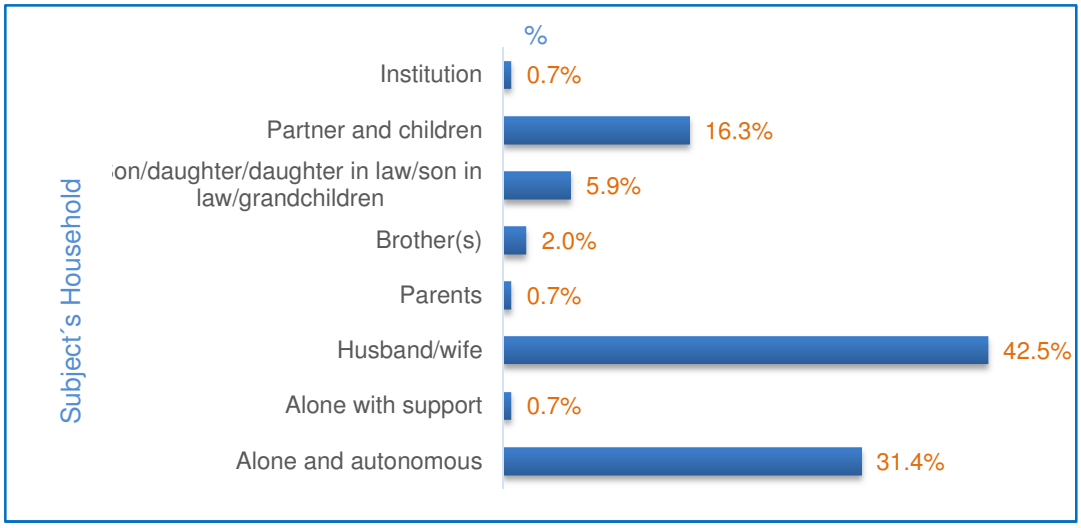
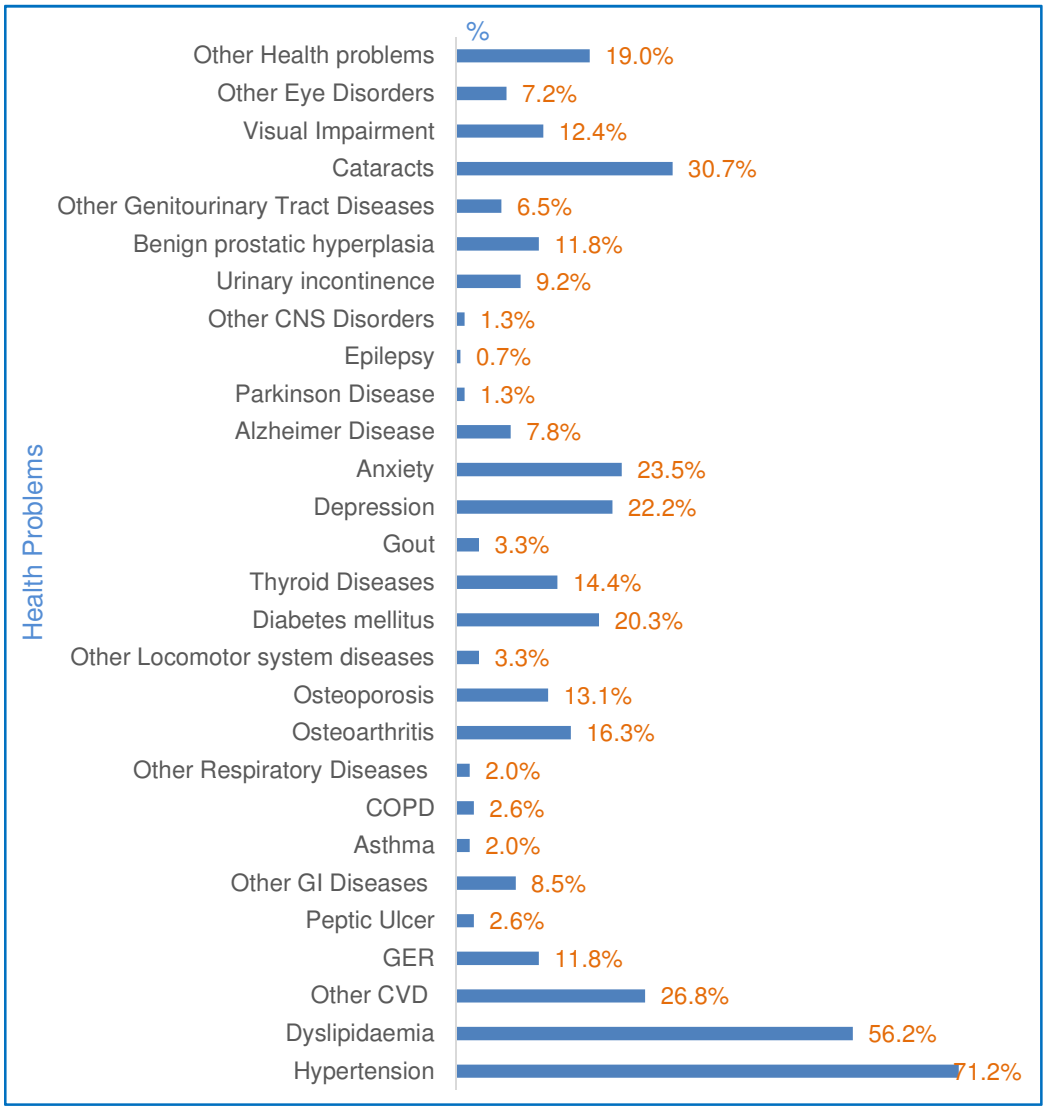


Figure 7: Characterization of subjects´ household.

Subjects have cardiovascular disease such as hypertension (71.2%; n=109), dyslipidaemia (56.2%; n=86), endocrine diseases such as diabetes *mellitus* (20.3%; n=31), nervous system disorders such anxiety (23.5%) and depression (22.2%) and cataracts (30.7%) (Figure 8).



Legend: CNS – Central nervous system; COPD – Chronic obstructive pulmonary disease; CVD – Cardiovascular disease; GER – Gastroesophageal reflux disease.

Figure 8: Health problems characterization.

The mean score for subjects' health literacy was 14.48±3.03, the lowest score was 4, a median of 15 and 25th and 75th percentiles, respectively, 13 and 17 points, with 37.9% (n= 58) of subjects showed having low health literacy (score equal or lower than 14) (Table 43).

Table 43: Characterization of health literacy score.

Score	N	%	Score	N	%
4.0	1	0.7	12.0	10	6.5
5.0	1	0.7	13.0	5	3.3
6.0	1	0.7	14.0	17	11.1
7.0	2	1.3	15.0	24	15.7
8.0	4	2.6	16.0	25	16.3
9.0	3	2.0	17.0	30	19.6
10.0	7	4.6	18.0	16	10.5
11.0	7	4.6	*Total*	153	100.0

The item in which subjects presented the greater number of incorrect answers was item 13 “directed” (32.7%), item 18 “syphilis” (32.0%), item 7 “dose” (21.6%) and item 11 “nutrition” (20.3%). Subjects indicated “Don´t know” more often in the following items: item 18 “syphilis” (24.2%), item 5 “kidney” (18.3%) and item 9 “constipation” (17.0%) (Table 44).

Table 44: Characterization of subject´s answers to the questionnaire.

	Correct answer	Incorrect answer	Don´t know
Item	% (N)	% (N)	% (N)
Occupation	90.2 (138)	9.8 (15)	0.0 (0)
Seizure	77.1 (118)	14.4 (22)	8.5 (13)
Infection	87.6 (134)	8.5 (13)	3.9 (6)
Medication	98.0 (150)	1.3 (2)	0.7 (1)
Alcoholism	66.7 (102)	15.0 (23)	18.3 (28)
Kidney	94.1 (144)	2.6 (4)	3.3 (5)
Dose	72.5 (111)	21.6 (33)	5.9 (9)
Miscarriage	89.5 (137)	8.5 (13)	2.0 (3)

Table 44 *(Continued)*

	Correct answer	Incorrect answer	Don´t know
Item	% (N)	% (N)	% (N)
Constipation	73.2 (112)	9.8 (15)	17.0 (26)
Pregnancy	94.1 (144)	5.9 (9)	0.0 (0)
Nerves	77.8 (119)	20.3 (31)	2.0 (3)
Nutrition	79.7 (122)	15.7 (24)	4.6 (7)
Directed	57.5 (88)	32.7 (50)	9.8 (15)
Hormones	76,5 (117)	16.3 (25)	7.2 (11)
Abnormal	88,9 (136)	7.8 (12)	3.3 (5)
Diagnosis	90.2 (138)	9.2 (14)	0.7 (1)
Haemorrhoids	92.2 (141)	3.3 (5)	4.6 (7)
Syphilis	43.8 (67)	32.0 (49)	24.2 (37)

Only 10.5% (n= 16) of the subjects indicated all the correct answers for the 18 items.

Health literacy score was higher for younger subjects (p<0.001), for those using a lower number of daily medicines (p=0.009), or taking a decreased number of medicine´s units (p=0.013) and using medicines more frequently (p=0012) (Table 45).

Table 45: Health literacy score and subject´s characteristics correlation.

Variables	r	p value
Age	-0.504	<0.001
Marital status	-0.188	0.02
Qualifications	0.262	0.001
Household	0.324	<0.001
Number of daily units	-0.211	0.013
Number of daily medicines	-0.220	0.009
Frequency of use of medicines	0.203	0.012

The health literacy score was lower for subjects with less qualifications (p<0.001), being more prevalent in patients having either the 1st, or 3rd cycles of basic education, or without any education degree (Table 46).

Table 46: Characterization of health literacy score and subject´s qualifications.

Qualifications	Health Literacy			
	Low HL N (%)	Not Low N (%)	Mean (SD)	p value
Can read and/or write without having education degree	8 (6.8)	4 (3.4)	11.58 (4.1)	p<0.001
1st cycle of basic education (4th grade)	16 (13.6)	15 (12.7)	13.06 (3.05)	
2nd cycle of basic education (junior)	0 (0.0)	7 (5.9)	14.86 (0.7)	
3rd cycle of basic education (9 years)	14 (11.9)	44 (37.3)	14.53 (2.64)	
Secondary education (12th grade)	3 (2.5)	23 (19.5)	15.69 (2.92)	
Professional course/technological (Level III)	0 (0.0)	7 (5.9)	16.43 (1.4)	
Higher education	0 (0.0)	12 (10.2)	16.83 (0.94)	
Total			14.48 (3.03)	

Legend: HL – Health literacy; SD – Standard deviation.

Older subjects (≥65 years) presented a lower score of health literacy (p<0.001), having an average score of 13.4±3.2 (median=14.0). The average score for younger patients (<65 years) was 15.95±1.96 (median=16.5).

Polymedicated subjects, using 5 (five) or more medicines, showed a lower score of health literacy (p=0.027), presenting an average score of 13.98±3.0 (median=14.0). Subjects using less than 5 medicines presented an average score of 14.94±3.0 (median=16.0).

The internal consistency analysis was performed using the Cronbach's alpha, which presented a value of 0.812, considering the 18 items.

The reliability for the measurements was analysed using the intraclass correlation coefficient (ICC). The ICC was 0.802 (95%CI 0.75-0.85) which suggests a statistically significant ($F=5.05$ $p<0.001$) interrater reliability, classified as excellent.

4.2 ReMeD Study

4.2.1 Sample Characterization

There were 118 patients included in the study, 45.8% (n=54) female and 54.2% (n=64) male, with a mean age of 66.2±10.41 years. Their ages ranged between 35 and 88 years, and presented a median of 67 years.

Most patients were over 65 years (56.8%; n=67), with a similar distribution for both genders (Figure 9).

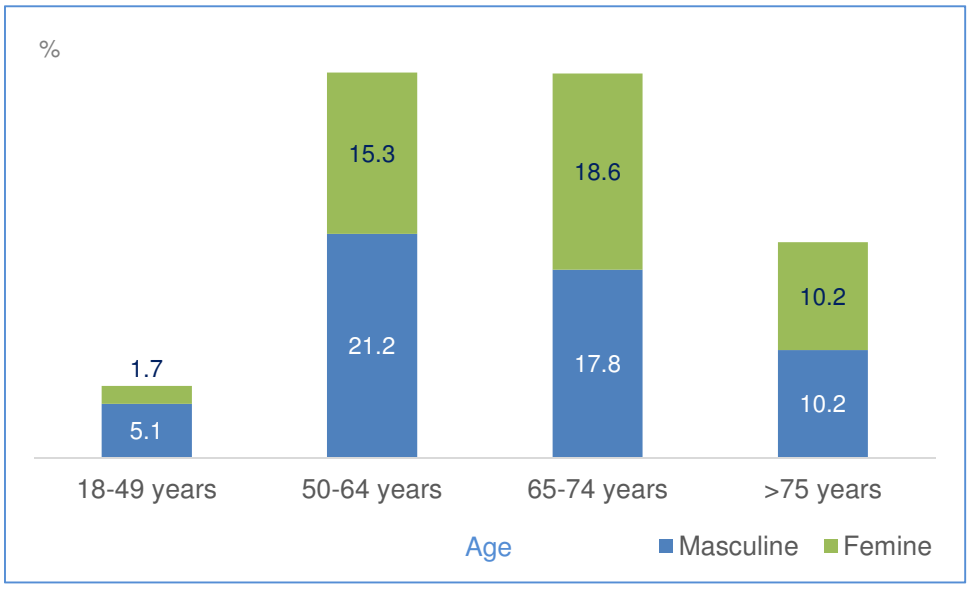


Figure 9: Characterization of patients´ age by gender.

Patients were mainly retired (71.2%; n=84), 3.4% (n=4) were retired with activity, and 20.4% (n=24) were employed.

About 74.6% (n=88) of patients were married, most of them lived with her wife/husband (54.2%; n=64), 11.9% (n=14) lived alone and were autonomous, and only 1 patient (0.8%) lived alone with support. It is noteworthy that about 12.7% (n=15) of patients lived with relatives from another family generation (children, grandchildren, or other). None of the patients included in this study was institutionalized.

More than one third of patients had only the four years of education (38.1%; n=45), and 2.5% could not read or write as described in Figure 10.

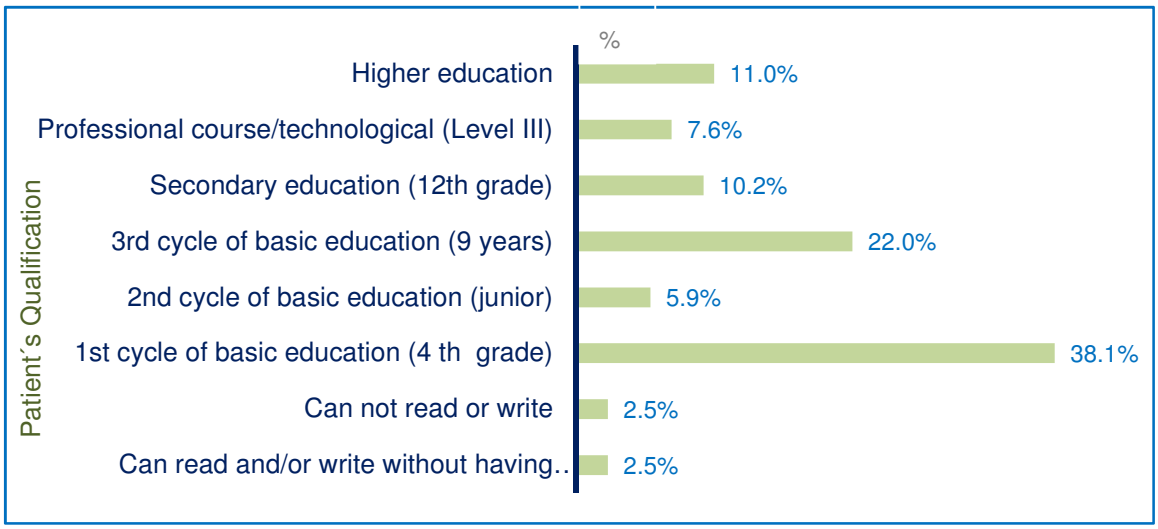


Figure 10: Characterization of patients´ qualifications.

The number of female patients with lower qualifications (less than 9 years of schooling) was higher (28.8%) than male patients (20.3%), but this difference was not statistically significant (p> 0.05).

In the overall sample no statistically significant difference was observed between qualifications and patient´s age (years) (p>0.05).

However, the number of older patients (≥65 years) having the first cycle of basic education (4th grade) was higher compared to younger patients (p=0.041).

Patients were followed at the AEDMADA clinic on average about 44.18±34.28 months (median=41.5 months). The longest time a patient was followed was over 8 years (103 months).

4.2.2 Patient´s Clinical evaluation

Clinical Profile

The characterization of patient´s health problems was conducted using the ICD-10 classification (http://apps.who.int/classifications/icd10/browse/2016/en).

Each patient had a mean of 4.78±1.94 (median=4) health problems, with a maximum of 11 health problems identified per patient.

Health problems which presented a higher prevalence were those belonging to Chapter IV - Endocrine, nutritional and metabolic diseases, Chapter IX - Diseases of the circulatory system), Chapter VII - Diseases of the eye and adnexa and Chapter V - Mental and behavioural disorders (Table 47).

Most prevalent diagnosis were diabetes *mellitus* (90.7%), hypertension (81.4%), disorders of lipoprotein metabolism and other lipidaemias (77.1%) (Table 47).

Table 47: Characterization of health problems.

*ICD-10**	Disease	N	%
I	B16 - Acute Hepatitis B	1	0.8
III	D50 - Iron deficiency anaemia	1	0.8
IV	E10 - Type 1 diabetes *mellitus*	6	5.1
	E11 - Type 2 diabetes *mellitus*	101	85.6
	E03 - Other hypothyroidism	2	1.7
	E78 - Disorders lipoprotein metabolism and other lipidaemias	91	77.1
	E79 - Hyperuricemia	3	2.5
	Other endocrine, nutritional and metabolic disorders	5	4.2
V	F32 - Depressive episode	14	11.9
	F41 - Anxiety disorders	17	14.4
	F51 - Non-organic sleep disorders	5	4.2
	Other disorders	3	2.5
VI	G20 - Parkinson Disease	3	2.5
	G40 - Epilepsy	2	1.7
	Other mental and behavioural disorders	8	6.8

Table 47 *(Continued)*

*ICD-10**	Disease	N	%
VII	H25 – Senile cataract	9	7.6
	H52 – Disorder of refraction and accommodation	26	22
	Other diseases of the eye and adnexa	16	13.6
VIII	Other diseases of the ear and mastoid process	5	4.2
IX	I10-Hypertension	96	81.4
	Other diseases of the circulatory system	27	22.9
X	J44 - Other chronic obstructive pulmonary disease	2	1.7
	J45 - Asthma	1	0.8
	Other diseases of the respiratory system	11	9.3
XI	K21 - Gastro-oesophageal reflux disease	9	7.6
	K90-93 - Other diseases of digestive system	20	16.9
XII	L40 - Psoriasis	1	0.8
XIII	M6 - Coxarthrosis	4	3.4
	M17 – Gonarthrosis	14	11.8
	M19 – Other arthrosis (excl. post-traumatic)	2	1.7
	M81 - Osteoporosis	1	0.8
	Other dis. of musculoskeletal syst. and connective tissue	20	16.9
XIV	N39 – Other disorders of urinary system	2	1.7
	N40 - Hyperplasia of Prostate	16	0.6
	Other diseases of the genitourinary system	12	10.2
XIX	T78 - Allergy, unspecified	6	5.1

*Legend: * - Chapter; Dis – disease; Sist – system.*

Older patients (≥65 years) presented an increased number of health problems (5.2±1.87) compared with younger patients (4.3±1.88), which proved to be statistically significant (p=0.003).

The number of health problems diagnosed per patients was higher for patients being followed at the AEDMADA clinic for a longer period (p=0.012; r=0.204), hypertense patients (p<0.001), patients with a very high cardiovascular risk (p=0.0228) and patients without physical activities habits (p=0.044).

Patients without physical activity habits presented an average of 5.18±2.16 health problems, while patients who practiced physical activity presented a lower average number of health problems (4.3±1.4) (p=0.045).

Characterization of biomarkers and other risk factors for cardiovascular diseases

Blood Pressure

ReMeD patients presented an average value of systolic blood pressure (SBP) of 151.38±20.02 mmHg and 79.93±11.48 mmHg for diastolic blood pressure (DBP). Over two thirds of these patients presented uncontrolled blood pressure values (61.0%; n=72).

In the age range of 65-74 years patients presented a higher prevalence (28.0%) of uncontrolled BP compared to patients in the range of 50-74 years (19.5%) (p=0.003) (Table 48).

Table 48: Characterization of blood pressure control and patient´s age.

	Age (years)									
	18-49		**50-64**		**65-74**		**≥ 75**		**TOTAL**	
BP control	N	%	N	%	N	%	N	%	N	%
Controlled	5	4.2	20	17.0	10	8.5	11	9.3	46	39.0
Uncontrolled	3	2.5	23	19.5	33	28.0	13	11.0	72	61.0
Total	8	6.7	43	36.5	43	36.5	24	20.3	118	100.0

Legend: BP – Blood pressure.

In patients who had not been previously diagnosed with hypertension about half (52.2%; n=12) had uncontrolled blood pressure values, with a mean value of 146.09±21.97 for SBP and 82.91±11.06 for DBP.

Patients with a diagnosis of hypertension, only about a third (36.5%; n=35) showed controlled blood pressure values. Patients having a controlled blood pressure, achieved a lower value both for SBP (p<0.001) and DBP (p<0.001), compared to patients with uncontrolled blood pressure (Table 49).

Table 49: Characterization of blood pressure values and blood pressure profile control for hypertensive patients.

BP control	SBP	DBP
	Mean ± SD	Mean ± SD
Controlled	132.5±7.18	74.43±9.3
Uncontrolled	163.4±15.8	83.4.2±11.41
p value	<0.001	<0.001

Legend: BP – Blood pressure; DBP – Diastolic blood pressure; SBP – Systolic blood pressure; SD – Standard deviation.

More than half (59.8%; n=64) of the diabetic patients had uncontrolled blood pressure, with a mean value for SBP of 150.40±20.05 mmHg and 79.48±11.25 mmHg for DBP.

Blood pressure control showed no statistically difference for hypertense patient´s gender, despite the average of systolic blood pressure was higher in men (153.2±18.73 and 151.20.57 for female) (p>0.05).

Glycemic Profile

Near half of patients had hyperglycemia values in the parameters of fasting glucose (51.7%) and postprandial glucose (43.2%). All non-diabetic patients (n=11) presented a good control of glycemic profile, with normoglycaemia values for fasting and postprandial glucose.

The glycemic profile reached in diabetic patients enrolled in this study is described in Table 50.

About half of diabetic patients presented a controlled glycemic profile (46.7%; n=50), and a median for HbA_1c of 7.73±1.4 %. More than one third of diabetic patients (39.3%) presented a HbA1c value ≥ 8%.

Table 50: Characterization of diabetic patients glycemic profile.

Parameter				Mean±SD
Fasting glucose	Hypoglycaemia: 1.9%; n=2 Normoglycaemia: 41.1%; n=44 Hyperglycaemia: 57%, n=61			148.5±51.1 mg/dL
Post prandrial glucose	Hypoglycaemia: 0.9%; n=1 Normoglycaemia: 51.4%; n=55 Hyperglycaemia: 47.7%; n=51			184.5±67.4 mg/dL
HbA1c	< 6.5 6.5 and 7 ≥ 7 and 8 ≥ 8	16.8% 18.7% 25.2% 39.3%	(n=18) (n=20) (n=27) (n=42)	7.73±1.4 %
Legend: HbA1c - Glycated haemoglobin; SD – Standard deviation.				

The mean value for HbA1c registered in female patients (median=7.85%) was higher than those showed in male patients (median=7.45%), altought this difference was not statistically significant (p>0.05). Also a higher rate of glycemic profile control was achieved in male patients (26.3%) compared to female pateints (15.3%), but not statiscally significant.

No statistically significant difference were found between patient´s glycemic profile control, blood pressure and lipid profile control (p>0.05).

Lipid Profile

Only about a third (22.9%; n=27) of the patients had a controlled lipid profile (Table 51).

Table 51: Characterization of patients´ lipid profile.

Parameter	Values	Mean±SD (mg/dL)
Total cholesterol	Normal value: 72% ; n=85 Above the reference value: 28%; n=33	174.8± 38.8
LDL-C	< 70 mg/dL: 10.2% (n=12) 70 – 100 mg/dl: 35.6% (n=42) 100 - 115 mg/dL: 22.0% (n=26) ≥ 115 mg/dL: 32.2% (n=38)	104.2±34.1
HDL-C	Normal value: 69.5%; n=82 Below the reference value: 30.5%; n=36	49.4±13.3
Tryglicerides	Normal value: 78.8%; n=93 Above the reference value: 150 – 200 mg/dL: 16.1%; n=19 >200 mg/dL: 5.1%; n=6	126.1±64.5

Legend: HDL-C – High density lipoprotein cholesterol; LDL-C – Low density lipoprotein cholesterol; SD – Standard deviation.

Diabetic patients showed a high prevalence of uncontrolled lipid profile (78.5%; n=84), a mean value for LDL-C of 103.4±32.0 mg/dL and 171.73±36.6 mg/dL for total cholesterol. The majority were being treated with lipid-lowering drugs (62.6%; n=67).

An uncontrolled lipid profile was observed in male patients (45.8%) more often than in female patients (34.4%), although this difference wasn´t statistically significant (p>0.05):

Male patients with a diagnosis of dyslipidaemia presented a higher prevalence of previous cardiovascular events (17.6% vs 4.4% for female) (p=0.015).

Smoking Habits

Most Patients were non-smoking (72.9%; n=86), and those that smoked (9.3%; n=11) showed an average intake of 12.27±12.52 cigarettes per day (Figure 11).

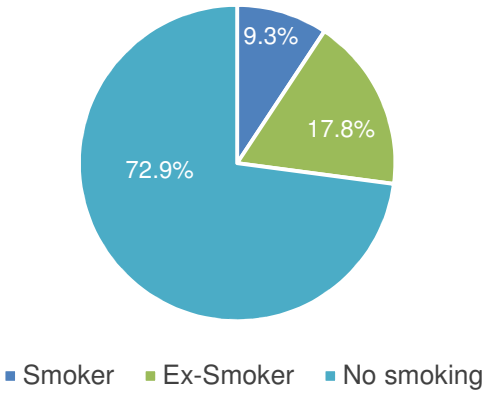


Figure 11: Characterization of patients' smoking habits.

Male patients and younger patients (<65 years) showed a significant higher prevalence in smoking habits compared to the female patients (p<0.001) (Table 52).

Table 52: Characterization of smoking habits, gender and patients´ age.

Smoking habits	Gender			Age		
	Feminine	Masculine	p value	< 65 years	≥ 65 years	p value
	N (%)	N (%)		N (%)	N (%)	
Smoker	0 (0.0%)	11 (9.3%)	<0.001	7 (5.9%)	4 (3.4%)	<0.001
Ex-Smoker	2 (1.7%)	19 (16.1%)		16 (13.6%)	5 (4.2%)	
No smoking	52 (44.1%)	34 (28.8%)		28 (23.7%)	58 (49.2%)	
Total	54 (45.8%)	64 (54.2%)		51 (43.2%)	67 (56.8%)	

Physical Exercise

More than half of patients (57.6%; n=68) indicated not to practice regular physical exercise. For those who practiced, the median was 3 times per week, with an average duration of 66.2±36.08 minutes.

About 13.6% of patients reported to practice physical exercise at least 5 days a week, and among these, male patients showed a higher prevalence (p=0.09) (10.2%), compared with a prevalence of only 3.4% for female patients.

Several physical activity types were practiced by patients, although mainly walking (38.0%) and gymnastic aerobic (32.0%), as described in Figure 12.

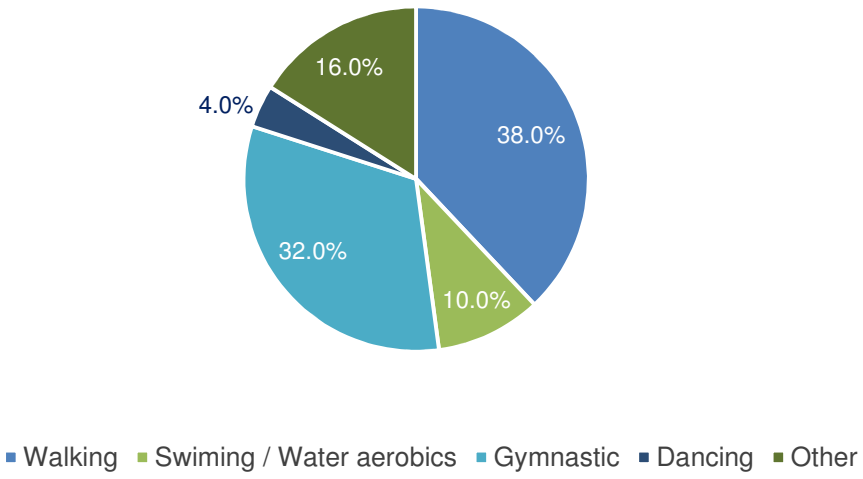


Figure 12: Characterization of patients´ physical exercise practice.

Patients who indicated not to practice physical exercise showed a higher prevalence of dyslipidaemia (p=0.016), diabetes (p<0.001) and previous cardiovascular events (p<0.001).

The number of patients practicing physical exercise and controlled blood pressure and controlled glycemic profile was greater those that did not exercise, however this difference was not statistically significant (p>0.05).

Body Mass Index (BMI)

Only about 18.6% (n=22) of patients had a BMI value considered normal, with a mean value of 28.64±4.7 Kg/m^2; most patients were overweight or obese (BMI≥25 Kg/m^2) (80.5%; n=95) (

Figure 13).

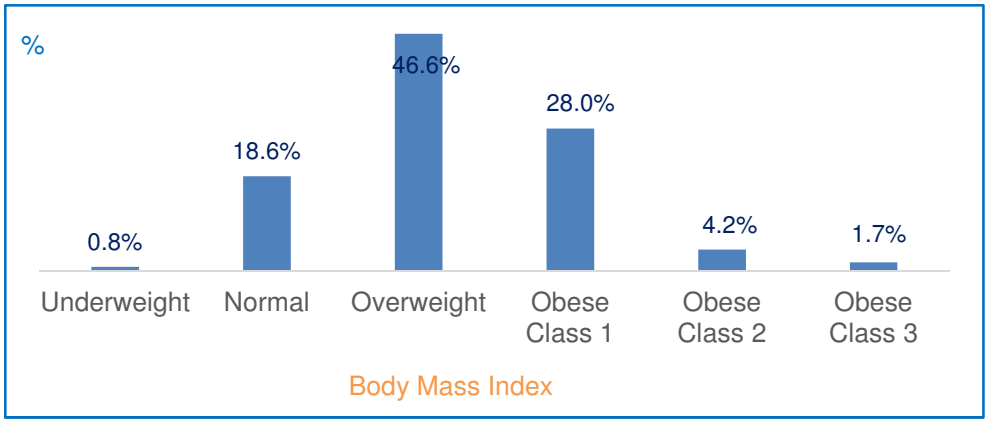


Figure 13: Characterization of patients´ body mass index (BMI).

No significant difference was identified between BMI and patient´s age (p>0.05), despite patients 65 years and older presented a higher prevalence of BMI ≥ 25 Kg/m^2, no statistically significant difference were observed for age (Table 53) or gender.

Table 53: Characterization of body mass index per patient´s age.

BMI classification	< 65 years	≥ 65 years	p value
	N (%)	N (%)	
Underweight	0 (0.0)	1 (0.85)	0.465
Normal	13 (11.0)	9 (7.65)	
Overweight	21 (17.8)	34 (28.8)	
Obese Class 1	14 (11.9)	19 (16.1)	
Obese Class 2	2 (1.7)	3 (2.5)	
Obese Class 3	1 (0.85)	1 (0.85)	
Obese Class 4	0 (0.0)	0 (0.0)	
Obese Class 5	0 (0.0)	0 (0.0)	

Legend: BMI – Body mass index.

Patients with a diagnosis of dyslipidaemia presented an increased prevalence of body mass index (BMI) ≥25 kg/m^2 (69.5%) compared to patients having a BMI<25Kg/m^2 (7.6%) (p<0.001).

Dietary Habits

The majority (97.5%: n=115) of patients affirmed to eat fruit every day (7 days per week), eating less than 3 fruit pieces per day (53.0%; n=61), 3-5 pieces (45.2%; n=52) or more than 5 pieces (1.8%; n=2).

Also regarding vegetable intake patients affirmed to eat vegetables every day (7 days per week) in 72% (n = 85) of cases, where most indicated to consume less than three portions daily (96.6%; n = 114).

Olive oil was the fat most often used to prepare their own meals (94.1%; n=111).

Previous Cardiovascular Events

Nearly a fifth of the patients (17.8%; n=21) had already a previous cardiovascular event, being stroke (33.3%; n=7) and acute myocardial infarction (28.6%; n=6) the most prevalent among those patients (Figure 14).

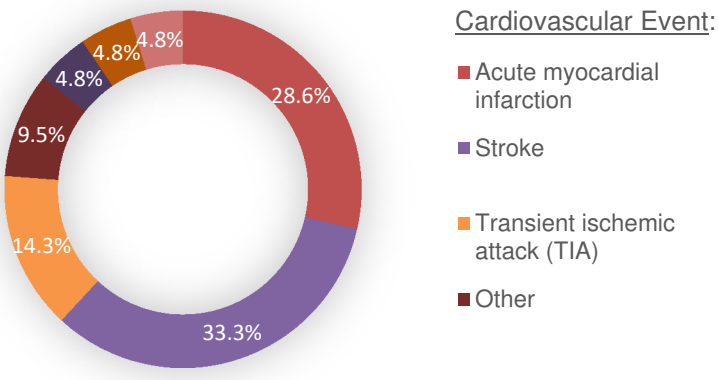


Figure 14: Characterization of previous cardiovascular events.

Older patients (≥65 years) reported a lower number of previous cardiovascular events (p=0.014) presenting an average of 1.9±0.27 events while younger patients an average of 1.74±0.44 previous cardiovascular events.

Furthermore, male patients had suffered a higher number of cardiovascular events (p=0.027) (13.6% for male and 4.24% for female). Beside that, patients without smoking habits had a lower rate of cardiovascular events (p=0.042).

Male hypertense patients presented an increased number of previous cardiovascular events (p=0.039) with a prevalence of 15.8% for male patients and 4.2% for female patients.

Patients with lipidaemia disorders presented a higher prevalence of cardiovascular events (p=0.03).

Family History

Family history of cardiovascular events only occurred in 16.4% (n=19) of the patients included in this study.

No statistically significant difference were achieved for familiy history of premature cardiovascular events and socio-demographic and clinical variables, nor to the ocorrence of cardiovascular events (p>0.05).

Cardiovascular Risk Assessment

Using a qualitative cardiovascular (CV) risk assessment methodolgy, it was found that most patients had a “Very high CV risk” (89.8%; n=106) (

Figure 15).

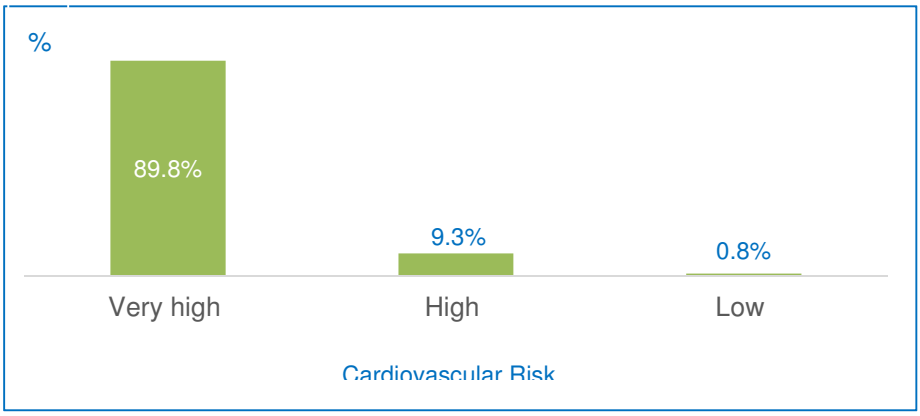


Figure 15: Cardiovascular Risk Assessment.

Patients with very high cardiovascular risk were mostly male (p=0.010) (51.7%), and were followed in the AEDMADA clinic for a longer period (p<0.001) on average for 50.4±31.95 months. Those with high risk had been followed on average for 9.4±25.7 months. Moreover, patients with very high cardiovascular risk had a higher prevalence of hypertension (p<0.001), diabetes (p<0.001), microvascular complications of diabetes (p<0.001) and uncontrolled lipid profile (p=0.026).

Microvascular complications (Diabetic patients)

Almost a quarter of diabetic patients already had microvascular complications (23.4%; n=25), being retinopathy the most frequent in the diabetic´s patients included in the study (Table 54).

Table 54: Prevalence of diabetes microvascular complications.

Microvascular complications	Prevalence
Diabetic retinopathy	17.8%; n=19
Nephropathy	3.8%; n=4
Neuropathy	9.3%; n=10

Patients with diagnosis of diabetes for a longer period achieved a higher prevalence of microvascular complications (p<0.001).

An increased number of health problems was depicted for patients with diabetes microvascular complications (p=0.026), having an average of 5.44±2.1 health problems. Patients without microvascular complications presented an average of 4.7±1.9 health problems.

No other variables (socio-demographic or clinical) showed a statistically difference for the existence of diabetes microvascular complications.

4.2.3 Pharmacotherapeutic Profile

In the 118 patients enrolled in this the study it was identified a total of 791 medicines and 21 food supplements and other health products (FS). Each patient was using a mean of 6.70±3.03 medicines per day, presented a median of 6 medicines and 25th and 75th percentiles, respectively, 4 and 9 medicines. Per day each patient was taking a mean of 7.63±3.92 (median=7) units, taking at least 1 unit and a maximum of 21 units per day, corresponding to 7.93±3.99 (median=7) doses per day per patient.

Polypharmacy (patients taking 5 or more medicines) was found in about three-quarters of patients (73.8%; n=89) (Table 55), and about 82.1% of older patients (65 years and older) were polymedicated (p=0.019).

Table 55: Number of medicines per patient.

	Patients (number)	**< 65 years**	**≥65 years**
Medicines (number)	N	N (%)	N (%)
Up to 4 medicines	31 (26.3)	19 (16.1%)	12 (10.2%)
5 to 10 medicines	75 (63.6)	27 (22.9%)	48 (40.7%)
More 10 medicines	12 (10.1)	5 (4.2%)	7 (5.9%)
Total	118 (100.0)	51 (43.2%)	67 (56.8%)

Only one in seven patients (15.2%) was using food supplements (FS), others only one food supplement (14.4%; n=17), obtaining an average of 0.18±0.5 FS per patient.

Elderly patients (≥ 65 years) used a higher number of daily medicines, taking a daily mean of 7.16±2.8 (median=7) medicines, 0.21±0.6 food supplements, 8.27±3.8 (median=8) units and 8.5±3.9 (median=8) doses. Globally, 82% (n=55) were polymedicated (≥5 medicines per day), and only about one-sixth of patients were using food supplements (16.4%; n=11).

In 10.2% (n=12) of the patients included this study, a previous situation of intolerance and / or drug allergies had already occurred.

The most prevalent medicines used by this patient´s sample were from group C-Cardiovascular system, A-Alimentary tract and metabolism, and N-Nervous system (Table 56).

Table 56: ATC classification of medication profile.

ATC Classification (level 1)	**N**	**%**
A - Alimentary tract and metabolism	251	31.7
B - Blood and blood forming organs	43	5.4
C - Cardiovascular system	280	35.4
G - Genito urinary system and sex hormones	21	2.7
H - Systemic hormonal preparations, excl. sex h. and insulins	43	5.4
J - Anti-infective for systemic use	4	0.5
M - Musculo-skeletal system	29	3.7
N - Nervous System	97	12.3
P - Antiparasitic products, Insecticides and repellents	1	0.1
R - Respiratory System	18	2.3
S - Sensory Organs	4	0.5
V - Various	1	0.13
Total Medicines (number)	791	100.0
Total Food Supplements and other health products	21	100.0
Legend: ATC – Anatomical, Therapeutic and Chemical.		

Among medicines used by patients, at least three quarters had been used for more than a year (75.8%; n=615), and most (66.9%) had been already used for at least 24 months (Table 57).

Table 57: Characterization of medicines use period.

Time (months)	**N**	**%**
0-6	133	16.4
7-12	64	7.8
≥ 12 - 24	72	8.9
≥ 24	543	66.9
Total	812	100.0

Antihypertensive drugs were used by 83.9% (n=99) of patients (mean of 1.51±0.78). Most patients used one (1) antihypertensive drug (63.6%; n=63), 24.2% (n=24) used two (2) antihypertensive drugs, 10.1% (n=10) used three (3) and 2.1% (n=2) used four (4) antihypertensive drugs.

About 88.1% of older patients (≥ 65 years) were using antihypertensive drugs, using a higher number of these drugs compared to younger patients (p=0.013).

The antihypertensive drug subgroup with highest prevalence of use in the sample study was “C09AA – Agents acting on the renin-angiotensin system; ACE Inhibitors, Plain” (23.38%), followed by “C09DA - Agents acting on the renin-angiotensin system; Angiotensin II antagonists, combinations; Angiotensin II antagonists and diuretics“ (18.1%) and “C08CA – Calcium channel blockers; Selective Calcium channel blockers with mainly vascular effects; Dihydropyridine derivatives” (13.64%). (Table 58).

Table 58: Classification of antihypertensive drugs used by patients.

ATC Classification (level 4)	**N**	**%**
C02AC - Antiadrenergic agents, centrally acting; Imidazoline receptor agonists	1	0.7
C03BA – Diuretics; Low-Ceiling Diuretics, excl. Thiazides; Sulfonamides, plain	7	4.4
C03CA – Diuretics; High-Ceiling Diuretics; Sulfonamides, plain	5	3.3
C03DA – Diuretics; Potassium sparing agents; Aldosterone antagonists	1	0.7
C03EA – Diuretics: Diuretics and potassium-sparing agents in combination; Low-ceiling diuretics and potassium-sparing agents	1	0.7
C07AB – Beta Blocking agents; Beta blocking agents, selective	16	10.4
C07AG - Beta Blocking agents; Alpha and beta blocking agents	3	1.9
C08CA – Calcium channel blockers; Selective Calcium channel blockers with mainly vascular effects; Dihydropyridine derivatives	21	13.6
C08DA - Calcium channel blockers; Selective channel blockers; Phenyl.deriv.	1	0.7
C08DB - Calcium channel blockers; Selective Calcium channel blockers with direct cardiac effects; Benzothiazepine derivatives	1	0.7
C09AA – Agents acting on the renin-angiotensin system; ACE Inhibitors, Plain	36	23.4
C09BA - Agents acting on the renin-angiotensin system; ACE Inhibitors, combinations; ACE Inhibitors and diuretics	10	6.5
C09BB - Agents acting on the renin-angiotensin system; ACE Inhibitors, combinations; ACE Inhibitors and calcium channel blockers	5	3.3
C09CA - Agents acting on the renin-angiotensin system; Angiotensin II antagonists, plain	14	9.1
C09DA - Agents acting on the renin-angiotensin system; Angiotensin II antagonists, combinations; Angiotensin II antagonists and diuretics	28	18.1
C09DB - Agents acting on the renin-angiotensin system; Angiotensin II antagonists, combinations; Angiotensin II antagonists and calcium channel blockers	4	2.6
Total	154	100

Legend: ATC – Anatomical, Therapeutic and Chemical; Phenyl.deriv - Phenylalkylamine derivatives.

About two thirds of antihypertensive drugs used were agents acting on the renin-angiotensin system (63.0%; n=97), being approximately half angiotensin converting enzyme inhibitors (33.1%; n=51) and the other half acting as antagonists of angiotensin II receptors (29.9%; n=46). Within this group which acts on the renin-angiotensin system about half (48.45%; n=47) corresponded to drugs associations.

Oral antidiabetic drugs (OADs) were used by 77.97% (n=92) of patients, and 86% of diabetic patients, most of those using one (1) drug (43.9%; n=47) or two (2) drugs (30.8%; n=33). Three (3) OADs were used by 10.8% and four (4) by 1.0% of the patients.

The oral antidiabetic class most often prescribed was “combination of oral blood glucose lowering drugs” (31.6%; n=49) and biguanides (24.5%; n=38). The class of “dipeptidyl peptidase 4 inhibitors (DPP-4)” was used by one fifth of the patients (18.1%; n=28), as described in Table 59.

Table 59: Characterization of oral antidiabetic drugs.

ATC Classification (level 4)	**N**	**%**
A10BA - Biguanides	38	24.5
A10BB - Sulfonylureas	23	14.8
A10BD - Combinations of oral blood glucose lowering drugs	49	31.6
A10BF - Alpha glucosidase inhibitors	5	3.2
A10BG - Thiazolidinedione	4	2.6
A10BH - Dipeptidyl peptidase 4 (DPP-4) inhibitors	28	18.1
A10BX - Other blood glucose lowering drugs, excl. insulins	8	5.2
Total	155	100.0
Legend: ATC – Anatomical, Therapeutic and Chemical.		

In ATC group A10BX (Other blood glucose lowering drugs, excl. insulins) liraglutide is included, which is a blood glucose lowering agent for parenteral administration and not orally. Among diabetic patients, 6 (5.6%) were being treated with this drug.

Insulin treatment was used by 38.98% (n=46) of the patients, and 43% of diabetic patients, using mostly (17.8%; n=19) one or two insulins (17.8%; n=19), and 7.5% (n=8) were using 3 types of insulins. The characterization of the insulins used by diabetic patients is described in Table 60.

Table 60: Characterization of insulins.

ATC Classification (level 4)	**N**	**%**
A10AB - Insulins and analogues for injection, fast-acting	19	23.75
A10AC - Insulins and analogues for injection, intermediate-acting	8	10.0
A10AD - Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	25	31.25
A10AE - Insulins and analogues for injection, long-acting	28	35.0
Total	80	100.0
Legend: ATC – Anatomical, Therapeutic and Chemical.		

About 12.15% (n=13) of diabetic patients were treated with insulin only, while 30.84% (n = 33) used insulin and oral antidiabetic drugs (OADs). Nearly half of diabetic patients were only medicated with oral antidiabetic drugs (55.15%, n=59).

For patients using a higher number of insulins, the HbA1c value was lower ($p<0.001$; $r=-0.377$).

Two (2) diabetic patients were not currently being treated with any antidiabetic drug, since they had achieved control of glycemic profile.

Patients with a controlled glycemic profile used significantly fewer number of insulins, as well as those whose presenting controlled blood pressure values (Table 61).

Table 61: Characterization of the number of insulins and disease control (blood pressure, glycemic profile and lipid profile).

	Number of insulins		
	Mean (SD)	Median	p value
Blood Pressure			
Controlled	0.44 (0.91)	0.0	0.03
Uncontrolled	0.79 (0.99)	0.0	

Table 61 *(Continued)*

	Number of insulins		
	Mean (SD)	Median	p value
Glycemic profile			
Controlled	0.29 (0.58)	0.0	0.00
Uncontrolled	1.16 (1.11)	1.0	
Lipid profile			
Controlled	0.33 (0.66)	0.0	0.08
Uncontrolled	0.76 (1.02)	0.0	

Legend: SD – Standard deviation.

Female patients used a lower number of antidiabetic drugs (oral antidiabetic drugs and insulins) compared to male patients, although this difference was not statistically significant (p>0.05).

Patients that experienced a previous cardiovascular event were using a higher number of antidiabetic drugs (p=0.005), having a prescription for 2.48±0.87 antidiabetic drugs, compared to 1.85±1.18 for patients who had no report of previous cardiovascular event.

Additionally, patients presenting microvascular complications from diabetes were using a higher number of antidiabetic drugs (p=0.003), taking an average of 2.36±1.11 antidiabetic drugs, while patients without clinical diagnosis of microvascular events used an average of 2.1±0.98 antidiabetic drugs.

A longer follow-up period in the AEDMADA clinic was reported for those patients using a higher number of antidiabetic drugs (p<0.001; r=0.438).

Antidyslipidemic drugs were used by 76.3% (n=90), of which most (93.33%; n=84) used 1 antidyslipidemic drug, and 6.67% (n=6) used 2 antidyslipidemic drugs. More than two thirds were using an antidyslipidemic drug from the subgroup of “HMG CoA reductase inhibitors” (Table 62).

Table 62: Characterization of antidyslipidemic drugs.

ATC Classification (level 4)	**N**	**%**
C10AA - HMG CoA reductase inhibitors	71	73.2
C10AB - Fibrates	17	17.53
C10BA - HMG CoA reductase inhibitors in combination with other lipid modifying agents	9	9.28
Total	97	100.0

Legend: ATC – Anatomical, Therapeutic and Chemical; HMG coA – Hydroxymethylglutaryl-coenzyme A.

Patients using polypharmacy ($p<0.001$) and having a body mass index ≥25 Kg/m^2 ($p<0.001$) had a prescription for a significant higher number of antidyslipidemic drugs.

Antithrombotic agents were used by 29.7% (n=35) of patients, which using one (1) drug (91.4%; n=32) or two (2) drugs (8.6%; n=3) (Table 63).

Table 63: Characterization of antithrombotic agents.

ATC Classification (level 4)	**N**	**%**
B01AA - Vitamin K antagonists	2	5.1
B01AC - Platelet aggregation inhibitors excl. heparin	35	89.8
B01AE - Direct thrombin inhibitors	2	5.1
Total	39	100.0

Legend: ATC - Anatomical, Therapeutic and Chemical.

Male patients used a greater number of antithrombotic agents (0.44±0.59) compared to female patients (0.19±0.39) ($p=0.012$).

Polymedicated patients showed a statistically significant higher number of prescribed antithrombotic agents ($p<0.001$).

Patients having a diagnosis of dyslipidaemia used an increased number of antithrombotic agents (p=0.001; r=0.309).

Also a higher number of antithrombotic agents was used by patients taking more antihypertensive drugs (p=0.015; r=0.224).

4.2.4 Analysis of Medication Review outcomes

4.2.4.1 Humanistic outcomes:

Medication Adherence

According to the results obtained from the two tools used to assess medication adherence [Haynes-Sackett test (297) and MAT scale (296)], most patients were adherent to the medication, by 76.3%% and 72.0% respectively (Table 64).

Table 64: Characterization of patient´s medication adherence.

	Haynes-Sackett test			MAT scale		
	N	%	Mean±SD	N	%	Mean±SD
Adherent	90	76.3	87.62±18.07	85	72.0	5.13±0.52
Non-adherent	28	23.7		33	28.0	
Total	118	100.0		118	100.0	

Legend: MAT – Measure Treatment Adherence; SD – Standard deviation.

Patients reported having forgotten to take their medication “sometimes” (28.8%) and “often” (16.1%), and being careless with the hours of taking medication “sometimes” (19.5%) and “often” (8.5%).Most patients indicated to “never” stopped medication because they felt better (63.6%), though 16.9% did this “sometimes” and 3.4% “often”, while only 9.3% reported to have stopped medication “sometimes” for feeling worse and 2.5% stopped “often”. Regarding

taking more pills on their own initiative after having felt worse, only 12.7% did this “sometimes” and 1.7% did often. About 10.2% of the patients declared to discontinue therapy for failing the end of drugs and 1.7% “often” did it. Almost half of patients (44.9%) have stopped medication without a doctor´s recommendation, and 11.9% stated to act like this “often” (Table 65).

Table 65: Characterization of medication adherence according MAT scale.

	Always	Almost always	Often	Some times	Rarely	Never	**Total**
A	0 (0.0)	0 (0.0)	19 (16.1)	34 (28.8)	61 (51.7)	4 (3.4)	118 (100.0)
B	0 (0.0)	0 (0.0)	10 (8.5)	23 (19.5)	23 (19.5)	62 (52.5)	118 (100.0)
C	0 (0.0)	0 (0.0)	4 (3.4)	20 (16.9)	19 (16.1)	75 (63.6)	118 (100.0)
D	0 (0.0)	0 (0.0)	3 (2.5)	11 (9.3)	18 (15.3)	86 (72.9)	118 (100.0)
E	0 (0.0)	0 (0.0)	2 (1.7)	15 (12.7)	27 (22.9)	74 (62.7)	118 (100.0)
F	0 (0.0)	0 (0.0)	2 (1.7)	12 (10.2)	26 (22.0)	78 (66.1)	118 (100.0)
G	0 (0.0)	0 (0.0)	14 (11.9)	53 (44.9)	43 (36.4)	8 (6.8)	118 (100.0)

A. Have you ever forgotten to take medication for their disease?
B. Have you ever been careless with the hours of taking medication for their disease?
C. Have you ever stopped taking medication for his illness, because he was better?
D. Have you ever stopped taking medication for his illness, on its own initiative, after having felt worse?
E. Have you taken a second or more pills for his illness, on its own initiative, after having felt worse?
F. Ever discontinued therapy for their disease for failing to end the drugs?
G. Have you ever stopped taking medication for their disease for some other reason than the statement of the doctor?

Legend: MAT – Measure Treatment Adherence.

Medication adherence was most pronounced for patients taking 5 to 10 medicines per day, as the results obtained by using both tools to assess

medication adherence, showed a significant difference relative to the number of medicines used by patients (p<0.001) (Table 66).

Table 66: Medication adherence according to number of medicines used.

Medication Adherence	Up 4 medicines	5 to 10 Medicines	11 to 16 Medicines	p value
	% (N)	% (N)	% (N)	
Haynes-Sackett Test				
Non-Adherent	11.9% (14)	11.0% (13)	0.9% (1)	0.001*
Adherent	14.4% (17)	52.5% (62)	9.3% (11)	
Total	26.3% (31)	63.5% (75)	10.2% (12)	
MAT Scale				
Non-Adherent	12.7% (15)	12.7% (15)	2.5% (3)	0.013*
Adherent	13.6% (16)	50.8% (60)	7.6% (9)	
Total	26.3% (31)	63.5% (75)	10.1% (12)	

Legend: MAT - Measure Treatment Adherence.

Polymedicated patients (5 or more medicines) presented a higher score of medication adherence with an average score of 90.7±13.45 and 5.2±0.46 respectively, considering Haynes-Sackett test (p=0.036) and MAT scale (p=0.037). Patients using less than 5 medicines presented an average score of 78.97±4.94 and 4.94±0.62, respectively.

No significant difference were achieved for medication adherence (results from both assessment tools) relative to socio-demographic variables, neither to glycemic profile, blood pressure or lipid profile control (p>0.05).

Adherent patients used an increased number of daily units, number of daily doses and presented a higher number of health problems per patient, considering the results obtained using Haynes-Sackett test, compared to non-adherent patients (Table 67).

Table 67: Number of daily units, daily doses, health problems and medication adherence.

Medication Adherence	Haynes-Sackett test			MAT scale		
	Daily Units	Daily Doses	Nr Health Problems	Daily Units	Daily Doses	Nr Health Problems
	Mean ± SD (Median)			Mean ± SD (Median)		
Non-Adherent	5.98±5.0 5.0	6.25±4.3 5.0	4.0±1.5 4.0	7.1±4.7 6.0	7.5±4.9 6.0	5.0±1.9 5.0
Adherent	8.15±3.6 7.57	8.46±3.8 8.0	5.06±1.97 5.0	7.9±3.6 7.0	8.1±3.6 7.0	4.7±1.9 4.0
p value	0.001	0.002	0.007	0.082	0.141	0.403

Legend: MAT - Measure Treatment Adherence; Nr – Number; SD – Standard deviation.

Patients using antihypertensive drugs presented a greater medication adherence of 89.38±15.18% according to Haynes-Sackett test (p=0.02) and 5.18±0.46 (p=0.011) according to MAT scale. Patients not using antihypertensive drugs showed a medication adherence of 78.44±27.6 and 4.4±0.72, respectively.

Patients using 2 or more oral antidiabetic drugs (OAD) exhibited a higher adherence compared to patients using only one OAD (Table 68).

Table 68: Medication adherence and number of oral antidiabetic drugs.

	Medication Adherence			
	Haynes-Sackett Test		MAT scale	
	Mean ± SD	Median	Mean ± SD	Median
<2 OAD	85.97±19.1	95.24	5.07±0.55	5.14
≥2OAD	90.3±16.2	94.34	5.24±0.45	5.29
p value	0.038		0.054	

Legend: MAT - Measure Treatment Adherence; OADs: oral antidiabetic drugs; SD – Standard deviation.

Medication adherence showed no significance difference for HbA1c values ($p>0.05$).

Patient Medication Knowledge

Patient knowledge about medication was assessed using an algorithm considering issues identified regarding the medicines used: name, drug´s strength, therapeutic indication, administration time, unit(s) number and storage conditions.

In about half of the medicines, patients were unable to indicate the name of the medication (50.9%), and in about three-quarters (75.7%) of the medicines the patients were not capable to indicate drug's strength. The therapeutic indication was not known by the patient or was incorrect in about a quarter of medicines (23.6%). In about 9.0% of medicines the patients have been identified problems related to administration time and in 7.8% of medicines issues related to the number of units to use. The storage conditions were incorrect in about 57.5% of the medicines (Table 69).

Table 69: Characterization of patients´ medication knowledge.

	N	%
Name		
✓ **Knows the name**	399	49.1
✓ **Does not know the name**	413	50.9
Drug´s strength		
✓ **Knows drug´s strength**	197	24.3
✓ **Does not drug´s strength**	615	75.7
Therapeutic Indication		
✓ **Knows the correct therapeutic indication**	541	66.6
✓ **Does not know the correct therapeutic indication**	63	7.8
✓ **Does not know the therapeutic indication**	128	15.8
✓ **The information on the therapeutic indication is not complete**	80	9.9

Table 69 *(Continued)*

	N	%
Administration time		
✓ **Correct administration time**	739	91.0
✓ **Incorrect administration time**	73	9.0
Units Number		
✓ **Correct number**	749	92.2
✓ **Incorrect number**	63	7.8
Storage Conditions		
✓ **Correct storage**	290	35.7
✓ **Incorrect storage**	467	57.5
✓ **Lack of information on medication storage**	55	6.8

About a quarter of patients (25.4%; n=30) showed a low medication knowledge (<50%), with an average rate of 62.77±16.01 of correct information about the medicines they were using.

An increased number of health problems was observed in patients with a low level of medication knowledge (p=0.029), and also a lower score of health literacy (p=0.039) (Table 70).

Table 70: Medication knowledge, number of health problems and health literacy.

	Nr Health Problems		Health Literacy	
	Mean±SD	Median	Mean±SD	Median
Low MK	5.53±2.18	5.0	12.23±4.45	13.5
Not Low MK	4.57±1.77	4.0	14.6±2.48	15.0
p value	0.029		0.039	

Legend: MK: Medication Knowledge; SD – Standard deviation.

No significant differences were achieved for medication knowledge regarding socio-demographic variables, patient´s medication adherence, disease control

(hypertension, diabetes and dyslipidaemia) and number of medicines used per patient (p>0.05).

The number of hospitalizations was higher in patients with low level of medication knowledge (mean=1.31±0.87; median=1.0), compared to patients who did not have this lack of knowledge (mean=1.0±0.0; median=1.0) (p=0.043).

Patients getting help managing medication presented a lower score for medication knowledge (mean=57.7±15.4; median=55.9) over patients without any support (mean=64.98±15.87; median=65.91) (p=0.026).

Patient Disease Knowledge

Patients indicated to have a diagnosis of hypertension, on average, for 10.73±7.87 years.

The optimal values for blood pressure were correctly identified by 67.7% of hypertense patients, and almost all of those had measured their blood pressure in the last 12 months (99.0%). Only 16.7% indicated to perform occasional measurements and most of them performed at least a monthly measurement (70.8%). Nearly half of patients (48.0%) were not able to correctly indicate possible complications of uncontrolled blood pressure (Table 71).

About 80.2% (n=77) of hypertensive patients indicated to have a tensiometer at home allowing them to measure blood pressure in the household.

Table 71: Patients´ knowledge about hypertension.

	N	%
Optimal value for blood pressure?		
▪ **Correct**	65	67.7
▪ **Incorrect**	17	17.7
▪ **Does not Know**	14	14.6
Total	96	100.0

Table 71 *(Continued)*

	N	%
Did you measure your blood pressure in the last 12 months?		
▪ **Yes**	95	99.0
▪ **No**	1	1.0
How many times?		
▪ **At least once a day**	19	19.8
▪ **At least once a week**	32	33.3
▪ **At least once a month**	17	17.7
▪ **Every six months**	6	6.3
▪ **Every 3 months**	6	6.3
▪ **Occasional**	16	16.7
Total	96	100.0
The patient is able to indicate two complications of uncontrolled hypertension?		
▪ **Yes, can identify 2 complications.**	28	29.2
▪ **Only one complication was identified.**	22	22.9
▪ **Patient knows that complications can be harmful but is not able to name it.**	9	9.4
▪ **The patient is not able to identify complications.**	30	31.3
▪ **Patient identified as a complication of the disease a side effect of medication (e.g. hypotension) or a symptom.**	7	7.3
Total	96	100.0

Patients who reported having diabetes *mellitus*, had this diagnosis for about 13.2±9.3 years. Most of these patients (70.1%) were able to identify the correct range for fasting blood glucose, but could not identify the target range for post-prandial blood glucose (94.4%). Patients indicated having measured blood glucose in the last 7 days on average 5.24 + 2.66 days, and 68.2% (n=73) indicated to have measured blood glucose every day, stating they had been indicated, by health professionals, to measure their blood glucose on average 6.14 + 1.98 days (during 7 days), and in 83.2% (n=89) of cases were advised to daily measure blood glucose. A statistically significant difference between the number of measurements performed by the patients and the number of measurements indicated by health professionals in the last 7 days was

achieved, the latter being higher than the number of measurements actually performed by the patients (Table 72).

It is noteworthy that 33.6% of patients diagnosed with diabetes, identified as a potential complication of the disease side effect(s) from medication (e.g. hypoglycaemia) or a disease symptom.

In diabetic patients, 99.1% indicated to have had a glycemic control device at home.

Table 72: Patients´ knowledge about diabetes.

	N	%
Which is target range for fasting blood glucose?		
▪ **Correct**	75	70.1
▪ **Incorrect**	18	16.8
▪ **Does not Know**	14	13.1
Total	107	100.0
Which is target range for post-prandial blood glucose?		
▪ **Correct**	6	5.6
▪ **Incorrect**	4	3.7
▪ **Does not Know**	97	90.7
Total	107	100.0
The patient is able to indicate two potential complications of uncontrolled blood glucose?		
▪ **Patient can identify 2 potential complications**	16	15.0
▪ **Only one complication was identified**	9	8.4
▪ **Patient knows that complications can be harmful but is not able to name it**	12	11.2
▪ **The patient is not able to identify potential complications**	34	31.8
▪ **Patient identified as a complication of the disease a side effect of medication (eg hypoglycaemia) or a symptom**	36	33.6
Total	107	100.0

No statistically significant differences were identified in patients with low health literacy compared to those who did not have low literacy relative to patient´s

socio-demographic characteristics, medications adherence, number of medicines used, health literacy score and glycemic profile control (p>0.05).

Patients indicated to have been diagnosed with dyslipidaemia on average for 7.42±5.82 years. About two-thirds of these patients couldn´t identify the optimal value for the total cholesterol (66.0%; n = 60), and more than half (58.2%; n=53) of these patients were not able to identify possible complications of uncontrolled cholesterol (Table 73).

Table 73: Patients´ knowledge about dyslipidaemia.

	N	%
Optimal value for total cholesterol?		
▪ **Correct**	31	34.1
▪ **Incorrect**	16	17.6
▪ **Does not Know**	44	48.4
Total	91	100.0
The patient is able to indicate two potential complications of uncontrolled total cholesterol?		
▪ **Patient can identify 2 potential complications**	24	26.4
▪ **Only one complication was identified**	14	15.4
▪ **Patient knows that complications can be harmful but is not able to name it**	6	6.6
▪ **The patient is not able to identify potential complications**	47	51.6
Total	91	100.0

A lack of knowledge regarding diseases such as hypertension, diabetes and dyslipidaemia was identified in many of the patients, respectively, in 61% (n=72), 78% (n=92) and 60.2% (n=71).

Health Literacy

Almost half of the patients (43.2%; n=51) were identified with “low health literacy”, with a mean of 13.97±3.24 points as the result for the application of SAHL-PT.

Patient´s health literacy score was higher for patients under 65 years (p<0.001) with a mean score of 14.86±2.83 (median=15.0) compared to patients ≥ 65 years, who presented an average of 13.3±3.64 (median=14.0). For higher level of qualifications an increased score of health literacy was obtained, with patients having secondary education (12th grade) and higher education presenting the greater score for health literacy (p=0.003) (Table 74).

Table 74: Health literacy and patients´ qualifications.

Qualifications	Mean	SD	Median	p value
Cannot read or write	6.3	2.9	8.0	0.001
Can read and/or write without having education degree	10.0	4.6	9.0	
1st cycle of basic education (4th grade)	12.8	3.26	12.0	
2nd cycle of basic education (junior)	15.3	1.5	15.0	
3rd cycle of basic education (9 years)	14.3	2.7	15.0	
Secondary education (12th grade)	16.4	1.24	16.5	
Professional course/technological	15.1	1.36	15.0	
Higher education	16.5	0.97	16.0	

Legend: SD – Standard deviation.

Patient´s health literacy presented a higher score (mean=14.57±2.5; median=15.0) for patients without a low level of medication knowledge (p=0.043) compared to patients presenting a low level of medication knowledge (mean=12.2±4.45; median=13.5).

Moreover, patients without lack of knowledge about dyslipidaemia (p=0.003) presented a higher score for health literacy (mean=15.55±2.4, media=16.0) than those with lack of knowledge about dyslipidaemia (mean=13.45±3.18, median=14.0).

Patients with uncontrolled lipid profile showed a higher score for health literacy (mean=15.1±3.0; median=16.0) than patients with controlled lipid profile (mean=13.73±3.25; median=15.0) (p=0.041).

The number of health problems reported by patients having a low health literacy score (mean=4.96±1.91) was greater than the number of health problems diagnosed for patients not having low health literacy score (mean=4.7±1.94), despite no statistically significant difference (p> 0.05).

Patients presenting low health literacy score showed an increased HbA1c value (7.75±1.2; median=7.6) compared to those without low health literacy score (7.6±1.5; median=7.3). Also a lower health literacy score (mean=13.68±3.44) was identified for patients presenting a higher prevalence of uncontrolled blood pressure compared to those with controlled blood pressure (mean=14.64±2.66), despite no statistically significant difference (p> 0.05).

Self-perceived health status

Patients considered their health status positively in 33.1% of the cases ("good" or "excellent") and 53.4% as "acceptable" (Table 75).

Table 75: Characterization of self-perceived health status.

Classification	N	%
Very Bad	3	2.5
Bad	13	11.0
Acceptable	63	53.4
Good	37	31.4
Excellent	2	1.7
Total	118	100.0

The number of medicines was higher for patients having a worse perspective of their own health status, having a statistically significant difference for patients considering their health as “very bad” and “bad” (p=0.025) (median=15.0 and 8.0 medicines, respectively), as well as for those considering “very bad” and “acceptable” (p=0.001) (median=15.0 and 7.0, respectively) and between those reporting health status as “bad” and “good” (p=0.001) (median=15.0 and 6.0 medicines, respectively).

Patients with a positive perspective of their health status presented an increased score of health literacy (p=0.018; r=0.218). For those with a "bad" perception of health status an average of health literacy score of 12.85±2.19 (median=13.0) was achieved, compared to those with a “good” perception of health status that presented a higher average score of 14.81±3.08 (median=16.0).

4.2.4.2 Economic outcomes:

Number of medicines

The number of medicines prescribed and used by patients was previously described in the section 4.2.3 - Pharmacotherapeutic profile, as well as the number of units and daily doses.

Patients followed for a longer period in the AEDMADA clinic were treated with a higher number of medicines (p=0.001). Polymedicated patients were followed for a median of 53 months and patients taking less than five medicines were followed for a median of 19 months.

The number of Physicians following patients was higher (mean2.76±1.02; median=3) for patients under polymedication compared to those using less than 5 medicines (mean=2.03±0.87; median=2) (p<0.001).

Patients presenting greater number of health problems were using a higher number of medicines (mean 5.31±1.9; median=5) compared to those with a lower number of health problems (mean 3.42±1.15; median=3) ($p<0.001$).

Patients having help with medication were using an increased number of medicines (mean=8.0±3.28; median=8) than those who did not indicate to receive help with medication (mean=6.13±2.74; median=6) ($p=0.006$).

In cases of patients who had suffered a cardiovascular event, the number of medicines used was greater (mean=8.48±2.46; median=9) compared to those who did not report a previous cardiovascular event (mean=6.32±3.0; median=6). ($p=0.001$).

In the case of patients who practiced physical exercise regularly the number of medicines used for these patients was lower (mean=5.76±2.55; median=5) than in patients who did not practice regular physical exercise (mean=7.4±3.17; median=7.5) ($p = 0.003$).

Number of hospitalizations

Only in 15% of the patients reported having experienced a hospitalization in the previous 12 months, with a total of 23 admissions. This event occurred mostly once (88.89%, n=16) in the previous year, with an average of 8.17±8.95 days of hospitalization, a minimum of 1 day and a maximum of 30 days. Only one patient indicated to be hospitalized on three (3) occasions and one in four (4) occasions.
About 15.9% (n=17) of diabetic patients had been hospitalized in the last 12 months, mostly only one time (88.2%; n=15).

Patients who underwent inpatient the previous 12 months were treated with a higher number of medicines (mean=8.39±3.24; median=8.0) compared to those patients who were not hospitalized during this period (mean=6.4±2.9; median=6.0) ($p = 0.024$).

The number of hospitalizations for patients presenting microvascular complications of diabetes was higher (mean=0.56±1.0) compared to those who have not yet had these complications (mean=0.098±0.3) (p=0.004).

Diabetic patients being treated with insulins presented a higher number of hospitalizations (mean=0.29±0.78) compared to those not using insulin (mean=0.14±0.35) (p=0.037).

Patients with a negative perception of their health presented an increased length of hospitalization (p=0.03), as well as patients who had already a prior cardiovascular event (p=0.006) (Table 76).

Table 76: Length of hospitalization, self-perceived health status and previous cardiovascular event.

Self-perceived health status	**Length of hospitalization** (days)			
	Mean± SD	**N**	**Median**	p value
Very Bad	17.5±17.68	2	17.5	0.03
Bad	11.0±7.0	3	14.0	
Acceptable	8.43±9.74	7	5.0	
Good	3.33±2.88	6	2.5	
Excellent	0.0±0.0	0	0.0	
Total	8.17±8.95	18	5.0	
Previous cardiovascular event	**Mean**	**N**	**Median**	p value
Yes	17.0±9.31	4	15.0	0.006
No	5.64±7.83	14	4.0	
Total	8.17±8.95	18	5.0	

Legend: SD – Standard deviation.

Number of Physicians following patient

Patients were followed mainly by two (36.4%) or three (34.7%) Physicians, while a small number of patients was followed by four (11.9%), five (1.7%) and six (1.7%) Physicians. Most patients (77.1%) was attending consultations with General Practitioners and specialists in the area of diabetology such as internal medicine (Table 77).

Table 77: Characterization of Physicians´ specialities.

Physician speciality	N	%
Cardiology	22	18.6
Endocrinology	2	1.7
General Practice	91	77.1
Internal Medicine	102	86.4
Neurology	3	2.5
Ophthalmology	35	29.7
Other	34	28.8
Pneumology	1	0.8
Urology	6	5.1

Polymedicated patients reported to be consulted by a higher number of Physicians ($p<0.001$).

Patients being followed by an increased number of Physicians used a higher number of medicines ($p<0.001$; $r=0.404$), and also a higher number of daily units ($p<0.001$; $r=0.404$) and daily doses ($p<0.001$; $r=0.448$).

Patients 65 years and older were consulted by a higher number of Physicians, compared to younger patients (<65 years), although the difference was not statistically significant ($p>0.05$).

Rate of reimbursement of medicines.

Patients were mostly covered by the Portuguese general medicine reimbursement system (75.4%; n=89), while only 14.4% (n=17) were covered by the special system for drug reimbursement and 10.2% (n=12) by other health subsystems.

Patient´s gender (p=0.001), qualifications (p=0.018), number of Physicians (p=0.027) and number of health problems (p=0.043) presented a significant difference relative to patient´s rate reimbursement of medicines. Many of the patients covered by the general medicine reimbursement system were male (57.3%; n=51) and most patients covered by the special system for drug reimbursement were female (82.35%; n=14).

Patients that couldn´t write or read were all covered by the special system for drug reimbursement (n=3).

A total of 3 Physicians were the most frequent number of these professionals following study patients covered by the special system for drug reimbursement (47.1%; n=8), whereas patients covered by the general medicine reimbursement system were more frequently followed by 2 Physicians (41.6%; n=37).

No significant difference was found between medicines reimbursement and patient´s medication adherence (p>0.05).

4.2.4.3 Clinical outcomes:

Negative Clinical Outcomes

A total amount of 360 negative clinical outcomes (NCOs) were identified, being those present in 99.2% (n=117) of the patients included in this study. An average of 3.05±1.13 NCOs per patient, a median of 3 NCOs, 25th and 75th percentiles, respectively, 2 and 4 NCOs, for patients presenting NCOs a minimum of 1 (one) NCO and a maximum of 7 NCOs was detected.

The most frequent NCOs were related to “Disease control” (52.8%) and “Untreated conditions” (38.1%), being less frequent those related to “Safety” (9.2%) (Table 78).

Table 78: Characterization of Negative Clinical Outcomes (NCOs).

NCO	N	%	Mean±SD	Median
Disease Control	190	52.8	1.64±0.82	2.0
Safety	33	9.2	0.23±0.5	0.0
Untreated Conditions	137	38.1	1.2±0.7	1.0
Total	360	100.0	3.05±1.13	3.0

Legend: NCO – Negative clinical outcomes; SD – Standard deviation.

The prevalence of negative clinical outcomes (NCOs) was higher for diseases from Chapter IV - Endocrine, nutritional and metabolic diseases (67.5%) and Chapter IX - Diseases of the circulatory system (22.3%) (Table 79), coinciding with the diseases with greater prevalence in the study sample (Table 47).

Negative clinical outcomes of “disease control” were found more frequently in disorders of lipoprotein metabolism and other lipidaemias (18.1%), hypertension (16.4%) and diabetes *mellitus* (15.8%). Outcomes relative to “untreated conditions” presented a higher prevalence in others disorders of endocrine, nutritional and metabolic diseases (30.8%) and hypertension (2.5%) while NCOs relative to “safety” were most frequent in others disorders of the digestive system (3.2%) and other disorders of endocrine, nutritional and metabolic diseases (2.5%).

Table 79: Characterization of negative clinical outcomes and diseases.

Chapter *	Disease	Disease Control		Safety		Untreated Conditions		Total	
		N	(%)	N	(%)	N	(%)	N	(%)
III	Anaemia	1	0.3	0	0.0	1	0.3	2	0.6
IV	Diabetes	57	15.8	0	0.0	0	0.0	57	15.8
	Dyslipidaemias	65	18.1	0	0.0	22	6.1	87	24.2
	Other	1	0.3	9	2.5	89	24.7	99	27.5
V	Depressive dis.	2	0.6	0	0.0	1	0.3	3	0.8
	Insomnia	1	0.3	0	0.0	0	0.0	1	0.3
	Other	0	0.0	2	0.6	2	0.6	4	1.1
VI	NS - Other	0	0.0	2	0.6	0	0.0	2	0.6
IX	Hypertension	59	16.4	1	0.3	9	2.5	69	19.2
	Other	2	0.6	2	0.6	7	1.9	11	3.1
XI	Other	1	0.3	11	3.1	2	0.6	14	3.9
XIII	Other	0	0.0	2	0.6	1	0.3	3	0.8
XIV	BPH	1	0.3	0	0.0	0	0.0	1	0.3
	Other	0	0.0	1	0.3	2	0.6	3	0.8
XIX	Allergy, Unsp.	0	0.0	3	0.8	1	0.3	4	1.1
	Total	190	52.8	33	9.2	137	38.1	360	100

*Legend: * ICD-10 Chapter; BPH – Benign prostatic hyperplasia; Dis. – Disorders; Unsp. – Unspecified; NS – Nervous system.*

About a fifth (21.5%) of the medicines and supplements used by patients, for those who had negative clinical outcomes, the most frequent NCOs were relative to the “control of disease” (80.5%) and the remaining outcomes related to “security” (19.5%).

Considering socio-demographic variables, no statistically significant difference was identified regarding the number of NCOs identified in patient´s medication review.

The average number of NCOs found in patients aged 65 years or older was higher (mean=3.06±1.04; median=3.0) than the number of NCOs achieved in younger patients (mean=3.04±1.25), although this difference was not statistically significant (p>0.05).

For the various specific types of negative clinical outcomes, in “disease control” a statistically significant difference was achieved for the follow-up period in AEDMADA clinic (p=0.037; r=0.193). Moreover, in NCOs of “safety” a higher number of negative outcomes (p=0.030) was observed for female patients (mean=0.34±0.59; n=53) compared to male patients (mean=0.14±0.39; n=64). For NCOs related to “untreated conditions” no association were identified within the socio-demographic variables.

In cases where there was an uncontrolled blood pressure (p<0.001; r=0.347), uncontrolled glycemic profile (p<0.001; r=0.476), increased HbA1c values (p<0.001; r=0.349) and previous cardiovascular events (p=0.028; r=0.202), patients presented higher prevalence of NCOs.

Those patients with hypertension (p=0.007; r=0.245), diabetes *mellitus* (p=0.017, r = 0.219) and previous cardiovascular event (p=0.002; r=0.284) had a significantly higher number of NCOs relative to "disease control".

Patients with a disorder of lipid metabolism showed an increased number of NCOs relative to “untreated conditions” (p=0.017; r=0.219).

Patients with polypharmacy presented an increased number of NCOs, with a statistically significant difference achieved for both “disease control” and “untreated conditions” negative outcomes (Table 80).

Table 80: Characterization of negative clinical outcomes and polypharmacy.

		NCOs (number)		
		Mean±SD	**Median**	**p value**
NCOs *(total number)*	<5 medicines	2.9±1.14	3	0.307
	≥5 medicines	3.1±1.13	3	
“Disease control”	<5 medicines	1.29±0.69	1	0.003
	≥5 medicines	1.76±0.83	2	
“Safety”	<5 medicines	0.13±0.34	0	0.254
	≥5 medicines	0.26±0.54	0	
“Untreated conditions”	<5 medicines	1.48±0.93	1	0.016
	≥5 medicines	1.09±0.56	1	

Legend: NCOs – Negative clinical outcomes; SD – Standard deviation.

The number of daily units (p=0.023; r=0.210) and the number of daily doses (p=0.033; r=0.196) were in higher number for patients with increased number of NCOs.

Moreover, a greater number of antidiabetic drugs (oral antidiabetic drugs and insulins) (p=0.001; r=0.305) were being taken patients manifesting an increased number of NCOs.

For NCOs relative to "disease control" significant differences were identified for the number of medicines (p = 0.001; r=0.297), daily units (p = 0.00; r=0.316), daily doses (p = 0.00; r=0.328).

For polymedicated patients (≥5 medicines) a higher number of NCOs (mean=3.1±1.13; median=2) relative to "disease control" (p=0.003) was identified, when compared to those patients using a lower number of medicines (mean=1.76±1.14; median=1).

A lower number of NCOs (mean=1.09±0.56; median=1) relative to "untreated situations" were identified for patients using polypharmacy, compared to those using a lower number of medicines (mean=1.48±0.93; median=1) (p=0.012).

The number of NCOs identified was higher for patients having uncontrolled blood pressure, uncontrolled glycemic profile, increased values of HbA1c and for those who had a previous cardiovascular event (Table 81).

Table 81: Characterization of negative clinical outcomes and clinical variables correlation.

Clinical variables	NCOs (total)		NCOs "disease control"		NCOs "untreated conditions"	
	r	p value	r	p value	r	p value
Number of health problems	0.077	0.406	0.100	0.280	-0.086	0.353
Hypertension	0.103	0.266	0.245	0.007	0.168	0.070
Diabetes *mellitus*	0.116	0.210	0.219	0.017	0.070	0.450

Table 81 *(Continued)*

Clinical variables	NCOs (total)		NCOs "disease control"		NCOs "untreated conditions"	
	r	p value	r	p value	r	p value
Blood pressure control	0.347	<0.001	0.358	<0.001	0.156	0.092
Glycemic profile control	0.476	<0.001	0.532	<0.001	0.238	0.013
Lipid profile control	0.115	0.216	0.231	0.012	0.032	0.734
HbA1c values	0.349	<0.001	0.375	<0.001	0.211	0.024
Previous CV event	0.202	0.028	0.284	0.002	0.006	0.945

Legend: CV – Cardiovascular; NCO – Negative clinical outcome.

Patients presenting a larger number of NCOs of "disease control" had a diagnosis of hypertension (p=0.007), diabetes *mellitus* (p=0.017), and a lower control on blood pressure (p<0.001), lipid profile (p=0.012), and glycemic profile (p<0.001), as well as higher values of HbA1c (p<0.001).

The number of NCOs relative to "safety" showed no statistically significant differences in the clinical variables.

When patients presented a diagnosis of dyslipidaemia a higher number of NCOs of "untreated conditions" were observed (p=0.017), as well as patients with uncontrolled glycemic profile (p=0.013) and higher HbA1c values (p=0.024) also showed a higher number of such NCOs.

Regarding the analysis of parameters included in the humanistic outcomes from medication review, no statistically significant differences were found concerning the number of NCOs other than the knowledge of the disease relative to dyslipidaemia (p=0.015) (Table 82). Patients who presented a lack of knowledge for this disease (dyslipidaemia) presented an average of 3.07±1.03 (median=3) NCOs and patients without this characteristic presented an average of 2.55±1.06 (median=2.5) NCOs (p=0.015).

Table 82: Negative clinical outcomes and humanistic outcomes correlation.

Humanistic Outcomes	r	p value
Medication Adherence (MAT scale)	-0.078	0.403
Medication Adherence (Haynes-Sackett test)	-0.028	0.762
Medication Knowledge	-0.040	0.669
Lack of knowledge (Hypertension)	0.018	0.860
Lack of knowledge (Diabetes *mellitus*)	0.006	0.952
Lack of knowledge (Dyslipidaemia)	0.252	0.015
Disease Knowledge (Total)	-0.127	0.171
Health Literacy	-0.082	0.377
Help with your medications	-0.051	0.585
Self-perceived health status	-0.054	0.560

Legend: MAT - Measure Treatment Adherence.

Regardless of no statistically significant differences obtained for patients with low health literacy score, low medication knowledge, non-adherent patients to medication, patients having help with medication and negative perceptions for health status, for those patients an increase in the number of NCOs was achieved ($p>0.05$).

Considering economic outcomes (Table 83), a statistically significant difference was identified for the number of Physicians consulted by patients ($p=0.018$; $r=0.208$) and patient´s medication reimbursement rate ($p=0.045$; $r=0.185$), relative to the number of NCOs.

Table 83: Negative clinical outcomes and economic outcomes correlation.

Economic Outcomes	r	p value
Medication reimbursement	0.185	0.045
Number of total of medicines	0.151	0.104
Number of hospitalizations	0.037	0.692
Number total of Physicians	0.218	0.018

For NCOs relative to “disease control”, patients with longer hospitalizations presented a higher number of these negative outcomes (p=0.033; r=0.503). Considering the NCOs relative to “safety” only the “number of Physicians consulted by patients” presented a significant difference (p=0.001; r=0.302), with patients being followed by a higher number of Physicians presenting a higher number of this type of NCO.

For the NCOs relative to “untreated conditions” no significant differences were identified within the parameters included in the scope of economic outcomes.

Drug-Related Problems

A total of 552 drug-related problems (DRPs) were identified among patient´s medication, whereas DRPs were pointed out by 95.8% (n=113) of patients, with an average of 4.7±2.9 (median=4) DRPs per patient.

The most prevalent DRPs were related to “Drug selection” (38.2%), followed by “Medicine´s use process” (27.9%) and “Dose selection” (20.7%), as described in Table 84.

Table 84: Characterization of drug-related problems (DRPs).

DRP Scope	N (%)	Type	N	%
Drug selection	211 (38.2)	Inappropriate drug (incl. contra-indicated)	101	18.3
		No indication for drug	66	12.0
		Inappropriate combination of drugs, or drugs and food	27	4.9
		Synergistic/preventive drug required and not given	17	3.1
		Duplicate drug	0	0.0
Dose selection	114 (20.7)	Drug dose too low	66	12.0
		Drug dose too high	9	1.6
		Dosage regimen not frequent enough	32	5.8
		Dosage regimen too frequent	2	0.4
		Dose adjustment is required (pharmacokinetics)	1	0.2
		Dose adjustment is required (improvement of disease state)	4	0.7

Table 84 *(Continued)*

DRP Scope	N (%)	Type	N	%
Drug form	1 (0.2)	Inappropriate drug form	1	0.2
Treatment duration	34 (6.2)	Duration of treatment too short	2	0.4
		Duration of treatment too long	32	5.8
Medicine´s use process	154 (27.9)	Inappropriate timing of administration and/or dosing intervals	73	13.2
		Drug underused (intentional)	34	6.2
		Patient forgets to use drug (unintentional)	15	2.7
		Drug not used at all	31	5.6
		Wrong drug used	1	0.2
Patient Medication knowledge	30 (5.4)	Low medication knowledge rate	30	5.4
Other	8 (1.4)	Other	8	1.4
Total	552 (100.0)		552	100.0

Analysing the type of DRPs identified, “Inappropriate drug” (18.3%), “Inappropriate timing of administration and/or dosing intervals” (13.2%), “No indication for drug” (12.0%) and “Drug dose too low” (12.0%) were the most frequent types identified in patient´s medication.

The analysis of drug related problems (DRPs) per medicine (drug´s ATC and food supplements) did not include DRPs relative to “Medicines knowledge” whereas the evaluation of the patient's knowledge about medicines was calculated for the total number of medicines used by the patient.

The total number of NCOs did not presented a statistically significant difference relative to the number of DRPs (p=0.151). However, a significant difference was achieved between the number of DRPs relative to “Drug selection” (p=0.026; r=0.315) and the total number of NCOs, as well for NCOs related to "disease control" (p=0.010; r=0.237).

The number of DRPs presented a significant difference ($p<0.001$) with the number of health problems ($p<0.001$; $r=0.496$).

Also for the number of antihypertensive drugs ($p=0.005$; $r=0.259$), oral antidiabetic drugs ($p=0.028$; $r=0.202$) and antiplatelet drugs ($p=0.043$; $r=0.186$), statistically significant differences were achieved relative to the number of DRPs.

A greater number of drug-related problems of “drug selection” was achieved for patients using an increased number of antidiabetic drugs (oral and insulins) ($p=0.029$; $r=0.201$) and antiplatelet drugs ($p=0.002$; $r=0.286$), as well as for patients with uncontrolled blood pressure ($p=0.019$) with an average number of this type of DRPs of 2.06±1.91 and 1.17±1.0 for patients with controlled blood pressure.

Furthermore, an increased number of DRPs of “dose selection” was achieved for patients using a higher number of antidyslipidemic drugs ($p=0.013$; $r=0.228$) and a lower number of insulins ($p=0.010$; $r=-0.237$).

Patients who had a prior cardiovascular event presented a greater number of DRPs of "dose selection" ($p=0.020$), as well as those who had a diagnosis of dyslipidaemia ($p=0.007$) with an average of 1.07±1.0 DRPs of this type and 0.63±1.11 for those who had no diagnosis of this health problem.

An increased number of DRPs of “medicine´s use process” was detected for patients using a higher number of oral antidiabetic drugs ($p=0.043$; $r=0.287$), and for patients using a higher number of antiplatelet drugs a greater number of DRPs of “medicine´s use process” ($p=0.045$; $r=0.285$) was found.

Considering the type of DRP, the highest prevalence of DRPs (37.2%) was identified in medicines belonging to the C group (Cardiovascular System), A group (Alimentary Tract and Metabolism) (27.0%) and N group (Nervous System) (17.2%) (Table 85).

Table 85: DRP prevalence for ATC group A, C and N.

DRP Type	ATC (Level 1)					
	A Group N (%)		C Group N (%)		N Group N (%)	
Inappropriate drug (incl. contra-indicated)	22	4.2	44	8.4	15	2.9
No indication for drug	19	3.6	8	1.5	15	2.9
Inappropriate combination of drugs, or drugs and food	9	1.7	12	2.3	3	0.6
Synergistic/preventive drug required and not given	2	0.4	13	2.5	1	0.2
Duplicate drug	0	0,0	0	0,0	0	0.0
Inappropriate drug form	0	0.0	0	0,0	1	0.2
Drug dose too low	12	2.3	28	5.4	12	2.3
Drug dose too high	1	0.2	4	0.8	1	0.2
Dosage regimen not frequent enough	3	0.6	16	3.1	6	1.1
Dosage regimen too frequent	2	0.4	0	0.0	0	0.0
Dose adjustment is required	0	0.0	0	0.0	1	0.2
Dose adjustment is required (improvement of disease state)	2	0.4	2	0.4	0	0.0
Duration of treatment too short	0	0.0	0	0.0	1	0.2
Duration of treatment too long	7	1.3	0	0.0	21	4.0
Inappropriate timing of administration and/or dosing intervals	28	5.4	29	5.6	6	1.1
Drug underused (intentional)	15	2.9	12	2.3	4	0.8
Patient forgets to use drug (unintentional)	3	0.6	8	1.5	1	0.2
Drug not used at all	10	1.9	15	2.9	2	0.4
Wrong drug used	0	0.0	1	0.2	0	0.0
Other	6	1.1	2	0.4	0	0.0
Total	141	27.0	194	37.2	90	17.2

Legend: ATC – Anatomical, Therapeutic and Chemical; DRP – Drug-related problem.

The problem “Inappropriate drug” presented a higher prevalence in medicines such as A10BH (Dipeptidyl peptidase 4 (DPP-4) inhibitors) (1.34%); C07AB (selective Beta blocking agents) (1.72%), C10AB (Lipid modifying agents – Fibrates) (1.34%), N05BA (Anxiolytics, Benzodiazepine derivate) (1%).

A higher prevalence was achieved for DRP “No indication for drug” with increased prevalence in A02BC (Proton pump inhibitors) (2.9%), and B01AC (antithrombotic agents, Platelet aggregation inhibitors excl. heparin)

(2.3%). Additionally to this type of problem under the "Drug selection" the problem "No indication for drug" was the second most frequent.

The pharmacotherapeutic groups with the highest prevalence were the N (Nervous system) group (2.9%), A (Alimentary tract and metabolism) group (3.6 %) and B (Blood and blood forming organs) group (2.3%). In A group, the subgroups with the outstanding number of problems were A02BC (Proton pump inhibitors) (2.9%) and B01AC (Antithrombotic agents, Platelet aggregation inhibitors excl. Heparin) (2.3%).

Considering DRPs relative to “Dose selection”, most prevalent problems were “Drug dose too low” (12.6%) and “Dosage regimen not frequent enough” (6.1%) For the problem “Dosage regimen not frequent enough” the drug´s group with more problems were C group (Cardiovascular system) (3.1%) and N group (Nervous system) (15.1%).

In the scope of “Medicine´s use”, the “Inappropriate timing of administration and/or dosing intervals” was the DRP with higher prevalence (13.2%), followed by “Drug underused (intentional)” (6.2%) and “Drug not used at all” (5.6%). For the first type of problem, the subgroup C08CA (Selective calcium channel blockers with mainly vascular effects, Dihydropyridine derivatives) (1.7%) and A02BC (Proton pump inhibitors) (2.9%) were the drug subgroups with highest number of DRPs.

Problems of “intentional non-adherence” were more frequent in the drug subgroups A10BA (Blood glucose lowering drugs, biguanides) and C10AA (Lipid modifying agents, HMG CoA reductase inhibitors), both with 1.15%. The subgroups C09AA (angiotensin-converting-enzyme inhibitors) and C10AA (Lipid modifying agents, HMG CoA reductase inhibitors) verified an increased number of DRPs relative to “Drug not taken at all” (1.3% for both).

DRPs relative to medication adherence were higher in the intentional (6.5%) character than in the unintentional (2.9%).

“Drug dose too low” was the more evident DRP in the subgroups C10AA (Lipid modifying agents, HMG CoA reductase inhibitors) (2.7%) and N05BA (Anxiolytics, Benzodiazepine derivate) (1.15%).

Older patients (≥65 years) presented a higher number of DRPs (5.52±2.89; median 5) compared to younger patients (mean=3.57±2.48; median=3) ($p<0.001$). In this group of patients, the most prevalent DRPs were relative to "Drug selection" (40.4%), "Medicine´s use process" (29.5%) and "Dose selection" (21.8%).

The type of DRPs most observed in older patients, were "Inappropriate drug" (19.3%), "Inappropriate timing of administration and/or dosing intervals" (14.0%), "No indication for drug" (12.6%) and "Drug dose too low" (12.6%).
Taking into account the humanistic outcomes from medication review, only the patient´s medication knowledge showed a statistically significant difference ($p=0.012$; $r=-0.229$) with the number of DRPs, with an average of 5.87±2.69 problems for the patient who had low medication knowledge and 4.27±2.85 problems for patients without low medication knowledge ($p=0.003$) (Table 86).

Table 86: Characterization of drug-related problems and humanistic outcomes correlation.

Humanistic Outcomes	r	p value
Medication Adherence (MAT scale)	0.046	0.620
Medication Adherence (HS test)	-0.137	0.140
Medication Knowledge	-0.229	0.012
Lack of knowledge (Hypertension)	-0.053	0.608
Lack of knowledge (Diabetes)	-0.061	0.529
Lack of knowledge (Dyslipidaemia)	-0.133	0.203
Disease Knowledge (Total)	-0.005	0.960
Health Literacy	-0.068	0.466
Help with your medications	0.008	0.932
Self-perceived health status	0.027	0.768

Legend: MAT – Measure Treatment Adherence.

Patients that were non-adherent to medication, patients who achieved a low health literacy score and those having a lack of disease knowledge presented a higher number of DRPs, although no statistically significant differences were observed (p>0.05).

Moreover, patients manifesting a more negative perception of their health status had a higher number of detected DRPs, although without statistically significant differences (p>0.05).

Analysing economic outcomes resulting from medication review (Table 87), a statistically significant difference was found for the number of DRPs with patient´s medication reimbursement (p=0.02; r=0.284 and with the number of Physicians following the patient (p=0.007; r=0.246). Also a higher number of DRPs were identified for patients taking an increased number of medicines (p<0.001; r=0632)

Table 87: Drug-related problems and economic outcomes correlation.

Economic Outcomes	r	p value
Medication reimbursement rate	0.284	0.02
Number of total of medicines	0.632	<0.001
Number of hospitalizations	0.137	0.138
Number total of Physicians	0.246	0.007

Patients who had attributed the general system of reimbursement of medicines had a statistically significant lower number of DRPs (p=0.006) and patients having the special system of medicine´s reimbursement showed a higher number of DRPs (median=6.0).

The number of DRPs detected increased with the number of medications used by the patient, and displayed a higher average value for patients using 11 or more medicines (Table 88).

Table 88: Characterization of drug-related problems and number of medicines.

Medicines (number)	Mean±SD	Median	N	p value
Up 4 medicines	2.61±1.94	2.0	31	0.006
5 to 10 Medicines	5.05±2.77	5.0	75	
11 to 16 Medicines	7.67±1.87	8.0	12	
Total	4.68±2.88	4.0	118	

Legend: SD – Standard deviation.

For patients with a greater number of hospitalizations a higher number of DRPs was achieved, although this difference was not statistically significant (p>0.05).

About 19.4% of older patients (≥ 65 years old) were using potentially inappropriate medication (PIMs), 17 drugs (3.5%) were identified as inappropriate according Beers criteria adapted to Portuguese language (196). Those older patients using PIMs were using mostly one (1) PIM (69.2%).

Potentially inappropriate medication (PIM) more often identified was “long term benzodiazepine” (29.4%) and “long term NSAID” (17.6%), although the more commonly identified PIMs were independent of diagnosis, with only 2 PIMs identified as inappropriate for a specific diagnosis (Table 89).

Table 89: Characterization of potentially inappropriate medication (PIM) according Beers criteria.

PIM		N	%
Independent of diagnosis	Long term benzodiazepine	5	29.4
	Stimulant laxatives	2	11.8
	Long term NSAID, COX-2 nonselective	3	17.6
	Amiodarone	2	11.8
	Muscle relaxants and antispasmodics	2	11.8
	Indomethacin	1	5.9

Table 89 *(Continued)*

PIM		N	%
Considering Diagnosis	Coagulation disorders (acetylsalicylic acid)	1	5.9
	Arrhythmias (amitriptyline)	1	5.9
	Total	17	100.0

Legend: COX-2 – Cicloxigenase- 2; NSAID – Non-steroidal anti-inflammatory drug.

Polymedicated patients (5 or more medicines) were treated with at least one PIM in 21.8% (n=12) of the cases, however no statistically significant difference was achieved (p>0.05).

The use of inappropriate drugs increased significantly with the number of medicines used by patients (p=0.047), and also with the number of drug related problems (p=0.049). No significant statistically differences were found for the number of negative clinical outcomes, or humanistic outcomes (p>0.05).

Risk situations for negative clinical outcomes

Risk conditions for NCOs were identified in 74.6% (n=88) of patients, a total of 293 risk situations and a mean of 2.48±2.31 (median=2.0) per patient. Most patients had up to four (4) risk situations (60.2%) (Figure 16).

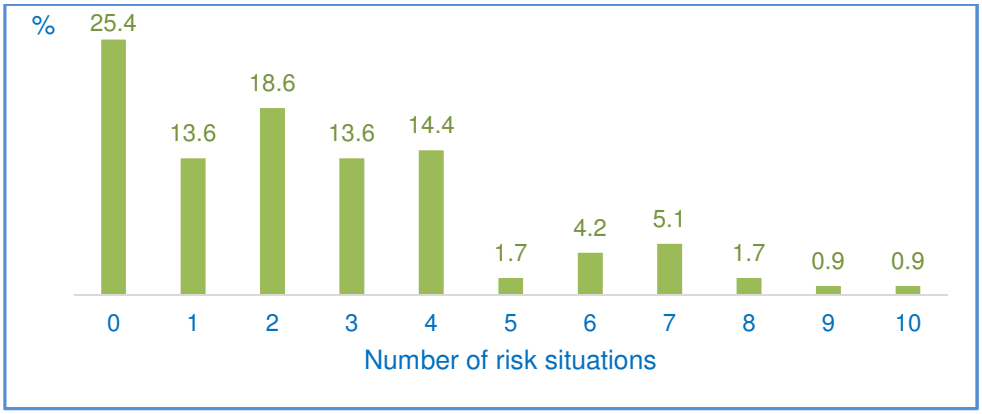


Figure 16: Number of risk situations for negative clinical outcomes.

The number of risk situations for NCOs presented a statistically significant difference for patient´s age (p<0.001) (Table 90), showing an increase with patient´s age, while no other significant differences were identified for socio-demographic parameters.

Table 90: Risk situations of negative clinical outcomes (NCO) and patient´s age.

Age class (years)	**Risk situations of NCOs** (number)				
	Mean	SD	N	Median	p value
18-49 years	0.75	1.75	8	0.0	0.0004
50-64 years	1.95	2.1	43	2.0	
65-74 years	2.70	2.1	43	2.0	
≥ 75 years	3.63	2.8	24	3.0	
Total	2.48	2.3	118	2.0	

Legend: NCO - Negative clinical outcomes; SD - Standard deviation.

Patients ≥65 years presented a higher number of risk situations (3.03±2.37) than younger patients (1.76±2.05) (p=0.001).

Most frequent risk situations were relative to the occurrence of the following DRPs: “no indication for drug” (17.4%), “inappropriate drug” (16.1%), “inappropriate timing of administration and/or dosing interval” (15.1%), “drug dose too low” (12.5%) and “duration of treatment too long” (9.9%).

For the first type of DRP referred above, the drug subgroups most prevalent were B01AC - platelet aggregation inhibitors excluding heparin (26.4 %) and A02BC – proton pump inhibitors (22.6%). Also the problem “inappropriate timing of administration and/or dosing interval” was more prevalent for drugs from the subgroup A02BC – proton pump inhibitors (50.0%).

The drug subgroup N05BA – anxiolytics: benzodiazepine derivate, showed a higher number of problems relative to “duration of treatment too long” (58.1%).

Risk situations relative to “drug selection” showed a statistically significant difference for patient´s age (p<0.001; r=0.355) and patient´s professional situation (p=0.026; r=0.199). Patients ≥65 years presented an average of 2.28±1.9 risk situations compared to younger patients (<65 years) with an average of 1.14±1.2 risk situations.

In older patients, a higher number of risk situations of “drug selection” was detected (p=0.029; r=0.201), patients ≥65 years presented an average of 1.16±1.23 and 0.71±0.86 risk situations for patients under 65 years.

An increased number of risk situations relative to “treatment duration” (p=0.027; r=0.203) was detected for female patients, with an average of 0.39±0.6 and 0.2±0.54 for male patients.

Risk situations relative to "medicine's use process" stands out a statistically significant increase on the "inappropriate timing of administration and / or dosing intervals" for patients followed for longer in clinical AEDMADA (p=0.010, r=0.236).

A statistically significant difference was found for risk situations of "drug underused (intentional)" and patient´s qualifications (p=0.005; r=-0.258), with a lower number of this type of risk situation for patients having the 1st cycle (mean 0.47±0.66) compared to patients with 12th grade (mean 0.83±0.29) (p=0.048).

The number of risk situations achieved no statistically significant difference for the humanistic outcomes from the medication review (Table 91).

Table 91: Risk situations for NCOs and humanistic outcomes correlation.

Humanistic Outcomes	r	p value
Medication Adherence (MAT scale)	0.105	0.290
Medication Adherence (Haynes-Sackett test)	0.040	0.668
Medication Knowledge	0.055	0.555
Lack of knowledge (Hypertension)	0.045	0.668
Lack of knowledge (Diabetes)	0.110	0.258
Lack of knowledge (Dyslipidaemia)	0.170	0.102
Disease Knowledge (Total)	0.090	0.335
Health Literacy	0.076	0.413
Help with your medications	0.033	0.721
Self-perceived health status	0.090	0.334
Legend: MAT – Measure Treatment Adherence.		

Patients taking a higher number of medicines, those who had a greater number of hospitalizations in the previous year, and consulting a large number of Physicians achieved an increase number of risk situations for negative clinical outcomes (Table 92).

Table 92: Risk situations for NCOs and economic outcomes correlation.

Economic Outcomes	r	p value
Number of total of medicines	0.645	<0.001
Number of hospitalizations in the last year	0.255	0.005
Number total of Physicians	0.193	0.037
Medication reimbursement	0.107	0.249

The number of risk situations was higher for polymedicated patients (≥5 medicines) ($p<0.001$), presenting an average of 3.1±2.35 and patients using a

lower number of medicines presented an average of 0.87±1.15 risk situations. Also patients taking an increased number of daily units ($p<0.001$) and daily doses ($p<0.001$) presented a higher number of risk situations.

Furthermore, an increased number of oral antidiabetic drugs ($p=0.037$), antihypertensive drugs ($p=0.003$), antidyslipidemic drugs ($p=0.025$) and number of antithrombotic drugs ($p=0.001$) were used by the patients that presented a higher number of risk situations. However, no statistically significant difference was found for the number of insulins ($p>0.05$).

Patients with a higher number of hospitalizations ($p=0.006$), with more Physicians consulted ($p=0.037$), increased number of health problems ($p<0.001$), as well as uncontrolled glycemic profile ($p=0.002$) and increased HbA1c values ($p=0.004$) showed an increased statistically significant number of risk situations for NCOs.

4.2.4.4 Potential Interventions

A total of 507 potential interventions were identified, an average of 4.3±1.74 per patient (median=4.0), with 25^{th} and 75^{th} percentile of 3.0 and 5.0 respectively, with a maximum of 12 interventions per patient.

Four (28.8%) or three (19.5%) potential interventions were more often identified per patient. In about two thirds of patients three, four or five potential interventions (66.1%) were the most common numbers of potential interventions, and only one patient had any potential intervention identified.
The potentials interventions with highest prevalence were “other intervention” (52.6%) and “at prescriber level” intervention (27.9%), with a median of two (2) and one (1) interventions per patient, respectively (Figure 17).

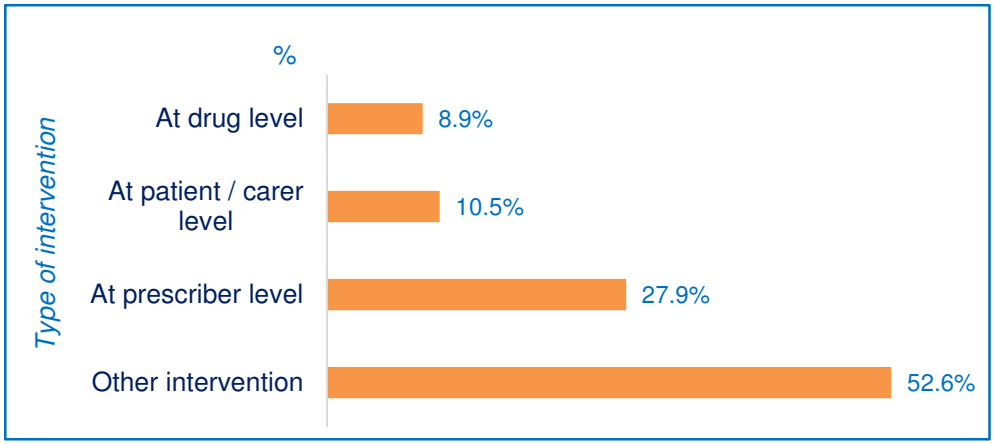


Figure 17: Characterization of potential interventions.

A median of 1 intervention per health problem/situation was identified. The majority of potential interventions was identified for situations presenting negative clinical outcomes (76.3%). Approximately 44% of the interventions were marked for NCOs of “disease control” ($p<0.001$), 26.8% of “untreated situations” ($p<0.001$) and 5.5% of “safety” ($p=0.004$). The remaining identified interventions (23.7%) were identified for health problems that did not have negative clinical outcomes at the time of completion of the medication review. The number of potential interventions increased with the number of diagnosed health problems ($p=0.007$; $r=0.248$). Patients using 5 or more medicines showed a higher number of potential interventions at drug level ($p=0.037$; $r=0.226$), with an average of 0.54±0.8 interventions and 0.26±0.63 for patients using less than 5 medicines.

A statistically significant difference was observed for the number of potential interventions and the number of marked drug-related problems (DRPs) ($p<0.001$), presenting an increased number of DRPs relative to “drug selection” ($p=0.041$), “dose selection” ($p=0.032$), “treatment duration” ($p=0.001$) and “medicine´s use process” ($p=0.017$).

Health problems/clinical situations with more identified potential interventions were dyslipidaemias (27.0%), obesity and other hyperalimentation (18.7%), hypertension (17.4%) and type 2 diabetes *mellitus* (15.0%) (Table 93).

No significant differences were achieved for the number of potential interventions relative to socio-demographic variables (gender, age, marital status, household, qualifications, professional situation and follow-up period in AEDMADA clinic) ($p>0.05$).

Table 93: Characterization of potential interventions and health problems/clinical situations.

		Health Problems/ Clinical situations					
		E78	**E65-E68**	**I10**	**E11**	**F41**	**K90-K93**
Type of intervention *[number of potential interventions (%)]*	**At prescriber level**	30(21.9)	1(1.1)	53(60.2)	23(30.3)	14(82.4)	4(26.7)
	At patient / carer level	24(17.5)	0(0.0)	8(9.1)	20(26.3)	2(11.8)	4(26.7)
	At drug level	6(4.4)	1(1.1)	9(10.2)	16(21.1)	1(5.9)	4(26.7)
	Other intervention	77(56.2)	93(97.9)	18(20.5)	17(22.4)	0(0.0)	3(20.0)
	Total (N)	137(100)	95(100)	88(100)	76(100)	17(100)	15(100)
	Total (%)	27.0	18.7	17.4	15.0	3.4	3.0

Legend: E11 – Type 2 diabetes mellitus; E65-E68 – Obesity and other hyperalimentation; E78 – Disorders of lipoprotein metabolism and other lipidaemias; F41 - Anxiety disorders; I10 – Hypertension; K90-K93 - Other diseases of digestive system.

The number of potential interventions increased with the number of medicines used by patients ($p=0.022$; $r=0.210$) and the number of daily units ($p=0.032$; $r=0.197$), as well as with their HbA1c value ($p=0.023$; $r=0.213$).

Patients with controlled glycemic profile presented a lower number of potential of identified interventions (mean=3.88±2.04; median=4) compared to patients

with uncontrolled glycemic profile (mean=4.47±1.48; median=4) (p=0.038; r=0.201).

Also for patients who had a normal BMI (mean=3.36±1.56; median=3.5) a lower number of potential interventions (p=0.048; r=0.183) were identified.

Patients with a higher number of identified potential interventions at the prescriber level showed an increased number of drug-related problems of the types “duration of treatment too long” (p=0.001; r=0.304), “inappropriate drug” (p=0.015; r=0.223) and “drug dose too high” (p=0.040; r=0.190).

4.2.5 Predictive factors for clinical outcomes

In order to analyse the association between the variables in this study, a list of variables was used as independent variables to construct multiple linear regression models for clinical outcomes (Table 94).

Table 94: List of independent variables used in multiple linear regression.

Patient´s age Older patients (≥65 years) Polypharmacy Professional situation Dyslipidaemia diagnosis Previous CV event Glycemic profile control Blood pressure control	HT diagnosis and using ≥4 drugs Using ≥3 medicines regularly Medication knowledge Medication reimbursement Nr of antidiabetic drugs Nr of antidyslipidemic drugs Nr of antihypertensive drugs Nr of antiplatelet drugs	Nr of daily doses Nr of daily units Nr of hospitalizations in the last 12 months Nr of insulins Nr of medicines Nr of oral antidiabetic drugs Nr of Physicians High risk medication*

*Legend:*Nonsteroidal anti-inflammatory drugs, antiplatelet drugs or diuretics; CV – Cardiovascular; HT – Hypertension; Nr – Number.*

For the independent variables that do not have a normal distribution its logarithmic (log10) equivalent was used, in order to achieve a variable with normal distribution.

Establishing the number of negative clinical outcomes as the dependent variable, the number of Physicians consulted by patients, the glycemic profile control and blood pressure control were included as independent variables. The number of daily units and number of daily doses were excluded from the list of independent variables to be considered, due to their interrelation and their association with the number of Physicians. In addition, the number of insulins and previous cardiovascular events were excluded from the list of independent variables to be considered, due to their interrelation and association with the glycemic profile control.

Table 95 shows the results of the multiple regression analysis for the model created considering NCOs as dependent variable.

Table 95: Predictive model for negative clinical outcomes.

Regression model	b	Standard error	β	p	r^2
Negative clinical outcomes as the dependent variable, F=18.6 p<0.001					
Constant	-0.307	0.48		0.525	0.351
Number of Physicians	0.24	0.09	0.21	0.010	
Blood pressure control	0.70	0.20	0.28	0.001	
Glycemic profile control	1.03	0.18	0.45	<0.001	

This model shows that number of Physicians consulted by patients, blood pressure control, and glycemic profile control predicted some of the variation in negative clinical outcomes (NCOs). According to the r^2 values, these factors predicted 35.1% of the variation in the negative clinical outcomes.

The glycemic profile control variable had a greater effect on the dependent variable (NCOs), although the variable blood pressure control also presented a

considerable weight, whereas the number of Physicians showed a significant but lower effect.

All independent variables established presented a statistically significant effect ($p<0.05$) on the dependent variable in the purposed model.

On the overall, this model shows that most of the variation in negative clinical outcomes can be due to other variables not assessed or to the interaction between variables.

Considering drug-related problems (DRPs) the dependent variable, older patients (≥65 years), the number of antidiabetic drugs and the number of antihypertensive drugs were used as independent variables to construct multiple linear regression models for drug-related problems (DRPs). The number of daily units, number of daily doses, number of antiplatelet drugs, number of Physicians consulted by the patient and the rate medicines reimbursement rate were excluded from the list of independent variables to be considered, due to their interrelation and their association with the number of medicines. The number of oral antidiabetic drugs was also excluded from the list of independent variables to be considered due to their interrelation and association with the number of antidiabetic drugs. Table 96 shows the results of the multiple regression analysis for the model created considering DRPs as dependent variable.

Table 96: Predictive model for drug-related problems.

Regression model	b	Standard error	β	p	r^2
Drug-related problems as the dependent variable, F=25.98 p<0.001					
Constant	0.865	0.538		0.111	0.479
Number of medicines	0.713	0.084	0.75	<0.001	
Age ≥ 65 years	1.33	0.411	0.23	0.002	
Antidiabetic drugs	-0.527	0.194	-0.21	0.008	
Antihypertensive drugs	-0.546	0.259	-1.69	0.037	

This model shows that the number of medicines, age ≥65 years, number of antidiabetic´s drugs and number of antihypertensive drugs significantly predicted some of the variation in drug-related problems. According to the r^2 values, these factors predicted 47.9% of the variation in the drug-related problems results.

The number of antihypertensive medicines and number of medicines used by patients had a greater effect on the dependent variable (DRPs), although the variable number of antidiabetic´s drugs and older patients also had a considerable weight.

All independent variables established presented a statistically significant effect ($p < 0.05$) on the dependent variable in the purposed model.

On the overall, this model show that almost half of the variation in the results of the drug-related problems could be due to other variables not assessed.

4.2.6 Analysis of eligibility criteria to conduct medication review in Australia, Canada and England

Applying to the sample of patients included in the study ReMeD the inclusion criteria for conducting current medication review in Australia, held by the Pharmaceutical Society of Australia, a statistically significant difference was achieved for negative clinical outcomes with patients taking more than 12 doses of medicine per day and for those attending a number of different Physicians (Table 97).

Although results from medication review performed to ReMeD study patients didn´t achieved a statistically significant difference in the number of negative clinical outcomes (NCOs) for patients using ≥5 medicines, this difference was statistically significant in the number of identified drug-related problems and the number of risk situations for NCOs.

Drug related problems presented a statistically significant difference for patients taking five or more regular medicines, taking more than 12 doses of medicine per day, experiencing symptoms suggestive of an adverse medicine reaction and attending a number of different doctors, *i.e.* for all criteria except for "experiencing significant changes to their medicine regiment (in the last three months)", "recently discharged from hospital" and "having difficulty managing their own medicines because of low level of health literacy and language skills or impaired sight" ($p>0.05$).

Table 97: Comparison of eligibility criteria for medication review programs in Australia.

	Program	Criteria	Clinical Outcomes		p value
Australia	Home Medication Review	Currently taking five or more regular medicines	< 5 medicines	≥ 5 medicines	
			NCOs Mean 2.9± 1.15 (median 3) **DRPs** Mean 2.61±1.94 (median 2) **Risk** Mean: 0.87±1.15 (median 0)	**NCOs** Mean 3.1±1.13 (median 3) **DRPs** Mean 5.41±2.81 (median 5) **Risk** Mean: 3.06±2.35 (median 3)	0.307 <0.001 <0.001
		Taking more than 12 doses of medicine per day	< 12 doses / day	≥ 12 doses / day	
			NCOs Mean 2.93±1.12 (median 3) **DRPs** Mean 4.09±2.49 (median 4) **Risk** Mean: 2.01±2.01 (median 2)	**NCOs** Mean 3.62±2.93 (median 3) **DRPs** Mean 7.38±3.07 (median 7) **Risk** Mean: 4.67±2.39 (median 4)	0.008 <0.001 <0.001
		Experiencing significant changes to their medicine regimen (in the last three months) #[1]	Yes	No	
			NCOs Mean 3.0±1.0 (median 3) **DRPs** Mean 3.67±2.5 (median 4) **Risk** Mean: 2.0±2.0 (median 2)	**NCOs** Mean 3.05±1.14 (median 3) **DRPs** Mean 4.7±2.9 (median 4) **Risk** Mean: 2.5±2.33 (median 2)	0.599 0.828 0.986
		Recently discharged from hospital#[2]	Yes	No	
			NCOs Mean: 3.0±1.14 (median 3) **DRPs** Mean: 5.89±3.6 (median 5) **Risk** Mean:5.33±1.64 (median 5)	**NCOs** Mean: 3.06±1.14 (median 3) **DRPs** Mean:4.46±2.69 (median 5) **Risk** Mean: 2.19±2.07 (median 2)	0.686 0.140 0.007

Table 97 *(continued)*

	Program	Criteria	Clinical Outcomes		p value
Australia	Home Medication Review	Taking medicine with a narrow therapeutic index or that requires therapeutic monitoring#[3]	**NCOs** Mean 3.17 ± 0.75 (median 3) **DRPs** Mean 6.36±2.88 (median 6) **Risk** Mean 4.0±2.68 (median 4.5)	**NCOs** Mean 3.0 ± 1.97 (median 3) **DRPs** Mean 6.0±1.75 (median 6) **Risk** Mean 4.0±2.68 (median 4)	0.780 0.783 1.000
		Experiencing symptoms suggestive of an adverse medicine reaction	Yes	No	
			NCOs Mean 3.26±1.23 (median 3) **DRPs** Mean 5.52±3.08 (median 5) **Risk** Mean: 2.5±2.38 (median 2)	**NCOs** Mean 2.93±1.06 (median 3) **DRPs** Mean 4.21±2.67 (median 4) **Risk** Mean: 2.46±2.29 (median 2)	0.891 0.021 0.271
		Having difficulty managing their own medicines because of low level literacy and language skills or impaired sight #[4]	Yes	No	
			NCOs Mean 3.08±1.04 (median 3) **DRPs** Mean 4.98±2.76 (median 5) **Risk** Mean: 2.65±2.22 (median 2)	**NCOs** Mean 3.03±1.2 (median 3) **DRPs** Mean 4.45±2.9 (median 4) **Risk** Mean: 2.35±2.38 (median 2)	0.745 0.212 0.330
		Attending a number of different doctors, both General Practitioners and specialists #[5]	Yes	No	
			NCOs Mean 3.34±1.24 (median 3) **DRPs** Mean 5.29±3.01 (median 5) **Risk** Mean: 2.81±2.42 (median 3)	**NCOs** Mean 2.76±0.93 (median 3) **DRPs** Mean 4.07±2.63 (median 4) **Risk** Mean: 2.15±3.16 (median 2)	0.018 0.020 0.126

Legend: DRPs – Drug-related problems; NCOs – Negative clinical outcomes; Risk – Risk situation for negative clinical outcomes.

#[1] – Patients using medicines for a period less than 6 months were considered; #[2]Patients that have been hospitalized in the last 12 months were considered; #[3] – According to INFARMED: cyclosporine, Levothyroxine sodium, Tacrolimus), in this analysis only levothyroxine was used by patient´s study; #[4] – Analysis was performed considering patient´s health literacy; #[5] – Patients attending more than 2 different doctors were considered.

In the case of "experiencing significant changes in medicine regimen" it was considered in the ReMeD study the patients that were using medicines for a period less than 6 months, while for patients "recently discharged" were only considered patients who had undergone hospitalization in the last 12 months. The number of ReMeD study patients that used "medicines with narrow therapeutic index" was greatly reduced.

A statistically significant difference was achieved in the group of patients who fulfilled at least one of the eligibility criteria for holding medication review concerning NCOs ($p = 0.024$), number of DRPs ($p = 0.001$) and number of risk for NCOs ($p = 0.001$).

Considering the current eligibility criteria for medication review in Canada, a statistically significant difference was observed for the number of NCOs relative to the inclusion criteria for the program MedsCheck and MedsCheck living with diabetes, with an increased number of NCOs and DRPs for patients using 3 or more medications for a chronic condition (Table 98).

Also a significant higher number of NCOs was identified for patients diagnosed with type 1 or type 2 diabetes and taking one or more medication for treating diabetes.

Table 98: Analysis of eligibility criteria for medication review programs in Canada.

	Program	Criteria	Clinical Outcomes		p value
Canada (Ontario)	MedsCheck	Minimum of 3 prescription medications for a chronic condition [#1]	< 3 medications	≥ 3 medications	
			NCOs Mean: 2.9±1.06 (median 2) **DRPs** Mean: 3.23±2.71 (median 2) **Risk** Mean: 1.32±1.91 (median 0)	**NCOs** Mean: 3.08±1.15 (median 3) **DRPs** Mean: 5.01±2.83 (median 5) **Risk** Mean: 2.75±2.32 (median 2)	0.018 0.020 0.128
	MedsCheck for Ontarians living with Diabetes	Individuals diagnosed with type 1 or type 2 diabetes and taking 1 or more medications for treating diabetes.	Yes	No	
			NCOs Mean: 3.1±1.14 (median 3) **DRPs** Mean: 4.74±2.9 (median 5) **Risk** Mean: 2.54±2.33 (median 2)	**NCOs** Mean: 2.46±0.88 (median 3) **DRPs** Mean: 4.15±2.82 (median 3) **Risk** Mean: 2.54±2.33 (median 2)	0.045 0.454 0.422

Legend: DRPs – drug-related problems; NCOs – negative clinical outcomes; Risk – risk situation of negative clinical outcomes.
#[1] – Patients with 3 or more medicines, including antihypertensive, antidiabetics, antidyslipidemic and antiplatelets drugs, were considered.

For the eligibility criteria applied to medication review service in England (Medicines Use Review), no statistically significant difference were reached with the number of NCOs and the established criteria. However, a statistically significant higher number of DRPs was achieved for “patients taking high risk medicine” and “patients at risk of or diagnosed with cardiovascular disease and regularly being prescribed at least four medicines” (Table 99).

Furthermore, an increased number of risk situations for NCOs were identified for patients who met all the eligibility criteria, except for “patients who are prescribed two or more medicines for respiratory disease” ($p>0.05$).

Table 99: Analysis of eligibility criteria for medication review programs in England.

	Prg	Criteria	Clinical Outcomes		p value
England (NHS)	Medicines Use Review (MUR)	▪ Patients taking "High risk medicine": NSAIDs, anticoagulants (including low molecular weight heparin), antiplatelets or diuretics #[1]	Yes	No	
			NCOs Mean: 3.1±1.24 (median 3) **DRPs** Mean: 5.4±2.76 (median 5) **Risk** Mean: 3.3±2.3 (median 3)	**NCOs** Mean: 3.0±1.02 (median 3) **DRPs** Mean: 3.98±2.9 (median 3) **Risk** Mean: 1.78±2.1 (median 1)	0.924 0.002 <0.001
		▪ Patients who are prescribed two or more medicines for respiratory disease (adrenoreceptor agonists, antimuscarinic bronchodilators, theophylline, compound bronchodilator preparations, corticosteroids, cromoglicate and related therapy, leukotriene receptor antagonists and phosphodiesterase type-44 inhibitors) #[2]	yes	No	
			NCOs Mean: 2.67±1.5 (median 3) **DRPs** Mean: 5.05±1.7 (median 6) **Risk** Mean: 3.0±0.0 (median 3)	**NCOs** Mean: 3.06±1.1 (median 3) **DRPs** Mean: 4.67±2.9 (median 4) **Risk** Mean: 2.47±2.34 (median 2)	0.747 0.576 0.376

Table 99 *(Continued)*

	Prg	Criteria	Clinical Outcomes		p value
England (NHS)	Medicines Use Review (MUR)	▪ Patients recently been discharged from hospital who had changes made to their medicines while they were in hospital. #[3]	Yes	No	
			NCOs Mean: 3.0±1.1 (median 3) **DRPs** Mean: 5.9±3.6 (median 5) **Risk** Mean:5.3±1.6 (median 5)	**NCOs** Mean: 3.1±1.14 (median 3) **DRPs** Mean:4.46±2.7 (median 4) **Risk** Mean: 2.19±2.07 (median 2)	0.686 0.140 0.007
		▪ Patients at risk of or diagnosed with cardiovascular disease and regularly being prescribed at least four medicines	Yes	No	
			NCOs Mean: 3.12±1.4(median 3) **DRPs** Mean: 5.35±2.9(median 5) **Risk** Mean:3.0±2.42 (median 2)	**NCOs** Mean: 2.9±1.09 (median 2) **DRPs** Mean: 3.03±2.1 (median 2) **Risk** Mean:1.2±1.37 (median 1)	0.182 <0.001 <0.001

Legend: DM-med: number of medicines used to treat Diabetes (oral antidiabetic drugs and insulins); DRPs – drug-related problems; NCOs – negative clinical outcomes; NHS – National Health Service; Nr - number; NSAIDs – Non-steroidal anti-inflammatory drugs; Prg – Program; Risk – risk situation of negative clinical outcomes.
#[1] – According to patient´s drug profile the following ATC groups were considered for AINEs: M01AB, M01AC, M01AE, M01AH, M01AX; anticoagulants: B01AA, B01AC, B01AE, B03AA, B03AB, B03AD, B03BB; diuretics: C03BA, C03CA, C03DA, C03EA;
#[2] – According to patient´s drug profile the following ATC groups were considered: R03AC, R03AK, R03BB, R03DC;
#[3] - Patients that have been hospitalized in the last 12 months were considered.

Despite no statistically significant differences were identified for all the eligibility criteria considered relative to the number of NCOs, DRPs and risk situations for NCOs, for patients who fulfilled at least one of eligibility criteria for holding medication review a statistically significant difference in the number of NCO ($p = 0.049$), number of DRPs ($p = 0.001$) and number of risk situations for NCOs ($p = 0.001$) was identified.

5 DISCUSSION

5.1 Adaptation of an instrument to assess health literacy to the Portuguese language

The main goal of the adaptation to Portuguese language of the “Short Assessment of Health Literacy - Spanish and English (SAHL-S&E)” was to obtain a tool that could be useful to identify patients with low health literacy, since it is a relevant factor that can affect subject´s health outcomes. (305–308)

The internal consistency of the instrument (0.812) was considered as “good”, indicating that reliability of the test scores was similar among sample. (284,309,310)

Moreover, a positive correlation was achieved for the score test and subject´s qualifications, as also found in the validation of the Short Assessment of Health Literacy - Spanish and English (SAHL-S&E), for Spanish-speaking and English-speaking populations. These results could mean the test is suitable for use in the Portuguese speaking population with low qualifications. (273)

In the analysed sample, a low health literacy level was identified in 37.9% of subjects. This was consistent with the expected outcome, taking into account the qualifications of the subjects included in the study, where about 32.7% of the subjects did not have the minimum level of education (9 years) defined as the minimum education in Portugal. (311)

Low health literacy is often correlated to negative health outcomes, such as identified by Souza *et al*. (2014) in a Brazilian older population with type 2 diabetes, where an association between low health literacy and patients showing an increased HbA1c values was found. (272)

The SAHL-PT test uses the literary ability and readability for terms associated with health, and can be considered a good instrument for screening of low health literacy subjects. As a result, this test is a very useful resource to identify situations of low health literacy.

Since there are no instruments available, with the same purpose of this test, validated for the Portuguese population, it was not possible to determine any correlation with other measuring instruments available for health literacy. Moreover, in the questionnaire adaptation procedures, a second application of questionnaires (retest) was not performed, which is a limitation of the applied methodology. However, since the patients included in this project were recruited from community pharmacies, it was not practicable the return of all subjects for a new application of the questionnaire.

5.2 ReMeD Study

5.2.1 Sample characterization and clinical evaluation

The AEDMADA clinic, which was where our study was performed, aims to support diabetic patients and their families on providing differentiated healthcare. Currently the clinic does not provide services to institutionalized patients, so there were no patients with this feature included in the study. Since only outpatients were included, and were mainly diabetic patients, the study sample should not be considered representative of the general Portuguese population.

Nevertheless, even if it was not our main goal, the comparison of our sample to the Portuguese population was performed in order to compare patient´s characteristics and health outcomes.

As expected, regarding the socio-demographic characteristics, while in the Portuguese population only about 19% are 65 years and older, most of our sample (56.8%) was above that age. Regarding gender, the results obtained were more similar to the general population, as in our study about 45.8% of the sample was female. Similar differences were found when comparing the Portuguese population and the Algarve resident population: 19.5% of the residents belong to the age group of 65 years and older, and 51.93% of the Algarve population was female and 48.07% male. (312)

According to the reported data from Census 2011, in the Algarve region, about 57.5% of the population was professionally active, compared to the 23.8% in the ReMeD, as expected due to the increased age of the AEDMADA users. (312) Patient´s qualifications showed some differences in their levels of qualification comparing the ReMeD patients to the resident population of this region, with an increased number of subjects with 1st cycle of basic education (38.1% in the sample *vs* 26% in the Algarve region population) and a lower number of illiterate subjects (5% in the sample *vs* 11% in the Algarve region population). (313)

Considering the specific characteristics of our study setting, and comparing the results of the Portuguese TEDDI CP study, which aimed to characterize type 2 diabetic patients followed in primary care units in Portugal, regarding gender distribution and marital status (74.6% of TEDDI CP patients being married or cohabitating) they were relatively similar to those obtained in the ReMeD study. (283) Also regarding qualification level, a similar distribution was achieved in the ReMeD patients, as would be expected since the ReMeD population is mostly diabetic.

Also as expected, considering the type of patients followed in the AEDMADA clinic, we detected a very high prevalence of diabetic patients in the study sample (90.7%). In the Portuguese general population diabetes mellitus presents a prevalence of 13.1% (patients between 20 and 79 years old). (23) The prevalence of diabetic patients is not 100%, as would be expected, since the AEDMADA clinic also follows relatives of diabetic patients who do not have diabetes.

Hypertension presented a prevalence of 81.4% in the study sample, and around 42% for the general Portuguese population. (15,18) Similar to the observed in the ReMeD population, also in the TEDDI CP study, a similar prevalence for hypertension (80.3%) was found. (283)

Accordingly, an increased prevalence of lipid disorders (77.1%) was achieved in the ReMeD study, compared to the results obtained from the general

Portuguese population identified in the VALSIM study (47%), that enrolled patients from primary health care. (282)

As expected, considering ReMeD patient´s profile, an increased rate of chronic diseases or prolonged health problems was found in the ReMeD patients, as in the Portuguese population aged between 65 to 74 years (65%; 66% in women and 62% men). (9)

The high number of morbidities, mainly chronic diseases, identified in the study population along with the advanced age allows to signal a population that may require intervention and may potentially benefit from a medication review service.

Biomarkers and other Risk Factors for Cardiovascular Diseases

Blood Pressure

Considering the results from the last Portuguese prevalence study on hypertension, held in 2011/2012, a similar rate to those found in the ReMeD study was achieved for BP control (42.5%). (18) Probably the patient centered services provided by the clinic could contribute to this degree of control, as well as an increased use of antihypertensive drugs and wider information provided to the Portuguese population.

Regarding exclusively the Portuguese diabetic population, a prevalence of 37.7% of patients presents a blood pressure value <130/80 mmHg, very similar to the one obtained in the ReMeD study for patients with a controlled blood pressure (40.2%). (23) However, in our study, the reference values considered were 140/85 mmHg for diabetic patients and 130/85 mmHg for those with nephropathy. (24)

Accordingly, although the rate of control of hypertension has been increasing in the last decade in Portugal, this pathology still presents a high prevalence, being one of the main factors that contribute to the high rate of morbidity and

mortality due to cardiovascular events. (10,18) An intervention strategy, with the participation of the Pharmacist, aiming the control of blood pressure values would be an asset for this population.

Glycemic Profile

Diabetic patients included in the study sample presented a longer mean of diagnosis duration (13.2±9.3 years), compared to the median of 7 years observed in the Portuguese TEDDI-CP study, probably due to the specificity of the service provided to diabetic patients. (283)

When comparing diabetic patients enrolled in the ReMeD study to those referred in the Portuguese report from 2014, the former showed a higher mean value of HbA1c (7.7%). Also, a higher prevalence of patients with a HbA1c ≥ 8% was found in the ReMeD patients (39.3% ReMeD *vs*. 20% Portuguese report). (23) These results suggest that probably most clinic diabetic patient´s are those who have more difficulty in achieving control of the glycemic profile, therefore needing more intervention to improve the degree of control. However, it is important to note that this national report only contains the values of HbA1c of diabetic patients who had records for this parameter and according to the information contained in the report, only 81.9% of diabetic had consultation records and only 85.3% of these patients had registration of this biochemical parameter. (23)

Lipid Profile

Patient´s lipid profile was analysed individually, considering patient´s global cardiovascular risk. In the ReMeD study sample a very low degree of control of the lipid profile was found (14.4%), while in the Portuguese VALSIM study the prevalence of controlled levels of LDL-C was 61.6%. Nevertheless, hypercholesterolemia (increased thotal cholesterol) was observed in 47% of the Portuguese patients included in VALSIM study, and in only 28% of ReMeD patients. (282) Although the national study VALSIM used as a reference parameter the value of total cholesterol and not the value of c-LDL as used in

the ReMeD study, the results from our study are indicative of an imminent need for intervention to improve patient´s lipid profile.

Similarly, the degree of control of lipid profile found both in the national report for diabetes (2014) and in the Portuguese TEDDI-CP study, was higher than those found in the diabetic patients enrolled in the ReMeD study. (23,283)

This lower degree in the lipid profile control might be attributed to the high number of diabetic patients included in the ReMeD study (90.7%) that present other cardiovascular risk factors, classifying them with a very high global cardiovascular risk (89.8%), which according to current guidelines advise a LDL-C below than 70 mg/dL to reduce the risk of cardiovascular events. (295)

In order to achieve improved results regarding the lipid profile, intervention is absolutely necessary and could be initiated through a medication review, in order to identify the issues associated with medication used by each patient.

Other Risk Factors for Cardiovascular Diseases

Besides the risk factors mentioned above, other were analysed.

Patients enrolled in the ReMeD study were mainly non-smokers (72.9%). Interestingly, this was also found in other Portuguese studies such as VALSIM study (hypertension prevalence in primary care) and TEDDI-CP study (type 2 diabetes patients in primary care). (283,314)

Despite the low prevalence of smokers in our sample, this is still undoubtedly a group where a pharmaceutical intervention in the field of smoking cessation could be performed, in order to contribute to the reduction of the overall cardiovascular risk of patients.

Regarding another modifiable risk factor, in the ReMeD study, only about half of patients reported to practice regular physical exercise. A Portuguese report about physical activity published in 2011 described a positive correlation in the amount of minutes per day of sedentary activity with individual´s age, where

36% of the subjects reported not to practice any kind of physical exercise. (33) The elderly Portuguese population has already been recognized as one of the most sedentary (76%) among several European countries. (315)

The results presented regarding the practice of physical exercise by the ReMeD patients also suggest a need for intervention in the implementation of this habit on a regular basis, and adapted to the patients' age and physical condition.

Obesity has been widely identified as a *major* risk factor for cardiovascular diseases. (316)

About 35% of our sample aged 18-64 years was overweight (BMI 20-24.9 Kg/m^2), while 25.5% were obese (BMI ≥ 25 Kg/m^2). A similar prevalence of 39.4% for overweight and 14.2% for obesity was observed in a survey (2003-2005) in the Portuguese population between 18-64 years. (317)

Also overweight (49.2%) and obesity (39.6%) has been pointed in the Portuguese report about diabetes (2014), but higher than those observed in the ReMeD patients. (23)

Towards these results, the decrease in patients' BMI is also a marked need, requiring an adequate intervention to patient´s characteristics and physical condition.

Surprisingly, most ReMeD patients reported the consumption of fruit and vegetables on a daily basis, and to use olive oil to prepare their meals. Considering that the majority of patients included in this study were 65 years or older, it was expected that many reported a daily and regular consumption of soup and fruit at least in one of the meals, since many patients come from rural areas and have their own fruit and vegetables production. Accordingly, the consumption of vegetables and fruits has been already pointed out as high in the populations of the west Mediterranean, compared to other European areas. (318)

In addition, the consumption of olive oil is also a very ingrained habit in the Portuguese population, as it is purchased from national production essentially. (318,319)

The adoption of Mediterranean diet, which includes the consumption of extra virgin olive oil has been associated to an increased effectiveness in the reduction of cardiovascular diseases (primary and secondary prevention). (320)

Due to their potential relevance in clinical results, the analysis of specific dietary habits adopted by the patients would be an interesting area for future research, in a potential partnership with other health professionals in the area of nutrition..

The causes of hospitalizations suffered by diabetic patients were similar to those found in the national report about diabetes (2014), being 28.8% of hospitalizations caused by stroke and 32.7% by myocardial infarction. (23)

Also the prevalence of cardiovascular events found in the ReMeD sample was similar to those described in a Portuguese exploratory descriptive cross-sectional study, using data from the fourth national health survey (2005-2006), which identified a prevalence of 2.31% for stroke, 2.13% for ischemic heart disease and 6.23% for cardiovascular disease. (321)

The family history of premature cardiovascular events was shown to be associated to a higher risk of early cardiovascular disease. (26) This risk factor was verified in 16.4% of the ReMeD patients, although the association was not verified in our study sample. The existence of this unmodifiable risk factor may be a useful point to identify target patients for intervention, in order to prevent the development of cardiovascular disease or minimize its negative impact on patient health.

Cardiovascular Risk Assessment

Regarding the cardiovascular risk assessment, about 90.7% of patients had a diagnosis of diabetes in our study, and of these 83.2% were hypertensive and

73.8% presented dyslipidaemia, which makes the majority of patients having a very high cardiovascular risk. (295)

Being circulatory diseases the main cause of death in Portugal (10), intervention aimed to reduce cardiovascular risk, with intervention directed to the achievement of control on the various risk factors should be a priority in the ReMeD study population.

***Microvascular complications* (Diabetic patients)**

Almost a quarter of diabetic patients included in the ReMeD study already had detectable microvascular complications (23.4%; n=25), 76% of which had a previous diagnosis of diabetic retinopathy. The national report about diabetes (2014) did not quantify the prevalence of these complications in diabetic patients, and only included data on the number of visits performed under the "diabetic retinopathy screening program" and the prevalence of diabetes in patients with chronic renal failure. (23)

The monitoring of the degree of control of the glycemic profile of diabetic patients is of extreme importance for the non-occurrence of these microvascular complications. Thus, the identification of situations of non-control and adequate intervention is a contribution to minimize the appearance of these possible complications.

5.2.2 Pharmacotherapeutic Profile

Each patient included in the ReMeD study was using an average of approximately 7 medicines, 8 units and 8 doses per day, with polypharmacy (5 or more medicines) being observed in 73.8% of the patients.

Polypharmacy can be associated to an increase in negative clinical outcomes in patients, such as can cognitive impairment, decline of functional status,

mortality and morbidity associated to falls, alteration of the patient's nutritional status, among others. (322)

Particularly in patients 65 years and older, who are expected to spend more than half of their life expectancy with polypharmacy (323), managing their medication should be considered as an important contribution.

Similarly, a Portuguese cross-sectional study conducted in nursing homes including institutionalized patients aged 65 years or above, and taking at least one daily medication, identified a rate of polymedication in about 76.6% of patients, with more than half (51.8%) of patients taking 6-10 medicines per day. (146) This suggests that the ReMeD sample has characteristics of a polymedicated population.

Most drugs used by ReMeD patients were from group C-Cardiovascular system, A-Alimentary tract and metabolism, and N-Nervous system, with antihypertensive drugs being used by 83.9% of the patients. Other studies have shown similar results, either in populations of elderly patients followed in units of primary health care in Portugal, or in patients who participated in medication review programs. (197,324)

In our study, hypertense patients used mainly one antihypertensive drug (63.6%), whereas 24.2% used two antihypertensive drugs, which were mainly agents acting on the renin-angiotensin system. These patients are at risk of suffering drugs side effects and potential drug-drug interactions (325), being the methodology used in the ReMeD study useful for the identification and monitoring of these events.

The high prevalence of hypertense patients treated with associations of drugs acting on the renin-angiotensin system (48.45%; n=47) can be justified by the high prevalence of patients with very high cardiovascular risk (89.8%), showing they are being treated according to the guidelines applicable in Portugal for the treatment of hypertension. (287,326)

As expected, in our study, diabetic patients were treated with oral antidiabetic (78.0), and most of those were using either one (51.1%) or 2 OADs (35.9%). Most were using an association of oral blood glucose lowering drugs (31.6%) and biguanides (24.5%), while 39.0% were using insulin (mainly only one type, 41.3%). Every drug treatment has possible side effects, which in some cases can be avoided if identified promptly.

In an observational multicenter study, aimed to explore the routine of clinical practice in Spain and Portugal, diabetic patients, particularly those receiving OADs, identified the unwanted loss of body weight and hypoglycaemia as the most valued parameters regarding their medication, which patients were willing to pay to avoid. (327) The identification, prevention and monitoring of side effects of OADs such as hypoglycaemia may be an outcome of the medication review service, which have already been recognized as a relevant issue by diabetic patients.

Regarding antidyslipidemic agents, about three quarters of the ReMeD patients were prescribed with this type of drugs (76.3%), a higher prevalence compared to the 47% of patients who used statins in the Portuguese VALSIM study conducted in primary health care users in Portugal (2013), but similar to those in the TEDDI-CP study, in which about 72% of the enrolled patients used lipid-lowering drugs. (282,283) This shows that a medication review service would probably benefit a hight proportion of our study sample and the aged population in general, which usually presents an increased use of this group of drugs. (197)

Almost one third (29.7%) of the ReMeD study sample had a prescribed anticoagulant/antiplatelet drug, similar to Eiras *et al*. (2016) findings, wherein 30% of older patients (≥ 65 years) from a Portuguese primary care center were using antithrombotic drugs. (197)

The patient´s medication analysis performed during ReMeD study allowed to identify situations such as polymedication that can contribute to health negative

outcomes. Likewise, this analysis enabled the identification of drugs that present an increased risk for the occurrence of negative outcomes.

5.2.3 Analysis of Medication Review outcomes

The methodology adopted to perform medication review (MR) and the nomenclature used is not universally systematized, being different in different countries and even between different research groups in this field. Although some MR programs include follow-up interventions as an activity, most of them are focused in the clinical outcomes. (94,142,151,159,324)

Since the applied methodology was developed specifically for this pilot project in the context of clinical practice, the results will be discussed individually for each type of outcomes: humanistic, economic and clinical.

5.2.3.1 Humanistic outcomes

Medication Adherence

ReMeD patients presented a high medication adherence rate and were using a higher number of medicines, similar to what was described in a review about therapies adherence in patients with a diagnosis of type 2 diabetes. (328)
In this study, a high adherence rate was observed in patients using medication for chronic diseases such as oral antidiabetic drugs and antihypertensive drugs. Others have found a similar pattern, when evaluating a group of older patients (≥65 years), using 3 (three) or more concomitant medicines, in a retrospective cohort study held in type 2 diabetes patients having at least one prescribed oral antidiabetic agent, in which the medication adherence to antidiabetic drugs was evaluated using the proportion of days covered (≥80%) over 12 months. (329) This high rate of medication adherence can be considered as a positive point to decrease the number of MACE (*major* adverse cardiovascular events). Patients

seem to be more sensitive about taking their chronic medication, however, should not devalue the importance of medication adherence to the remaining treatments.

Since several methodologies can be used to assess medication adherence, the use of two or more tools simultaneously has been pointed as the most accurate way to perform this assessment. (226)

For that reason, in the ReMeD study, the assessment of medication adherence included MAT scale, that allowed to identify, despite the high rate found for the overall adherence to medication (~74%), patients' attitudes regarding medication use such as those taken when they felt worse, better, and when they had no medication available. Interestingly, Campbell *et al*. found 30% of clinic outpatient aged 65 years and older showing low adherence rate and 28.5% that stopped taking medication when feeling worse, a similar value obtained in the ReMeD study considering patients that reported to act like this "often", "sometimes" and "rarely" representing a total prevalence of 27.1%. (330)

In addition, the use of the tool "Haynes Sackett test" was also used, allowing to identify the medicines in which the medication adherence rate was lower, thus allowing to point out which drugs / therapeutic areas in which patients are more or less compliant with the prescription.

Medication adherence rate has not been consistently included as an outcome of the medication review, as verified by Renaudin *et al*. (2016). (331) Nevertheless, this parameter seems to be an outcome to consider when conducting a medication review, since non-adherence can be associated to a higher number of negative outcomes such as hospitalization, emergency department visit or even death. (332) Moreover, an improvement in medication adherence can be achieved after the completion of a medication review. (331,333)

All the facts formerly presented indicate that it is definitively an advantage to include medication adherence assessment in the outcomes of the medication review, as done in the ReMeD study.

Patient Medication Knowledge

About a quarter of the ReMeD patients (25.4%) showed a low medication knowledge (MK).

Regarding the Portuguese population, a cross-sectional study conducted in community pharmacies in the Lisbon Metropolitan area (Portugal), using the transcultural adaptation to European Portuguese of the questionnaire PKM-PT-PT, showed that 65.9% of patients didn´t know the medication they were using. Compared to the ReMeD patients, the latter had higher rates of MK, such as "therapeutic goal" (70.9%) and "process of use" (36.7%), while "safety" (1.9%) and "conservation" (5.8%) were those with the lowest rate. (334)

Also similar results to those obtained in the ReMeD study were achieved by Romero-Sanchez *et al*. (2016) in subjects requesting medicines at community Spanish pharmacies, in which they identified an inadequate medication knowledge in 71.9% of the patients, with 65.7% having no medication knowledge and 6.2% insufficient medication knowledge. (233)

Patients knowledge about medication has been associated to poor blood glucose control in type 2 diabetes patients, with patients over 65 years and increased HbA1c level being associated to lower rate of MK. (237)

When analysing the ReMeD study results considering MK, a deficiency in the identification of drugs (name and drug strength) was clearly identified. It is then important, as a result of the medication review, to draw up a list of medicines and give it to each patient so they can carry it with them whenever they access health services or whenever they need to show a health professional the medicines they are taking.

Moreover, the identification of patients with low MK score may serve to signal patients to be included in therapeutic education programs. A significant improvement in MK can be reached after a medication review and being provided with a counselling session by Pharmacists, as shown by Goh *et al*. (2014), in patients from policlinics in Singapore using 5 or more chronic medicines and referred to MR by the prescribers due to adherence or knowledge issues. (333)

Farsaei *et al*. (2011) also showed that an improvement was achieved in diabetes management, in type 2 diabetic patients, including a significant decrease in HbA1c through the implementation of an educational program which included several subjects, such as OADs, adherence, diabetes dairy log and pill box usage, conducted by Pharmacists after a period of three months of intervention. (335)

Over time, some methodologies have emerged for the evaluation of medication knowledge, although not all of them including the same evaluation parameters and approaches. In some studies the tools used to assess MK are only applied to one drug per patient (240,336). In the ReMeD study this assessment was applied to all medicines used by patients. Although this methodology becomes exhaustive, it allows to better identify the items in which the patients presented more weaknesses regarding the knowledge of each medicine, compromising their full benefits. This approach enables to draw up a plan according to the patients' difficulties regarding MK. However, the methodology used to assess MK in the ReMeD study was not previously validated, which should be done in the future.

Patient Disease knowledge

A lack of knowledge regarding diseases such as hypertension, diabetes and dyslipidaemia, was identified in most patients, respectively, in 61%, 78% and 60.2% of the cases. The medication review program applied to the patients of the ReMeD study allowed the identification of patients who needed additional

knowledge about the management of their disease, namely in the monitoring of biochemical and/or physiological parameters and potential complications of the disease.

Providing self-management education on diabetes (DSME), depending on the way provided, either promoted by one person or by a team, was shown to contribute to an improvement of HbA1c levels in diabetic´s patients. (337)

Importantly, the Portuguese National Plan until 2020 (Portugal 2020) includes the development and implementation of education programs for health and self-management of the disease (338), which could be an opportunity to launch the implementation of a MR service.

As a result of the medication review, the identification of patients that can be included in education programs for health and self-management of the disease can be achieved.

Health Literacy

Almost half of ReMeD patients (43.2%) were identified to have "low health literacy", and a low score was associated to older patients (≥65 years). An association between patient´s health literacy and patient´s age, with older patients presenting less qualifications (less than high school), being 2.4 times as likely to report fair or poor health literacy, was also identified. (339)

Moreover, patients having one or more chronic diseases were found to present a lower health literacy, especially among older patients, such as found in our study. (8,340)

A worse control of diseases has already been associated with low level of health literacy, as achieved in the control of blood pressure in hypertensive patients by Willens *et al*. (2013). (341) Also a lower control of glycemic profile has been achieved in diabetic patients with lower score of health literacy. (342,343)

Patients presenting a low health literacy have been associated with an increase difficulty in the interpretation of labels (prescription medications and nutrition)

and health messages, referred as a key factor for disease knowledge, self-efficacy, contributing to improvements in health outcomes in diabetic´s patients. (8,272,344)

The identification of patients with low health literacy score, as included in the ReMeD study, enables the identification of patients that could present an increased risk of uncontrolled diseases, such as those with higher prevalence in this study and in the Portuguese population. In addition, it also allows identifying groups of patients that may benefit from therapeutic education programs.

It has been recently identified that an improvement on the outcomes of patients regarding medication adherence and medication knowledge could result from the interventions in low health literate populations that include an additional aid for written information on a personalized approach. (279)

Since patients with limited health literacy increase health care costs, the identification of these patients could potentially contribute to a reduction in health costs. (345)

Although the tool used in the ReMeD study aims to identify patients with low health literacy, this may be useful to adjust the patient-pharmacist communication, since it could be a barrier to understanding medicines instructions and consequently medication adherence.

Self-perceived health status

Patients included in our study rated their health status positively, mainly (53.4%) as “acceptable”, a similar result of the obtained in the Portuguese “Study of Satisfaction of Users of the Portuguese Health System” (2015), in which the population considered their health status positively (65.2%), considering it "good" in 36.0% of the cases and 31.5% as “acceptable”. (346)

Importantly, a more negative health status has been associated to a lower health literacy level leading to an increased number of negative health outcomes. (8)

Patients being followed for a longer period in AEDMADA clinic presented a significant difference regarding patient´s self-perceived health status (p=0.024) compared to those being followed for a shorter period, which may indicate that the fact that the patients are followed for a longer time provides them with a more positive opinion of their health status.

The self-perceived health status can provide some information about the patient's image of their health status and the way that the patients approach the disease.

Globally, the humanistic outcomes, although they may not have explicit clinical significance, seem to contribute to identify factors that may improve the health outcomes of the patients, hence the importance of their inclusion in the medication review process.

5.2.3.2 Economic outcomes

Number of medicines

With respect to the number of medicines, the ReMeD patients were using a mean of 7 medicines per day. Several studies, although exclusively enrolling patients over 65 years using polypharmacy, have found a relatively similar number, including a Spanish project of pharmacotherapy with follow-up conducted in nursing homes (mean of 6.4 medicines), and the conSIGUE project, a program of medication review with follow-up held in Spanish community pharmacies (mean of 8.32±3.1 chronic medicines). (158,347,348)

The consumption of more drugs commonly represents an increase in costs both for the patients and the health system, as it has been observed in the consumption of medicines in Portugal. (47) Furthermore, the increase in the number of medicines used by patients contribute to a higher complexity of medication regimen, which can lead to a poor management in patient´s

medication and the emergence of clinical negative outcomes, so it is important to consider this parameter as an economic outcome. (146)

An outcome provided from the medication review can include the identification of patients with high therapeutic complexity, enabling the definition of the appropriate measures that lead to a reduction of the complexity, as well as the improvement of health outcomes.

In the ReMeD study the therapeutic complexity was not considered as an outcome. However, the methodology used to collect medication data allows to identify the main issues related to the medicines use.

Number of hospitalizations

Diabetic patients enrolled in the ReMeD study showed a prevalence of hospitalizations (15.9%) similar to the general population of Portuguese diabetic patients, which had a rate of 15.4% (more than 24 h hospitalization) in 2014. Moreover, considering hospitalization days, the numbers are at a similar range. In 2014, the average number of hospitalization days recorded for diabetic patients was 4.5 days for hospitalizations > 24h and 11.3 days for all the hospitalizations length, while the mean number of hospitalization in the ReMeD sample for diabetic patients was 8.4 days (considering only hospitalizations > 24h). (23)

The number of visits to the emergency department, although not included in the ReMeD outcomes, should be included as an economic outcome, since such visits may represent an increase of the costs for the health system, which are not included in the regular care process and that can be associated to the use of medication.

The analysis of the impact on hospital admissions performed in the conSIGUE project achieved a significant decrease in medication-related hospitalizations in patients receiving medication review with follow-up (MRF) relative to the control group, as well as lower probability of being hospitalized (3.7 times higher in the

control group) and lower costs in hospitalizations, justifying the potential of this MR service, which would benefit both patients and government by decreasing costs for the NHS. (349)

Hospitalizations suffered by the patients can drive towards the increased of poor disease control which may be associated with medicine´s use, whether due to adverse reactions or drug´s ineffectiveness.

This economic outcome has to be considered in the calculation of the costs associated with health negative outcomes and disease burden, and subsequently as one potential indicator on the economic impact of the medication review service, as used previously by other authors. (141,349,350)

Number of Physicians following patient

In the ReMeD study, patients were followed mainly by 2 or 3 Physicians, attending consultations mostly with General Practitioners and specialists in the area of diabetology, which suggests that most patients were followed by several professionals, and possibly at various levels of care. The management of the disease by a group of health professionals can be beneficial if this approach is done in an integrated way. However, if this does not happen, it may possibly become a limitation and contribute to an increase in negative clinical outcomes.

The activity of medication reconciliation in the hospital setting, held by Pharmacists at hospital transition, has been already associated to a lower number of hospital revisits related to adverse drug events and also lower emergency department visits. (351)

Moreover, it was shown that a lower number of Physicians following a certain patient is positively correlated with their increased independence in daily activities, less comorbidities, and less hospitalization episodes. (352)

The identification of patients who are being followed by different Physicians and at different levels of health care (public and private, for example) could be useful allowing their signalling during the medication review, so that discrepancies could be respectively analysed.

Rate of reimbursement of medicines

In our study, patients were covered mostly by the Portuguese general medicine reimbursement system (75.4%), whereas only 14.4% were covered by the special system for drug reimbursement (lower co-payment on the purchase of medicines). (46) This last group has less financial capacity to support health costs, including medicines, but it will have access to reimbursed medicines at lower prices than most of the other groups.

Interestingly, the co-payment level has been previously identified as a predictor of medication adherence for antihypertensive medications, in a retrospective observational study conducted in members of an American care organization, showing a significant increased compliance among patients with pharmacy claims for drugs that required lower co-payments. (353)

This economic outcome, while not having a direct impact on patients' health, may allow the identification of patients with limitations in the acquisition of medicines and health services, particularly those that are not reimbursed, which can lead to health negative outcomes.

5.2.3.3 Clinical outcomes

The clinical outcomes obtained from the review of the medication can assume diverse designations, depending on the methodology used for this service, as well as according to the concepts of outcomes considered by each research group. In the ReMeD study we considered three types of clinical outcomes: NCOs, DRPs and Risk situation of NCOs.

Negative Clinical Outcomes (NCOs)

The number of NCOS identified per patient in the ReMeD study (3.05±1.13) were similar to those found in a Spanish study where a medication review with follow-up was performed, conducted in a community pharmacy of the province of Gipuzkoa, during a period of 18 months. In the referred Spanish study, an average of 3.1±2.5 NOMs (Negative Outcomes related to Medicines) were

identified per patient, mostly regarding effectiveness (47.3%), followed by safety (36.5%) and necessity (16.2%). (142) The concept of NOM considered by these authors included "uncontrolled health problems that appear due to the use or nonuse of medicines". (142)

In a controlled trial including type 2 diabetic patients from Brazilian community pharmacies, most frequent negative clinical outcomes (mean: 2.3±1.6) were ineffectiveness of the drug therapy (68.1%), and the need for additional pharmacotherapy or the use of unnecessary drugs, being identified in 15.1% of the outcomes. (354) In the ReMeD study, the diabetic patients also presented a larger number of NCOs, particularly those with uncontrolled glycemic profile.

A Medication Review Management (MRM) program conducted through home visits in Jordan, used a different approach which considered the identification of treatment-related problems (TRP), described by AbuRuz *et al*. (2006) as "*an event or circumstance involving patient treatment that actually or potentially interferes with an optimum outcome for a specific patient*"(132). (355) The TRPs identified included: unnecessary drug therapy, untreated conditions, ineffective/incomplete drug therapy, inappropriate dosage regimen, adverse drug effects, actual or potential drug interactions, non-adherence to non-pharmacological and pharmacological therapy and suboptimal monitoring. (355)

An interesting point of this classification system of TRPs is the inclusion of untreated conditions that require pharmacological or non-pharmacological therapy. Sometimes the necessary approach for the treatment of some clinical situations may include the adoption of non-pharmacological measures, such as for the treatment of dyslipidaemia or obesity. (356) Non-pharmacological interventions should have priority in the intervention plans drawn up by the Pharmacist, in order to achieve improvement in patient´s health outcomes.

In the ReMeD study, the highest prevalence of NCOs were related to "disease control", and in these the most observed were related to disorders of lipoprotein metabolism and other lipidaemias (18.1%), hypertension (16.4%) and diabetes (15.8%). These findings are in agreement with results obtained in the analysis of the degree of control of the biochemical and physiological parameters

described in the previous chapter “Results 4.2.2 Patient´s clinical evaluation”. Patients included in ReMeD study showed a low rate of lipid profile control (14.4%), the blood pressure values were controlled in only a third of patients (30.5%), and the control rate of glycemic profile in diabetic patients was reached in about half of patients (41.5%). Therefore, a high number of NCOs were expected regarding “disease control”.

Moreover, in the ReMeD study a high prevalence of NCOs related to “Untreated conditions” was identified (38.1%), which may suggest a very positive point of this methodology. This situation has already been mentioned by Hurkens *et al*. (2016), noting that situations of “indication without medication” were frequently missed, even when the professionals had access to information regarding laboratory results, reason for admission and medical history conducted. (357)

Most of the methodologies applied in the MR focus on the analysis by medicines, hence the designation often used in the clinical outcomes presented as results, such as “medication related problems” and “drug-related problems”, (135,159,358).

In the ReMeD study, the approach adopted was based on clinical situation, since the clinical evaluation of the patient is usually based on the data related to their clinical history, including the pathologies already diagnosed and the symptoms / signs presented by each patient. Furthermore, the selection of the treatment is made according to their clinical state and diagnoses. Thus, we did not, like other research groups, use an approach per medicine, using the explicit concept of effectiveness of prescribed / used therapy, which should not be done per drug, but by clinical situation, since for example in clinical situations that several drugs are prescribed simultaneously, it becomes difficult to identify the relative effectiveness of each medicine.

However, through the approach used in the ReMeD study, the analysis of the medication is also performed, thus fulfilling one of the points described as purpose of the medication review identified by the PCNE: "a structured evaluation of a patient's medicines with the aim of optimizing medicines use and improving health outcomes ". (96)

***Drug-Related Problems* (DRPs)**

In the ReMeD study an average of 4.7±2.9 drug-related problems (DRPs) was identified per patient, with DRPs being appointed in 95.8% of the patients included in the ReMeD study.

Likewise, a "brown bag medication review", which included patients 60 years or older taking at least 5 medicines, found an average of 4.3±2.8 DRPs, a value similar to those obtained in the study ReMeD. (359) However, it is important to note that the methodology used for the classification of DRPs was PCNE 6.2 classification system, where the ADEs (adverse drug events), for example, are considered a DRP and not a negative clinical outcome. In the referred study, the most frequent causes identified for DRPs were relative to "drug selection" (40%), "dose selection" (28%), "participant problems" (14%) and "drug use or administration process" (11%), which in the ReMeD study were also the scopes with higher prevalence. (359)

For issues identified as DRPs in the ReMeD study, another study conducted in a University Hospital in Sweden at admission time, between January 2007 and March 2008, patients presented similar results relative to "inappropriate drug", and "inappropriate treatment duration", using MAI criteria. (134) The authors used the "Lund Integrated Medicines Management model" (LIMM), including medication reconciliation upon admission and discharge, and medication review and monitoring, by a multi-professional team, including a clinical Pharmacist, while the ReMeD study was conducted exclusively at outpatients. (134) In addition, the criteria used to identify the suitability of the medication were also different. The suitability of the therapy in the ReMeD study was mainly performed according to the guidelines produced and adopted in Portugal, therefore it is difficult to standardize the criteria for different countries.

A group of Portuguese Pharmacists conducted a descriptive observational cross-sectional study carried out in six Portuguese nursing homes. In this study, a median of 14.5 DRP per patient was achieved, being the most prevalent "Adverse Drug Event, non-allergic" (49.51 %), "Drug treatment more costly than

necessary" (19.11 %), "Effect of drug treatment not optimal" (14.82 %) and "Unnecessary drug treatment" (6.16 %). (145) The system adopted for the drug-related problems classification was the II Granada Consensus. (172) The number of DRPs identified in this sample was superior to those in the ReMeD study, however the referred study included only institutionalized patients ≥65 years and using 5 or more medicines. The average number of drugs used in these patients was 10 medicines, and a median of 11 dosages per day. Furthermore, from the identified DRPs only 2.1% were manifested, whereas the remaining were merely potential DRPs. (145) In the former study, the identified DRPs were mainly potential DRPs while in the REMED study those identified were explicit rather than potential. Moreover, in referred study issues related to medication adherence and patient medication knowledge were not identified by the researchers, probably due to patients being instutionalized.

In a Spanish program including medication review with follow-up in a community pharmacy, Ocampo *et al*. identified an average of 4.5 DRPs per patient, during the follow-up period. The most frequent DRPs identified were "adverse effects probability" (21.2%), followed by "non-adherence" (15.6%) and "inappropriate dose, frequency and/or duration of treatment" (15.5%). (142) Similar results were found in the ReMeD study considering issues identified relative to medicine´s use process (adherence) and dose selection (inappropriate dose).

Norwegian Pharmacists who participated in the project developed by Granas *et al*. (2010) identified a lower number of DRPs in a medication review conducted in type 2 diabetes patients (in a community pharmacy setting). (182) DRPs were categorized using a modified PCNE classification system, considering 5 main areas: adverse reactions, drug use problems, other drug-related problems, drug choice problem, dosing problem, and drug interactions. Furthermore, this study included an evaluation group to review retrospectively all DRPs identified by the Pharmacists, which identified 76 additional DRPs even in patients who had no previous identified DRPs. (182) This approach held by an evaluation group of reviewing the DRPs identified by the Pharmacists may be interesting and allow a uniformity in the clinical approach.

Different results were reported from other studies, such as those identified in patients from five hospitals of all sectors of health services (public, private, and military), where a high average of 11.2±6.2 DRPs per patient was found. Those patients enrolled presented at least one chronic medical condition and received at least two medications. (360) The most prevalent DRPs reported were “a need for additional or more frequent monitoring”, “inappropriate adherence to self-care activities or nonpharmacological therapy”, and “the patient was not given instruction in or did not understand nonpharmacological therapy or self-care advice”, showing a different profile than those obtained in the ReMeD study regarding the identification of issues with medicines (DRPs). (360)

In the ReMeD study a high prevalence in the problem of “Inappropriate drug” was identified in the use of DPP-4 inhibitors. The Portuguese guideline, from the General Health Direction, for the treatment of type 2 diabetes *mellitus* patients, indicates that insulin secretagogues (sulphonylureas, glinides, and DDP-4 inhibitors) should be suspended as soon as complex insulin regimens in addition to basal insulin (or insulin premix) are prescribed and maintaining treatment with metformin. (291) Nevertheless, recent systematic review and meta-analysis, identified DPP-4 inhibitors to be an advantage in addition to any type of insulin therapy in type 2 diabetes, by reducing both fasting and post-prandial glucose levels through increasing insulin secretion and decreasing glucagon secretion while not contributing to the increase bodyweight and risk of hypoglycaemia, used alone or in combination with metformin. (361) Additionally, other reviews indicate the combination of DPP-4 inhibitors with insulin as a safe procedure, obtaining a smooth decrease on the HbA1c levels (0.6%), whereas the risk of hypoglycaemia was not increased, and presenting a neutral effect on the weight gain. (362,363) Since the latest update of the Portuguese guideline for the pharmacological approach in type 2 diabetes *mellitus* was produced in 2013, an updated review according to international guidelines should be achieved.

In addition, in the analysis of ReMeD patient´s medication, drugs from the B01AC subgroup (antithrombotic agents, platelet aggregation inhibitors excl.

heparin) showed a high rate of DRPs relative to “No indication for drug”. According to the literature, the risk of vascular mortality is not significantly changed with the treatment with aspirin for primary prevention of cardiovascular events, as well as in individuals with multiple risk factors, the use of clopidogrel in combination with aspirin *vs*. aspirin didn´t show a significant improvement in cardiovascular outcomes. (26) Antithrombotic therapy in individuals without cardiovascular disease is not a recommendation from the European Society of Cardiology, neither from the Portuguese General Direction of Health. (26,364) This suggests that in some ReMeD patients, prescribers should review the use of this medication.

ReMeD patient´s medicines containing drugs from the subgroup C08CA (calcium channel blockers, d, such as lercanidipine), presented some DRPs (1.7%; n=9) relative to “Inappropriate timing of administration and/or dosing intervals”. It is important to note that these drugs present a high first-pass metabolism, and the absolute bioavailability of lercanidipine administered orally to patients in the post-prandial conditions, is about 10%, although the bioavailability is about 30% when administered in the fasted state, so it is recommended the administration before meals. (365) Pharmaceutical counselling on the timing of administration of these drugs should be considered as a consequence of the medication review.

Likewise, drugs from the subgroup A02BC (proton pump inhibitors) presented a pronounced prevalence (2.9%) of DRPs relative to “Inappropriate timing of administration and/or dosing intervals” in the ReMeD patients. Importantly, proton pump inhibitors, such as pantoprazol, may have the absorption affected by the concomitant food intake, leading to an increased variability of latency period. (366) In some other cases, as with the esomeprazole, food intake delays absorption, although these effects have no significant influence on the effect of esomeprazole in intragastric acidity. (367)

Recently, a national campaign was launched by INFARMED to alert against the risk of a prolonged use of proton pump inhibitors. (368) The study and analysis

of proton pump inhibitors use may constitute an area of future research and intervention by the Pharmacist.

Drug subgroup C10AA (Lipid modifying agents, HMG CoA reductase inhibitors) presented, in our study, an increased prevalence of problem relative to “intentional non-adherence” (1.15%). These results go in agreement with previous studies that have already shown that elderly patients are normally more prone to non-adherence in the use of lipid lowering agents than younger or middle-age patients. (320) Moreover, Ferrajolo *et al*. (2014), in an Italian population-based study, identified the use of statins for primary prevention as a predictive factor for nonadherence, and that those patients had higher probability (64%) to be more non-adherent than those who started statins on secondary prevention (210)

For drugs from the former subgroup C10AA, issues entitled “drug dose too low” presented a high prevalence (2.7%). In the decision of the pharmacological treatment of dyslipidaemias the choice of statin and respective dose should first be made on the basis of global cardiovascular risk presented by the patient and then depending on the individual objectives to be achieved for the individual LDL cholesterol levels, according to the guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), and adopted by the General Direction of Health (DGS) in Portugal. (292,369,370) The data obtained from the ReMeD patients, suggests that in the patients where this issue was identified, they should be referred to their Physician for reassessment of dyslipidaemias treatment, including the drug selected, dose and the existence of adverse reactions.

Similarly, the drug subgroup N05BA (Anxiolytics, Benzodiazepine derivates) also presented a high prevalence of problems relative to “drug dose too low” in ReMeD patients. Benzodiazepine and similar drugs are indicated for the treatment of anxiety and insomnia and should not be routinely used in the symptomatic treatment of mild to moderate anxiety or insomnia. (371) The benzodiazepine dose should always be individualized based on the severity of symptoms and the individual patient response, proceeding to a reassessment

within a period not exceeding 4 weeks. (371,372) Considering alprazolam as an example, the recommended dosage for an anxiety state is 0.25 mg to 0.5 mg three times daily increasing, if necessary, for a total of 3 mg per day. (373) Some patients from the ReMeD study were using a lower dose than recommended in the SmPC of the respective medicine. In addition, and very importantly, patients presenting this issue should be referred to their Physician for reassessment of the insomnia treatment.

Considering the high consumption of benzodiazepines in the Portuguese population (374), it would be useful to implement a joint strategy with prescribers in order to reduce the use and the misuse of these drugs.

The identification of inappropriate medication can be performed using several tools, developed and validated by various authors. According to Beers criteria (196), about a fifth of ReMeD patients were using potentially inappropriate medication (PIM), a lower prevalence than the one achieved in another Portuguese observational cross-sectional survey conducted in elderly subjects in community pharmacies in Lisbon district (38.5%). (375) Nevertheless, as found in the ReMeD study, the most prevalent PIMs were long acting benzodiazepines, and also the number of PIMs used was significantly higher in patients using an increased number of medicines. (375)

Another Portuguese observational and cross-sectional study, held in November 2012, including older subjects (≥ 65 years) consulted in a Family Unit Care in the area of Oporto, identified an increased number of PIM (37.0%). (376) In the referred study, the 2012 Beers criteria was used as a reference, which covers other PIMs such as sliding-scale insulin, which was not part of PIMs 2002 list, although they have not yet been adapted for Portugal. (194)

A more recent Portuguese study, held by Alves da Costa *et al*. (2016), analysed a sample of polymedicated (≥ 5 medicines), older patients (≥ 65 years) resident in Portuguese nursing homes to assess the prevalence of PIMs, and used Beers criteria [Portuguese version (2008) and American version (2012)], and STOPP/START criteria (Screening Tool of Older Person's Prescriptions /

Screening Tool to Alert doctors to Right Treatment). Using the first tool, this study found that 60.3% of patients were using PIMs, and using the second tool 85% of the patients were using PIMS, a substantially higher prevalence than found in the ReMeD study (19.4%). (205) Patients included in the ReMeD study over 65 years were using polypharmacy in 82% (n=55) of cases. The most prevalent PIMs independent of diagnosis found in the home resident sample, using Portuguese version of Beers criteria (2008), were short-acting benzodiazepines, laxatives, and muscle relaxants, very similar to what was found in the ReMeD study. (205)

The Beers criteria are one of several tools to detect PIM in elderly patients, however their operationalization for Portugal has not yet been performed for the most recent versions of this tool. As verified by da Costa *et al*., the tool selection for the detection of PIM has influence on the results obtained, and the Portuguese version of Beers criteria allows to detect a lower number of PIM compared to the last American version or the START/STOPP criteria. (205) Moreover, the Beers criteria does not include missing medication, which can be identified in situations such as the prevention of cardiovascular events using the START / STOPP criteria. It would be useful to operationalize these tools, in their latest version, for the Portuguese reality, thus allowing an additional way to identify issues related to the medication use in the elderly, which is a growing age group in the Portuguese population. These tools seem to be a very relevant contribution to include in computer applications embedded in the IT resources that are already used by the Portuguese health institutions.

Globally, the identification of DRPs, although there is no consensus in this concept, seem to be a fundamental point in the medication review process. Regardless of the nomenclature used, the identification of issues in the medicines used by patients is of extreme importance in order to enable Pharmacists to identify patient centered interventions.

Risk situations for negative clinical outcomes

The risk situations (rNOMs) were noted whenever the patient did not present NCOs, although an issue was identified with some of the drugs used (DRPs). In the ReMeD sample these risk situations were identified in about three-quarters of the patients.

The number of risk situations identified in the ReMeD study were associated with an increase in the age of the patients, polypharmacy, use of antithrombotic agents, polymorbidity, and use of oral antidiabetic drugs, factors that had already been identified as a risk factor for the occurrence of DRPs by Kaufmann *et al*. (2015). (377) Other risk factors, classified as “important”, were also identified by these authors, such as dementia, cognitive situation, low IQ, confused patient, antiepileptics, combinations of NSAID and oral anticoagulants, insulin, missing information, half-knowledge of the patient, the patient does not understand the goal of the therapy, medication with a narrow therapeutic window, and non-adherence. (377)

This clinical outcome, although it does not translate to an explicit negative outcome, allows to signal the patients that present a higher risk for the occurrence of these NCOs. Petrovic *et al*. (2016) already recognized that the assessment of appropriateness in geriatric pharmacotherapy should include a screening to identify patients at risk of DRPs and adverse drug reactions (ADRs) and should include, in addition to the clinical outcomes of patients, capacities obtained from a health care team, that would allow avoiding potential negative outcomes that could be harmful to patient´s quality of life. (378) Therefore, the identification of the existing issues in the use of the medication (DRPs), may enable a corrective intervention and prevent the occurrence of future NCOs, and should consequently be an outcome of the medication review.

5.2.3.4 Potential Interventions

In the ReMeD study, the potential interventions identified with the highest prevalence were “other interventions” and interventions “at prescriber level”, a scenario with some similarity to the one found in a project including a medication review with follow-up held in a community pharmacy (Gipuzkoa, Spain) in 2015, where the main interventions were implemented at prescriber level (63.7%) and at patients level of educational interventions (36.3 %). (142)

Also in the Spanish study conSIGUE, about 50% of the interventions in all study periods were intended to prescribers, a greater amount of potential interventions in this scope than those identified in the ReMeD study (27.9%). (379) However, the conSIGUE study was conducted in the field of community pharmacy, including only patients aged 65 years and older and using polypharmacy (5 or more medicines). (379)

Based on these results, it is clear the importance of this activity in a multidisciplinary team, with better accessibility and direct contact with other health professionals, enabling faster intervention to achieve improved health outcomes. The Pharmacist´s intervention has been referred by Riordan *et al*.as a path to improve medication appropriateness in older adults, with greater impact on the results when there is Pharmacist collaboration with the Physicians acting in primary care. (380)

In the ReMeD study, disorders of “lipoprotein metabolism and other lipidaemias” and “obesity and other hyperalimentation” presented the highest rate of potential “other interventions”, regarding actions such as non-pharmacological interventions and referral to other professionals. These results show patient´s need for non-pharmacological interventions in diseases such as dyslipidaemias and obesity, which present a high prevalence in the Portuguese population.

An intensive lifestyle intervention is highly relevant in patients with type 2 diabetes, especially when associated with medication management, as identified in the Look AHEAD trial, which was developed with the aim of assessing the effects of weight loss through behavioural means on

cardiovascular morbidity and mortality (intensive multi-component lifestyle intervention versus diabetes support and education). (381)

The predictive variables identified for the weight loss in overweight type 2 diabetes adults were the following: baseline variables fasting glucose, anxiety, numb feeling in extremities, insulin dose and waist-to-hip ratio. (382) A large part of the ReMeD population study may be a good target for a weight loss program prepared by a nutritionist in conjunction with other health professionals, since about one-sixth of the population was diagnosed with anxiety and about 40% was using insulin.

It should be also highlighted the number of potential interventions proposed for the ReMeD patients under the anxiety disorders treatment scope, which are essentially at the prescriber level. In the case of the treatment of this medical disorder, clinical guidelines indicate that treatment with benzodiazepines calls up a maximum duration of 8 to 12 weeks, including a discontinuance period being subsequently reviewed in a specialized consultation, and should not rely on the use of more than one benzodiazepine anxiolytic. (371) Some patients included in the ReMeD did not meet these recommendations, which is reflected by the increased number of potential interventions at the level of prescriber with the number of drug-related problems such as "too long duration of treatment" and "inappropriate drug". A reassessment of the anxiety treatment should be performed by prescribers, also considering the inclusion of non-pharmacological measures in the treatment.

The ReMeD patients presenting a diagnosis of type 2 diabetes *mellitus* showed the highest rate of no intervention purposed, which can be intuitive since the patients included in this study were recruited in a clinic focused on the study, treatment and monitoring of patients with diabetes, which may justify a reduced need for interventions under this health problem. Nevertheless, the proposed interventions at various levels presented themselves in a similar order of magnitude, with potential interventions proposed within the prescriber and the

patient being the most prevalent, which may point to an important multifactorial approach for these patients.

5.2.4 Predictive factors for clinical outcomes associated to medication review

For the model considering negative clinical outcomes as dependent variable, blood pressure control and glycemic control were the parameters with a heavier effect in the number of negative clinical outcomes.

Clinical outcomes associated with uncontrolled diseases or ineffectiveness of treatment have been reported by several authors as the main clinical outcomes of medication review in a community pharmacy setting as well as in clinical or residential context. (142,144,355)

Also in the Spanish conSIGUE project, about 28.5% of health problems identified in the intervention group were uncontrolled, and about 45.7% of negative results associated with medication were related to ineffectiveness at the first period of the study. (379)

Future research should include target groups of patients to carry out medication review, hypertense and diabetic patients, since these groups are probably at greatest risk of negative clinical outcomes.

According to the results, the model considering drug-related problems as a dependent variable, the number of medicines, older patients (≥65 years) and number of antidiabetic drugs could predict about 47.9% of the variable results.

Several of the studies in which a MR was conducted, included as target populations people aged 65 years and over, although with specific methodologies, having been recognized improvement in the outcomes of patients. (141,158,383)

A correlation between the number of pharmaceutical care issues and the number of medicines was also described by Krska *et al*. (2001), in a randomized controlled trial conducted in older patients. (383)

in addition, the reduction of medicines number has been reported as one of the main outcomes from medication review. (141,158)

The number of medicines used by patients and the discrepancies between prescribed and taken medications were identified as predictive factors for an advantage to patients undertaking medication review by Rose *et al*. (2016). For this analysis it was considered the acceptability of the Physician to implement pharmaceutical recommendations and factors influencing Physicians' acceptance. Also older patients with multimorbidity, polymedication and a cardiovascular disease experience, were identified as subjects that can benefit from medication review. (384)

Considering predictive factors for clinical outcomes identified in the ReMeD study, target groups to undertake medication review should include, in future research, older patients (≥65 years), polymedicated patients and patients using antidiabetic drugs.

5.2.5 Comparison of eligibility criteria for medication review programs in Australia, Canada and England

The eligibility criteria established for the various medication review programs showed to have some points in common, namely the number of medicines used by patients and the number / type of pathologies.

In Australia, several groups of researchers have tried to improve the medication review process over recent years. A systematic review regarding the outcomes from clinical medication review (CMR) service held in community setting in Australia, identified that most of the studies included in the analysis were conducted in patients at risk for negative outcomes from medication use (n=40).

Moreover, others studies were carried out in groups of elderly patients (n=10), and further studies were conducted in patients with specific clinical conditions (eg, chronic heart failure, chronic obstructive pulmonary disease, diabetes and others) or with specific humanistic characteristics as problems in medication adherence, culturally and linguistically diverse. (159)

The eligibility criteria for conducting a medication review in Canada under the MedsCheck program, only include a criteria based on the number of medications used by patients for chronic conditions. If these criteria were applied to the sample of patients included in ReMeD study, about 85% of patients would meet these criteria.

An analysis of MedsCheck annual (MCA) provided in Canada from 2007-2013, identified an increased number of MCA provided among this 6-year period in patients aged over 66 years compared to younger subjects (42% vs 31%), with a higher prevalence of hypertension, heart failure and cancer in the older patients (≥66 years) cohort and most of those having at least one dispensing of an antihypertensive or antidyslipidemic drug during the previous year before MCA. (324)

Canadian researchers developed and validated a tool called “Medication Risk Assessment Questionnaire” (MRAQ) to identify patients at risk for DTPs, in a community pharmacy environment, consisting of five questions to be self-answered by the patient, with a good value of reliability ($k = 0.91$, $p<0.01$). (385)

Pammett *et al*. (2016) reported a higher number of moderate-severity drug-therapy problems (DTPs) in eligible patients for medication review according to provincial criteria compared to those who did not accomplish the eligibility criteria for all provincial programs available in Canada. (386)

Despite the eligibility criteria for the MCA service in Canada being less restrictive than those applied in other countries, the profile of individuals who benefited from this service seems to be similar to that found in the groups that benefit from similar programs in other countries.

The Medicines Use Review service, available in the United Kingdom (UK), has more specific eligibility conditions than the existing programs in the two previous countries (Australia and Canada), including patients using "High risk medicines" "Medicines for respiratory disease" and patients "At risk or diagnosed with cardiovascular disease and using regularly at least 4 medicines", and also as defined for the two other countries under analysis, patients recently discharged from hospital with changes in medicines (during hospitalization).

The criteria for this specific service available in community pharmacies in England, which comply with the conditions for their provision, are closely related to the results obtained previously, resulting in potentially advantageous for improving health outcomes, which allowed the funding authorized by the National Health Service (NHS) to pharmacies for providing this service with these features focused in practical use of medicines. (119)

In 2001, a randomized controlled trial conducted in Scotland that enrolled patients 65 years and older using at least 4 (four) medicines and having at least 2 (two) chronic health problems, already identified "pharmaceutical care issues" (PCI), having identified diuretics and other medications used in the cardiovascular system related to possible PCI, and also referred the need of access to patients records to enable identification of some PCI. (383)

The main goal common to all countries and services is an attempt to identify groups that may benefit from this medication review activity, whether the medication used, patient´s clinical outcomes or their personal characteristics that may influence the treatment and thus lead to negative results in the health status of the individual.

The methodology and the team involved in the conduction of a medication review are key points, since it may influence the data obtained and consequently the outcomes of this activity.

Willeboordse *et al*. (2016) compared information about patient´s medication use and drug-related problems using a questionnaire and a face-to-face interview,

with results showing an agreement on results obtained by both methods, but a higher number of reported drug-related problems obtained in the interview than the questionnaire. Although the results were similar for younger patients with proper health literacy, for older patients with more diseases and lower health literacy the interview was the methodology that allowed more accurate results. (387) This suggests that, in the case of the ReMeD study, and considering the age characteristics of the population, the approach through interview that was used was the most appropriate.

The eligibility criteria adopted to date in these three countries do not invalidate that there are other target groups that may benefit from the medication review.

Each country / community identifies the eligibility criteria according to the needs of its population, the purpose of which is to identify individuals who may be at greater risk of negative health outcomes. Not always these criteria allow the identification of all individuals who can benefit from this service. It is therefore important to establish the appropriate criteria for each population and to monitor the results obtained and to update these criteria according to the health outcomes of the individuals.

6 CONCLUSION

In order to contribute to the improvement of patient´s health outcomes, particularly associated to the medication use, this study aimed to develop a methodology to analyse the outcomes of the process of medication use through medication review (ReMeD study).

The adaptation to Portuguese language of the “Short Assessment of health literacy – Spanish and English” (SAHL-S & E) was one of the objectives for this investigation. A good value of internal consistency (Cronbach's alpha) and intraclass correlation coefficient was reached, in addition to an excellent and statistically significant interrater reliability, in the Portuguese version. Therefore, the tool achieved (SAHL-PT) seems easy to apply and appropriate to screen subjects who have low health literacy.

The ReMeD study was conducted in a sample of 118 patients, where around half of the patients were male (54.2%) and older than 64 years (56.7%), and most were married (74.6%) and lived with family members (87.3%). About half of the sample had qualifications below the 9th grade, and patients were followed in the AEDMADA clinic on average for 3.5 years.

Clinically, we can conclude that patients within the sample presented could benefit from an intervention plan, due to the high number of morbidities identified and low rate of control for risk factors of cardiovascular diseases. This screening for patients with negative health outcomes, including low degree of control of chronic diseases and those to minimize the development of diabetes complications, can be an asset of medication review service.

The analysis of the pharmacotherapeutic profile identified a population mainly using polymedication (73.8%), and therefore at risk of suffering negative outcomes associated with medication.

The outcomes of medication review (MR), for the ReMeD population, were presented in the humanistic, economic and clinical scope.

Considering the humanistic outcomes, an increased rate of medication adherence was observed. However, the assessment of medication adherence during medication review allows to identify medicines with lowest rate of adherence and identify patients who reported not taking medications under certain circumstances, such as when they felt better or worse or to identify specific medicines in which there is a lack of adherence. A low medication knowledge score was identified in a quarter of the patients, this assessment enable to signal patients that should be included in therapeutic educational programs and those who may need help identifying their medications.

The identification of a lack of knowledge for disease such as hypertension, diabetes and dyslipidaemia, allows the identification of patients' specific needs in terms of disease management.

Patients identified as having low health literacy could be useful to identify patients at risk of uncontrolled disease, patients that could benefit from therapeutic education programs and for which an adjustment is required in the patient / health professional communication.

Economic outcomes are parameters that may contribute to identify actions that could improve patient´s savings on their medication as well as to recognize the economic impact of negative clinical outcomes. Considering these outcomes, we can conclude that patients used a median of six (6) medicines, seven (7) units and seven (7) doses per day, with polypharmacy being present in most of the patients, which may indicate an increased therapeutic complexity, and intervention can be identified as necessary. Almost three quarters of the patients (71.1%) were followed by more than 1 Physicians, which could lead to an increase discrepancies in patient´s medication and contribute to health negative outcomes, and these should be analysed during medication review. The previous hospitalizations identified contributes to the burden of disease and to the increase in health costs. Pointing patients with a special rate of medicines reimbursement could help identify patients with financial difficulties in acquiring medicines.

The clinical outcomes obtained with the approach applied, performed by clinical situation, enables the identification of the treatment´s outcomes with clinical significance, and later to define actions that allow to achieve the intended clinical objectives. Although this is not an approach used globally in the review of medication process, this methodology allows the direct analysis of the impact of therapeutic on patient´s health outcomes.

The identification of the issues (DRPs) associated with the medication used, enables the Pharmacist to achieve patient´s necessities regarding medication management and also to collect information that will be useful to share with other team care professionals and to define a patient´s centered intervention.

The methodology used enabled signalling patients at risk of suffering a NCO, which could contribute to a preventive Pharmacist´s intervention, correcting the issue identified and preventing the occurrence of patient harmful.

The identification of the potential intervention adopted in this methodology allows a purpose of an individualized work plan to be established on a patient´s centered approach, and may serve as a basis for future patient monitoring/intervention activities performed by the Pharmacist or the referral to other health professionals.

The number of Physicians, blood pressure control and glycemic profile control were identified as predictive factors for negative clinical outcomes, enabling to predict 35.1% of the variation in NCOs. Still, the number of medicines, patient´s age ≥65 years, the number of antidiabetic drugs and the number of antihypertensive drugs allowed to predict 47.9% of variation in DRPs.

In future research, older patients (≥65 years), polymedicated patients, diabetic and hypertense patients should be included as target groups to undertake medication review.

Some of the eligibility criteria established for the medication review programs available in Australia, Canada and England could probably be applied in the ReMeD population. However, each service, according to its target population,

should establish its criteria based on the identified specific needs and health outcomes, for which the knowledge of the population-specific health outcomes is fundamental.

The ReMeD study was conducted in a clinical context, having direct contact with patients, access to their medical record and in communication with other health professionals, which was the key to successfully implement this study.

The methodology used, including a patient´s clinical centered approach allows to identify clinical situations with negative results and to target points of intervention, either by the Pharmacist or other health professionals involved. The analysis of medicine´s use included in the ReMeD study, allowed to detect issues related to the medicines used by patients, and also enables to signal the needs and difficulties of these patients with medication. Furthermore, the identification of risk situations for the occurrence of NCOs may allow a better performance of the Pharmacist acting to prevent the manifestation of negative outcomes and worsen health outcomes.

This approach can definitively be useful to the development of new strategies aimed to improve patient's medication use and the empowerment for disease management. An opportunity to a Pharmacist´s intervention arises in the scope of therapeutic education and health promotion, disease prevention and control of disease progression.

7 FUTURE RESEARCH

In the future, a validation of this methodology, applied by other Pharmacists in collaboration with other health professionals, should be done, as well as an evaluation of the inter-reliability of the method.

Furthermore, an economic evaluation of the costs of the service provided is needed, including the assessment of the time spent in the medication review process, in order to allow the calculation of the relative cost of the professional responsible (Pharmacist) for this service. Also the quality of life assessment could be included, in order to allow a future cost analysis and to estimate the costs and potential price of providing and implementing the service of medication review. Moreover, the evaluation of the patients' satisfaction with the service should be also included as an outcome, allowing to understand patient´s perspective and capital gains, being identified by the users of the service.

In the near future, the implementation of this medication review service is planned in a primary health care unit belonging to the public health system. It could aim the medication review in patients diagnosed with hypertension or type 2 diabetes, to identify and analyse the clinical, humanistic and economic outcomes associated with the use of medication. From this analysis, an individual report would be prepared per patient, would be sent to the patient's attending Physician, indicating the issues identified and respective intervention proposals. Subsequently, the acceptance rate of the proposed intervention would be analysed. One year later, a new medication review would be performed and the respective results would be analysed, comparing to those obtained in the first analysis.

Another planned project is the implementation of medication review in residential care units, which includes subjects aged 65 or over. It would be applied, as a pilot project, to 30 residents in a residential care unit in Olhão (Faro district). This pilot project would allow the adequacy of the methodology of medication review to the resident´s characteristics and specify needs, as well as

the available clinical data and the integration of the Pharmacist role in this setting.

Still as a consequence of the ReMeD study outcomes a need for a "medication list" tool was identified, allowing patients to always carry the information about the medication used. A pilot study would be carried out where this tool would be used, initially assessing the patient's medication knowledge prior to the delivery of the list and 3 months after the intervention.

The medication review activity will be a relevant area to explore in the future of the activity of the Pharmacist in Portugal, and the research in this area should continue.

8 LIMITATIONS

The ReMeD study was conducted in a clinical setting primarily intended for the treatment, monitoring and care of diabetic patients. This population has, for this reason, particular characteristics and outcomes targeted in the area of diabetes and other frequent chronic health problems often associated with it.

The methodology used to assess medication knowledge in the ReMeD study did not include items within the dimension of security, as included in some other tools available for this purpose. In fact, these items were originally included in the questionnaire, but the answers given by the patients couldn't be considered valid for inclusion in the tool used. Most patients failed to respond when placed on the question about adverse effects of the drug, or on the drug´s therapeutic goals. Due to its relevance to the outcomes, medication knowledge assessment was performed for all medicines used by the patient, although most studies published only included the evaluation of medical knowledge for one medicine per patient. Unfortunately, this became a most lengthy and difficult process to the patient, where hence he probably failed to properly identify the specific side effects and potential interactions to each drug. In a future approach, this assessment should be made not so exhaustively for all drugs, but individually to each specific group of drugs.

The number of visits to the emergency department should has been included as an economic outcome, since these visits could be identified as an additional increase in the costs for the health system, which are normally not included in the regular care process and can be associated to the use of medication.

The existing state of organization of the patients' clinical file is not properly systematized. Although the records are mainly integrated on a digital file they are also made on paper in some cases. In addition, patients are mostly followed by several Physicians, which makes it more difficulty to integrate all clinical information. It would be useful to reorganize the collection of patients' clinical data and, if possible, to create a mechanism for sharing information among all

health professionals who follow these patients at the various levels of healthcare.

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10 APPENDICES

Appendix A **: Questionnaire for SAHL-PT adaptation**

1. AGE: _____years

2. GENDER: Male Female

3. WEIGHT: _____kg HEIGHT: _____cm

4. MARITAL STATUS:

5. QUALIFICATIONS:

7. PROFESSIONAL SITUATION:

8. HOUSEHOLD:

9. HEALTH PROBLEMS:

10. MEDICATION:

Number of medicines used daily:

Number of daily units (cps, cáps, other):

Appendix B **: SAHL-PT Test (Portuguese)**

	Chave ou Distração		
1. emprego	__trabalho	__educação	__não sei
2. convulsões	__tontura	__tranquilidade	__não sei
3. infeção	__morte	__vírus	__não sei
4. medicamento	__instrumento	__tratamento	__não sei
5. alcoolismo	__adição	__recreio	__não sei
6. rim	__urina	__febre	__não sei
7. dose	__dormir	__quantidade	__não sei
8. aborto	__perda	__matrimonio	__não sei
9. obstipação	__bloqueado	__solto	__não sei
10. gravidez	__parto	__infância	__não sei
11. nervos	__aborrecido	__ansiedade	__não sei
12. nutrição	__saudável	__gases	__não sei
13. indicado	__instrução	__decisão	__não sei
14. hormonas	__crescimento	__harmonia	__não sei
15. anormal	__diferente	__similar	__não sei
16. diagnóstico	__avaliação	__recuperação	__não sei
17. hemorroidas	__veias	__coração	__não sei
18. sífilis	__contracetivo	__ preservativo	__não sei

Appendix C **: Informed consent form**

Informed Consent

Title of the Research Project:

*Evaluation of health outcomes associated with medication in Southern Portugal using a novel approach for **med**ication **re**view:* **ReMeD study**.

The main objectives of this research project are: Assessment of cardiovascular risk in the population of users of AEDMADA; Characterization of pharmacotherapeutic profile; Analysis of the degree of control of risk factors for cardiovascular diseases (hypertension, diabetes, dyslipidemia); Identification of negative clinical outcomes; Identification of drug related problems; Identification of risk situations for negative clinical outcomes in the use of medication.

Data will be collected regarding socio-demographic parameters and the following parameter values: weight, height, blood pressure, pulse, blood glucose, HbA_1c, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, smoking, medication use and others as applicable.

Questionnaires will be used to assess medication adherence, degree of health literacy and medication use.

The collection of these data will be performed during an interview.

I, _____, declare that I consent my participation in this research project.

By giving my consent I declare that:

I agree with the goals of the research project and my involvement in it; All doubts about the project have been fully clarified; I understand that at any time I can give up to participate in the project without affecting my relationship with the researchers or AEDMADA; I understand that my participation is confidential and information about me will not be used so that my identity is revealed; Participate in this project is completely voluntarily; I know I can at any time stop the interview and, if I wish, my participation will not be included in the study.

Faro, _____ 20___

(Patient Signature) (Investigator Signature)

Appendix D **: ReMeD Questionnaire**

QUESTIONNAIRE	
Socio-demographic Data	
Name	
Age(years)	
Gender	
Marital Status	
Household	
Qualifications	
Professional Situation	
Biochemical and physiological parameters; Lifestyle.	
Weight	
Height	
BP	SBP: DBP:
Pulse	
Lipid Profile	Total Colesterol: Date: c-LDL: Date: C-HDL: Date: Triglycerides: Date:
Glycemic profile	Fasting glycemia: Date: Postprandial glycemia : Date: HbA_{1c}: Date:
Smoking Habits	Smoker ___ Nr cigarettes/day: ___ Ex-Smoker ___ No-smoking ___
Physical Exercise Habits	Do you practice physical exercise regularly? Yes No How many times a week? How long each session?
Food Habits	In a typical week how many days ate fruit? How many pieces of fruit eaten one of these days? In a typical week how many days ate vegetables? How many portions of vegetables eaten in those days? What kind of fat do you use most often to prepare your own meals?

Clinical Profile	
Health Problems	Diseases of the circulatory system: 1- Hypertension 2 - Other: Digestive Diseases: 1- GER Disease 2 – Peptic ulcer 3 - Other: Diseases of the Respiratory System: 1- Asthma 2 - DPOC 3 - Other: Diseases of the Musculoskeletal System and connective tissues: 1 - Osteoarthrosis 2 - Osteoporosis 3 - Other: Endocrine, nutritional and metabolic Diseases: 1 - Diabetes *mellitus* 2 – Hypothyroidism 3 – Hyperthyroidism 4 – Dyslipidaemia 5 – Hyperuricaemia 6 - Other: Mental and Behavioural Disorders: 1- Depression 2 – Anxiety 3 – Alzheimer Disease 4 - Other(s): Diseases of Nervous System: 1 – Parkinson Disease 2 – Epilepsy 3 – Alzheimer Disease 4 - Other(s): Diseases of the Genitourinary System: 1 – Urinary incontinence 2 – Benign prostate hyperplasia 3 – Other: Diseases of the Eye and Adnexa: 1 – Cataracts 2 – Visual impairment 3 – Other: Others:
Diabetes Microvascular Complications	Retinopathy Yes No; Nephropathy Yes No; Neurophaty Yes No
CV events	Any **cardiovascular event**? (stroke, myocardial infarction, transitory ischemic attack, other)? Yes No Do you have any family (1st degree) with premature cardiovascular event/disease (men <55 years, women <65 years)? Yes No
Hospitalizations	Have you been hospitalized in the last year? Yes No How many times? _____How long?_____Cause? _____
Falls	Have you fallen in the last 12 months? Yes No; Where? Do you had any broken bones from the fall? Yes No; Where?
Complaints	
Other	- Who renews the prescriptions?

Pharmacotherapeutic Profile										
	#01		#02		#03		#04		#05	
Medicine										
Drug´s Strenght	K NK		K NK		K NK		K NK		K NK	
Medicine´s Name	K NK	Can Cannot	K NK	Can Cannot	K NK	Can Cannot	K NK	Can Cannot	K NK	Can Cannot
Regimen										
When do you take?										
Howmany units/time?	____ units		____ units		____ units		____ units		____ units	
Why are you taking?										
How long?										
Medicines´ effects	**(+)**	**(-)**	**(+)**	**(-)**	**(+)**	**(-)**	**(+)**	**(-)**	**(+)**	**(-)**
Nr days taken (7d)?	____ days		____ days		____ days		____ days		____ days	
Nr days missed (7d)?										
Where do you keep?										
Medicine bother you?	Yes / No How ?		Yes / No How ?		Yes / No How ?		Yes / No How ?		Yes / No How ?	
Who prescribed?										
Comments										

Medication Adherence

Haynes-Sackett (Haynes *et. al*, 1980)

- **Most people have difficulty taking medication. Do you have difficulty taking your medication?** yes No

Yes (tablets missed last 7 days / number indicated tablets) × 100; Non-adherent: <80%

MAT – Medida de Adesão aos Tratamento (Delgado & Lima, 2001)

a) Alguma vez se esqueceu de tomar os medicamentos para a sua doença?
Sempre Quase sempre Com frequência Por vezes Raramente Nunca

b) Alguma vez foi descuidado(a) com as horas da toma dos medicamentos para a sua doença?
Sempre Quase sempre Com frequência Por vezes Raramente Nunca

c) Alguma vez deixou de tomar os medicamentos para a sua doença por se ter sentido melhor?
Sempre Quase sempre Com frequência Por vezes Raramente Nunca

d) Alguma vez deixou de tomar os medicamentos para a sua doença, por iniciativa, após se ter sentido pior?
Sempre Quase sempre Com frequência Por vezes Raramente Nunca

e) Alguma vez tomou mais um ou vários comprimidos para a sua doença, por sua iniciativa, após se ter sentido pior?
Sempre Quase sempre Com frequência Por vezes Raramente Nunca

f) Alguma vez interrompeu a terapêutica para a sua doença por ter deixado acabar os medicamentos?
Sempre Quase sempre Com frequência Por vezes Raramente Nunca

g) Alguma vez deixou de tomar os medicamentos para a sua doença por alguma razão que não seja a indicação do médico?
Sempre Quase sempre Com frequência Por vezes Raramente Nunca

Medication Management	Do you have someone to help with your medications? Yes No If yes, how?
Self-perceived health status(PT)	How do you consider, currently, your health? Very poor Poor Fair Good Excellent

Health Services Access

Medication reimbursement system	NHS ____ NHS – R ____ Other: ____
Who is the doctor (s) that makes your follow-up?	General Practice_____ Specialist_____ Which? _____

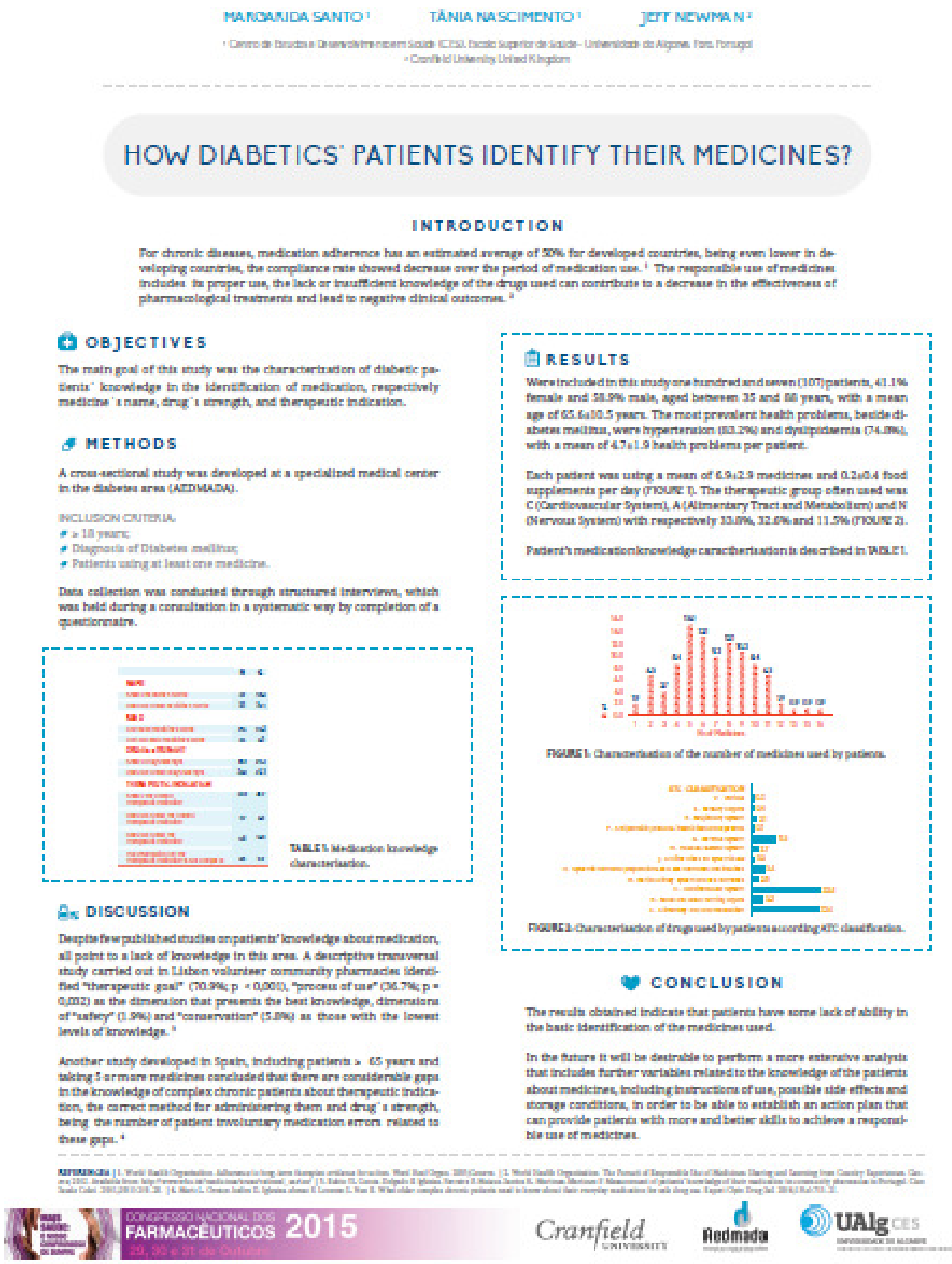
Patient knowledge about disease

Hypertension	▪ How **many years** have hypertension? _____ years
	▪ What is the **optimal value** for your blood pressure?_____ mmHg ▪ Could you point **two possible complications** of hypertension? _____ ▪ Have you measured your blood pressure in the **last 12 months**? Yes No ▪ If yes, how many times? _____ ▪ Do you have tensiometer at home? Yes No

Patient knowledge about disease *(continued)*	
Diabetes	▪ How **many years** do you have diabetes? _____ years
	▪ Do you know the **optimal values** for your Glycemia? Yes No Fasting _____ Postprandial _____ ▪ Do you have glucometer at home? Yes No ▪ How many days you measured your glycemia in the last 7 days? 0 1 2 3 4 5 6 7 ▪ How many times a week was appointed to measure glycemia by your doctor, nurse or pharmacist? 0 1 2 3 4 5 6 7 ▪ Could you point **two possible complications** of uncontrolled glycemia? _____
Dyslipidaemia	▪ How **many years** do you have dyslipidaemia? _____ years
	▪ Do you know the **optimal value** for total cholesterol? Yes No ▪ **Optimal value** ? _____ ▪ Could you point **two possible complications** of uncontrolled cholesterol values? _____

Appendix E : **Publications**

E.1.1 **Portuguese National Congress of Pharmacists**



(Lisbon, October 2015)

E.1.2 National Congress of Diabetes

(Vilamoura, March 2016); http://unidospeladiabetes.pt/

E.1.3 Manuscripts in progress to submit [potential journal]

- "Adaptation to Portuguese language (Portugal) of the Short Assessment of Health Literacy - Spanish and English (SAHL-PT)" [Public Health Journal (Revista de Saúde Pública); IF:1.283]
- "Assessment of medication knowledge in a diabetic population" [Research in Social and Administrative Pharmacy; IF: 1.936]
- Analysis of medication review outcomes in clinical setting" [International Journal Clinical Pharmacy; IF: 1.339]