Journal of Geriatric Cardiology (2015) 12: 239–245

Research Article · Open Access ·

Attainment of multifactorial treatment targets among the elderly in a lipid clinic

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Abstract

Objective To examine target attainment of lipid-lowering, antihypertensive and antidiabetic treatment in the elderly in a specialist setting of a University Hospital in Greece. **Methods** This was a retrospective study including consecutive subjects ≥ 65 years old (n = 465) with a follow-up ≥ 3 years. Low-density lipoprotein cholesterol (LDL-C), blood pressure (BP) and glycated hemoglobin (HbA1c) goal achievement were recorded according to European Society of Cardiology/European Atherosclerosis Society (ESC/EAS), European Society of Hypertension (ESH)/ESC and European Association for the Study of Diabetes (EASD) guidelines. **Results** The LDL-C targets were attained by 27%, 48% and 62% of very high, high and moderate risk patients, respectively. Those receiving statin + ezetimibe achieved higher rates of LDL-C goal achievement compared with those receiving statin monotherapy (48% *vs*. 33%, $P < 0.05$). Of the diabetic subjects, 71% had BP < 140/85 mmHg, while 78% of those without diabetes had BP < 140/90 mmHg. A higher proportion of the non-diabetic individuals (86%) had BP < 150/90 mmHg. Also, a higher proportion of those with diabetes had HbA1c < 8% rather than < 7% (88% and 47%, respectively). Of note, almost one out of three non-diabetic individuals and one out of ten diabetic individuals had achieved all three treatment targets. **Conclusions** Even in a specialist setting of a University Hospital, a high proportion of the elderly remain at suboptimal LDL-C, BP and HbA1c levels. The use of drug combinations could improve multifactorial treatment target attainment, while less strict targets could be more easily achieved in this population.

J Geriatr Cardiol 2015; 12: 239–245. doi:10.11909/j.issn.1671-5411.2015.03.004

Keywords: Blood pressure; Goal achievement; Glycated hemoglobin; Low-density lipoprotein cholesterol

1 Introduction

Cardiovascular (CV) disease remains the primary cause of death worldwide.[1] Advancing age, smoking, hypercholesterolemia, hypertension and diabetes are the leading causes of CV morbidity and mortality.[1] A wealth of evidence of large randomized clinical trials has established that lowering low density lipoprotein cholesterol (LDL-C) and blood pressure (BP), along with good glycemic control in individuals with diabetes reduce the risk of CV events.[1–3] However, proposed goals by the guidelines are difficult to achieve in clinical practice.[4–6] We have previously reported that even in the setting of a lipid clinic, only one out of four very high risk patients achieved the optimal LDL-C target < 70 mg/dL and 42% of those at high CV risk had LDL-C < 100 mg/dL.[4,7] In the US, 31% of the hypertensive individuals and 36% of those with diabetes do not reach the BP and glycemic targets, respectively.[5,6] Data are limited regarding the rates of goal achievement of lipid-lowering, antihypertensive and antidiabetic treatment in the elderly.[8,9]

In two previous publications, we presented data for the lipid goal achievement of patients attending a Lipid Clinic of a University Hospital.[4,7] In this report, we studied only the older outpatients and present data for LDL-C target attainment, but also for BP and glycemic control. In addition, the rates of the less strict BP and glycemic target achievement, recently recommended in the elderly,[2,10] were recorded along with the incidence of treatment side effects.

2 Methods

The study details have been previously described.[4] Briefly, this was a retrospective study including consecutive adult patients followed for more than or equal to three years. The study was conducted in the outpatient Lipid Clinic of the University Hospital of Ioannina, Greece. The study protocol was approved by the institutional committee.

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Received: November 5, 2014 **Revised:** January 21, 2015
Accepted: March 2, 2015 **Published online:** April 7, 2015

All subjects were of Greek origin. For the purposes of the present analysis, only subjects aged ≥ 65 years old were included. Demographic characteristics along with clinical and laboratory data were recorded at baseline and last visit. These included: (1) anthropometric indices [body mass index (BMI)]; (2) age, gender and smoking status; (3) BP readings; (4) lipid profile, including total cholesterol (TCHOL), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), LDL-C and non-high density lipoprotein cholesterol (non-HDL-C); (5) fasting glucose and glycated hemoglobin (HbA1c); and (6) serum creatinine as well as liver and muscle enzyme levels.

Prescribed medications were also recorded, with particular emphasis on lipid lowering treatment (i.e., statins, fibrates, ezetimibe, omega-3 fatty acids and colesevelam). Median dose of each statin along with the rates of combination statin therapy with ezetimibe were recorded. Antihypertensive drugs were classified into the following groups: monotherapy, combination of 2, 3 or ≥ 4 BP lowering agents. Antidiabetic drugs were classified into the following categories: (1) metformin monotherapy; (2) metformin + another oral glucose lowering agent; (3) oral glucose lowering agents without metformin; and (4) insulin ± oral antihyperglycemic drugs.

Rates of adverse events of the multifactorial treatment were also recorded: increase of the liver enzymes > 3 times the upper limit of normal values (ULN) and increase of the creatine phosphokinase (CK) > 10 times the ULN, myalgias, hypotension, gastrointestinal disorders and hypoglycemia.

Subjects classified into 'very high', 'high' and 'moderate' CV risk groups and were treated for dyslipidemia according to the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS).[1] The corresponding LDL-C targets were < 70 mg/dL (1.8 mmol/L), < 100 mg/dL (2.6 mmol/L) and < 115 mg/dL (3 mmol/L) for the three groups, respectively.[1]

BP goals were those recommended by the European Society of Hypertension (EHS)/ESC.[2] A systolic blood pressure (SBP) target of < 140 mmHg was used, while the corresponding target of diastolic blood pressure (DBP) target was < 90 and < 85 mmHg for the non-diabetic and diabetic subjects, respectively.[2] A less strict SBP target (< 150 mmHg) is also recommended for those older than 80 years.[2]

Diagnosis of diabetes was based on the criteria proposed by the ESC and the European Association for the Study of Diabetes (EASD).[3] The HbA1c targets were < 7%, while a less stringent goal (7.5% to 8%) has recently been recommended for the older diabetic patients.[10]

Rates of LDL-C target attainment across CV risk groups according to the ESC/EAS guidelines were recorded, while correlations between lipid lowering treatment and LDL-C goal achievement were performed. Similar analyses were performed regarding BP and HbA1c targets, according to the ESH/ESC and ESC/EASD guidelines, respectively.

For categorical values, frequency counts and percentages were applied. Chi square tests were used for comparisons of categorical values between the two groups. Continuous numeric variables were expressed as mean ± SD and median (range) if Gaussian or non-Gaussian distributed, respectively. Continuous variables were tested for the lack of normality by the Kolmogorov-Smirnov test. Paired-sample *t*-tests (parametric and non-parametric) were performed for comparisons within groups. Independent sample *t*-tests (parametric and non-parametric) were performed for the comparison of continuous numeric variables between the two groups. Multivariate analysis of variance (MANOVA) was used for the comparison of the dependent variable of interest between three or more groups. Two-tailed significance was defined as $P < 0.05$. Data analysis was performed with SPSS 21.0 software (SPSS, IBM corp., Armonk, New York).

3 Results

3.1 Study population

Four hundred and sixty five subjects were eligible and followed for a mean of eight years. Demographic, clinical and laboratory characteristics of the study population are shown in Table 1. Briefly, the majority of the subjects were at very high CV risk according to the ESC/EAS guidelines (68%). Diabetes was the most prevalent disease (31%), followed by chronic kidney disease (CKD) (23%), stroke (15%) and coronary heart disease (CHD) (15%).

3.2 Treatment

Lipid-lowering treatment is thoroughly described in Table 2. Of the patients, 98% were receiving statins (80% statin monotherapy and 20% combination of statin + ezetimibe), 5% omega-3 fatty acids, 4% fibrates and 1% colesevelam. Some patients were receiving more than two drugs, e.g., statin plus ezetimibe plus fibrate. The statin of choice was atorvastatin, followed by rosuvastatin and simvastatin (Table 2).

Angiotensin II receptor blockers (ARBs) were the first choice of BP lowering drugs, followed by calcium channel blockers, thiazides and β-blockers. In addition, the majority of the hypertensive participants were receiving a double or triple combination of BP lowering agents (Table 2).

Table 1. Demographic, clinical, and laboratory characteristics of the study population at the most recent visit (n = 465).

Age, yr	73 ± 6
Sex (male), %	41
Smoking, %	8
Body mass index, kg/m^2	28.8 ± 4.3
Waist, cm	103 ± 10
Metabolic syndrome, %	62
Diabetes, %	31
Fasting glucose, mg/dL	107 ± 24
HbA1c, %*	7.1 ± 1.0
eGFR, mL/min per 1.73 m^2	69 ± 16
Systolic blood pressure, mmHg	133 ± 13
Diastolic blood pressure, mmHg	76 ± 8
TC, mg/dL	173 ± 33
TG, mg/dL	112 (22–405)
HDL-C, mg/dL	56 ± 14
LDL-C, mg/dL	93 ± 27
Non-HDL-C, mg/dL	117 ± 30
Lipid-lowering treatment, %	95
Antihypertensive treatment, %	89
Antidiabetic treatment, %	29
Cardiovascular risk, %#	
Very high	68
High	28
Moderate	4
Disease group, %	
Diabetes	31
CKD	23
Stroke	15
CHD	15
PAD	8
Carotid stenosis	6
Aneurysm	3

Values are expressed as mean ± SD or percent except for triglycerides which are expressed as median (range). To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol, by 0.01129 for triglycerides and by 0.05549 for glucose. * For diabetic patients. #Cardiovascular risk was defined according to the ESC/EAS guidelines for the management of dyslipidemias.[1] CHD: coronary heart disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; EAS: European Atherosclerosis Society; ESC: European Society of Cardiology; HbA1c: glycated hemoglobulin; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non-high density lipoprotein cholesterol; PAD: peripheral arterial disease; TC: total cholesterol; TG: triglycerides.

In diabetic subjects, metformin was the first drug of choice, followed by dipeptidyl peptidase-4 (DDP-4) inhibitors and sulfonylureas (Table 2). The majority of patients with diabetes were receiving metformin plus another oral antihyperglycemic drug or metformin monotherapy (46% and 35%, respectively).

Table 2. Drug treatment at the most recent visit.

Lipid lowering treatment	
Statins	98
Atorvastatin, % (median dose)	46 (20 mg)
Rosuvastatin, % (median dose)	26 (20 mg)
Simvastatin, % (median dose)	24 (40 mg)
Fluvastatin, % (median dose)	2 (80 mg)
Pravastatin, % (median dose)	1 (40 mg)
Ezetimibe, %	21
Fibrates, %	4
Coleveselam,%	1
Omega-3 fatty acids, %	5
Statin + ezetimibe, %	20
Antihypertensive treatment	
ARB, %	79
Calcium channel blockers, %	61
Thiazides, %	58
β-blockers, %	40
ACE inhibitors,%	9
Aldosterone receptor antagonists, %	8
Centrally acting drugs, %	3
Combinations of antihypertensive drugs	
≥ 4 drugs, %	15
3 drugs, %	34
2 drugs, %	35
Monotherapy, %	16
Antidiabetic treatment	
Metformin, %	89
DPP-4 inhibitors, %	32
Sulfonylureas, %	21
Pioglitazone, %	13
Insulin, %	13
Combinations of antidiabetic drugs	
Metfromin + oral antidiabetics, %	46
Metformin monotherapy, %	35
Insulin ± oral antidiabetics, %	13
Oral antidiabetics without metformin, %	6

ARB: angiotensin II receptor blockers; ACE: angiotensin-converting-enzyme inhibitor; DDP-4: dipeptidyl peptidase-4. Antihyperglycemic drug or metformin monotherapy (46% and 35%, respectively).

3.3 Changes in study participant metabolic profile and adverse events

Multifactorial treatment improved overall patient metabolic profile, as shown in Table 3. Significant reductions in TCHOL, TG, LDL-C and non-HDL-C were noted. Also, a small though significant increase in HDL-C was found. SBP

Table 3. Metabolic profile of study participants (mean follow-up equal to 8 years).

	Baseline visit	Last visit
Fasting glucose, mg/dL	134 ± 43	126 ± 32
HbA1c, %[#]	7.8 ± 1.4	7.1 ± 1*
eGFR, mL/kg per 1.73 m^2	74 ± 15	69 ± 16*
AST, U/L	21 (11–344)	22 (9–144)
ALT, U/L	20 (3–201)	20 (6–240)
γGT, U/L	17 (5–142)	17 (5–333)
ALP, U/L	73 (23–210)	58 (23–210)*
CK, U/L	91 (16–485)	95 (20–645)
TC, mg/dL	251 ± 57	173 ± 33*
TG, mg/dL	132 (41–750)	112 (22–405)*
HDL-C, mg/dL	54 ± 13	56 ± 14*
LDL-C, mg/dL	165 ± 49	93 ± 27*
Non-HDL-C, mg/dL	196 ± 55	117 ± 30*
SBP, mmHg	148 ± 19	133 ± 13*
DBP, mmHg	86 ± 13	76 ± 8*

*P < 0.05 for paired comparison; [#]For diabetic patients. Values are expressed as mean ± SD except for non-parametric data which are expressed as median (range). To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol, by 0.01129 for triglycerides and by 0.05549 for glucose. ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; CK: creatine phosphokinase; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; γGT: gamma glutamyltranspetidase; TC: total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non-high density lipoprotein cholesterol; SBP: systolic blood pressure.

and DBP significantly declined by 15 and 10 mmHg, respectively. Finally, HbA1c significantly declined by 0.7% in the diabetic individuals (Table 3).

No significant changes were noticed in liver enzymes, except for a decrease in alkaline phosphatase by 21%. Finally, renal function declined by 5 mL/min per 1.73 m^2 during the 8-year follow-up period (Table 3).

Low rates of adverse events were demonstrated in individuals receiving lipid-lowering treatment; the corresponding rates were 2.3% for myalgias, 1.6% and 0.2% for increase in liver enzymes and CK, respectively. The rates of adverse events for those receiving antihypertensive treatment were 4.8% for leg swelling, 0.7% for hypotension and 0.5% for cough. Finally, 2.2% and 1.0% of those taking antidiabetic therapy experienced hypoglycemia and gastrointestinal disorders, respectively.

3.4 Multifactorial treatment target attainment

Rates of multifactorial treatment goal achievement are thoroughly described in Table 4. Patients at very high CV risk were less likely to achieve optimal LDL-C levels compared with those at high and moderate risk, respectively (27% *vs*. 48% *vs*. 62%, P < 0.05). Individuals on combination treatment with statin + ezetimibe were more likely to achieve optimal levels of LDL-C according to the ESC/EAS guidelines compared with those on statin monotherapy (48% *vs*. 33%, P < 0.05 for the comparison between the two groups). Across CV risk groups, the favourable impact of combination therapy on LDL-C target attainment was most evident in subjects at very high CV risk (the respective rates were 46% *vs*. 23%, P < 0.05). Despite not being significant, a similar trend was noticed in individuals at high (56% *vs*. 52%) and moderate CV risk (92% *vs*. 60%).

Table 4. Rates of multifactorial treatment target attainment at the most recent visit.

Risk factors	Subjects	Treatment targets	Target attainment, %
LDL-C	Very high risk	< 70 mg/dL	27
	High risk	< 100 mg/dL	48*
	Moderate risk	< 115 mg/dL	62*
BP	Non diabetic	< 140/90 mmHg	78
	Diabetic	< 140/85 mmHg	71
HbA1c	Diabetic	< 7%	47

*P < 0.05 for the comparison with patients at very high risk. To convert from mg/dL to mmol/L multiply by 0.02586 for cholesterol. BP: blood pressure; HbA1c: glycated hemoglobin; LDL-C: low density lipoprotein cholesterol.

The rates of BP target attainment in the diabetic patients were similar to those noticed in the individuals without diabetes (Table 4). A higher proportion of the latter group (86%) achieved the less strict BP target < 150/90 mmHg.

Almost half of the patients with diabetes had HbA1c levels < 7%, while a higher proportion had HbA1c < 7.5% or < 8% (68% and 88%, respectively) (Table 4). Higher rates of overall control of CV risk factors were noticed in the non-diabetic subjects compared with those with diabetes. Of the non-diabetic individuals, 28% had optimal LDL-C and BP levels according to the ESC/EAS and ESH/ESC guidelines, while 13% of those diagnosed with diabetes had achieved all proposed LDL-C, BP and HbA1c targets.

4 Discussion

The present analysis shows that a high proportion of the elderly attending a specialist clinic failed to achieve the current targets of the lipid-lowering, antihypertensive and antidiabetic treatment. One out of four patients had optimal LDL-C levels according to the ESC/EAS guidelines, 76% of those diagnosed with hypertension achieved the proposed BP targets by the ESH/ESC, while only half of those with

diabetes had HbA1c < 7%. Finally, almost one out of three non-diabetic individuals and one out of ten diabetic individuals achieved all treatment targets.

4.1 Attainment of multi-factorial treatment targets

Reduction of LDL-C is considered to be the principal goal for the management of dyslipidemias and cardiovascular disease prevention.[1] Nevertheless, the rates of the achievement of these targets are far from optimal in clinical practice.[4,11] Advancing age is a known risk factor for CV disease.[1] Higher than 80% of CHD-related mortality occurs in patients ≥ 65 years of age.[1,12]

It has been demonstrated that the combination treatment of statin plus ezetimibe provides a more effective therapeutic option for LDL-C lowering in the elderly compared with statin monotherapy.[13] In this analysis, individuals receiving statin + ezetimibe achieved higher rates of LDL-C goal achievement compared with those receiving statin monotherapy. Therefore, the additional use of ezetimibe should be considered in the elderly in order to achieve the 'difficult' LDL-C targets proposed by the recent ESC/EAS guidelines.[14] In this context, novel treatment modalities, such as antibodies against PCSK9, are promising therapeutic options on lowering LDL-C in the future.[15]

High BP is a well-established independent risk factor for CV disease and its prevalence increases with age, since more than 60% of individuals older than 65 years old are diagnosed with hypertension.[16] Lowering high BP reduces the CV risk morbidity and mortality.[2] However, a large proportion of hypertensive individuals fail to achieve the proposed BP targets in clinical practice,[6] which is more prominent in the elderly.[17] In a community-based cohort study based on all Framingham Heart Study Examinations attended in the 1990s, the BP control rates (BP < 140/90 mmHg) for male patients aged 60–79 and > 70 years old were 36% and 38%, respectively. The corresponding rates for the females were 28% and 23%, respectively.[17] A similar low rate of BP target attainment (36%) was noticed in hypertensive patients in the Second Australian National Blood Pressure (ANBP2) after taking antihypertensive treatment and followed for a median of 4.1 years.[18] Higher rates were observed in the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial and the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial, where the corresponding rates were 66% and 67%, respectively.[19,20] In our cohort, a higher proportion of hypertensive individuals (76%) had optimal BP levels according to ESH/ESC guidelines. This could be attributed to the fact that these data come from a specialist clinic.

Recent changes in the recommendations for BP targets in the elderly have been an area of discussion.[21] Some studies demonstrated that the BP target < 140/90 mmHg in older individuals might not be more beneficiary compared with a less strict one (< 150/90 mmHg), while the former increases the adverse event risk.[22–24] In addition, it was noticed that the elderly hypertensive patients were more likely to reduce the SBP between 150 mmHg and 140 mmHg, rather than achieve the stricter target of SBP < 140 mmHg.[22–24] In agreement a higher proportion of the non-diabetic patients had BP levels < 150/90 mmHg rather than < 140/90 mmHg in our study. Therefore, the less aggressive lowering of BP is more 'achievable' in the older patients.

It has been estimated that almost one out of three diabetic patients achieve a good glycemic control in the US or Europe.[5,25] In our cohort, a higher but still low proportion of the diabetic subjects (47%) achieved the HbA1c target < 7%.

Professional organizations have recently emphasized on the individualization of the HbA1c targets.[26] The limited, available evidence suggests that a near-normal glycemic target should be achieved in the younger diabetic patients with a relatively recent onset of diabetes to prevent complications.[8,26] Recent trials indicated that higher targets should be considered in the elderly, since intensive glycemic control is not more beneficiary on macrovascular outcomes compared with the standard therapy.[8,26] In our cohort, a higher proportion of diabetic subjects (88%) achieved the HbA1c target < 8%. In this context, a less strict glycemic target could be more easily achieved in clinical practice.

4.2 Strategies confronting poor multi-factorial target attainment

Our results showing suboptimal treatment and CV risk factor control in the elderly are similar to those of older studies.[8,9] In those cohorts 74%–89% of the diabetic patients aged ≥ 65 years had SBP < 140 mmHg, 8%–52% had LDL-C < 100 mg/dL and 76%–83% had HbA1c < 8%.[8,9] The corresponding rates of BP and LDL-C target attainment in those without diabetes were 75% and 55%, respectively.[9] Thus, despite the available modern treatment options, no significant changes in the rates of target achievement in the elderly have occurred over the years. There are several reasons that might account for this poor goal achievement in clinical practice. Firstly, patient adherence to treatment plays a major role.[4,18,26] The advancing age is related with an increased number of concomitant diseases. Therefore, the complexity of the prescribed scheme, such as the increased number of prescribed medications might decrease patient compliance.[27] Thus, patient education and the availability fixed-dose combinations may improve their adherence.[27]

Secondly, the fear of adverse effects and the reluctance of physicians to use the most potent treatments may play a role.[4,18,26] In our cohort the rates of adverse events were low, while no changes were noticed in liver enzymes except for a decrease in alkaline phosphatase by 21%. In addition, considering the expected decline of about 1 mL/min per 1.73 m^2 per year (or 8 mL/min per 1.73 m^2 over the 8-year study period),[4] eGFR declined by 5 mL/min per 1.73 m^2 in our cohort. These results come in agreement with other studies demonstrating that multifactorial treatment, including statin therapy, may have a favourable impact on liver and kidney function.[28,29]

Nevertheless, the most potent therapies were not preferred in our study. High-dose statin treatment was not used, while only 20% of the subjects were receiving combination treatment of statin + ezetimibe. In addition, only half of the diabetic subjects were receiving a combination therapy of oral antidiabetic drugs and 13% were on insulin treatment. Combination therapy with statin + ezetimibe led to higher rates of LDL-C target attainment, while the majority of the elderly were taking combination of antihypertensive drugs to decrease their BP.

In conclusion, even in a setting of a specialist clinic, a high proportion of elderly patients remain at suboptimal LDL-C, BP and HbA1c levels. The use of drug combinations could improve multifactorial target achievement. Less strict targets could be achieved more easily in this population.

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