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ORIGINAL ARTICLE

Treatment with Free Triple Combination Therapy of Atorvastatin, Perindopril, Amlodipine in Hypertensive Patients: A Real-World Population Study in Italy

Valentina Perrone[1] · Chiara Veronesi[1] · Marco Gambera[2] · Giulio Nati[3] · Francesco Perone[4] · Paola Fausta Tagliabue[5] · Luca Degli Esposti[1] · Massimo Volpe[6,7]

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Abstract

Introduction Polytherapy is often required to treat the comorbidity of hypertension and hyperlipidemia. Fixed-dose co-formulation, rather than free combinations, simplifies medication taking and also improves adherence to medication, which is the key for a successful management of these conditions.

Aim To determine the number of patients potentially eligible for treatment with triple fixed-dose atorvastatin/perindopril/amlodipine (CTAPA), and to estimate if an unmet medical need exists among CTAPA free combination treated patients.

Methods This observational retrospective study was based on administrative databases of 3 Italian Local Health Units. The cohort comprised adult patients with at least one prescription of amlodipine and perindopril (either as free combination or co-formulated) and atorvastatin during 2014. Follow-up period started on the date of prescription of the 3 molecules (index date) and lasted 1 year. Adherence to CTAPA was analyzed during follow-up, by using the proportion of days covered (PDC).

Results 2292 patients (9.1 per 10,000 beneficiaries) had a prescription for CTAPA as free combination. Only 1249 (54.5%) were adherent to the therapy (PDC $\geq$ 80%); among them, a small percentage required dosage modification. The number of patients with CTAPA increased during the study period. Discontinuation of drugs prescribed the year before interested 582 patients in 2014, and 522 in 2015. Considering the Italian national population ($n = 60{,}782{,}668$), it was estimated that 69,542 hypertensive patients could be eligible for fixed-dose CTAPA during 2014.

Conclusions Real-world analysis among patients with free combination therapy can be applied to estimate the eligible population for fixed combination, and to evaluate the appropriateness of their prescriptions. Moreover, fixed-dose CTAPA could effectively improve adherence, which was calculated to be low in the free combination cohort.

Keywords Single pill fixed combinations · Atorvastatin/perindopril/amlodipine · Real-world setting

✉ Valentina Perrone
valentina.perrone@clicon.it

1 Health Economics and Outcomes Research, Clicon S.r.l., Via Salara, 36, 48121 Ravenna, Italy

2 Local Pharmaceutical Service, Bergamo Local Health Authority, Bergamo, Italy

3 Italian Society of General Practice, Roma, Italy

4 Local Health Unit, Caserta, Italy

5 General Practitioner of Agenzia di Tutela e Salute della provincia di Bergamo, Bergamo, Italy

6 Division of Cardiology, Department of Clinical and Molecular Medicine, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy

7 IRCCS Neuromed, Pozzilli, Italy

1 Introduction

Cardiovascular diseases (CVD) are the most common cause of death worldwide. The recent World Health Organization (WHO) estimates that 17.7 million people died from CVDs in 2015, representing 31% of all global deaths [1].

Efforts are being extended to investigate ways to optimally manage risk factors for CVD and to improve medical interventions for reducing the clinical burden associated with the development of the disease [2]. High blood pressure and high levels of blood lipids are two of the most commonly co-occurring cardiovascular (CV) risk factors, as they are often present in the same individuals [3]. More than 64% of patients with high blood pressure also have high blood lipid levels, and conversely, almost 47% of patients with high

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lipid levels also have high blood pressure [4]. The combination of hypertension and hyperlipidemia is associated with a higher rate of CV events [5].

Scientific evidence suggests that the combination of blood pressure lowering drugs (angiotensin-converting enzyme (ACE) inhibitor and calcium channel blocker) with a lipid lowering agent (statin) could reduce major CV events such as heart attacks [4, 6, 7].

Patient adherence to medications is vital to ensure the successful treatment of asymptomatic conditions such as hypertension and hypercholesterolemia [8]. In this view single pill fixed combinations simplify medication taking and can definitely improve medication adherence compared with free drug association therapy [9, 10]. In general, it is more likely to achieve better compliance with the use of single-pill formulation especially in patients receiving several drugs due to comorbid conditions. With this approach therapeutic targets are more easily achieved and also the number and daily assumptions of prescribed pills is reduced [11].

We address here the potential need of triple fixed-dose combination of atorvastatin/perindopril/amlodipine (CTAPA), which is used to treat high blood pressure and/or stable coronary artery disease in adults who present elevated cholesterol levels (primary hypercholesterolemia) or combined or mixed hyperlipidemia.

The objectives of the present study were to determine how many patients are eligible for treatment with triple fixed-dose CTAPA (being treated with free combination of the same active ingredients) and to estimate whether there is an unmet medical need among patients in treatment with CTAPA as free combination in an Italian real-world setting.

2 Methods

2.1 Data Source

This was an observational retrospective study based on administrative databases (DBs) of the Local Health Units (LHUs) of three Italian Region (Lombardia, Lazio, Campania) including about 2.5 million health-care assisted subjects. The following DBs were analyzed: Beneficiaries' DB (including patients characteristics), Medication Prescription DB (including data on prescription of drugs reimbursed by the INHS, including the name of the drug, ATC code, dispensing date), Hospital Discharge DB [including primary and secondary diagnoses at hospital discharge coded according to the International Classification of Diseases IX, Revision, Clinical Modification (ICD-9-CM)] and Diagnostic test and Specialist visit DB (including data on outpatient specialist services).

Each patient is identified in the DBs by an anonymous code, which permitted electronic linkage between these DBs. Data were extracted by the staff of the Regions and their databases were anonymized in full compliance with the Italian code of protection of personal data (Legislative Decree 196/03, http://www.camera.it/parlam/leggi/deleghe/03196dl.htm). No identifiers related to patients were provided to the researchers. All the results of the analyses were produced as aggregated summaries, which are not possible to assign, either directly or indirectly, to the individual patients. Informed consent was not required for using encrypted retrospective information. According to the Italian law [12], this study protocol has been notified to the local Ethic Committee of the Region involved in the study and each Region Ethics Committee approved the analysis and the overall study protocol.

2.2 Cohort Definition

All adult patients (≥ 18 years) treated with amlodipine (ATC code C08CA01) and perindopril (alone, ATC code C09AA04, and in combination with indapamide, C09BA04, or amlodipine, C09BB04) and atorvastatin (C10AA05) between 01/01/2014 and 31/12/2014 (inclusion period) were included. Free drug associations of perindopril with indapamide and perindopril with amlodipine were also considered and identified for the presence of the prescription of these drugs at the same time (± 3 months). Index-date was defined as the date (± 3 months) the prescription of the three active ingredients (atorvastatin, perindopril, amlodipine) were detected during the inclusion period. All included patients were characterized during a 12-month period preceding the index-date (characterization period) and followed-up the 12 months after index-date (follow-up period). Patients who moved to another Region during follow-up were excluded from the analysis.

2.3 Variables and Outcomes Definition

Patients were characterized on the basis of demographic characteristics (age, gender), drug prescriptions and hospital admissions. The following drugs were analyzed (at least two prescriptions): antidiabetics (ATC code A10), lipid-lowering agents (ATC code C10), anti-hypertensive agents (ATC codes C02, C03, C07, C08, C09), drugs used in cardiac therapy (ATC code C01); and the following CV-related diseases (both primary and secondary diagnosis at discharge): hypertensive disease (ICD-9-CM codes 401–405), ischemic heart diseases (ICD-9-CM codes 410–414), heart failure (ICD-9-CM code 428), cerebrovascular diseases (ICD-9-CM codes 430–438), peripheral vascular diseases (ICD-9-CM codes 440–442).

Adherence to medications and dosage of drug modification were analyzed during the follow-up period. Treatment adherence was calculated by using the proportion of days

covered (PDC), i.e. the ratio between the number of days of medication supplied and 365 days, multiplied by 100. According to PDC patients were categorized as non-adherent (PDC < 40%), partially adherent (PDC = 40–79%) and totally adherent (PDC ≥ 80%). The variation in drug dosage, as compared to the dosage prescribed at index date, was evaluated only for patients totally adherent (PDC ≥ 80%).

Patients treated with CTAPA were defined in three groups: naïve-patients if they had no prescriptions for CTAPA during the characterization period, patients who continued treatment during the follow-up period, and patients who discontinued the treatment during the follow-up period.

2.4 Statistical Analyses

Continuous variables were reported as mean and standard deviation (SD), whereas categorical variables were expressed as numbers and percentages. All statistical analyses were performed using SPSS Windows version 18.0.

3 Results

A total of 2292 adult patients (9.1 per 10,000 beneficiaries) received free combination of CTAPA. Mean age was 69.3 (± 10.5) years, 56.3% were male. Table 1 illustrates demographic and clinical characteristics of the included patients.

Only 54.5% ($n = 1249$) of patients treated with CTAPA were totally adherent (PDC ≥ 80%) during the follow-up period (Fig. 1), considering both the fixed (already-established) and free (extemporaneous) preparation of perindopril and amlodipine. Analysis of dosage modification was performed only among totally adherent patients ($n = 1249$) and considering the single molecule of atorvastatin and the extemporaneous and fixed combinations of perindopril with indapamide or amlodipine (Table 2). Dose changes were mostly needed in patients treated with atorvastatin (13.1%), followed by those treated with fixed combination of perindopril with amlodipine (11.7%) and fixed combination of perindopril with indapamide (7.8%). In general, a low percentage of patients required a dose change during the follow up period.

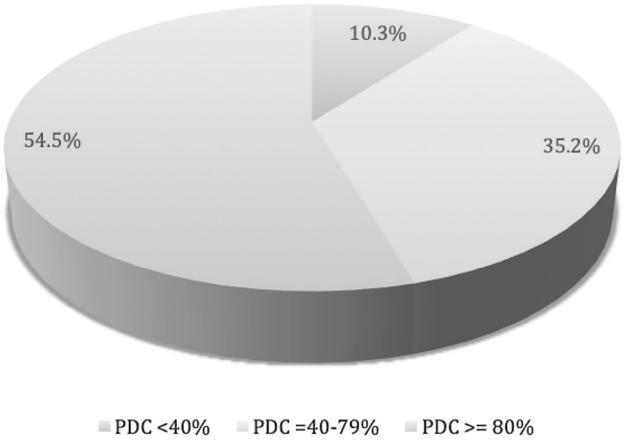

Fig. 1 Treatment adherence according to PDC during follow-up among hypertensive patients treated with the free combination of CTAPA

During the study period (2013–2015), the number of patients in treatment with the free combination of CTAPA increased from 1700 to 2330 (Fig. 2). 1174 patients were naïve to the CTAPA treatment in 2014, whereas in 2015 there were only 819. Among patients treated with free combination of CTAPA in 2014, nearly half (48.8%) continued treatment initiated in 2013. Among patients treated with CTAPA as free combination in 2015, 35.6% continued over the 3-year study period and 28% continued during 2014–2015.

In 2014, 582 patients discontinued treatment initiated in 2013, while in 2015 there were 288 patients who discontinued the treatment initiated in 2013 and 522 patients who discontinued the treatment initiated in 2014. Taking into consideration the Italian population as a whole

Table 1 Baseline characteristics of hypertensive patients treated with the free combination of atorvastatin/perindopril/amlodipine

	Study population $N = 2292$ (100)
Age, mean (sd)	69.3 (10.5)
Male, *n* (%)	1290 (56.3)
Antidiabetic drugs, *n* (%)	784 (34.2)
Lipid-lowering drugs, *n* (%)	1755 (76.6)
Anti-hypertensive drugs, *n* (%)	2134 (93.1)
Cardiovascular agents, *n* (%)	367 (16.0)
Cardiovascular-related diseases, *n* (%)	304 (13.3)
Type of the formulation of combined perindopril and amlodipine	
Fixed (already-established) combination	1962 (85.6)
Free (extemporaneous) combination	330 (14.4)

Table 2 Dosage variation of the different therapeutic strategies for the considered drugs of the triple treatment among adherent patients (1249)

Therapeutic strategies	%
Perindopril + indapamide (free combination)	2.6
Perindopril + amlodipine (free combination)	1.8
Atorvastatin	13.1
Perindopril + indapamide (fixed combination)	7.8
Perindopril + amlodipine (fixed combination)	11.7

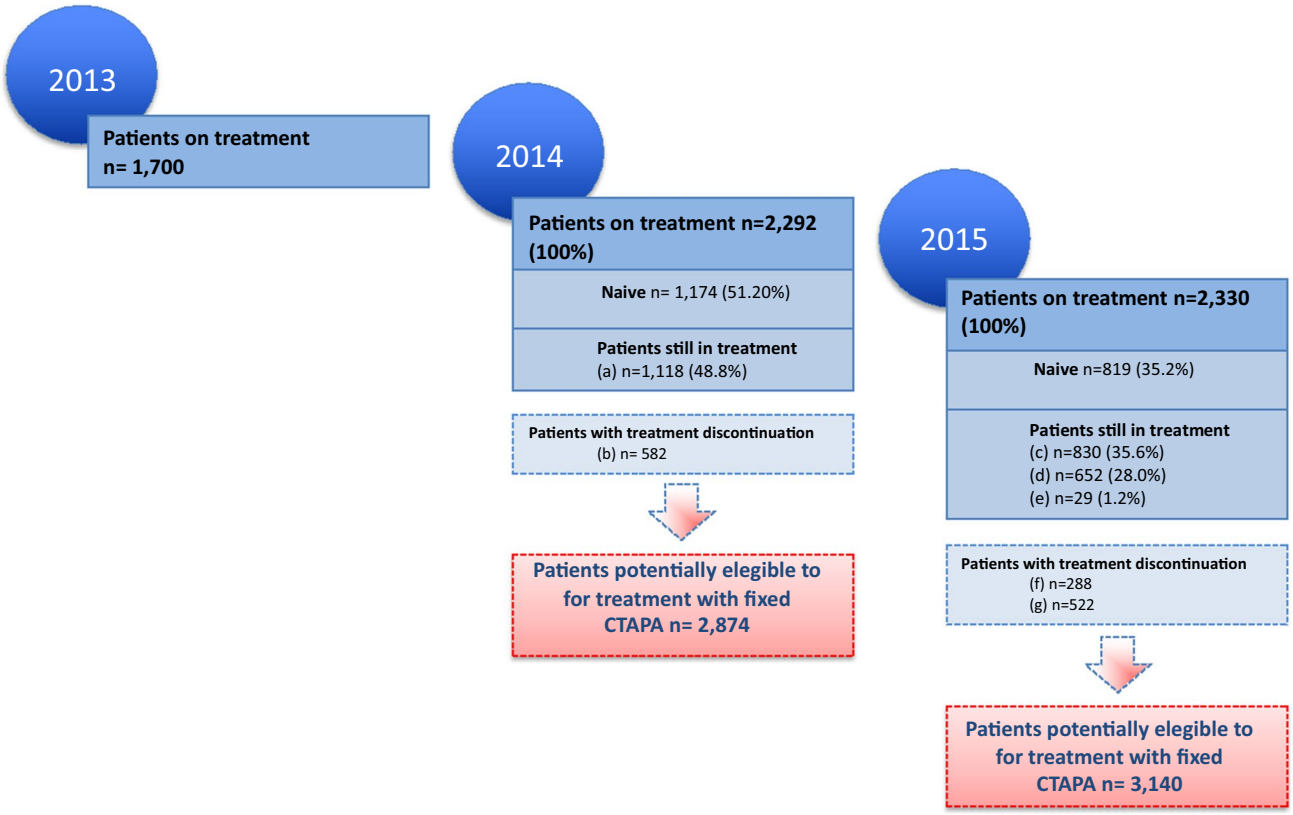

Fig. 2 Prevalence of free combination of CTAPA treatment in hypertensive patients during the individual years of the study period. (a) Patients with triple treatment prescription during 2013 and 2014; (b) Patients with triple treatment prescription during 2013 and without triple treatment prescription during 2014; (c) Patients with triple treatment prescription over the 3-year study period; (d) Patients with triple treatment prescription during 2014 and 2015; (e) Patients with triple treatment prescription during 2013 and 2015; (f) Patients with triple treatment prescription during 2013–2014 and without triple treatment prescription during 2015; (g) Patients with triple treatment prescription during 2014 and without triple treatment prescription during 2015. *CTAPA* fixed combination of atorvastatin/perindopril/amlodipine

($n = 60{,}782{,}668$) [13] and based on the data from this study, we have estimated that 69,542 [as sum of patients who continued treatment ($n = 55{,}459$) plus patients who discontinued treatment ($n = 14{,}083$)] hypertensive patients were potentially eligible for treatment with fixed CTAPA during 2014.

According to data updated to 2018, number of patients potentially eligible for treatment with fixed CTAPA increased year by year, from 2013 to 2018, but with a decreasing rate. According to the last update, first semester 2018 respect to first semester 2017, the annual increase of patients potentially eligible for treatment with fixed CTAPA was approximately 3.4%.

Estimates of the growing number of patients potentially eligible for treatment with fixed CTAPA in the coming years should take into account the trend of annual increase at a decreasing rate observed over the past years.

Consequently, considering most recent years, the annual increase of patients potentially eligible for treatment with fixed CTAPA was negligible.

4 Discussion

In the present investigation a cohort of patients in treatment with free CTAPA were retrospectively analyzed to determine how many patients are potentially eligible for treatment with triple fixed-dose combination of the same active drugs and to estimate if there is an unmet medical need among patients in treatment with atorvastatin/perindopril/amlodipine as free combination in an Italian real-world setting.

This retrospective analysis in an unselected Italian population under clinical practice setting showed that 2292 patients (9.1 per 10,000 beneficiaries) were in treatment with CTAPA as free combination.

Patients with coexisting moderate hypertension and moderate dyslipidemia increase the risk of developing CV events more than patients with isolated marked elevations in blood pressure or cholesterol levels alone. Appropriate control is associated with a proportional reduction of CV death, stroke and non-fatal heart failure. Calcium channel blockers and ACE inhibitors in combination

and the use of statins are recommended for hypertensive patients in current guidelines based on published data [11].

Studies based on real-world data showed that in an Italian setting the percentage of patients treated appropriately with antihypertensive or lipid-lowering drugs is at least sub-optimal [14–17]. We found that the percentage of patients adherent (proportion of days covered ≥ 80%) was 54.5% ($n = 1249$). Our findings are also consistent with previous investigations [12] that demonstrated a significant proportion of patients discontinued the pharmacological treatment prescribed, already in the first year after the beginning of the treatment. Indeed, in 2014, 582 patients discontinued treatment initiated in 2013. From our results, considering the Italian national population ($n = 60{,}782{,}668$), we estimated that 69,542 (as sum of patient who continued treatment ($n = 55{,}459$) plus patients who discontinued treatment ($n = 14{,}083$) hypertensive patients were potentially eligible for treatment with fixed CTAPA during 2014.

The literature data show that a fixed association of antihypertensive treatments and lipid metabolism control has a significant clinical relevance in terms of reaching target levels, suggested by current guidelines, both for arterial hypertension that for LDL cholesterol [11]. It is well documented in the literature that greater adherence to treatment is linked with a lower incidence of major CV events [18]. The combination of two or more active principles in a fixed dose combination drugs could improve both qualitatively and quantitatively the prescription appropriateness in primary and secondary prevention, as well as improving the levels of adherence to therapy over time [19–22].

In this context, an improved communication between patients and clinicians and the use of combined therapies may substantially increase the adherence rates to pharmacological treatment of hypertension and hypercholesterolemia.

5 Conclusions

Free combination of CTAPA were prescribed to 9.1 per 10,000 beneficiaries during 2014 and only 54.5% of them were adherent to the treatment. Dosage modification was needed in less than 15% of the study cohort. Considering the Italian population, 69,542 hypertensive patients were potentially eligible for treatment with fixed CTAPA during 2014.

Real-world analysis of patients using free combinations appears to be a useful tool to estimate potentially eligible population for fixed combination and also the appropriateness of their prescriptions. Given the observed low adherence to free combination CTAPA, the use of fixed combination could provide an opportunity to improve adherence.

Compliance with Ethical Standards

Conflict of interest Manuscript development was supported by unconditional funding from Servier. MV received honoraria for speaking bureau or scientific consulting Servier.

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