Adv Ther (2023) 40:1765–1772
https://doi.org/10.1007/s12325-023-02451-y

ORIGINAL RESEARCH

Adherence to Triple Single-Pill Combination of Perindopril/Indapamide/Amlodipine: Findings from Real-World Analysis in Italy

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Received: November 30, 2022 / Accepted: February 1, 2023 / Published online: February 24, 2023

ABSTRACT

Introduction: Single-pill combination therapy for hypertension is recognized to improve adherence to treatment. However, less is known about the benefits of triple single-pill combinations. This retrospective observational analysis aimed to assess changes in adherence when treatment was switched from perindopril (PER)/indapamide (IND) + amlodipine (AML) to PER/IND/AML single-pill combination, in Italian clinical practice.

Methods: This analysis used data extracted from administrative databases of Italian healthcare entities. Adult patients receiving PER/IND/AML were selected, and the prescription date was considered as the index date. Among them, those who had a prescription for PER/IND + AML during the 12 months before the index date and a prescription of PER/IND/AML during 6 months of follow-up were included. Adherence was calculated as the proportion of days covered (PDC: PDC < 40%, non-adherent; PDC = 40–79%, partially adherent; PDC ≥ 80%, adherent).

Results: Among the identified patients, 158 were exposed users and were included in the analysis. When patients were compared before and after switch to triple single-pill combination, the proportion of adherent patients was significantly higher with PER/IND/AML single-pill combination (75.3%) than with PER/IND + AML combination (44.3%) ($P < 0.05$). Conversely, the proportion of non-adherent patients was lower with the PER/IND/AML single-pill combination (14.6%) vs PER/IND + AML (17.7%) ($P < 0.001$).

Conclusion: This real-world analysis showed that switching to a triple single-pill combination could offer an opportunity to improve adherence to antihypertensive treatment in real-life clinical practice.

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PLAIN LANGUAGE SUMMARY

Medication adherence is defined by the World Health Organization as the "extent to which a person's behavior (in taking medication) corresponds with agreed recommendations from a healthcare provider". Low levels of medication adherence in hypertension have been linked with increased disease burden and with higher costs for patients. Patients with hypertension whose blood pressure is poorly controlled often need to receive more than one pill. Nevertheless, having to take many pills may result in poor adherence, i.e., patients not taking their treatment as prescribed. Combining multiple drugs into a single pill for the management of hypertension is known to improve adherence; however, limited evidence exists about the benefits of triple single-pill combinations compared with equivalent free combinations in real clinical practice. This analysis evaluated changes in adherence before and after patients switched from a three-drug therapy of perindopril/indapamide single-pill + amlodipine (PER/IND + AML) to perindopril/indapamide/amlodipine (PER/IND/AML) taken as a single pill. In this analysis, real-world data from Italian administrative databases covering around 11% of the Italian population were used. Overall, 158 patients were included. More patients were found to be adherent after switch to PER/IND/AML single pill (75.3% vs 44.3% of PER/IND + AML combination). Partially adherent and poorly adherent patients were fewer with PER/IND/AML single-pill combination (10.1% and 14.6%, respectively) compared to PER/IND + AML combination (38.0% and 17.7%, respectively). These findings indicate that switching to a simplified therapy in which all three drugs are taken in one pill may offer an opportunity for increasing the number of patients that are adherent to their medication.

Keywords: Hypertension; Adherence; Perindopril; Indapamide; Amlodipine; Triple single-pill combination therapy

Key Summary Points

Why carry out this study?

Many patients with hypertension do not attain blood pressure control on two antihypertensive agents and require additional medication.

To reduce the pill burden and improve adherence, triple single-pill combinations are available, but data on their benefits compared with equivalent free combinations outside the clinical trial setting are limited.

This real-world analysis used data from Italian administrative health databases to evaluate changes in adherence when treatment was switched from a three-drug therapy comprising perindopril/indapamide single-pill + amlodipine (PER/IND + AML) to a PER/IND/AML single-pill formulation.

What was learned from the study?

The proportion of fully adherent patients was significantly higher with the PER/IND/AML single-pill compared with the PER/IND + AML combination.

Simplifying the antihypertensive treatment regimen by using a triple single-pill combination may offer an opportunity to improve adherence in real-life clinical practice.

INTRODUCTION

The control of cardiovascular (CV) risk factors, particularly arterial hypertension, and the achievement of the related therapeutic goals are key factors in the treatment of CV conditions. Poor control of hypertension leads to progressive target organ damage and impacts on CV mortality. Real-world studies indicate that, in Italy, only 30–40% of patients undergoing

pharmacological treatment are adequately controlled [1]. Suboptimal adherence to antihypertensive treatment is an important cause of poor blood pressure control [2]. Moreover, poor adherence is associated with increased risk of CV events, comorbidities and mortality, and increased healthcare resource consumption and related costs [3]. Therefore, efforts directed at improving adherence should be recognized as an integral part of hypertension management. Pill burden may affect medication adherence, as it has been reported that increasing the number of antihypertensive medications is associated with a higher rate of nonadherence [3]. In this context, we have conducted a real-world analysis to evaluate changes in adherence when treatment was switched from perindopril/indapamide single-pill + amlodipine (PER/IND + AML) to PER/IND/AML single-pill formulation, in Italian clinical practice.

METHODS

This observational retrospective analysis used the administrative databases (demographic, pharmaceutical, hospitalization, and outpatient service databases) of a sample of local health units (LHU) covering around 11% of the Italian population. These databases store all data concerning the healthcare resources reimbursed by the Italian National Health Service (INHS). All adult patients (at least 18 years of age) treated with PER/IND/AML as single-pill combination during the study period (2010 to 2020) were screened for eligibility in the study. The date of first detection for this prescription was defined as the index date. Exposed users, defined as those receiving PER/IND + AML combination during 12 months before the index date, were included in the study (Fig. 1). All these patients had data available from at least 1 year before the index date (characterization period) to 6 months afterwards (follow-up). Patients were excluded if they moved to another region or died during the 6 months of follow-up. Adherence was evaluated as proportion of days covered (PDC), i.e., the ratio between the number of days of medication supplied and days of observation, multiplied by 100, by using the following cutoffs: PDC < 40% (non-adherent); PDC = 40–79% (partially adherent); PDC ≥ 80% (adherent). PDC is considered as one of the most reliable methods to measure adherence in chronic therapies, and these cutoffs are widely used in the literature to evaluate levels of adherence [4, 5]. Adherence to PER/IND + AML combination was calculated as the number of days covered by all three drugs (in two tablets) in the 6 months prior to the index date, and adherence to PER/IND/AML single-pill combination was calculated as the days covered by single-pill combination in the 6 months after the index date. Statistical significance was defined as $P < 0.05$. All analyses were performed using Stata SE version 12.0 (StataCorp, College Station, TX, USA).

Ethics Statement

To guarantee patients' privacy, an anonymous univocal numerical code was assigned to each subject included in the study, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). This code allowed the electronic linkage between all different databases. No identifiers related to patients were provided to the authors. All the results of the analyses were produced as aggregated summaries, which are not possible to assign, either directly or indirectly, to individual patients. Informed consent was not required (pronouncement of the Data Privacy Guarantor Authority, General Authorization for personal data treatment for scientific research purposes – no. 9/2014), and the LHU ethics committees approved the study.

RESULTS

In this analysis, of the 50,679 patients with PER/IND/AML single-pill formulation identified, only 158 were exposed users and were included in the analysis. Exposed users were defined as those receiving a prescription for PER/IND + AML during the 12 months before the index date (i.e., PER/IND/AML single-pill prescription date and 6 months of follow-up period with PER/IND/AML. Mean age was 67.9 years, and

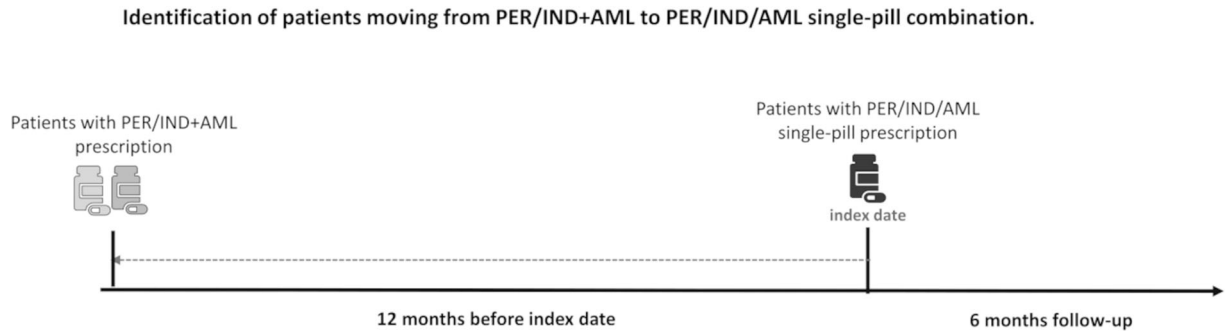

Fig. 1 Study design

most patients (65.8%) were in the age range of 60–79 years; male patients accounted for 63.9%. Other antihypertensive treatments were previously prescribed to 59.5% of patients, and lipid-lowering agents to 55.7%, most of which were statins.

The proportion of adherent patients was significantly higher with PER/IND/AML single-pill combination than with PER/IND + AML combination (75.3% vs 44.3%, P value < 0.05) (Fig. 2). Partially adherent patients were detected more often while on PER/IND + AML (38.0%) than on single-pill combination (10.1%) ($P < 0.001$), while the proportion of poorly adherent patients was lower with the single-pill combination (14.6%) vs PER/IND + AML (17.7%) ($P < 0.001$).

DISCUSSION

Suboptimal adherence strongly contributes to poor blood pressure control [6, 7]. However, in the real word, in ambulatory patients with multiple diseases who are often treated with multiple drugs, suboptimal adherence is still highly prevalent [8], and only half of patients with hypertension persist with their treatment after 1 year [7]. It has been reported that biochemically confirmed non-adherence increases with the number of drugs taken, and in one study of 1348 patients with hypertension from

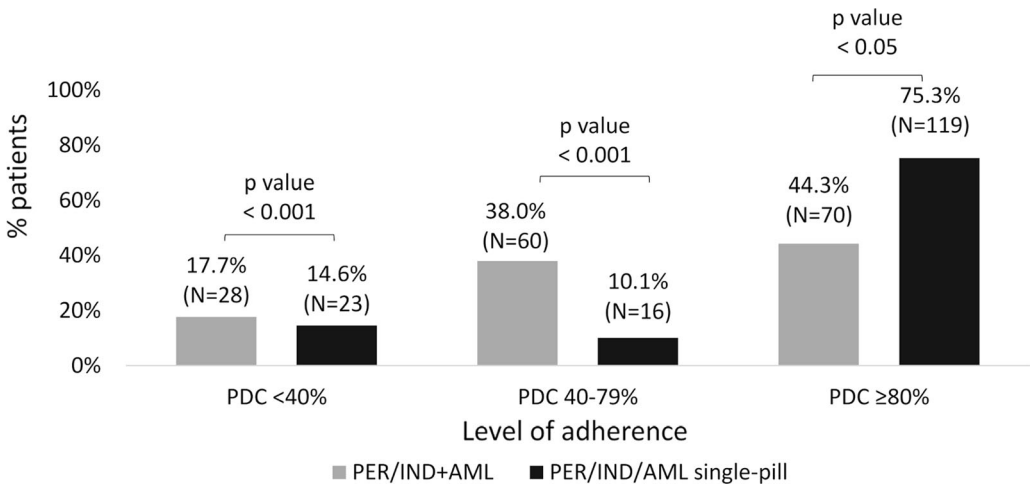

Fig. 2 Adherence before and after switching from PER/IND + AML to PER/IND/AML single-pill combination. The prescription of PER/IND + AML and PER/IND/AML single-pill combination was identified by using Anatomical Therapeutic Chemical (ATC) codes C09BA04b + C08CA01, and C09BX01, respectively

two European countries, non-adherence was detected in 79.3% of patients treated with six drugs or more [8].

Hence, regimen simplification represents one of the strategies to pursue the improvement of adherence to antihypertensive medication. A recent meta-analysis of studies that measured adherence to antihypertensive medication (including randomized controlled trials, observational studies, and retrospective database analyses) reported that in 78% of studies, adherence significantly improved in patients receiving single-pill combinations versus free equivalent combinations [2]. Furthermore, 88% of the studies showed that patients receiving single-pill combinations had significantly improved persistence or were significantly less likely to discontinue therapy than patients receiving a free combination. There were also significantly greater reductions in blood pressure with the single-pill combination, suggesting that the improved adherence associated with the simplified regimen had led to better blood pressure control.

Adherence in clinical practice can differ markedly from the clinical trial setting and retrospective analyses are an accepted way to assess adherence in routine clinical practice [9]. Selecting an optimal antihypertensive regimen can be difficult given the multiple options available. It is therefore important to examine the relative clinical effectiveness of different drug classes and their combinations in the real-world setting, particularly as patient profiles often differ from those included in trials. The wide accessibility of healthcare utilization databases in electronic format, such as used in the current study, has greatly simplified this process and confirmed the benefits of single-pill combination therapy for improving adherence [9].

Consequently, the World Health Organization (WHO) recommends single-pill combinations as the emerging best practice for safe, effective, rapid, and convenient hypertension control, and single-pill combination antihypertensive medications have been added to the WHO essential medicines list [10]. Additionally, all recent guidelines place strong emphasis on the issue of non-adherence, notably by recommending single-pill combination therapy as the preferred strategy for initial two-drug combination treatment and the preferred use of single-pill combination therapy for most patients [11, 12]. In addition, it was observed that patients treated with three antihypertensive agents or more generally have more associated comorbidities and advanced disease [13]. Thus, their pill burden will be high, making adherence to all prescribed treatments even more challenging. The better adherence associated with single-pill combination therapy might be of particular interest in the case of polypharmacy regimens, e.g., in those presenting with several comorbid conditions requiring different associated treatments and in the elderly [2, 14]. This group of patients (elderly or with a multimorbid profile) are generally underrepresented in randomized clinical trials conducted worldwide.

However, data on triple single-pill combination treatment are limited, with a lack of direct comparisons between regimens and on the potential benefits of triple single-pill combinations versus the same free combination. The efficacy of the switch to the triple PER/IND/AML single-pill combination in patients with hypertension was demonstrated in the real-world PETRA study [15].

A recent observational study conducted in a real-life clinical setting found high adherence (a primary endpoint of this study) to treatment with the PER/IND/AML single-pill combination [16]. The simplification of the antihypertensive drug regimen by administration of one instead of three different pills, the rapid achievement of target blood pressure levels, and the low incidence of adverse events may explain the high levels of adherence observed. Similarly, in patients with grade 2–3 hypertension and high or very high cardiovascular risk who did not reach blood pressure target when using the free combination of PER, IND, and AML, there was an improvement in adherence when single-pill combination therapy was used.

Our results, reporting a significantly higher proportion of adherent patients after switching from a multiple-pill to a triple single-pill combination of PER/IND/AML, are in line with these findings.

The main limitation of the analysis is the small number of exposed patients included. A further limitation is the lack of data on factors that could have affected the level of medication adherence (i.e., social, economic, or clinical factors) not reported in the administrative database, as well as data on blood pressure level, which are not present within the databases. Furthermore, to calculate adherence, we have assumed that a patient takes one pill per day, as it is not possible to retrieve information on the actual intake of the patient from administrative databases. A strength of this study is the unselected population represented in real-life settings.

CONCLUSION

Switching to a triple single-pill combination could offer an opportunity to improve adherence to antihypertensive treatment in real-life clinical practice.

ACKNOWLEDGEMENTS

Funding. Open access funding provided by Alma Mater Studiorum - Università di Bologna within the CRUI-CARE Agreement. The study report was developed by Clicon S.r.l. Società Benefit and funded by Servier, France. The journal's Rapid Service and Open Access Fees was funded by Servier, France.

Medical Writing and Editorial Assistance. Medical writing assistance was provided by Melania Dovizio of Clicon S.r.l. Società Benefit and funded by Servier, France.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICJME) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and are accountable for the accuracy and integrity of the manuscript.

Disclosures. Claudio Borghi has received consultation fees and lecture honoraria from Servier, Novartis, Menarini Corporate, Novo Nordisk, Alfasigma, Sanofi. Pathiyil Balagopalan Jayagopal declares no conflict of interest. Alexandra Konradi: lecture honoraria from Servier, Novartis, Novo Nordisk, KRKA. Luiz Aparecido Bortolotto declares Advisory board member for Servier, Medtronics and Merck. Jacques R. Snyman has received consultation fees and lecture honoraria from Servier, Novartis, Novo Nordisk, Boehringer Ingelheim, Merck, AbbVie. Valentina Perrone and Luca Degli Esposti declare no conflict of interest.

Compliance with Ethics Guidelines. Informed consent was not required (pronouncement of the Data Privacy Guarantor Authority, General Authorization for personal data treatment for scientific research purposes – n.9/2014), and the LHU ethics committees approved the study: Comitato etico interprovinciale Area I (protocol number 63/CE/20 and 68/CE/20, approval date 3/12/2020); Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza (protocol number 1627, approval date 28/10/2020); Comitato Etico "Lazio 2" (protocol number 0179046/2020, approval date 28/10/2020); Comitato Etico Inter-aziendale Campania Sud (protocol number 51, approval date 02/09/2020 and protocol number 64, approval date 03/11/2020); Comitato Etico "Lazio 1" (protocol number 1166/CE Lazio 1, approval date 12/10/2020 and protocol number 1079/CE Lazio 1, approval date 23/09/2020); Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S.Camillo (approval date 28/07/2020); Comitato Etico per le province di L'Aquila e Teramo (protocol number 11, approval date 24/03/2021); Comitato Etico Regionale Umbria (protocol number 19414/20/ON, approval date 16/09/2020); Autorizzazione CE Imperia Comitato Etico Regionale della Regione Liguria (protocol number 024/2019, approval date 17/06/2019). This study was

performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The data sets generated and/or analyzed for this study are not publicly available as they include medical records of patients from a secondary source.

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