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Adherence to Triple-Free-Drug Combination Therapies among Patients with Cardiovascular Disease

Running head: Adherence to triple free drug combination therapies in primary care

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Abstract

Combination therapies are often needed to modify the concomitant risk factors for cardiovascular disease (CVD). Non-adherence to cardiovascular medications is a relevant concern, especially in polytherapy. We conducted a population-based, cohort study with the aim of quantifying the level of non-adherence and its related determinants in patients exposed to free three-drug combination therapies, namely concurrent use of angiotensin-converting-enzyme inhibitor (ACEi), calcium channel blockers (CCBs), and statins or of ACEi, statins, and low-dose aspirin. Within Health Search Database, we selected a cohort of adult patients concurrently prescribed with ACEi, CCBs, and statin, as well as those prescribed with ACEi, statins and low-dose aspirin, from the 1st January 2002 to the 31st December 2014. Non-adherent patients were concurrent users of triple free pill regimen with a proportion of days covered (PDC) <80% during 1-year follow-up; demographics and clinical determinants of 1-year non-adherence were identified by multivariate logistic regression. We found that more than half of patients prescribed with triple free drug combination therapy with ACEi plus CCB plus statins or ACEi plus statins plus low-dose aspirin, were found to be non-adherent to these treatments. Males and patients at high/very-high cardiovascular risk were more likely to be adherent, while depression and atrial fibrillation were associated with non-adherence. Our findings indicate that sex, cardiovascular risk, presence of atrial fibrillation and depression can influence adherence to polytherapy. In conclusion, given that patients suffering from multiple cardiovascular risk factors are at higher risk of fatal events, strategies are needed to improve medication adherence to combination therapies.

Keywords: Polytherapy; adherence; cardiovascular disease; primary health care

Introduction

Cardiovascular diseases (CVD) are the major cause of disability and death in Western countries, and their related epidemiological burden is also growing in developing countries.¹ CVD continues to be a global epidemic, as obesity, sedentary lifestyle and diabetes mellitus are becoming increasingly common. Furthermore, the underuse of cardiovascular medications is still a relevant concern.² All these issues need to be considered in the light of the growing aging of population. Namely, more than 60% of older adults suffer from at least two or more chronic diseases. Among them, CVD were the most common conditions.³ In this context, the cardiovascular triple free pill combination therapy has already demonstrated its effectiveness in preventing CVD acting on different and concomitant risk factors, such as hypertension, hyperlipidemia and/or platelets aggregation.^{4,5} However, regimen complexity is known to contribute to poor adherence.⁶ One of the biggest lacks of clarity on multiple-pill use for CVD prevention is associated to the poor knowledge of demographic and clinical determinants related to non-adherence. Given this background, this study was conducted to assess adherence levels in patients treated with triple free drug combinations, namely angiotensin-converting-enzyme inhibitor (ACEi) plus calcium channel blocker (CCB) plus statins and ACEi plus statins plus low-dose aspirin and to identify the determinants of non-adherence to these combination therapies.

Methods

We used the Health Search Database (HSD), a longitudinal observational database established in 1998 by the Italian College of General Practitioners and Primary Care, containing the electronic patient records from approximately 1,000 general practitioners (GPs) homogeneously distributed across Italy. Computer-based patient records collected by a selected group of 800 GPs, who met standard quality criteria regarding the levels of data entry (i.e. levels of coding, prevalence of selected diseases, rates of mortality, and years of recording), were included in the present study. These GPs covered almost 1 million patients, and were geographically distributed to include patients representative of the whole Italian population and to ensure the completeness and consistency of medical records. Records consisted of demographic details; medical information, such as diagnoses, drugs and diagnostic test prescriptions; specialist referrals; life-style characteristics and all-cause mortality. These data were linked through a unique anonymous code. All diagnoses were coded

according to the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM). To complement the coded diagnoses, GPs are enabled to add free text. Information on drug prescriptions includes the name of the prescribed drug (i.e., active substance and/or brand name), the dosage instruction (i.e. the Prescribed Daily Dosage: PDD) the correspondent Anatomical Therapeutic Chemical (ATC) code along with the related Defined daily dose (DDD), the date of prescription, and number of days' supply. The ATC/DDD is a validated classification system from the World Health Organization (WHO), considered the standard reference for coding medications in several countries. Every prescription was associated with specific diagnoses (i.e. indication of use). A number of epidemiological studies have been conducted using HSD.^{7,8} Furthermore, HSD collaborates with other databases under the principles of the European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)⁹.

We formed two study cohorts identifying all patients aged 18 years or older, prescribed with free combinations of ACEi (ATC codes: C09A*; C09BB*) plus CCB (ATC codes: C08*) plus statin (ATC codes: C10A*), or ACEi plus statin plus low-dose aspirin (ATC: B01AC06), from the 1st January 2002 to the 31st December 2014. For each medication class, we adopted PDD to identify the related dosages. As such, the overall prescribed amount (i.e. in mgs) was divided by the related PDD to provide duration (days) for each prescription. For the identification of triple free pill users eligible for calculation of adherence, an overlapping prescription was operationally defined as a prescription for 1 of the 3 components before or on the run-out date (prescription date plus days of supply) of the other 2 components. When fixed combinations were identified, an overlapping prescription was operationally defined as a prescription for 1 of the 2 components (including a fixed combination) before or on the run-out date (prescription date plus days of supply) of the other components.¹⁰ A patient was therefore considered exposed to triple free pill regimen whenever the concurrent use of the three components covered a minimum period of 60 days.¹¹ The start date of this 60-day period was defined as the study *index date*. Patients were followed up until the occurrence of one of the following events (whichever came first): death, end of the first year of follow-up, end of registration data with his/her GPs, end of data availability (31st December 2015). Patients with less than 1-year follow-up were excluded.

Adherence to triple free drug combination was calculated as proportion of days covered (PDC), which is obtained by dividing the cumulative days of medications use by the length of follow up. A PDC <80% was adopted to define patients as non-adherent to three-pill regimen. To identify the determinants of non-adherence to triple free drug combination therapy, patients' characteristics were assessed before or on the index date. Namely, we used the cardiovascular risk staging defined as mean/moderate (<5%), high ($\geq 5\%$ and <10%), and very high risk ($\geq 10\%$) according to the SCORE algorithm.¹² This method adopts a Weibull model which includes the patient's age, total cholesterol (TC), blood pressure (BP) and smoking, in women and men taken separately. The TC and BP values were defined in the year preceding the *index date*. The last registration of smoking habits was identified in the entire available period preceding the *index date*. The former smokers were considered as non-smokers. The SCORE algorithm was applied to patients in primary prevention, such as those with no prior cardiovascular event or other related conditions. Furthermore, patients with high cardiovascular risk were identified considering the following variables: i) type 2 diabetes with no complications, neither other cardiovascular risk factors such as low-density lipoprotein cholesterol (LDL-C) >130 mg/dL, current smoking, obesity (ICD-9-CM codes or body mass index ≥ 30 kg/m² (last measurement in year preceding or on the entry date or the registration of ICD-9-CM codes)); ii) metabolic syndrome; iii) familial hypercholesterolemia (ICD-9-CM codes coupled with the term familiar * in the code description); iv) other familial dyslipidemia (ICD-9-CM codes coupled with the term familiar*); v) hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg being registered in the year preceding or on the entry date); vi) moderate chronic kidney failure (glomerular filtration rate [GFR] ranging 30-59 mL/min/1.73 m² (last measurement before or on the entry date)). Patients with very-high cardiovascular risk were identified considering the presence of previous cardiovascular events (i.e. stroke, ischemic cardiomyopathy, peripheral vascular diseases, coronary bypass recorded by ICD-9-CM codes during 12 months before or on the index date), severe chronic kidney failure (GFR ranging ≤ 29 mL/min/1.73 m²) including dialysis and/or renal transplantation or free text "dialysis" or "renal transplant", and type 2 diabetes with complications or other cardiovascular risk factors such as LDL-C >130 mg/dL, current smoking, obesity (last measurement in year preceding or on the entry date and or the registration of ICD-9-CM codes). Other

comorbidities examined as candidate determinants included diagnosis of heart failure; atrial fibrillation; and depression; being recorded by ICD-9-CM codes in the entire period preceding or on the index date.

We performed descriptive statistics for continuous (mean (SD)), median (IQR) and categorical values (N and (%)). Univariate and multivariate logistic regressions were used to evaluate candidate determinants of non-adherence. Odds Ratio (OR) and related 95% Confidence Intervals (95% CI) were the measure of association. The selection of determinants was conducted using a stepwise approach according to a backward selection method by setting *p-values* to 0.10 and 0.15 for entering and exiting variables, respectively.

We conducted three sensitivity analyses to verify the robustness of the results. Firstly, the overlaps criteria and gaps (i.e. “grace period”) between two prescribing cycles were varied from 60 to 90 and 30 days. Secondly, considering the effect of socio-economic conditions on medication adherence, we adopted the official estimates of the Italian National Institute of Statistics (ISTAT) on the average salary (hourly rate, €) which is provided by ISTAT according age class (15-29; 30-49; ≥50), gender and geographic location (north-west, north-east, central, south and Island), to infer the effect of economic conditions on medications adherence¹³. Thirdly, in order to evaluate a possible association between medication adherence to ACEi/CCBs/statins and ACEi/statins/low-dose aspirin combination therapies, we adjusted the model for the year of index date.

All statistical analyses were performed using the software STATA version 13 (Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). This was a retrospective observational study, for which the approval by the Ethics Committee is not required (GU n. 76 March 31, 2008). All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

Overall, we identified 6,302 patients exposed to triple free drug combinations of ACEi plus CCBs plus statins (2.7%; among patients being prescribed with at least one of the medications forming the combination, n= 235,138) and 15,918 (6.7%; among patients being prescribed with at least one of the medications forming the combination, n= 237,892) patients exposed to triple free drug

combinations of ACEi plus CCBs plus statins and ACEi plus statin plus low-dose aspirin, respectively (**Table 1**). Most of them (>55%) were male and older than 45 years. Patients prescribed with ACEi/CCBs/statins were a little older than patients prescribed with ACEi/statins/low-dose aspirin. On average, patients reached the two different triple free drug combinations after 3.9 and 3.2 years, cumulating 314.5 (± 352.3) and 294.1 (± 307.4) days of exposure, respectively. As shown by SDs values, duration of use was featured by high variability.

Among patients eligible to calculation of adherence, 6,176 and 15,600 patients were exposed to ACEi/CCBs/statins and ACEi/statins/low-dose aspirin, respectively, with comparable characteristics in terms of sex and age (**Table 2**). Overall, 52.1% and 50.6% of patients were non-adherent to triple free combination therapy for ACEi/CCBs/statins and ACEi/statins/low-dose aspirin, respectively. On average, patients cumulated 257.9 (± 102.0) and 263.8 (± 96.5) days of exposure, for ACEi/CCBs/statins and ACEi/statins/low-dose aspirin use, respectively. In this context, we observed a high variability in terms of duration of use. For what concerns the concurrent treatments, 39.2% and 32.9% were those patients prescribed with more than five medications in ACEi/CCBs/statins and ACEi/statins/low-dose aspirin group, respectively. In particular, regarding ACEi/CCBs/statins group, 43.1% (95% CI 41.3 – 44.8) of non-adherent and 35.3% (95% CI 33.5 – 36.9) of adherent patients were prescribed with more than five medications. Similarly, considering non-adherent patients to ACEi/statins/low-dose aspirin combination, 36% (95% CI 34.95 – 37.1) and 29.9% (95% CI 28.9 – 30.9) of them resulted co-exposed with more than five medication. For what concerns the average number of pills being prescribed besides triple free drug combinations, 1,416.9 pills per year (95% CI 1,393 – 1,440.8) and 1,308.7 pills per year [95% CI 1,294.3 – 1,323.0) were prescribed in addition to ACEi/CCBs/statins and ACEi/statins/low-dose aspirin combination, respectively. Based on 95% CIs overlaps, no difference was found considering adherent and non-adherent patients exposed to ACEi/CCBs/statins (Non-adherent: 1,402.8 (95% CI 1,368.9 – 1,436.6) vs. Adherent: 1432.3 (95% CI 1,398.5 – 1,465.9)) and ACEi/statins/low-dose aspirin ((Non-adherent: 1,306.3 (95% CI 1,285.8 – 1,326.7) vs. Adherent: 1,311.2 (95% CI 1,290.9– 1,331.4)). There was no substantial difference between ACEi/CCBs/statins and ACEi/statins/low-dose aspirin group in terms of patients' clinical characteristics. Namely, patients were similarly distributed across CV risk strata, with the highest percentage in very-high cardiovascular risk (70.1% vs. 73.4%). Differently, a slightly higher

prevalence was observed for atrial fibrillation (6.4% vs. 4.5%) and depression (7.3% vs. 6.8%) in ACEi/CCBs/statins compared to ACEi/statins/low-dose aspirin.

Table 3 reported predictors of adherence to triple free drug combination therapy being investigated through ACEi/CCBs/statins group. In particular, males resulted significantly more adherent than females (greater than 27%), while no relation was found considering age. High and very-high cardiovascular risk were significantly associated with greater adherence ((high risk: OR: 1.35 95% CI (1.06 - 1.72); very-high risk: OR: 1.34 95% CI (1.06 - 1.68)). Similar results were obtained for the other triple free drug combination (ACEi/statins/low-dose aspirin). In addition, these patients resulted significantly less adherent when suffering from atrial fibrillation (lower than 18%) and depression (lower than 15%) (**Table 4**).

The results of sensitivity analysis, considering two different time-windows criteria to define overlaps and gaps between two prescribing cycles (i.e. from 60 to 90 and 30 days), showed no substantial difference from the primary analyses. As expected, the results indicated a longer and shorter duration of concurrent medications use adopting 30- and 90-day time-windows, respectively (**Supplementary Table 1 and Table 2**). In the second sensitivity analysis, evaluating predictors of adherence to triple free drug combinations for ACEi/CCBs/statins, we found that a 1-unit (1 €) increase for the hourly rate was significantly associated with greater adherence (OR: 1.14 95% CI (1.08 - 1.19)). A similar trend was obtained for the other triple free drug combination (ACEi/statins/low-dose aspirin) although we found a non-significant association ((OR: 1.07 95% CI (0.95 - 1.20)). Finally, adjusting the model for the year of index date (i.e., index data ≤ 2004 as reference category), we found growing ORs for medications adherence over the study years for ACEi/CCBs/statins group (OR: 1.16 95% CI (0.98 - 1.37), OR 1.24 95% CI (1.06 - 1.45), OR: 1.14 95% CI (0.98 - 1.32) for index date between 2005 and 2007, between 2008 and 2010, ≥ 2011 , respectively) and ACEi/statins/low-dose aspirin group (OR: 1.27 95% CI (1.13 - 1.42), OR 1.39 95% CI (1.25 - 1.54), OR: 1.01 95% CI (0.92 - 1.12) for index date between 2005 and 2007, between 2008 and 2010, ≥ 2011 , respectively), although no significant trend was found.

Discussion

We conducted a real-world retrospective cohort study aimed to quantify the level of adherence and its determinants, for patients exposed to two triple free drug regimens in primary care; namely, ACEi/CCBs/statins and ACEi/statins/low-dose aspirin combination. Our results indicated that 52.1% and 50.6% of patients were non-adherent to ACEi/CCBs/statins and ACEi/statins/low-dose aspirin, respectively. These results confirm that non-adherence is one of the most important hurdles to achieve effectiveness in preventing CVD. Our evidence is consistent with those reported by the WHO, which estimates that the prevalence of non-adherence to antihypertensive medications ranges between 30% to 50%¹⁴. Similar findings have been obtained considering a recent systematic review and meta-analysis which established that 45% of patients were non-adherent to antihypertensive medications¹⁵. A good adherence was associated with a reduction in hospitalization for myocardial infarction (MI), stroke, and hospitalization for heart failure.¹⁶ As reported in a recent systematic review and meta-analysis absolute risk differences for any CVD associated with poor medication adherence were 13 cases for any vascular medication, 9 cases for statins and 13 cases for antihypertensive agents, per 100,000 individuals per year¹⁷.

Adherence to medication could be influenced by multiple interrelating factors. In the last decades, several works have been published concerning the variables associated with non-adherence to cardiovascular medications. For example, Lemstra and Alsabbagh performed a meta-analysis of cohort studies providing estimates of risk indicators associated with non-adherence to antihypertensive medications¹⁸. They identifying nine variables: diuretics in comparison to ACEi and angiotensin receptor blockers (ARBs) and CCBs, ACEi in comparison to ARBs, CCBs in comparison to ARBs, those with depression or using antidepressants, not having diabetes, and a lower socioeconomic status. In our setting, we found that male sex and high/very high cardiovascular risk were determinants of adherence to ACEi/CCBs/statins and ACEi/statins/low-dose aspirin therapy. On the contrary, depression and atrial fibrillation were associated with non-adherence. These findings are consistent with those already published in several observational studies. In fact, differences in drug utilization were observed for all ages and medication types¹⁹. In general, women were less likely to be adherent in their use of chronic medications than men. A meta-analysis found that gender has an impact on adherence to cardiovascular medications, demonstrating that women had 10 percent greater odds of being non-adherent than men²⁰. In terms of cardiovascular risk and adherence levels, our results are

fairly consistent with data published by Poluzzi et al.²¹. In this study, patients at the highest cardiovascular risk, requiring a stricter adherence to therapy, showed a higher rate of medications daily coverage compared to patients at lower cardiovascular risk. Our findings confirm the role of depression as a cause of non-adherence, in particular those treated for CVD, who could forget/decide to skip taking their medications²². Indeed, around 50% of patients with CVD experienced at least one major or minor depression episode. The association between depression and non-adherence may be driven by a third factor, such as cognitive decline, which is frequently associated with depression and it has been associated with non-adherence as well²³. Given that, our cohort was mainly formed by elderly patients, the cognitive decline might have been a relevant component in those with depression.

Several studies described medications' underuse in patients with atrial fibrillation. As reported by Brieger et al.,²⁴, evaluating patients' adherence for secondary prevention of acute coronary syndrome after the first 6 months of follow up, atrial fibrillation were independently associated with lower likelihood of adherence. Furthermore, the use of anticoagulants in patients with atrial fibrillation might have enhanced non-adherence to other medications because of the complex therapeutic regimens of anticoagulants as well as the clinical relevance of drug-drug interactions.

In our study, we identified a lack of effect of age as determinant for adherence levels. This result differs from what has been observed in prior studies on adherence to cardiovascular medications²⁵. Nevertheless, our exposure categories were featured by similar health status given with the use of triple combinations ACEi/CCBs/statins or ACEi/statins/low-dose aspirin which were indicators of similar clinical complexity per se. Not surprisingly, more than 70% of patients were at very high cardiovascular risk at the baseline.

Our findings might support GPs to identify patients at risk of non-adherence knowing their demographic and clinical features. By doing so, specific software applications, such as clinical decision support systems (CDSS), might be developed to early identify patients at-risk of non-adherence in the first year of therapy. This approach should be easily implemented in primary care given the current and broad availability of electronic medical care charts which are mandatory for GP to provide patients care (D.M. 4 March 2009 (G.U. n. 146 del 26 June 2009); DPCM 26 March 2008 (G.U. 28 May 2008, n. 124). Through CDSS, GPs could choose the best strategy aimed to minimize the burden of non-adherence. They comprise the use of education materials on the relevance of

medication adherence, the advice on the use of supporting tools (i.e., mobile application), a greater interaction with pharmacists and nurses, as well as the simplification of drug regimens through the use of fixed combination pills (i.e., polypill), whenever patients are on target with free combinations^{4,10,26,27}.

As showed in a recent meta-analysis, polypill-based care was associated with an improve in medication adherence and this strategy could contribute significantly to the WHO goal of reducing CVD in the next years²⁸. Indeed, the ESC/ESH Guidelines for the management of arterial hypertension suggests that the treatment with polypill may be considered in patients with hypertension as substitution therapy²⁹.

The present study had several strengths. First, the Italian HSD, one of the largest general practice databases in Europe, contains reliable information on a large population assisted in primary care throughout Italy. All data herein reported result homogenous and country-representative, and can provide a deep insight of a real-world clinical setting. Second, in the HSD, information on drug exposure is prospectively recorded by GPs, thereby minimizing any recall bias.

This study has some limitations as well. As in other database studies evaluating medication adherence, GPs' prescriptions are used to estimate the measure of adherence. Therefore, we are not certain whether patients actually filled and ingested the prescribed medications. However, direct comparison with official reports on defined daily dosages (DDDs) for these medication classes showed consistent results with ours, so demonstrating no difference between prescribed and dispensed amounts. Although HSD does not possess any variable measuring socioeconomic inequalities, we adopted the official estimates of ISTAT on the average salary (hourly rate, €) which is provided by ISTAT according age class (15-29; 30-49; ≥50), gender and geographic location (north-west, north-east, central, south and Island). Furthermore, we examined a cohort of elderly patients who shared a certain degree of severity, given they were exposed to three concurrent medications. That being said, they should be more homogeneous for non-clinical features when compared with general population.

In conclusion, this study confirms that low medication adherence is one of the most important hurdles to overcome for enhancing the medication effectiveness in preventing CVD³⁰. This issue is particularly relevant in primary care, being GPs the main prescribers for CVD as well as for other

chronic conditions. Our data suggest that, in a real world-setting, strategies should be implemented to minimize the burden of non-adherence.

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All persons that contributed to this manuscript met the criteria for authorship and are listed as authors.

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Conflict of interest

FL and EM provided consultancies in protocol preparation for epidemiological studies and data analyses for Bayer, Alfa Sigma, and IBSA. DP and CC provided clinical consultancies for Bayer, Alfa Sigma, IBSA, and Teva. NL, GC, MS, AV and AB have no conflict of interest to disclose.

1. Anon. World Health Statistics 2009. Table 2: cause-specific mortality and morbidity. Available at: https://www.who.int/whosis/whostat/EN_WHS09_Table2.pdf. Accessed September 26, 2019.
2. Lonn E, Bosch J, Teo KK, Pais P, Xavier D, Yusuf S. The polypill in the prevention of cardiovascular diseases: key concepts, current status, challenges, and future directions. *Circulation* 2010;122:2078–2088.
3. Marengoni A, Melis RJF, Prados Torres A, Onder G. Multimorbidity: Epidemiology and Models of Care. *Biomed Res Int* 2016;2016:7029027.
4. Cimmaruta D, Lombardi N, Borghi C, Rosano G, Rossi F, Mugelli A. Polypill, hypertension and medication adherence: The solution strategy? *Int J Cardiol* 2018;252:181–186.
5. Bahiru E, Cates AN de, Farr MR, Jarvis MC, Palla M, Rees K, Ebrahim S, Huffman MD. Fixed-dose combination therapy for the prevention of atherosclerotic cardiovascular diseases. *Cochrane database Syst Rev* 2017;3:CD009868.
6. Castellano JM, Sanz G, Fernandez Ortiz A, Garrido E, Bansilal S, Fuster V. A polypill strategy to improve global secondary cardiovascular prevention: from concept to reality. *J Am Coll Cardiol* 2014;64:613–621.
7. Cricelli C, Mazzaglia G, Samani F, Marchi M, Sabatini A, Nardi R, Ventriglia G, Caputi AP. Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Public Health Med* 2003;25:254–257.
8. Filippi A, Vanuzzo D, Bignamini AA, Mazzaglia G, Cricelli C, Catapano AL. The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction. *Ital Heart J* 2005;6:311–314.
9. ENCePP. Resources Database. Available at: <http://www.encepp.eu/encepp/resourcesDatabase.jsp>. Accessed January 24, 2020.
10. Levi M, Pasqua A, Cricelli I, Cricelli C, Piccinni C, Parretti D, Lapi F. Patient Adherence to Olmesartan/Amlodipine Combinations: Fixed Versus Extemporaneous Combinations. *J Manag Care Spec Pharm* 2016;22:255–262.

11. Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. *Curr Med Res Opin* 2014;30:2415–2422.
12. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, Backer G De, Bacquer D De, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Witheimsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: The SCORE project. *Eur Heart J* 2003;24:987–1003.
13. ISTAT. Retribuzioni orarie dei dipendenti del settore privato. 2019. Available at: <http://dati.istat.it/Index.aspx>. Accessed January 24, 2020.
14. Sabate E. Adherence to long term therapies. Evidence for action. *World Heal Organ* 2003.
15. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs. *Medicine (Baltimore)* 2017;96:e5641.
16. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancina G. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011;29:610–618.
17. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, Stricker B, Mendis S, Hofman A, Mant J, Franco OH. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–2948.
18. Lemstra M, Alsabbagh W. Proportion and risk indicators of nonadherence to antihypertensive therapy: a meta-analysis. *Patient Prefer Adherence* 2014;8:211.
19. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of Patient Sex and Gender on Medication Use, Adherence, and Prescribing Alignment with Guidelines. *J Women's Heal* 2014;23:112–119.
20. Lewey J, Shrank WH, Bowry ADK, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: A meta-analysis. *Am Heart J* 2013;165:665-678.e1.
21. Poluzzi E, Strahinja P, Lanzoni M, Vargiu A, Silvani MC, Motola D, Gaddi A, Vaccheri A,

- Montanaro N. Adherence to statin therapy and patients' cardiovascular risk: a pharmacoepidemiological study in Italy. *Eur J Clin Pharmacol* 2008;64:425–432.
22. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch Intern Med* 2005;165:2508–2513.
23. Stoehr GP, Lu S-Y, Lavery L, Bilt J Vander, Saxton JA, Chang C-CH, Ganguli M. Factors associated with adherence to medication regimens in older primary care patients: the Steel Valley Seniors Survey. *Am J Geriatr Pharmacother* 2008;6:255–263.
24. Brieger D, Chow C, Gullick J, Hyun K, D'Souza M, Briffa T, CONCORDANCE Investigators. Improving patient adherence to secondary prevention medications 6 months after an acute coronary syndrome: observational cohort study. *Intern Med J* 2018;48:541–549.
25. Keenan J. Improving adherence to medication for secondary cardiovascular disease prevention. *Eur J Prev Cardiol* 2017;24:29–35.
26. Anon. Novartis Europharm Limited. Exforge HCT film-coated tablets: EU summary of product characteristics. 2014. Available at: http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_-_Product_Information/human/001068/WC500033641.pdf. Accessed September 27, 2018.
27. Anon. Les Laboratoires Servier. Triveram film-coated tablets: IT summary of product characteristics. 2016. Available at: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_000049_043427_RCP.pdf&retry=0&sys=m0b113. Accessed September 27, 2018.
28. World Health Organisation. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. *World Heal Organ* 2013. Available at: https://apps.who.int/iris/bitstream/handle/10665/94384/9789241506236_eng.pdf;jsessionid=0C538068B104B4D175949781C9915D30?sequence=1.
29. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, Simone G de, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M,

Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, Backer G De, Heagerty AM, Agewall S, Bochud M, Borghi C, Boutouyrie P, Brguljan J, Bueno H, Caiani EG, Carlberg B, Chapman N, Cífková R, Cleland JGF, Collet J-P, Coman IM, Leeuw PW de, Delgado V, Dendale P, Diener H-C, Dorobantu M, Fagard R, Farsang C, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;39:3021–3104.

30. Lapi F, Lucenteforte E, Moschini M, Bonaiuti R, Pirro M Di, Barchielli A, Benemei S, Belladonna M, Nesti N, Coppini R, Taras M, Vannacci A, Ungar A, Mugelli A. Representativeness of the “Fiesole Misurata”; study database for use in pharmaco-epidemiological investigations on adherence to antihypertensive medications. *Aging Clin Exp Res* 2013;25:433–445.

Table 1. Characteristics of patients according to type of triple free pill combination: ACEi/CCBs/statins and ACEi/statins/low-dose aspirin.

Characteristics	ACEi/CCB/statin (N=6,302)	ACEi/statin/low-dose aspirin (N= 15,918)
Women	2,609 (41.4%)	5,860 (36.8%)
Men	3,693 (58.6%)	10,058 (63.2%)
Age (years)		
<45	139 (2.2%)	406 (2.6%)
45-54	676 (10.7%)	1,932 (12.1%)
55-64	1,751 (27.8%)	4,416 (27.7%)
65-74	2,449 (38.9%)	5,859 (36.8%)
75-84	1,174 (18.6%)	2,982 (18.7%)
≥85	113 (1.8%)	323 (2.1%)
Age (years, mean ± SD)	66.2 ±9.93	65.8 ±10.33
Time to triple therapy (years)		
mean ±SD	3.9 ±3.36	3.2 ±3.2
median	3.06	2.25
minimum and maximum	0.0-12.83	0-12.87
p25 – p75	0.9-6.16	0.4-5.28
Triple therapy duration ^a		
mean ±SD	314.5 ±352.3	294.1 ±307.4
median	191.5	191
minimum and maximum	60 – 4,013	60 – 4,433

Characteristics	ACEi/CCB/statin (N=6,302)	ACEi/statin/low-dose aspirin (N= 15,918)
p25 – p75	130 - 343	134 - 328

ACEi= angiotensin-converting-enzyme inhibitor; CCB= calcium channel blocker; SD= standard deviation.

^a calculated on the first combination being identified

Table 2. Characteristics of patients eligible to calculation of adherence to triple free pill therapy: ACEi/CCBs/statins and ACEi/statins/low-dose aspirin.

Characteristics	ACEi/CCB/statin (N=6,176)	ACEi/statin/low-dose aspirin (N=15,600)
Proportion of days covered		
(PDC)		
Non-adherent (<80%)	3,217 (52.1%)	7,892 (50.6%)
Adherent (≥80%)	2,959 (47.9%)	7,708 (49.4%)
Women	2,547 (41.2%)	5,716 (36.6%)
Men	3,629 (58.8%)	9,884 (63.4%)
Age (years)		
<45	53 (0.8%)	241 (1.5%)
45-54	408 (6.6%)	1,313 (8.4%)
55-64	1,314 (21.3%)	3,493 (22.4%)
65-74	2,287 (37.0%)	5,588 (35.8%)

Characteristics	ACEi/CCB/statin (N=6,176)	ACEi/statin/low-dose aspirin (N=15,600)
75-84	1,785 (29.0%)	4,205 (27.0%)
≥85	329 (5.3%)	760 (4.9%)
Age (years, mean ±SD)	69.8 ±9.8	68.8 ±10.4
Triple therapy duration ^a		
mean ±SD	257.9 ±102.0	263.8 ±96.5
median	283	290
minimum and maximum	60-365.2	60-365.2
p25 – p75	165.0 - 362.5	173.0 – 361.0
Cardiovascular risk		
Mean/moderate	332 (5.4%)	1,016 (6.5%)
High	1,514 (24.5%)	3,135 (20.1%)
Very-high	4,330 (70.1%)	11,449 (73.4%)
Other conditions		
Heart failure	344 (5.6%)	890 (5.7%)
Atrial fibrillation	398 (6.4%)	701 (4.5%)
Depression	450 (7.3%)	1,066 (6.8%)

ACEi= angiotensin-converting-enzyme inhibitor; CCB= calcium channel blocker; SD= standard deviation.

^a calculated on the first combination being identified

Table 3. Determinants of 1-year adherence to triple free pill therapy with ACEi/CCB/statin.

	OR (95% CI)		p-value
	Crude	Adjusted	
Women	<i>1.00</i>	<i>1.00</i>	
Men	1.32 (1.20 - 1.46)	1.27 (1.15 - 1.42)	<0.001
Age (years)			
<45	<i>1.00</i>	<i>1.00</i>	
45-54	0.97 (0.54 -1.71)	1.01 (0.57 -1.79)	0.981
55-64	0.91 (0.52 -1.58)	0.96 (0.55 -1.67)	0.883
65-74	0.83 (0.48 -1.43)	0.89 (0.51-1.53)	0.667
75-84	0.76 (0.44 -1.32)	0.84 (0.48 -1.46)	0.528
≥85	0.62 (0.35 -1.11)	0.70 (0.39 -1.26)	0.226
Cardiovascular risk			
<i>Intermediate/Moderate</i>	<i>1.00</i>	<i>1.00</i>	
High	1.31 (1.03 -1.67)	1.35 (1.06 -1.72)	0.014
Very-high	1.33 (1.06 -1.67)	1.34 (1.06 -1.68)	0.013
Other conditions			
Heart failure	0.95 (0.77 -1.19)	-	
Atrial fibrillation	0.96 (0.78 -1.18)	-	
Depression	0.95 (0.78 -1.15)	-	

ACEi= angiotensin-converting-enzyme inhibitor; CCB= calcium channel blocker; CI= confidence interval; OR=

Odds Ratio; SD= standard deviation.

Table 4. Determinants of 1-year adherence to triple free pill therapy with ACEi/statin/low-dose aspirin.

	OR (95% CI)		p-value
	Crude	Adjusted	
Women	1.00	1.00	
Men	1.20 (1.13 - 1.28)	1.14 (1.06 - 1.22)	<0.001
Age (years)			
<45	1.00	1.00	
45-54	0.97 (0.74 - 1.28)	0.98 (0.74 - 1.29)	0.888
55-64	0.92 (0.71 - 1.19)	0.94 (0.73 - 1.22)	0.658
65-74	0.85 (0.66 - 1.11)	0.89 (0.69 - 1.16)	0.384
75-84	0.77 (0.59 - 0.99)	0.81 (0.62 - 1.05)	0.118
≥85	0.74 (0.55 - 0.99)	0.80 (0.60 - 1.08)	0.144
Cardiovascular risk			
<i>Intermediate/Moderate</i>	1.00	1.00	
High	1.27 (1.1 - 1.46)	1.30 (1.12 - 1.49)	<0.001
Very-high	1.35 (1.18 - 1.53)	1.35 (1.18 - 1.54)	<0.001
Other conditions			
Heart failure	0.86 (0.75 - 0.99)	0.90 (0.78 - 1.03)	0.132
Atrial fibrillation	0.78 (0.67 - 0.91)	0.82 (0.7 - 0.95)	0.009
Depression	0.81 (0.72 - 0.92)	0.85 (0.75 - 0.96)	0.011

ACEi= angiotensin-converting-enzyme inhibitor; CI= confidence interval; OR= Odds Ratio; SD= standard deviation.

Sample CRediT author statement

Niccolò Lombardi: Conceptualization, Writing - Original Draft. **Giada Crescioli:** Conceptualization, Writing - Original Draft. **Monica Simonetti:** Formal analysis. **Ettore Marconi:** Methodology, Writing - Review & Editing. **Alfredo Vannacci:** Writing - Original Draft, Supervision. **Alessandra Bettiol:** Writing - Original Draft. **Damiano Parretti:** Resources, Supervision. **Claudio Cricelli:** Resources, Supervision. **Francesco Lapi:** Conceptualization, Methodology, Writing - Review & Editing, Supervision.