

Impact of compliance with antihypertensive and lipid-lowering treatment on cardiovascular risk Benefits of fixed-dose combinations

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ABSTRACT: Despite the favorable impact of antihypertensive and lipid-lowering treatment on cardiovascular (CV) morbidity and mortality, patient compliance is frequently poor in clinical practice even in high risk populations. This leads to worsening of clinical outcomes and higher long-term health-care costs. Several measures have been proposed to improve compliance. Single-pill formulations that would contain various drugs treating CV risk factors can improve the compliance and lead to a long overdue reduction in vascular events. The aim of this review is to emphasize the lack of compliance with prescribed lipid-lowering and antihypertensive drugs along with its impact on CV mortality and morbidity

Συσχέτιση της συμμόρφωσης με την αντιυπερτασική και υπολιπιδαιμική θεραπεία και της μείωσης του καρδιαγγειακού κινδύνου Τα οφέλη των έτοιμων συνδυασμών

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ΠΕΡΙΛΗΨΗ: Παρά την ευνοϊκή επίδραση της αντιυπερτασικής και υπολιπιδαιμικής αγωγής στην καρδιαγγειακή νοσηρότητα και θνητιμότητα, η συμμόρφωση των ασθενών είναι συχνά ανεπαρκής στην κλινική πράξη ακόμα και σε άτομα υψηλού κινδύνου. Η μειωμένη συμμόρφωση με τη θεραπεία οδηγεί σε μείωση του οφέλους της αγωγής και υψηλότερο μακροπρόθεσμο κόστος υγειονομικής περιθαλψης. Πολλά μέτρα έχουν προταθεί για τη βελτίωση της συμμόρφωσης. Σκευασμάτα έτοιμων συνδυασμών φαρμάκων σε ένα δισκίο που περιέχουν διάφορα φάρμακα για τη θεραπεία των παραγόντων καρδιαγγειακού κινδύνου μπορούν να βελτιώσουν τη συμμόρφωση και να οδηγήσουν σε σημαντική μείωση των καρδιαγγειακών συμβαμά-

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and present the benefits of fixed-dose combinations in regard to patient compliance and CV risk.

Key words: Compliance, cardiovascular morbidity, mortality, antihypertensive treatment, hypolipidemic treatment, fixed-dose combinations, statins.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide.¹ Major risk factors for CVD include hypertension, dyslipidemia, smoking, age, male gender, diabetes mellitus, obesity and family history of premature CVD.^{2,3} A large scale of clinical trials and meta-analyses has shown that antihypertensive and lipid-lowering treatment reduces the risk of coronary heart disease (CHD), stroke and death.^{4–7} Nevertheless, adherence to antihypertensive and hypolipidemic treatment is poor in clinical practice.^{8,9} The aim of this review is to focus on the lack of compliance with prescribed lipid-lowering and antihypertensive drugs in clinical practice, present its impact on CVD morbidity and mortality and discuss the benefits of fixed-dose drug combinations in regard to patient compliance and CV risk.

2. Methods

We searched PubMed up to 30 September 2012 using combinations of the following keywords: compliance, CV morbidity, mortality, stroke, myocardial infarction, antihypertensive, single pill, compliance, adherence, combination therapy, lipid-lowering, hypolipidemic and statins. Original papers, review articles and case reports are included in the present review. The references of these articles were scrutinized for relevant articles. For articles not written in English, only the abstracts were considered.

3. Compliance with antihypertensive treatment

3.1. Benefits of reduction in blood pressure (BP)

Several large clinical trials have shown that reduction of elevated blood pressure (BP) by treatment reduces the risk of fatal and nonfatal cardiovascular events.^{10–14} Specifically, antihypertensive treatment reduced the

stroke. Σκοπός της παρούσας ανασκόπησης είναι να περιγράψει την έλλειψη συμμόρφωσης στα συνταγογραφούμενα υπολιπιδαιμικά και αντιυπερτασικά φάρμακα, καθώς και τις επιπτώσεις στην καρδιαγγειακή θνησιμότητα και νοσηρότητα. Επιπρόσθετα, παρουσιάζονται τα οφέλη των έτοιμων συνδυασμών σε σχέση με τη συμμόρφωση και τη μείωση του καρδιαγγειακού κινδύνου

Λέξεις ευρετηρίου: Συμμόρφωση, καρδιαγγειακή νοσηρότητα, θνησιμότητα, αντιυπερτασική θεραπεία, υπολιπιδαιμική θεραπεία, έτοιμοι συνδυασμοί, στατίνες.

risk of stroke by 35–40%, acute myocardial infarction (AMI) by 20–25% and heart failure by >50%.¹⁵ Reduction of systolic BP of just 2 mmHg can reduce the risk of CVD by 7–10%.¹⁵ These results have been incorporated into evidence-based guidelines for the treatment of hypertension.^{14,16,17} These guidelines recommend that BP should be reduced to <140/90 mmHg in patients with uncomplicated hypertension and to <130/80 mmHg in those with diabetes or chronic kidney disease.^{14,16,17}

3.2. Poor compliance with antihypertensive treatment

Despite the obvious benefits of BP control and the availability of many effective antihypertensive drugs, only a small proportion of hypertensive individuals are properly treated and even fewer achieve guideline targets.¹⁸ BP is inadequately controlled in one third to one half of patients receiving antihypertensive treatment in the United States and Canada and in 40–66% of patients with concurrent hypertension and diabetes.^{19–23} In the European Union BP is inadequately treated in more than two thirds of treated patients.^{22,24}

There are several factors responsible for the inadequate control of BP, such as the multifactorial nature of hypertension, the presence of concurrent medical conditions, and the presence of resistant secondary hypertension.^{25,26} A consensus however exists that the poor worldwide rate of BP control is largely due to patients frequently taking antihypertensive treatment in a highly irregular fashion or even permanently discontinue the prescribed drugs.^{27–35} It is estimated that 24–51% of hypertensive patients are non-compliant (compliance defined as drugs taken for >80% of the days in year) and 29–58% of hypertensive patients are non-persistent with therapy (persistence defined as remaining on treatment for 12 months).³⁶

The lack of compliance with antihypertensive treatment has been attributed to factors which are grouped into 5 categories: patient related, condition related, therapy related, health system related and socioeconomic factors.³⁷ Patients may not understand and be aware of the long-term consequences of elevated BP as hypertension is often asymptomatic.³⁶ In addition, complex medication regimens that include multiple drugs or multiple doses per day decrease patient compliance.³⁸ A meta-analysis of 11,485 patients showed that adherence rate was higher in patients with once-daily dosing of antihypertensive drugs compared with those on multiple dosing (91.4 vs 83.2%, respectively, P<0.001).³⁹

The consequences of poor adherence and compliance with antihypertensive therapy encompasses a higher risk of CVD, hospitalization and increased health care utilization cost.⁴⁰ Patients being highly compliant were 45% more likely to achieve BP goal in comparison with those showing medium or poor compliance.⁴¹ A large cohort of newly treated hypertensive patients (n=31,306) demonstrated that the risk of all-cause death, stroke, or AMI was significantly lower in patients with good [hazard ratio (HR)=0.69, P<0.001] and excellent adherence (HR=0.53, P<0.001) compared with those with poor adherence.⁴² Another study that evaluated the compliance with angiotensin-converting enzyme (ACE), angiotensin II blockers (ARBs) and/or b-blockers in patients with ischemic heart disease and diabetes mellitus (n=3998) demonstrated that patients with higher compliance had lower mortality rates (6.7%) compared with patients with poor compliance (12.1%) (P<0.01).⁴³ The impact of persistence on the primary prevention of AMI and stroke has also been analyzed.⁴⁴ Nonpersistence with antihypertensive therapy was associated with a 15% increase in the risk of AMI and a 28% increase in the risk of stroke in patients being watched initially for a 2-year period followed by an additional 2-year period or until a CV event occurred.⁴⁴ Likewise, a cohort study included 83,267 patients newly treated for hypertension in the primary prevention setting.⁴⁵ Taking >80% of the prescribed antihypertensive medication was associated with reduced risk for CV events compared with taking <80% [relative risk (RR)=0.90, 95% confidence intervals (CI) 0.86–0.95].⁴⁵ Interestingly, a post-hoc analysis of the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) study showed that mortality was significantly lower in compliant patients with congestive heart failure whatever the treatment (placebo or candesartan).⁴⁶ This may imply that compliance is a marker of a general "healthier" behavior. As far as hos-

pitalization risk is concerned, it has been demonstrated that the 1-year risk of hospitalization was significantly lower for patients who were highly compliant and adherent (80–100%) compared with those with poor compliance (<59%) (P<0.05).⁴⁷

3.3. Fixed-dose combinations improve compliance with antihypertensive treatment

Measures to increase compliance with antihypertensive treatment may reduce CV risk.⁴⁸ These include reducing the complexity of the prescribed scheme, such as the number of prescribed medications and once-daily dosing since patients prefer to take as few pills as possible.⁴⁹ Therefore, the use of once-daily single-pill combination therapy with effective and well-tolerated agents will reduce pill burden, simplify treatment regimens and improve treatment adherence, which will in turn help patients to reach and maintain their BP target.⁵⁰ Indeed, adherence to fixed-dose combinations of two or three agents given as a single pill is better than the adherence to free combinations of the same agents.^{51–53} A recent large study studying adherence to first-line antihypertensive drug class in a large Chinese population (n=147,914) demonstrated that more favorable adherence profiles were associated with initial antihypertensive prescriptions of fixed-dose combination therapies.⁵⁴ An older retrospective US database analysis compared compliance in 2754 patients receiving single-pill combination therapy (amlodipine/benazepril) with that in 2,978 patients receiving an ACE inhibitor and a long-acting calcium channel blocker (CCB) as separate drugs.⁵⁵ The single-pill combination group demonstrated better compliance (80.8% vs 73.8%, P<0.001) and significantly lower average annual cost of cardiovascular-related care per subject (P<0.001).⁵⁵ A meta-analysis (n=32,331) performed to assess compliance, persistence, BP control and safety associated with fixed-dose combinations compared with their free-drug components demonstrated that fixed-dose combinations were associated with a significant improvement in compliance and non-significant beneficial trends in BP and adverse effects.⁵⁶ Likewise, other studies demonstrated better patient compliance with single-pill combinations of two or three antihypertensive agents,^{57–60} along with better efficacy.^{61–63}

4. Compliance with lipid-lowering treatment

4.1. Benefits of lipid-lowering treatment

Dyslipidemia is one of the major CVD risk factors and lipid-lowering treatment, mainly statins, has well-established benefits in the primary and secondary preven-

tion of coronary heart disease and stroke.^{64,65} Analysis of data from primary prevention studies showed that statin therapy, on average, reduces the risk of total mortality by 7% and AMI by 27%.⁶⁶ Likewise, other studies demonstrated the benefit of statin therapy to both primary^{67–71} and secondary prevention of CHD events.^{72–76} On average, statin therapy reduces CVD events by 25% and total mortality by 16% in secondary prevention.⁷⁷

4.2. Poor compliance with lipid-lowering treatment

Despite the well-known favorable effects of lipid-lowering treatment on CVD morbidity and mortality, compliance with prescribed medications remains poor in everyday practice, especially in the primary care setting.^{78,79} A large cohort study in Canada (n=143,505) demonstrated that the 2-year compliance rates were 40.1% for patients with acute coronary syndrome, 36.1% for patients with chronic stable coronary artery disease and 25.4% for primary prevention individuals.⁸⁰ Overall, statin discontinuation rates after the first year of treatment vary between 15 and 60%.^{78,81,82} Of note, compliance with lipid-lowering therapy is lower in primary than in secondary prevention.⁸³

Responsible factors that contribute to poor compliance can be categorized into patient factors, physician factors, and health system factors.⁸⁴ For example, patients with other health problems might be more compliant because they have accepted the idea of a long-term treatment.⁸⁵ In addition, the number of tablets and the adverse effects associated with medication use may reduce compliance.^{86–88}

It has been suggested that poor adherence to lipid-lowering treatment increases CV morbidity and mortality.⁸⁹ A recent population-based retrospective cohort study (n=19,232) investigated the association between adherence to treatment and all-cause mortality and hospitalization for AMI or stroke.⁹⁰ Adherence to statins was low in 4,427 patients (23.0%), intermediate-low in 3,117 (16.2%), intermediate-high in 3,784 (19.7%), and high in 7,904 (41.1%).⁹⁰ High adherence was significantly associated with decreased risk of all-cause death, AMI, or stroke.⁹⁰ Specifically, compared with low adherence, the risk was lower in intermediate-low adherence ($HR=0.83$; 95% CI, 0.71–0.98; $P<0.05$), much lower in intermediate-high ($HR=0.60$; 95% CI, 0.51–0.70; $P<0.001$) and high adherence ($HR=0.61$; 95% CI, 0.54–0.71; $P<0.001$).⁹⁰ Another cohort study (n=90,832) investigated whether an association exists between statin adherence when used as primary prevention and risk of subsequent ischemic heart disease.⁹¹ Patients with low, intermediate, or high statin adherence had HR

(95% CI) values of 0.85 (0.72–0.98), 0.82 (0.71–0.95), and 0.81 (0.71–0.94) respectively, compared with patients with very low adherence.⁹¹ An interesting study conducted in primary prevention subjects (n=579) with ≥ 3 CVD risk factors showed that only a quarter of patients taking lipid-lowering drugs attained the therapeutic goal of low-density lipoprotein cholesterol (LDL-C) <130 mg/dL during all 3 study years.⁹² The CVD risk in individuals who partially achieved the therapeutic goal [odds ratio (OR)=2.4; 95% CI 1.01–5.39] or never during the study period (OR=2.99; 95% CI 1.26–7.08) was significantly higher compared with those who attained the therapeutic goal.⁹² Although this study did not evaluate the adherence to lipid-lowering treatment, lack of compliance with the prescribed drugs might be the reason for not achieving the therapeutic goals of LDL-C. Similarly, in patients with coronary heart disease, a 26% rate of noncompliance was found, which in turn was associated with an 85% increase in total mortality.⁹³ Another cohort study (n=137,217) showed that patients non-adherent to a statin regimen over a 3-year period (76% of the cohort) had by more than 40% higher odds of CV events, irrespective of risk factors, when compared with adherent patients.⁹⁴ Other studies have demonstrated the positive impact of increased adherence on CV risk.^{95,96} A large cohort study in Italy (n=84,262) demonstrated that interventions to increase the average level of adherence from 45% (baseline) to 50% ("soft" intervention) or to 90% ("hard" intervention) reduced the number of patients who experienced ischemic heart disease (from 38.9 to 38.4 or 35.8 events every 10,000 person-year, respectively).⁹⁵ A similar reduced incidence of major coronary events has also been noticed in diabetic patients with good adherence to statins.⁹⁷

4.3. Fixed-dose combinations improve compliance with lipid-lowering treatment

High levels of adherence and longer persistence with statins are associated with progressively increasing clinical benefits in primary and secondary prevention.⁹⁸ Simple measures, such as educating physicians and patients, distributing printed guidelines and brochures and completing a 1-page form, motivated physicians and patients to achieve multiple CVD risk factor goals.⁹⁹ Fixed-dose combinations might also improve patient compliance with lipid-lowering treatment.^{57,100} One fixed combination of lipid-lowering agents is the combination simvastatin/ezetimibe.¹⁰¹ Many studies have demonstrated that the fixed-dose combination of simvastatin with ezetimibe in one tablet is safe, tolerable and has better effectiveness on lowering LDL-C

compared with simvastatin monotherapy.¹⁰² In addition, a retrospective study used pharmacy and medical claims and laboratory result data from a national managed care dataset to evaluate patients who were newly prescribed simvastatin plus ezetimibe, simvastatin plus niacin, and lovastatin plus niacin either as single-pill combination or multi-pill combination.¹⁰³ Patients receiving single-pill combination were 32% (OR=1.32; 95% CI: 1.27–1.36; P<0.01) more likely to be adherent to treatment than patients receiving multiple lipid-lowering drugs separately.¹⁰³ Likewise, another study showed that adherence was significantly higher among patients initiating fixed-dose combination versus multi-pill combination dyslipidemia therapies.¹⁰⁴ Patients receiving separate pills of niacin/simvastatin and niacin/lovastatin were respectively 31.3% (95% CI: 22.9–39.5%) and 39.1% (95% CI: 26.7–49.4%) less likely to be optimally adherent than fixed-dose combination patients (P<0.01).¹⁰⁴ In addition, optimally adherent patients had 8% and 40% decreases in annual CVD-attributable total healthcare resource utilization (OR=0.92; 95% CI: 0.857–0.989; P=0.023) versus sub-optimally adherent patients.¹⁰⁴

4.4. Single-pill formulations

As mentioned above, compliance with both antihypertensive and lipid-lowering treatment is irreversibly related to CV risk. Also, fixed-dose combinations improve patient compliance. Hence, single-pill formulations may help since the simultaneous initiation of antihypertensive treatment and lipid-lowering treatment together with a reduced pill burden can increase the probability of good compliance.⁵² In this concept, the single pill amlodipine with atorvastatin (AML/ATOR) at various doses has been developed for patients with hypertension and dyslipidemia.^{105,106} The AML/ATOR has been associated with better compliance and adherence compared with two-pill regimens of amlodipine with atorvastatin or other statins.^{105,106} In a retrospective cohort study based on pharmacy claims data, patients newly initiated on a CCB (including amlodipine) or statin (including atorvastatin) simultaneously or within 30 days, regardless of sequence, were followed (n=4,703).⁸⁹ After 6 months, patients taking AML/ATOR were more adherent to treatment compared with those taking amlodipine and atorvastatin (OR=1.95, 95% CI, 1.80–2.13, P<0.0001) or other statins (OR=3.10, 95% CI, 2.85–3.38, P<0.0001) separately.¹⁰⁵ The concept of a 'polypill' which would contain different drugs to treat many of the CV risk factors has moved one step further by The Indian Polycap Study (TIPS).^{107,108} TIPS assessed the effects of 9 different pills containing either single

agents or combinations of 2, 3, 4 or 5 drugs, to evaluate their effects on risk factors such as blood pressure and cholesterol concentrations, along with the tolerability of administering a single pill to a relatively unselected group of patients.¹⁰⁷ The polypill which contained statin (20 mg simvastatin), 3 antihypertensive agents (12.5 mg thiazide, 50 mg atenolol and 5 mg ramipril) and 100 mg aspirin did what was intended.¹⁰⁹ The statin reduced LDL-C by 27 mg/dL (95% CI 0.62–0.78), the 3 antihypertensives reduced systolic blood pressure by 7.4 mmHg (95% CI 6.1–8.1) and diastolic blood pressure by 5.6 mmHg (4.7–6.4) and aspirin reduced the clotting ability of the blood.¹⁰⁹ The FOCUS (fixed-dose combination drug for secondary cardiovascular prevention) project will compare adherence to treatment in 1340 post-myocardial infarction patients either receiving a fixed-dose combination comprising aspirin (100 mg), ramipril (2.5 mg, 5 mg, or 10 mg) and simvastatin (40 mg) or receiving the same 3 drugs separately.¹¹⁰

Therefore, the polypill may have several advantages such as improved patient compliance, reduced cost of therapy and improved delivery of care by avoiding complex algorithms, increasing the ease of prescribing, and avoiding multiple steps for dose titration of each drug.¹¹¹ However, there are a few potential disadvantages and uncertainties of the polypill that have to be mentioned. For instance, there is no available data on the benefits and long-term safety of a polypill in primary prevention in individuals with average levels of risk factors.¹¹¹ Pharmaceutical formulation issues need to be documented due to the complex of the combination of 4 or 5 active components into a single polypill.¹¹¹ Furthermore, the clinical outcome of a polypill, patient compliance and the actual rates of adverse effects in a long-term treatment are still unknown.¹¹¹ Apart from the potential interference of a polypill with lifestyle since there are concerns that a single "magic bullet" for CVD prevention may lead people to abandon healthy lifestyle, a polypill might change the conventional thinking of the physicians, leading them to abandon the individualized, titrated, target-driven approach to CVD prevention.¹¹¹

5. Conclusion

Despite the undoubtable benefits of antihypertensive and lipid-lowering treatment to CV morbidity and mortality, patient compliance is frequently disappointing in clinical practice even in high-risk populations. Statin and antihypertensive withdrawal leads to unfavorable clinical outcomes and higher long-term healthcare costs. Several measures have been proposed

to improve compliance, such as reducing treatment complexity and the pill burden along with improving patient motivation. Indeed, fixed-dose combinations of antihypertensive and lipid-lowering drugs increase patient compliance. Therefore, single-pill formulations containing various drugs for CV risk factors may improve compliance and lead to a long overdue reduction in vascular events.

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