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CONSENSUS DOCUMENT

An Expert Opinion on the Role of the Rosuvastatin/Amlodipine Single Pill Fixed Dose Combination in Cardiovascular Prevention

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Abstract
Current cardiovascular disease prevention strategies are based on the management of cardiovascular risk as a continuum, redefining the therapeutic goals for each individual based on the estimated global risk profile. Given the frequent clustering of the principal cardiovascular risk factors, such as hypertension, diabetes and dyslipidaemia, in the same individual, patients are required to take multiple drugs to achieve therapeutic targets. The adoption of single pill fixed dose combinations may contribute to achieve better control of blood pressure and cholesterol compared to the separate administration of the individual drugs, mostly due to better adherence related to therapeutic simplicities. This paper reports the outcomes of an Expert multidisciplinary Roundtable. In particular, the rational and potential clinical use of the single pill fixed dose combination "Rosuvastatin-Amlodipine" for the management of concomitant hypertension/hypercholesterolemia in different clinical fields are discussed. This Expert Opinion also illustrates the importance of an early and effective management of total cardiovascular risk, highlights the substantial benefits of combining blood pressure and lipid-lowering treatments in a single-pill fixed dose combination and attempts to identify and overcome the barriers to the implementation in clinical practice of the fixed dose combinations with dual targets. This Expert Panel identifies and proposes the categories of patients who may benefit the most from this fixed dose combination.

Keywords Cardiovascular prevention · Fixed dose combination · Rosuvastatin/Amlodipine · Hypertension · Dyslipidaemia

1 Introduction

Cardiovascular diseases (CVD) have an enormous impact on global health, still representing the leading causes of morbidity and mortality worldwide [1].

In such a context, a huge effort has been made in the last decades by National Healthcare Systems, Scientific Societies as well as by individual physicians in their clinical practice to implement and extend effective preventive strategies with the aim to reduce the burden of CVD.

Current cardiovascular disease prevention strategies are based on the management of cardiovascular risk as a continuum, redefining the therapeutic goals for each individual based on the estimated global risk profile. Given the frequent

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clustering of the principal cardiovascular risk factors, such as hypertension, diabetes and dyslipidaemia, in the same individuals, patients are required to take multiple drugs to achieve therapeutic targets. [2]. Moreover, the presence of multiple risk factors (RFs) exponentially increases cardiovascular risk [3]. In a large observational study, the incidence of major cardiovascular events (MACE) was 6-fold greater in hypertensive men with elevated cholesterol concentrations and smoking habit compared to non-smokers subjects with high blood pressure (BP) with normal cholesterol levels [4].

Based on multiple evidence, it appears today quite reasonable to postulate that early preventive management strategies based on control of main RFs may contribute to prevent, or at least delay, the development of organ damage and may reduce the excess of cardiovascular risk [5].

1.1 Therapeutic Efficacy of Combinations

Several studies have demonstrated that concomitant treatment of hypertension and dyslipidemia with antihypertensive drugs and statins produce a synergistic and large reduction of cardiovascular risk as compared to the separate management of the same conditions taken separately [6–8]. Figure 1, which is modified from the MRFIT Study, a milestone of cardiovascular prevention history, shows that concomitant slight reductions of BP and cholesterol are expected to produce a reduction of cardiovascular risk quantitatively comparable to those attained with more marked individual reductions of BP or cholesterol [4].

In this regard, it should be also mentioned that statins have been shown to contribute to BP lowering in hypertensive patients, due to their capacity to inhibit vascular smooth muscle cell proliferation, to increase the bioavailability of nitric oxide, to downregulate type 1 angiotensin II receptors and endothelin-1 production, improving arterial compliance and reducing in large artery stiffness and vascular resistances [9–11]. An alternative interpretation of the BP effect of statin therapy associated with BP drugs was presented [9]. One thousand eight hundred twenty-seven hypertensive patients showed lower 24-h BP (− 2.8/− 7.1 mmHg), daytime (− 3.3/− 7.6 mmHg) and night-time BP (− 2.5/− 6.0 mmHg, all $P < 0.001$). They also showed better ambulatory BP control, even after adjustment for confounding factors. The analyses on the groups derived from the 'propensity score matching' (369 patients in each group) confirmed these results (OR = 1.8 for 24-h BP control; OR = 1⁄4 1.6 for daytime BP control; OR 1⁄4 1.7 for night-time BP control, all $P < 0.001$). The interpretation was that patients that were taking a statin, as shown by the lower cholesterol levels, despite the so called "nocebo" effect, were also more likely to be adherent to antihypertensive therapy [10].

In the SECURE trial, a treatment strategy for secondary prevention with a polypill containing aspirin, ramipril, and atorvastatin in older patients with recent myocardial infarction resulted in a lower risk of major adverse cardiovascular events than an usual-care strategy based on the separate administration of the various medications. The risk reduction observed in the polypill group may be explained at least in part, also in the opinion of the authors, by the increased adherence to treatment [12]. In such a context, adherence to prescribed therapy is defined as the number of refilled prescriptions (on time) over the total duration of the treatment, compliance consists in the number of taken medications (pills) and persistence is the time period during which each individual patients stay on therapy.

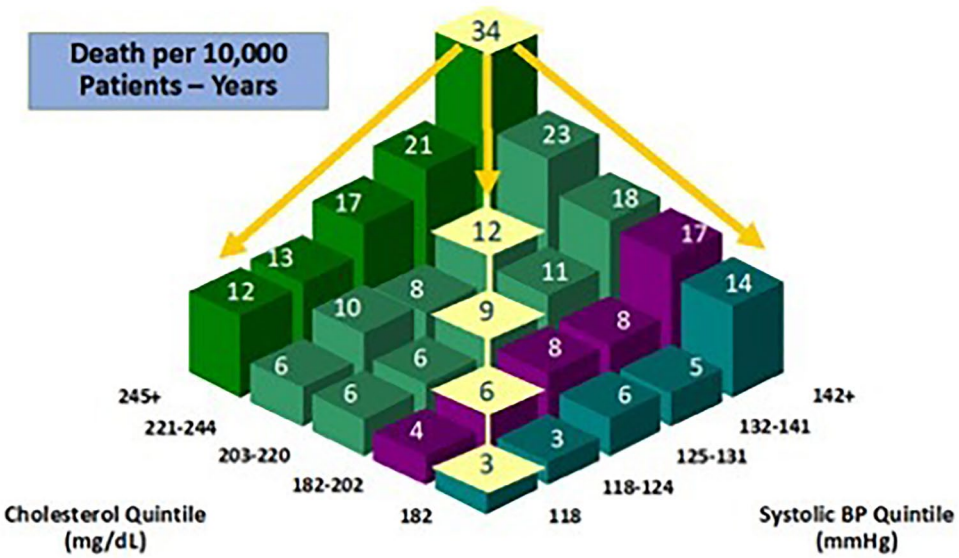

Fig. 1 Relationship between risk factors levels and cardiovascular mortality (Modified from Ref. [4]). Even mild elevations in blood pressure and cholesterol increases the risk of cardiovascular diseases. On the other hand, mild concomitant decreases of both risk factors levels significantly reduce cardiovascular risk, at a level comparable to that achieved with marked decreases of the individual risk factors

1.1.1 The Issue of Preserved Therapeutic Adherence

Several studies have demonstrated that adherence to virtuous lifestyle changes and pharmacological prescriptions is a critical component to achieve an adequate control of RFs and to reduce MACE [13]. In a population of hypertensive patients, those who adequately took prescribed BP-lowering agents (adherence > 80%) had a 11%, 10% and 22% lower risk of heart failure (HF), coronary artery disease (CAD) and cerebrovascular disease, respectively, compared to subjects with poor therapeutic adherence [14, 15].

An Italian study stratifying 242,000 patients with newly treated hypertension by the level of adherence (very low < 25%; low 26–50%; intermediate 51–75%; and high > 75%) showed that in the groups with intermediate and high adherence the risk of MACE was 20% and 25% lower, respectively, compared to those with low adherence [16].

In the US cohort of the Veterans Affairs Health System, patients with history of CVD who were poorly adherent to statin treatment had a 30% greater risk of cardiovascular death compared to adherent participants [17].

In a large meta-analysis including two million subjects from 44 studies showed that poor adherence was responsible for 9.1% of all registered MACE, whereas an adequate adherence to statin and BP lowering treatments was able to reduce by 45% and 29%, respectively, the risk of cardiovascular death [18].

The risk of CVD attributable to low adherence is exponentially amplified in people treated for multiple cardiovascular RFs. In a Finnish study including 58,000 patients, those were adherent to both statin and antihypertensive therapies presented a 1.8-fold lower risk of death from stroke compared to subjects non-adherent to statins but adherent to BP-lowering therapy, whereas individuals adherent only to statins had a 1.3-fold increased risk. Moreover, non-adherence to both medications was associated with a 7.4-fold increase in the risk of death from stroke compared with fully adherent patient [19].

A large body of evidence supports the inverse relationship between adherence and the complexity of prescribed regimens. In this view, international guidelines recommend combinations of two or more agents in a fixed dose combination (FDC) as first-line strategies for most patients [20–22].

More recently, the development of FDCs has been advocated also for the treatment of multiple clinical conditions requiring several agents to be used simultaneously in complex regimens.

Several randomized trials have demonstrated that FDCs improve BP and cholesterol control compared to the separate administration of the individual component drugs, with a favorable safety profile and comparable rates of adverse events [23]. These results have been confirmed also in trials (FOCUS, Kanyini-GAP, IMPACT and UMPIRE) conducted in patients with previous CVD or with an estimated high cardiovascular risk, which have shown that the use of a polypill improves adherence from 25% to 40% at 12 months [24–27]. A meta-analysis of the Single Pill to Avert Cardiovascular Event (SPACE) Collaboration showed that FDCs significantly reduced systolic BP (– 2.46 mmHg, 95%CI: – 4.55 to – 0.37 mmHg) and low-density lipoprotein cholesterol (LDL-c) (–0.09 mmol/L, 95% CI – 0.18 to 0.00) compared to separate individual agents [28].

In this view, the implementation of the polypill use has been increasingly suggested as an effective strategy to improve cardiovascular prevention. However, the use of polypill is less frequent in the context of CVD, due to the relatively low level of global pharmaceutical manufacturing investment, technical challenges and skepticism by clinicians about effectiveness, safety, potential fertility and flexibility. In such a context, it should be underlined that FDCs of different pharmacological classes have been demonstrated to be a safe approach not only as a substitution therapy for patients already receiving medications, but also as a "step-up" therapy in those who were not treated or partially treated [29–32].

In this context, the combination of two widely investigated and long established drugs such as Amlodipine and Rosuvastatin represents an attractive therapeutic solution for implementing cardiovascular preventive therapies.

In this Expert Opinion paper we discuss the potential clinical use fulness of the single pill FDC "Rosuvastatin-Amlodipine" for the management of concomitant hypertension/hypercholesterolemia in different clinical settings was discussed In the present paper we also provide a synthetic report of the multidisciplinary expert panel opinion regarding the importance of an early and effective management of total CVD risk, highlighting the substantial benefits of combining BP- and lipid-lowering treatments in a single-pill FDC, we also attempted to identify and to overcome the barriers to the persistently poor implementation of the dual target FDC in clinical practice in general and with specific regard to the "Rosuvastatin/Amlodipine" single pill FDC.

2 Rosuvastatin: Italian Regulatory Policy and New Perspectives

In Italy regulatory policy identifies Rosuvastatin (both in isolated form and in association with other molecules) as a second-line drug in the therapeutic management of dyslipidemias, allowing reimbursement by the Italian National Healthcare System only after the failure to achieve recommended therapeutic targets or in case of the occurrence of adverse events with a first-line lipid-lowering drug (including Atorvastatin, Pravastatin, Fluvastatin, Lovastatin and Simvastatin). In Italy, on the other hand, the

"legge n.24 2017" also called "Gelli-Bianco" rules about the legal consequences for the physician that not apply current guidelines, guidelines that indicate the use of high-intensity statin from the beginning in many patients with high or very high cardiovascular risk. This is why many physicians do prescribe rosuvastatin as first-line statin even if the low-cost might not be reimbursed.

Indeed, despite the regulatory provision about reimbursement, the analysis of the Italian Market has shown a progressive moderate increase of the prescriptions of Rosuvastatin alone and combined to Ezetimibe in a FDC in the last years. In this context, beside the remarkable efforts made by several pharmaceutical companies to promote the prescription of these combinations, their use in probably less broad than what could be expected. However, a pivotal role is currently played by the significant reduction, both in primary and secondary prevention, of lipid levels targets recommended by international guidelines on the basis of a wide literature [21, 22, 33]. Based on the remarkable scientific literature and authoritative studies performed on Rosuvastatin [34–42] in different clinical settings and published on leading international journals, a much larger number of patients could potentially benefit from the use of this effective and safe lipid-lowering drug to achieve the therapeutic goals currently recommended by all main international guidelines.

Indeed, as shown by several systematic reviews and meta-analyses [39–42], Rosuvastatin is the most effective among high-potency statins (with the exception of Pitavastatin, which however is not widely available) [43] in reducing both total and low density lipoprotein cholesterol (LDL-c). Furthermore, Rosuvastatin is also most effective in increasing high-density lipoprotein cholesterol (HDL-c) levels improving the overall metabolic profile of patients affected by metabolic syndrome. Indeed, the STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin) study showed that rosuvastatin significantly reduced non-HDL-C, apo B, and all lipid and apolipoprotein ratios assessed, compared to milligram-equivalent doses of atorvastatin and milligram-equivalent or to higher doses of simvastatin and pravastatin (all, $P < 0.002$). Rosuvastatin reduced non-HDL-C by 42.0–50.9% compared with 34.4–48.1% with atorvastatin, 26.0–41.8% with simvastatin, and 18.6–27.4% with pravastatin [36, 37].

Beside the class effect of statins to stabilize and slow-down the progression of atherosclerotic plaques, Rosuvastatin has been demonstrated to induce the regression of coronary lesions measured by intravascular ultrasound (IVUS) [44, 45]. Furthermore, in a study conducted with IVUS-virtual histology, Rosuvastatin reduced necrotic core and plaque volume and decreased thin-cap fibroatheroma rate independently from the dose of administration [46]. Finally, due to its combined lipid-lowering-anti-inflammatory effect [47], Rosuvastatin can reverse the carotid plaque burden in patients suffering from systemic inflammatory diseases such as rheumatoid arthritis [48].

In Italy only 1 out of 9 patients on statins is treated with Rosuvastatin while Atorvastatin is used more frequently partly because Atorvastatin is routinely selected for in-hospital treatment of acute coronary syndrome [49]. On the other hand, an early use of Rosuvastatin in acute settings, even at low-doses, is useful and effective to achieve more rapidly the recommended therapeutic targets, to improve prognosis and to implement adherence also in view of the good tolerability profile [34–42]. Indeed, it seems reasonable to believe that it is more likely to maintain lipid targets over time if they are reached as quickly as possible, with a high potency statins. In fact, international guidelines recommend using high potency statins such as Rosuvastatin and Atorvastatin at the highest tolerable dose to reach therapeutic goals [21].

3 The FDC Rosuvastatin-Amlodipine

In the context of hypertension management, the most recent European Guidelines recommend starting treatment with a dual combination of BP-lowering drugs (angiotensin converting enzyme inhibitors /angiotensin receptor blockers plus calcium channel blockers [CCB] or thiazide like diuretics) [20]. In these guidelines, Amlodipine represents 0ne of the first-line effective BP-lowering drugs and, in those patients who present the coexistence of dyslipidemia, the association with statins, in a FDC may appear as a reasonable and feasible solution in clinical practice, also in consideration of the long half-life of this dihydropyridine CCB which provides 24-hour BP lowering effect. In view of a "paradigm shift" towards an approach of a global cardiovascular risk management, this FDC may reduce not only BP and lipid levels, but also contribute to reduce cardiovascular events and mortality, by treating the patients in their complexity [50, 51]. Indeed, the association of Rosuvastatin-Amlodipine, addressing two major cardiovascular RFs simultaneously in a simple and effective way, meets the requirements implied by a more thorough cardiovascular prevention. Moreover, this combination provided in the single-pill formulation appears to be more effective in reducing both BP and lipid values than the two separate agents [51, 52]. Kim and colleagues showed that subjects who received the association Rosuvastatin-Amlodipine achieved the greatest reduction in systolic and diastolic BP levels and in LDL-c levels compared to those who were treated with only Rosuvastatin or Amlodipine. The percentage of patients in which systolic and diastolic BP levels decreased ≥20 mmHg and ≥10mmHg, respectively (about 74%), and in which LDL-c

targets were reached (about 92%) was also highest in the Rosuvastatin-Amlodipine group [51].

4 Potential Implications in Clinical Practice

Different categories of patients may take advantages from the single pill FDC Rosuvastatin-Amlodipine (Summarized in Table 1):

(1) Subjects at low estimated cardiovascular risk with both high-normal BP (SBP between 130 and 139 mmHg and DBP between 85 and 90 mmHg) or grade 1 hypertension (SBP between 140 and 159 mmHgand DBP between 90 and 99 mmHg), in which a single antihypertensive agent may be sufficient, and moderate dyslipidemia, in which treatment with ezetimibe is not required [53]. In these individuals, the concept that "the earlier, the better" may be appropriate, with great long-term cardiovascular benefits [54].
(2) Subjects with the "JUPITER" type phenotype, consisting in metabolic syndrome, high-normal BP and elevated high-sensitive C-reactive (hs-CRP) levels. In the JUPITER study [35], indeed, Rosuvastatin (20 mg/day) lowered LDL-c by 55% and hsCRP by 36%, significantly reducing the risk of MACE.
(3) Subjects with intermediate cardiovascular risk. In the HOPE-3 study conducted in 12,705 participants who did not have CVD and were at intermediate risk rosuvastatin 10 mg per day significantly reduced the first coprimary outcome of death from cardiovascular causes, nonfatal MI, or nonfatal stroke, and the second coprimary outcome of revascularization, HF, and resuscitated cardiac arrest [55].
(4) Patients with multiple comorbidities or treated with complex polytherapies, such as those with HIV on HAART [56], those who receive aromatase inhibitors [56], cancer patients in chemotherapy. In these categories, the use of a safe FDC could at least partially reduce the risk of assumption mistakes and of adverse interactions among the different drugs [56, 57].
(5) Patients who have experienced an ischemic stroke. Amlodipine plays a very important role in the prevention of ischemic stroke, as demonstrated by the ASCOT study [58]. Moreover, patients with cerebrovascular disease often need to take lipid-lowering therapy and Rosuvastatin has been shown to reduce by about 50% the recurrence of ischemic stroke [59, 60].
(6) Diabetic patients with high or very-high cardiovascular risk, in which both BP and lipid targets are very stringent according to the most recent Guidelines [61]. To pursue these ambitious objectives, Rosuvastatin, the most powerful high intensity statin with very solid evidence in diabetics, may be proposed as a first therapeutic choice [62]. Moreover, in diabetic patients the combination of the ACEi Benazepril + Amlodipine was superior in terms of cardiovascular endpoints (− 18%, HR 0.82, p = 0.02) compared to

Table 1 Different categories of patients may take advantages from this FDC of "Rosuvastatin-Amlodipine"

Category of patients who may benefit from the FDC "Rosuvastatin-Amlodipine"	Clinical features
Hard-To-Control Hypertensive Patients	Patients who do not achieve BP control with a double antihypertensive therapy in a FDC. A triple antihypertensive therapy in a "dissociated" form may be prescribed: two pills including four active medications
Substitution therapy	Patients who effectively take separately the two drugs especially in complex therapeutic regimens
Patients simultaneously affected by high-normal BP/grade 1 hypertension and moderate dyslipidaemia	Subjects at low estimated CV risk in which a single antihypertensive agent is sufficient to control BP and ezetimibe is not required to manage dyslipidaemia
"JUPITER" Patients	Patients presenting with metabolic syndrome, high-normal BP and elevated high-sensitive C-reactive levels regardless of lipid values
Patients on Polytherapies	Patients with multiple comorbidities on polytherapies (eg elderly, HIV patients on HAART, cancer patients in chemotherapy). The use of a safe FDC could reduce the risk of assumption mistakes and of adverse interactions
Patients who have experienced an ischemic stroke	Both amlodipine and Rosuvastatin play a very important role in the prevention and treatment of ischemic stroke
Diabetic patients	In diabetics both BP and Lipid targets are very stringent. To get these targets, Rosuvastatin is the most powerful high-intensity statin and Amlodipine is one of the antihypertensive agents of choice in diabetics

BP blood pressure, *CV* cardiovascular, *FDC* fixed dose combinations, *HIV* human immunodeficiency virus, *HAART* highly active antiretroviral therapy

the association of Benazepril + hydrochlorothiazide, with a lower risk of worsening of renal function [63]. Another important issue to consider is that increasing adherence and therapeutic compliance is essential to cope with chronic diseases such as diabetes. A retrospective cohort study conducted on 11,532 diabetic patients showed that those who adhered to the prescribed therapy had better BP, glucose and lipid control and a reduced risk of all-cause mortality (4.0% vs 5.9%, $p < 0.001$) and hospitalizations (19.2% vs 23.2%, $p < 0.001$) [64]. Another study showed that the costs related to hospitalization of diabetics are significantly higher in non-adherent patients [65]. Therefore, ensuring adequate therapeutic compliance is also sustainable in pharmacoeconomic terms. In such a context, a strategy that has proved extremely effective in improving therapeutic adherence is exactly the prescription of FDCs such as Rosuvastatin-Amlodipine [24, 30, 31].

(7) Patients already taking separately Rosuvastatin and Amlodipine with good results within a complex therapeutic scheme (substitution therapy)

(8) Patients who do not achieve BP control with a double antihypertensive therapy in a FDC. A triple antihypertensive therapy in a "dissociated" form can represent a solution. The combination of Rosuvastatin-Amlodipine could allow to manage concomitant RFs with just two pills including four active medications. For instance, through single-pill FDC with a renin angiotensin-system blocker plus a thiazide-like diuretic. The combinations of different FDC offers many advantages and is a novel way to reduce cardiovascular risk by enhancing adherence and persistence in drug therapy.

5 Conclusion

In conclusion, although not yet broadly adopted in the clinical practice, the single-pill FDC "Rosuvastatin-Amlodipine" represents a rational combination of two effective, evidence-based, safe and well tolerated drugs to approach the treatment of two major RFs like hypertension and hypercholesterolemia, hence reducing cardiovascular events and their related burden. This multidisciplinary Expert Panel composed by physicians with competence in the different areas prevention of cardiovascular disease believes that this FDC could prove to be an extremely useful approach in different clinical settings (e.g. diabetics, patients who have experienced an ischemic stroke, etc..) both for increasing drug adherence in complex patients suffering from multiple diseases and for reducing the global burden of cardiovascular disease.

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Declarations

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