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Dear Dr. Hamburg and Dr. Woodcock:

Public Citizen, representing more than 300,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352, and 21 C.F.R. §§ 10.30 and 201.56, to immediately require the following:

(1) The addition of a black box warning to the label for all medications containing angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), and aliskiren, indicating that the three drug classes, when used in any

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combination (an ACE inhibitor with an ARB, or either drug with aliskiren) present an increased risk of renal failure, symptomatic hypotension, and hyperkalemia, with no countervailing clinical benefit compared with any of the drug classes used alone. At present, combination therapy is addressed, wholly inadequately, in the labels of aliskiren and five (ramipril, telmisartan, valsartan, candesartan, and losartan) of the 18 ACE inhibitor/ARB drugs, and the warnings on these six drugs are dangerously insufficient.

(2) The mandatory distribution of FDA-approved patient Medication Guides for all medications containing ACE inhibitors, ARBs, and aliskiren, alerting patients to this risk. These guides should be dispensed prior to the administration of the first dose of these medications.

(3) The distribution by all manufacturers of these drugs of a "Dear Doctor" letter alerting physicians and other health care professionals to the risk, with instructions on optimal titration of ACE inhibitor, ARB, and aliskiren monotherapy as an alternative to combination therapy.

(4) The immediate removal of the following assertion in the Indications and Usage section of the candesartan (an ARB) label: "ATACAND [candesartan] also has an added effect on these outcomes [of reducing cardiovascular death and heart-failure hospitalizations] when used with an ACE inhibitor." This is based on a non-standardized clinical trial, and the label fails to include any mention of a more rigorous trial that showed no added benefit of combination therapy with candesartan on these same outcomes in patients taking standardized doses of the ACE inhibitor enalapril.

I. BACKGROUND

The renin-angiotensin-aldosterone system (RAAS) is one of the body's main mechanisms for regulating blood pressure. In response to low blood pressure, low blood volume, or low sodium concentration, the kidneys secrete renin, the first hormone in the RAAS axis that enzymatically cleaves the pro-hormone angiotensinogen to angiotensin I. Angiotensin I is then converted to angiotensin II by the angiotensin-converting enzyme (ACE) circulating in the blood. Angiotensin II acts as a potent vasoconstrictor and also triggers the release of aldosterone from the adrenal gland, which further increases blood pressure through direct vasoconstriction and sodium retention in the kidneys.

Both ACE inhibitors and ARBs lower blood pressure by inhibiting angiotensin II. ACE inhibitors decrease the production of angiotensin II through inhibition of ACE, while ARBs block the action of angiotensin II, once produced, through inhibition of the angiotensin II receptor. Aliskiren (which is discussed in further detail in Section II-D) is the first of a new class

of drugs called direct renin inhibitors, which inhibit the activity of renin further upstream in the RAAS pathway.

ACE inhibitors, ARBs, and aliskiren are all of great benefit when used alone in treating high blood pressure (hypertension). ACE inhibitors and ARBs are also vital in slowing the progression of several serious diseases, such as congestive heart failure (CHF), cardiovascular disease, and chronic kidney disease (CKD) and are among the top-selling medication classes in the country. In 2011, 164 million ACE inhibitor prescriptions (fifth most of any drug class) and 86 million ARB prescriptions (16th most) were dispensed[1] (in addition to 2.4 million aliskiren prescriptions[2]). ARBs alone generated $7.6 billion in revenue in 2011.[3]

An estimated 1.3 million people were on both ACE inhibitors and ARBs in the U.S. as of 2004.[4] A Canadian study found that 5.4% of new users of either ACE inhibitors or ARBs between 2002 and 2006 in a Canadian province, Alberta, were on both therapies.[5] An Irish study found that co-prescription of ACE inhibitors and ARBs had risen in Ireland over 30-fold between 2000 and 2009.[6]

The use of ACE inhibitor and ARB drugs together became common due to the theoretical belief that combination therapy may confer a synergistic benefit in patients with myriad conditions ranging from hypertension to CKD. ACE inhibitors suppress most, but not all, angiotensin II production and many patients may adjust to chronic ACE inhibitor therapy by partly overcoming the inhibition of ACE, producing more of the precursors to angiotensin II (renin and angiotensin I).[7] For these reasons, it was thought that the addition of an ARB to ACE inhibitor therapy would complement the latter's inhibition of angiotensin II production by blocking the hormone's action at the sites where it worked.

This is, however, a classic case of theory not translating into clinical significance. While combination therapy does have predictable effects on surrogate markers, including blood pressure and proteinuria, the evidence is clear that such added effects confer no clinical advantage over monotherapy in any patient population. Furthermore, combination therapy is dangerous. It has been shown to cause a higher incidence of serious adverse effects, some life-threatening, including symptomatic hypotension, renal dysfunction (in some cases requiring dialysis), and hyperkalemia, compared with treatment with either drug class alone. This unfavorable benefit-risk profile has been demonstrated consistently across multiple patient populations and medications studied in all adequately controlled trials to date.

Evidence is reviewed below for the various effects of ACE inhibitor/ARB combination therapy compared with monotherapy in patients with: (a) hypertension, (b) CHF and vascular disease (including in diabetics), and (c) proteinuria and CKD (including in diabetics). The single study related to use of either of these two drug classes with aliskiren in patients with diabetes is

discussed in Section II-D. This is followed by a request for a black box warning advising against use of combination therapy with any of these three drug classes.

II. STATEMENT OF GROUNDS

A. Hypertension

The evidence to date indicates that ACE inhibitor and ARB therapies, when used alone, reduce systolic and diastolic blood pressure (SBP and DBP, respectively) and improve clinical outcomes in hypertensive patients. When used together as combination therapy in these patients, both SBP and DBP are reduced further, but as seen in larger trials, this improvement in surrogate measures does not translate into any added clinical benefit, only additional harm to patients.

The candesartan and lisinopril microalbuminuria I and II (CALM I and II) studies were small, randomized trials that compared ACE inhibitor/ARB combination therapy to monotherapy in patients with hypertension and diabetes.[8,9]

The CALM I study, published in 2000, randomized 199 patients with microalbuminuria, hypertension, and type II diabetes mellitus (DM) to treatment of candesartan 16 milligrams per day (mg/day) or lisinopril 20 mg/day for 12 weeks, at which point patients were either assigned to continue with monotherapy or were placed on ACE inhibitor/ARB combination therapy for the remaining 12 weeks of the study.[10] The primary outcomes were changes in blood pressure and urinary albumin excretion. At 24 weeks, there was a significantly greater mean reduction in both SBP and DBP with combination treatment than in either candesartan or lisinopril monotherapy (adjusted mean difference for SBP 11.2 mm Hg, p=0.002, and 8.6 mm Hg, p=0.02; and DBP 5.9 mm Hg, p=0.003, and 5.6 mm Hg, p=0.005, for candesartan and lisinopril, respectively). Creatinine clearance was slightly decreased at 24 weeks in those treated with combination treatment (adjusted mean decrease 0.0735 milliliters per second [ml/sec], p=0.05) and lisinopril (0.0835 ml/sec, p=0.04) but not in the candesartan-treated group. Combination-therapy patients also experienced slight increases in potassium (0.30 millimoles per liter [mmol/L]) at 24 weeks. However, the validity of the study was limited by a large number of withdrawals (55 out of 199 patients) before the 24-week assessment.

The subsequent CALM II study, published in 2005, compared ACE inhibitor/ARB combination therapy to ACE inhibitor monotherapy in 75 patients with type 1 or type 2 DM and hypertension to determine long-term effects of combination therapy on SBP in patients with hypertension and diabetes.[11] All patients had an SBP level of 120-160 mm Hg while on lisinopril 20 mg/day and were randomized to treatment with either 40 mg/day lisinopril monotherapy or 20 mg/day lisinopril with 16 mg/day candesartan (combination therapy) for 12 months. One critical baseline difference between the groups was that 20 combination-therapy patients were on concomitant

antihypertensive thiazide therapy, compared with only eight in the monotherapy group. Unlike CALM I, CALM II found no significant differences in mean daytime, nighttime, or 24-hour SBP change between the combination-therapy and monotherapy groups, although there was a trend in favor of combination therapy in reducing SBP (the trial was likely underpowered to detect a significant difference). This was perhaps because the monotherapy control group was given a higher dose of lisinopril (40 mg/day) in CALM II than in CALM I (20 mg/day). There were also no significant differences in rates of adverse events, creatinine clearance, or serum potassium levels between the groups.

Shortly after the publication of CALM II, in 2005, a meta-analysis of randomized trials comparing combination therapy to monotherapy in the treatment of hypertension was published.[12] Twenty-four hour ambulatory blood pressure was reduced with combination therapy relative to ACE inhibitor (4.7/3.0 mm Hg; 95% CI: 2.9-6.5/1.6-4.3) and ARB (3.8/2.9 mm Hg; 95% CI: 2.4-5.3/0.4-5.4) monotherapies. Combination therapy also reduced blood pressure measured in the clinic by 3.8/2.7 mm Hg (0.9-6.7/0.8-4.6) and 3.7/2.3 mm Hg (0.4-6.9/0.2-4.4) compared with ACE inhibitor and ARB therapy, respectively. However, the majority of the studies used submaximal doses or once-daily dosing of shorter-acting ACE inhibitor monotherapy. When a longer-acting ACE inhibitor was used in one study, the additive effect of the ARB on blood pressure largely disappeared. Consistent with larger trials, combination therapy significantly reduced proteinuria by 30% and 39% compared with ACE inhibitor and ARB monotherapy, respectively. There were no significant differences in safety outcomes, although three studies did report a small increase in serum potassium (0.3 mmol/L) in combination-therapy patients.

However, all trials were exceedingly small, with fewer than 100 patients on combination therapy in any one study. The trials were also short term, ranging from four to 12 weeks, with one exception (one trial lasted 2.9 years). Therefore, almost all of the trials were not adequately powered to detect significant differences in rates of adverse events (or other clinically significant outcomes).[a] The authors concluded that there may be a small additive effect on blood pressure with combination therapy, but they did not recommend the routine use of such therapy before more adequate studies could be performed.

In a more recent trial, 54 patients with non-diabetic nephropathy on ACE inhibitor therapy (lisinopril 40 mg/day) were randomized in a double-blind crossover trial in four consecutive six-week periods to combination therapy with an ARB (valsartan 320 mg/day) or monotherapy with a placebo, each combined consecutively with a low-sodium or regular-sodium diet.[13] The primary outcome was proteinuria, with blood pressure a secondary outcome. Combination

[a] (p.885) The authors of the meta-analysis stated that, "perhaps with the exception of the study by Nakao et al [the trial lasting 2.9 years], none of these studies was of sufficient size and duration to properly assess the safety of combining ACEI and ARB."

therapy only significantly reduced mean DBP (p=0.02) but not SBP (p=0.12) compared with ACE inhibitor monotherapy. The addition of a low-sodium diet to ACE inhibitor monotherapy significantly reduced both SBP (p<0.001) and DBP (p<0.001) to a greater extent than combination therapy.

Summary of the evidence concerning combined ACE inhibitor/ARB effects on blood pressure

These studies of combination therapy in hypertensive patients were small and, for the most part, of short duration. Nevertheless, combination therapy seemed to confer a consistent reduction in both SBP and DBP, an observation confirmed in larger and longer-term trials comparing combination therapy to monotherapy in patients with cardiovascular disease, including CHF. However, unlike the trials presented above, these larger trials also definitively addressed the clinical significance of this blood pressure reduction and are discussed below.

B. CHF and Cardiovascular Disease

For patients with significant cardiovascular disease, including CHF, ACE inhibitor and ARB monotherapies are clearly beneficial, life-saving treatments. The authors of the 2008 Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), the latest trial showing such a benefit, observed that the evidence from prior randomized, controlled trials (RCTs) showed that ACE inhibitor and ARB therapies, used alone, reduced fatal and nonfatal cardiovascular events in patients with CHF, left ventricular dysfunction, vascular disease, hypertension, and diabetes.[14] However, ACE inhibitor/ARB dual therapy is more harmful than beneficial to those same patients. The largest long-term RCTs, including ONTARGET, comparing combination therapy to monotherapy in patients with CHF and cardiovascular disease are reviewed below.

Standardized versus non-standardized trials

Trials assessing ACE inhibitor/ARB combination therapies in patients with CHF and cardiovascular disease are classified in this petition either as standardized studies or non-standardized studies.

In standardized studies, patients were randomized to one of three treatment groups: ACE inhibitor/ARB combination therapy, ACE inhibitor monotherapy, or ARB monotherapy. All patients in each group were assigned to receive the same ACE inhibitor and ARB medication at identical doses, with patients stratified into subgroups in trials testing more than one dose of each therapy. Both patients and doctors were blinded to all treatment assignments.

In non-standardized studies, patients already on ACE inhibitor therapy at the start of the trial were randomized to one of two treatment groups: ARB therapy or a placebo. Patients were not randomized with respect to ACE inhibitor therapy but merely continued on pre-existing regimens consisting of different ACE inhibitor medications at varying doses, with some patients in one study on no ACE inhibitor therapy at all. Additionally, neither patients nor doctors were blinded to the ACE inhibitor treatment.

Thus, standardized and non-standardized trials were based on starkly different study designs. In standardized trials, randomization with respect to both ACE inhibitor and ARB therapies ensured that the role of confounding variables would be minimized, blinding to both therapies guarded against potential bias, and the standardization of both ACE inhibitor and ARB treatments allowed investigators to systematically compare the effects of differing regimens. The absence of these critical elements with respect to *both* ACE inhibitor and ARB therapies prevented such a comparison in non-standardized trials. For these reasons, the results of the standardized trials reviewed below are more valid indicators of the benefits and risks of combination therapy relative to monotherapy.

Standardized ACE inhibitor/ARB therapy combination trials in vascular disease with or without CHF

The 1999 Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial compared an ACE inhibitor/ARB combination therapy (enalapril 10 mg twice daily and candesartan at either 4 or 8 mg/day) with both ACE inhibitor (enalapril at 10 mg twice daily) and ARB (candesartan at 4, 8, or 16 mg/day) monotherapies in patients with New York Heart Association (NYHA) class II–IV CHF.[15] The trial was designed to look primarily at surrogate outcomes of ventricular function and neurohormonal levels but also assessed clinical outcomes. A total of 768 patients with an ejection fraction of less than 40% were randomized to one of the three therapies for 43 weeks.

Patients on combination therapy displayed significantly greater reductions in SBP and DBP relative to patients on monotherapy with either drug class. However, this difference in blood pressure reduction did not translate into a significant improvement in mortality, hospitalizations for CHF, hospitalizations for any reason, activity-related symptoms (by NYHA class), quality of life, or left ventricular ejection fraction (LVEF; although a trend toward improvement was present on this final outcome) when compared to ACE inhibitor or ARB monotherapy (perhaps due to a lack of power, as the trial was primarily designed to look at surrogate outcomes). In addition, patients on combination therapy had higher increases in mean serum potassium levels (0.13 mmol/L increase at 17 weeks; 0.11 mmol/L increase at 43 weeks) than those on ACE inhibitor therapy alone (0.00 mmol/L change at 17 weeks; -0.01 mmol/L decrease at 43 weeks; $p<0.05$). There were no significant differences in rates of renal dysfunction or symptomatic

hypotension, but this was, again, likely due to a lack of power (only 12 patients across all groups suffered either adverse event).

The Valsartan in Acute Myocardial Infarction (VALIANT) trial was a landmark study that compared ACE inhibitor/ARB combination therapy with both ACE inhibitor and ARB monotherapy in patients who had suffered acute myocardial infarction (MI) complicated by clinical or radiologic signs of CHF and/or evidence of left ventricular systolic dysfunction.[16] A total of 14,703 patients were randomized to groups of ACE inhibitor (captopril), ARB (valsartan), or ACE inhibitor/ARB (captopril/valsartan) combination therapies, and they were followed for a median of 24.7 months. ACE inhibitor monotherapy was begun at 6.25 mg/day and gradually increased to a target dose of 50 mg three times daily. ARB monotherapy was begun at 20 mg/day and gradually increased to a target dose of 160 mg twice daily. ACE inhibitor/ARB combination therapy was begun at 6.25 mg/day of captopril and 20 mg/day of valsartan and gradually increased to a target dose of 50 mg three times daily and 80 mg twice daily, respectively.

As with most other trials, those on ACE inhibitor/ARB combination therapy achieved minimally lower, or equivalent, systolic and diastolic blood pressures (125/75) compared with those on ACE inhibitor (127/76) or ARB monotherapies (127/75) ($p<0.001$ for combination versus ACE inhibitor therapy, for both systolic and diastolic comparisons). However, despite this lower blood pressure, ACE inhibitor/ARB combination therapy did not reduce overall mortality, the primary endpoint, relative to ACE inhibitor therapy (HR 0.98, 97.5% CI: 0.89, 1.09), or the rate of the secondary composite outcome of death from cardiovascular causes, recurrent MI, or hospitalization for CHF (HR 0.97, 97.5% CI: 0.89, 1.05). A post-hoc analysis did show that combination therapy was superior to ACE inhibitor monotherapy on one outcome: namely, reducing hospital admissions for either MI or CHF ($p=0.005$ for the comparison of the proportion of patients admitted, and $p=0.007$ for the comparison of the number of admissions, between the groups).

But ACE inhibitor/ARB combination-therapy patients had higher rates of drug discontinuation at one year than ACE inhibitor-only patients (19.0% vs. 16.8%; $p=0.007$) and ARB-only patients (19.0% vs. 15.3%; p-value not reported), and a higher rate of drug discontinuation due to adverse events than ACE inhibitor-only patients (9.0% vs. 7.7%; $p<0.05$) and ARB-only patients (9.0% vs. 5.8%; p-value not reported). Two adverse events, hypotension and renal dysfunction/increased serum creatinine levels, which led to either a reduction in, or permanent discontinuation of, one or more study drugs, occurred at a significantly higher rate in the ACE inhibitor/ARB combination-therapy group than in the ACE-only group.

The 2008 ONTARGET study was the largest trial to date assessing whether ACE inhibitor/ARB combination therapy results in superior cardiovascular outcomes relative to monotherapy.

ONTARGET compared ACE inhibitor/ARB (ramipril 10 mg/day and telmisartan 80 mg/day) combination therapy with either drug alone in patients with vascular disease or diabetes with end-organ damage.[17] Patients were followed for a median of 56 months. The primary endpoint was a composite of death from cardiovascular causes, MI, stroke, or hospitalization for CHF.

Those receiving ramipril/telmisartan combination therapy had lower mean SBP (2.4 mm Hg lower) and DBP (1.4 mm Hg lower) than those on ramipril alone over the study period. But again, this improvement in blood pressure with combination therapy did not result in lower rates of the primary outcome (relative risk [RR] 0.99, 95% CI: 0.92-1.07), or any individual component of the primary outcome, than ramipril alone. Overall mortality was also not significantly different between these two groups and was slightly higher in those on combination therapy (RR 1.07, 95% CI: 0.98-1.16, for combination versus ACE inhibitor therapy).

As with RESOLVD and VALIANT, the ACE inhibitor/ARB combination group in ONTARGET incurred an increased risk of adverse events. The combination-therapy group had significantly higher rates of drug discontinuation for any reason (29.3% in the combination group versus 24.5% in the ACE inhibitor-only group and 23.0% in the ARB-only group, $p<0.001$), and due to hypotensive symptoms (4.8% vs. 1.7% vs. 2.7%, $p<0.001$), syncope (0.3% vs. 0.2% vs. 0.2%, $p=0.03$), and renal impairment (1.1% vs. 0.7% vs. 0.8%, $p<0.001$; all p-values correspond to comparison of rates with combination versus ACE inhibitor-only therapy; see **Table 1**). Combination-therapy patients also had higher overall rates of renal impairment as reported by clinical investigators (13.5%) than those on ACE inhibitor (10.2%; $p<0.001$) or ARB (10.6%) therapy alone. (Renal adverse event details are described further in the section entitled "Proteinuria and CKD.") More patients had increases of greater than 5.5 mmol/L in their serum potassium level on combination therapy (480 patients) than either the ACE inhibitor-only group (283 patients) or the ARB-only group (287 patients; $p<0.001$ for comparison between combination and ACE inhibitor-only group).

The ONTARGET authors observed that the absence of any clinical benefit from the blood pressure reduction in the combination-therapy group mirrored the VALIANT findings. They speculated that this phenomenon may be due to the already well-controlled blood pressure profiles of the patients studied, rendering further marginal blood pressure reduction clinically insignificant. Another hypothesis was that the higher incidence of adverse effects with combination therapy compared with monotherapy offset any expected clinical benefits from the blood pressure reduction. Regardless of the possible mechanism, the authors concluded that "taken together, these two studies [VALIANT and ONTARGET] showed no additive [beneficial] effect for an ARB in conjunction with a full dose of a proven ACE inhibitor."

Addition of ARB to baseline ACE inhibitor therapy: Non-standardized ACE inhibitor/ARB "combination" trials in CHF

Two large RCTs have been conducted in which combination therapy was studied indirectly. ARB therapy was compared with a placebo in patients already on ACE inhibitor therapy; the trials did not standardize the specific type or dose of ACE inhibitor. As previously explained, the lack of standardization of ACE inhibitor therapy between the groups makes it more difficult to draw definitive conclusions from these studies, compared with standardized studies, on the relative merits of ACE inhibitor/ARB combination therapy versus monotherapy.

The 2003 Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity ("CHARM-Overall") trial was designed to test the addition of ARB therapy to standard medical therapy in patients with NYHA class II–IV CHF.[18] In CHARM-Overall, three groups of patients were studied: (a) patients with LVEF >40% ("CHARM-Preserved"),[19] (b) patients with LVEF≤40% who were on ACE inhibitor therapy at baseline ("CHARM-Added"),[20] and (c) patients with LVEF≤40% not on ACE inhibitor therapy at baseline ("CHARM-Alternative"). Only the CHARM-Added trial was able to evaluate the effect of ACE inhibitor/ARB combination therapy relative to ACE inhibitor monotherapy, as discussed below.[b]

In CHARM-Added, 2,548 of the CHARM-Overall patients with NYHA class II–IV CHF and LVEF≤40% on baseline ACE inhibitor therapy were randomized to treatment with an ARB (candesartan, initially at 4 or 8 mg/day, gradually titrated to a target dose of 32 mg/day) or a placebo.[21] The primary outcome of the study was the composite of cardiovascular death or unplanned hospital admission for CHF. Patients were followed for a median of 41 months. Fewer patients in the candesartan group (38%) experienced the primary outcome than in the placebo group (42%; covariate adjusted HR 0.85, p=0.010). Candesartan also reduced each of the individual components of the primary outcome, cardiovascular mortality and hospital admissions for CHF, individually, relative to placebo. The addition of candesartan caused a significant increase in adverse events related to drug therapy. Patients given the ARB experienced higher rates of creatinine increases (7.8% vs. 4.1% for placebo, p=0.0001), hyperkalemia (3.4% vs. 0.7%, p<0.0001), and (not significantly) hypotension (4.5% vs. 3.1%, p=0.079) leading to drug discontinuation. Consistent with other trials, patients on ARB/ACE inhibitor therapy discontinued the study drug due to "any adverse event or laboratory abnormality" at higher rates than those receiving ACE inhibitor plus a placebo (24.2% vs. 18.3%, p=0.0003).

The 2001 Valsartan Heart Failure Trial (Val-HeFT) randomized 5,010 patients with NYHA class II–IV CHF to ARB therapy (valsartan, initially at 40 mg twice daily, gradually titrated to a target

[b] In the CHARM-Preserved trial, only 19-23% of patients in both groups were on ACEIs [20% at baseline and study end in the ARB group; 19% at baseline and 23% at study end in the placebo group; see Yusuf et al. 2003], while in CHARM-Alternative, no patients were on ACEIs as a condition of study entry.

dose of 160 mg twice daily) or a placebo as an addition to standard therapy (any combination of ACE inhibitors, diuretics, digoxin, and beta-blockers).[22] Not all patients (only 93% in each group) were on ACE inhibitor therapy. There was no significant difference in mortality between the two groups. Patients receiving ARB therapy did have a reduced incidence of a combined endpoint of mortality and a range of morbidity outcomes (RR 0.87; 97.5% CI: 0.77, 0.97), which was largely due to a lower number of hospitalizations for CHF. ARB patients also showed improvements in activity-related symptoms (NYHA class), signs and symptoms of CHF, and quality of life ($p<0.01$ for all three outcomes).

Subgroup analyses were performed to distinguish between patients on any combination of ACE inhibitor and beta blocker therapy. Among patients on ACE inhibitor therapy and not on beta blockers, the addition of ARB therapy was effective in reducing rates of the combined mortality/morbidity endpoint and tended toward significance in reducing mortality. But, in patients on both ACE inhibitor and beta blocker therapy, the addition of an ARB was found to significantly increase mortality ($p=0.009$), which the authors speculated may have been due to excessive neurohormonal inhibition with all three drugs. It should be noted that there was no such interaction between ACE inhibitor and beta blocker therapy in the subsequently published CHARM-Added trial.[23]

There were no subgroup analyses by ACE inhibitor treatment status for adverse events. Patients on ARBs experienced higher rates, relative to placebo, of discontinuation due to adverse events (9.9% vs. 7.2%, respectively; $p<0.001$), with dizziness (1.6% vs. 0.4%; $p<0.001$), hypotension (1.3% vs. 0.8%; $p=0.124$), and renal impairment (1.1% vs. 0.2%; $p<0.001$) the most common adverse events leading to discontinuation in the ARB group. Mean changes in blood urea nitrogen (5.9 mg/dl ARB vs. 3.3 mg/dL placebo; $p<0.001$), creatinine (0.18 mg/dL vs. 0.10 mg/dL; $p<0.001$), and potassium (0.12 mmol/L increase versus 0.07 mmol/L decrease; $p<0.001$) serum concentrations were all greater in ARB-treated patients than in those getting a placebo.

Meta-analyses of standardized and non-standardized ACE inhibitor/ARB combination-therapy trials in CHF

Two meta-analyses have been published pooling data from four of the five major RCTs described above (RESOLVD, VALIANT, CHARM-Added, and Val-HeFT; ONTARGET was not included in either) to determine the relative efficacy and safety of combination therapy versus standard medical therapy (which included ACE inhibitors in almost all cases), in patients with CHF and left ventricular dysfunction.

The first was a 2007 meta-analysis by Phillips, et al., published just prior to ONTARGET's release, evaluating only the adverse effects of combination therapy.[24] The study analyzed all large RCTs (500 or more subjects with three or more months of follow-up) of ACE

inhibitor/ARB combination therapy in patients with symptomatic left ventricular dysfunction through 2006. Several adverse effects were analyzed, including worsening renal function, hyperkalemia, symptomatic hypotension, and drug discontinuation due to adverse events. Four studies (RESOLVD, VALIANT, CHARM-Added, and Val-HeFT) of 17,337 patients with a mean follow-up of approximately two years were included. Combination treatment significantly increased discontinuations because of adverse effects in both patients with CHF (RR 1.38 [95% CI: 1.22-1.55]) and those with acute MI with symptomatic left ventricular dysfunction (RR 1.17 [95% CI: 1.03-1.34]) on standard medical therapy, including ACE inhibitors alone. For both sets of patients, combination therapy also led to higher rates of worsening renal function (RR 2.17 [95% CI: 1.59-2.97] and RR 1.61 [95% CI: 1.31-1.98], for CHF and acute MI patients, respectively), hyperkalemia (RR 4.87 [95% CI: 2.39-9.94] and RR 1.33 [95% CI: 0.90-1.98], respectively), and symptomatic hypotension (RR 1.50 [95% CI: 1.09-2.07] and RR 1.48 [95% CI: 1.33-3.18], respectively).

In the second meta-analysis, published in 2010, Kuenzli, et al., evaluated both the efficacy and safety of combination therapy in the four major RCTs and four smaller trials, encompassing 18,061 patients in total. The meta-analysis included all RCTs comparing ARB/ACE inhibitor combination therapy with ACE inhibitor therapy alone in patients with left ventricular dysfunction or CHF, with follow-up of at least six months and with reported mortality and hospitalization outcomes.[25] The vast majority of trial subjects had NYHA class II–III CHF with mean LVEF ranging between 25% and 35%. Combination therapy did not reduce mortality, hospitalizations for any reason, or fatal or nonfatal MI compared with monotherapy. Although a reduction in hospitalization for CHF was found (RR 0.81, 95% CI: 0.72-0.91), there was significant heterogeneity across the trials reporting this outcome (p-value for heterogeneity = 0.04). Across many of the trials, adverse events were undefined, and/or reporting was inconsistent. Nevertheless, patients receiving combination therapy experienced significantly higher rates of worsening renal function, symptomatic hypotension, and permanent discontinuation of study drugs. Higher rates of hyperkalemia were also reported for the combination arm, though this did not reach statistical significance (RR 1.95, 95% CI: 0.85-4.48), and there was significant heterogeneity (p=0.007) across the trials reporting this outcome.

Summary of the evidence on ACE inhibitor/ARB combination therapy in CHF and cardiovascular disease

As noted in Section II-A, small trials in hypertensive and diabetic patients showed a small benefit of combination therapy over monotherapy in reducing SBP and DBP. The larger and longer-term CHARM-Added and Val-HeFT trials that added an ARB to existing (and non-standardized) ACE inhibitor therapy in patients with CHF confirmed a long-term reduction in blood pressure with combination therapy as well as an improvement in clinical outcomes, such as mortality and morbidity resulting from CHF.

However, only one of the two components of combination therapy, ARB therapy, was standardized in these trials. Different ACE inhibitor therapies at varying dosages were given to most patients, with others (7% of patients in Val-HeFT) not receiving any ACE inhibitor therapy at all. Thus, in the absence of randomization, blinding, and standardization of ACE inhibitor therapy, any conclusion as to the independent benefit or risk of ACE inhibitor/ARB combination therapy over ACE inhibitor monotherapy is extremely limited.

This design flaw of non-standardized trials is likely responsible for the contradictory benefit profiles seen in standardized versus non-standardized trials. When both ARB and ACE inhibitor therapies were standardized in terms of medication type and dosage in patients with significant cardiovascular disease and/or CHF, the apparent clinical benefits seen in the non-standardized trials disappeared. Although combination therapy still resulted in a minor improvement in blood pressure, this improvement did not translate into any clinically meaningful benefit on a range of outcomes. By contrast, combination therapy resulted in higher rates of the same adverse effects, including renal dysfunction, hypotension, and hyperkalemia in both non-standardized and standardized trials.

The absence of clinical benefit, when considered in light of the consistent harms of combination therapy relative to monotherapy, clearly tilts the balance in favor of monotherapy for patients with cardiovascular disease and CHF. The similarity of the findings (see **Table 1**) in the three standardized trials (including the two largest trials to date, VALIANT and ONTARGET, which studied two different patient populations) further validates this conclusion.

Table 1. Rates of Adverse Events in Patients with Cardiovascular Disease and/or CHF on ACE Inhibitor/ARB Combination Therapy versus Patients on Either ACE Inhibitor or ARB Monotherapy from Three Standardized Trials

			Trial		
			ONTARGET[26]	VALIANT[27]	RESOLVD[28]
Adverse Event*	Renal impairment	Rate†	1.1% vs. 0.7% vs. 0.8%	1.3% vs. 0.8% vs. 1.1%	0.6% vs. 0.0% vs. 0.6%
		RR‡	1.58 (<0.001) vs. ACE inhibitor	1.63 (<0.05) vs. ACE inhibitor	1.00 (NS) vs. ARB
	Hypotension	Rate	4.8% vs. 1.7% vs. 2.7%	1.9% vs. 0.8% vs. 1.4%	1.2% vs. 0.9% vs. 0.9%
		RR	2.75 (<0.001) vs. ACE inhibitor	2.38 (<0.05) vs. ACE inhibitor	1.33 (NS) vs. ACE inhibitor
	Hyperkalemia	Rate	5.6% vs. 3.3% vs. 3.4%	0.2% vs. 0.1% vs. 0.1%	NR** (no difference)
		RR	1.71 (<0.001) vs. ACE inhibitor	2.00 (NS) vs. ACE inhibitor	NR** (no difference)

*Rates of adverse events were defined slightly differently among the three standardized trials. In ONTARGET, renal impairment and hypotension rates were those that resulted in permanent discontinuation of the study drugs, while hyperkalemia rates represented the proportion within each group that had an increase in their serum potassium level of more than 5.5 mmol/L. In VALIANT, rates represented the proportion in which the adverse event resulted in the permanent discontinuation of treatment, with no threshold provided for hyperkalemia. In RESOLVD, rates represented the proportion within each group experiencing the adverse event, with hyperkalemia defined as the proportion of patients with serum potassium levels of 5.5 mmol/L or more. In all three trials, there were no standard definitions provided for renal impairment or hypotension, with both adverse events reported at the discretion of individual clinical investigators.

†Rates are expressed as a proportion of combination, ACE inhibitor, and ARB therapy patients, respectively, experiencing the adverse event.

‡RR = relative risk (with p-value, if available, or "NS" if RR was not statistically significant) of adverse event with combination therapy compared with either ACE inhibitor or ARB monotherapy, as obtained from article or calculated using rates.

**NR = values not reported, but "the proportion of patients with potassium levels ≥ 5.5 mmol/L was not significantly different among the treatment groups."[29]

C. Proteinuria and CKD

Among its many other functions, angiotensin II acts on the kidney to maintain glomerular blood pressure and filtration when renal blood flow is compromised by low systemic blood pressure, blood volume, or cardiac output by preferentially constricting the glomerular efferent arteriole (the vessel carrying blood away from the filters in the kidney known as glomeruli) more than the afferent arteriole (the vessel carrying blood to the glomeruli). Glomerular filtration rate (GFR) is thus maintained, leading to minimal to no increase in serum creatinine. Both ACE inhibitor and ARB therapies, by respectively inhibiting the production and action of angiotensin II, reduce glomerular blood pressure and filtration in the setting of decreased systemic blood pressure, blood volume, or cardiac output. This reduction in glomerular blood pressure and filtration frequently leads to a short-term decrease in renal "function" as evidenced by increased levels of serum creatinine. However, in part by relieving renal hypertension and preventing the progression of proteinuria, the drugs are known to have a beneficial effect on kidney function over the long term in patients with chronically high glomerular pressure at risk for CKD, such as those with diabetes. Thus, both ACE inhibitor and ARB monotherapy have been shown to be reno-protective over the long term. Any added advantage that ACE inhibitor/ARB combination therapy may confer over and above this monotherapy – on both surrogate and clinical endpoints – has been extensively studied.

A meta-analysis published by Kunz, et al. (2008), analyzed all standardized and non-standardized RCTs assessing the effect of ACE inhibitor and ARB therapy, alone and in combination, in reducing progression of proteinuria up to one year in patients with or without diabetes and with microalbuminuria and proteinuria at baseline.[30] Twenty-three trials compared ARB/ACE inhibitor combination therapy with ACE inhibitors alone, and 16 trials compared ARB/ACE inhibitor combination therapy with ARBs alone. While both ARBs and ACE inhibitors given alone resulted in a similar reduction in proteinuria, combination therapy resulted in a greater reduction than either ARBs (ratio of means 0.76 [95% CI: 0.68-0.85] over one to four months, and 0.75 [95% CI: 0.61-0.92] over five to 12 months) or ACE inhibitors (ratio of means 0.78 [95% CI: 0.72-0.84] over one to four months, and 0.82 [95% CI: 0.67-1.01] over five to 12 months).

However, the meta-analysis was limited in several respects. First, sample sizes were exceedingly small in most studies, with as few as 10 subjects in each arm of some. Second, and most important for the purposes of accurate risk-benefit calculations, an accurate estimate of adverse event occurrence with combination therapy versus monotherapy was impossible to ascertain, given inconsistent reporting and methodology across almost all trials. Finally, the study only assessed a surrogate marker (proteinuria) over a relatively short time period (one to 12 months). As the authors acknowledged, although proteinuria has been shown to correlate with progression of CKD, their study shed no new light on whether clinically relevant outcomes (such as the

progression to end-stage renal disease and need for dialysis) would benefit from combination therapy.

Around the time of the publication of the Kunz meta-analysis, results from ONTARGET were published that definitively assessed the clinical significance of a reduction in proteinuria.[31] In this standardized trial, 8,576 patients 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage were assigned to ramipril 10 mg/day, 8,542 to telmisartan 80 mg/day, and 8,502 to a combination of both drugs at these doses. Patients were followed for a median of 56 months. The primary renal endpoint was a composite of dialysis, doubling of serum creatinine, and death.

ONTARGET confirmed the results of Kunz's meta-analysis, as ACE inhibitor/ARB combination therapy did result in a significant reduction in both the risk of developing new proteinuria (12% reduction, p=0.003) and the risk of progression from a low level of proteinuria (microalbuminuria) at baseline to a high level of proteinuria (macroalbuminuria) (24% reduction, p=0.019) relative to ACE inhibitor monotherapy. However, as is the case with blood pressure and cardiovascular outcomes with combination therapy, this improvement in a surrogate marker did not confer any benefit in clinically meaningful outcomes.

Patients on combination therapy suffered higher rates of the primary endpoint of death, dialysis, or doubling of serum creatinine (hazard ratio [HR] 1.09, 95% CI: 1.01-1.18, p=0.037) and the secondary endpoint of dialysis or doubling of serum creatinine (HR 1.24, 95% CI: 1.01–1.51, p=0.038) relative to those on ACE inhibitor therapy alone. In separate ONTARGET results published in the *New England Journal of Medicine*, combination-therapy subjects had higher rates of renal impairment as reported by clinical investigators (RR 1.33, 95% CI: 1.22-1.44) and trended (not significantly) toward higher rates of renal failure requiring dialysis (RR 1.37, 95% CI: 0.94-1.98) than those on ramipril alone.[32] Consistent with these clinical outcomes, estimated GFR (eGFR) decreased more with combination therapy compared with ACE inhibitor therapy alone by the end of the study (−6.11 vs. –2.82 mL/min/1.73 m^2, p<0.0001).

In addition, a total of 406 patients (4.8%) on combination therapy permanently discontinued therapy due to hypotensive symptoms compared with only 229 on telmisartan (2.7%) and 149 on ramipril (1.7%). Combination-therapy patients also discontinued medication due to renal abnormalities at higher rates (1.1%) than those on either telmisartan (0.8%) or ramipril (0.7%); (RR 1.58, p<0.005 for combination therapy versus ramipril).

The most recent review of the effect of ACE inhibitor/ARB combination therapy on renal outcomes was by Maione, et al. (2011).[33] This review included 85 trials (including ONTARGET) comprising 21,708 patients with albuminuria and one or more cardiovascular risk factors, in which ACE inhibitor, ARB, or combination therapies were compared with placebo or one

another for cardiovascular and renal outcomes. Results were consistent with both the Kunz, et al., meta-analysis and the ONTARGET study, in that ACE inhibitor/ARB combination therapy reduced the risk of progression of microalbuminuria to macroalbuminuria when compared with ACE inhibitor or ARB monotherapy (two RCTs, 4,145 patients; RR 0.80, 95% CI: 0.69-0.92). However, as in ONTARGET, this surrogate benefit did not translate into improved clinical outcomes. Combination therapy did not result in any significant improvement in rates of end-stage kidney disease (ESKD) or doubling of serum creatinine compared with either ACE inhibitor or ARB monotherapy.

Adverse events were only reported in a few trials. There was a significant increase in rates of hypotension in ACE inhibitor/ARB combination-therapy patients compared with ACE inhibitor monotherapy patients (two RCTs, 2,742 patients; RR 2.21, 95% CI: 1.21-4.06), and a trend toward an increase in hypotension compared with ARB monotherapy patients (two RCTs, 2,786 patients; RR 1.38, 95% CI: 0.83-2.30). No other adverse events, including hyperkalemia, occurred significantly more frequently in the combination-therapy group; however, due to the low number of trials and patients reporting adverse events (for example, only two RCTs – one with 86 patients, the other with 90 patients – reported rates of hyperkalemia), the review may have been underpowered to detect such effects.

Standardized versus non-standardized trials: Limitations of RCTs in real-world practice?

Despite these unequivocal trial results showing more harm than benefit from combination therapy on a range of clinically relevant kidney outcomes, there may be a perception among some physicians that one cannot readily apply the results of such RCTs to everyday clinical practice. This is based on the reasoning that doctors in the real world, unlike those operating in rigid trial protocols, can individualize the dosing of both ACE inhibitors and ARBs, thereby reducing the risk of kidney problems and other adverse effects. However, this is ignoring the fundamental principle that the lack of standardization of ACE inhibitor dosing makes it impossible to assess what effect ARBs are having independent of ACE inhibitor therapy across the population.

A 2011 longitudinal, retrospective cohort study of elderly residents in Alberta, Canada, addressed this consideration.[34] A total of 32,312 patients age 66 or older (mean age 76.1 years) who were new users of an ACE inhibitor, an ARB, or ACE inhibitor/ARB combination therapy were evaluated for a primary composite outcome of death, doubling of serum creatinine, and end-stage renal disease requiring dialysis within six months of starting therapy, as well as two secondary outcomes of hyperkalemia (serum potassium $\geq$ 6.0 mmol/L) and medication discontinuation within six months of starting therapy. A total of 1,750 patients (5.4%) were on combination therapy. These patients were on significantly more concomitant medications (beta blockers, statins, calcium channel blockers, and diuretics) and had higher rates of baseline

albuminuria, nephrotic range proteinuria, and hypertension than monotherapy patients. All baseline characteristics were adjusted for in the final analyses.

Combination-therapy patients experienced higher rates of death, doubling of serum creatinine, or end-stage renal disease requiring dialysis (5.2 [95% CI: 3.4-7.9] events per 1,000 patients per month) than patients on either ACE inhibitor or ARB monotherapy (2.4 [95% CI: 2.2-2.7] events per 1,000 patients per month) (adjusted HR 2.36, 95% CI: 1.51-3.71). Higher rates of hyperkalemia were also seen with combination therapy (2.5 [95% CI: 1.4-4.3] events per 1,000 patients per month) compared with monotherapy (0.9 [95% CI: 0.8-1.0] events per 1,000 patients per month) (adjusted HR 2.42, 95% CI: 1.36-4.32).

This was a limited study due to its retrospective methodology and widely varying baseline characteristics between those on combination therapy and monotherapies, which introduced the possibility of residual confounding. Incidentally, the authors noted a disturbing finding that of the 1,750 patients on combination therapy, 1,512 (86.4%) did not have "trial-established" indications, such as CHF or proteinuria. As this petition shows, however, there are no "trial-proven" indications for which clinically relevant benefits are seen with combination therapy over monotherapy.

Summary of the evidence on combination therapy in proteinuria and CKD

Taken together, these results make it clear that, although ACE inhibitor/ARB combination therapy does appear to improve surrogate markers of CKD, such as urinary albumin concentration, there is no significant clinical benefit over using either drug class alone, in terms of survival, renal function, or progression to ESKD. Furthermore, such therapy is actually harmful, presenting increases in renal impairment, hyperkalemia, and hypotension.

The Combination Angiotensin Receptor Blocker and Angiotensin-converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D) trial is an ongoing study that will compare ACE inhibitor/ARB (lisinopril/losartan) combination therapy with ARB (losartan) therapy alone, on the progression of CKD in 1,850 patients with diabetes and overt proteinuria.[35] A subgroup analysis in ONTARGET found no clinical benefit of combination therapy over ACE inhibitor (ramipril) therapy alone in diabetics with overt nephropathy.[36]

D. Recent Safety Communication concerning Direct Renin Inhibitor Aliskiren Used in Combination with ACE Inhibitors or ARBs Confirms Risks of Combination RAAS Suppression

Aliskiren is the first, and so far only, drug in a new class of anti-hypertensives called direct renin inhibitors, which work by suppressing the activity of renin in the RAAS pathway. On April 20,

2012, the FDA released a safety communication concerning the severe adverse reactions seen when aliskiren was used in combination with ACE inhibitors or ARBs in a large RCT.[37] In the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE), 8,579 patients with type 2 diabetes with renal disease (defined either by the presence of albuminuria or reduced GFR) were randomized to treatment with aliskiren 300 mg daily or a placebo.[38] The trial was non-standardized, as patients were already taking variable types and doses of ACE inhibitor or ARB concomitant therapy. The purpose of ALTITUDE was to evaluate whether aliskiren, when added to conventional treatment, reduced complications of cardiovascular and renal disease in patients with diabetic nephropathy. The primary endpoint included a composite of cardiovascular death, resuscitated sudden death, nonfatal MI, nonfatal stroke, unplanned hospitalization for CHF, onset of end-stage renal disease, renal death, and doubling of serum creatinine concentration from baseline sustained for at least a month.

The trial was terminated early, after a median patient follow-up of 27 months, because the addition of aliskiren conferred no benefit on the primary outcome over placebo. Adverse events, however, were increased in the aliskiren arm. An adverse event profile identical to that seen with ACE inhibitor/ARB combination therapy was caused by aliskiren therapy combined with either ACE inhibitor or ARB therapy. Aliskiren-treated patients had higher rates (significance levels not reported) of renal impairment, hypotension, and hyperkalemia compared with those given a placebo.

Table 2. Incidence of Selected Adverse Reactions in ALTITUDE as Reported by the Investigators (table and accompanying text all run verbatim from the FDA's April 20, 2012, drug safety communication)[39]

	Aliskiren N=4283		**Placebo N=4296**	
	Serious Adverse Event* (%)	Adverse Event (%)	Serious Adverse Event* (%)	Adverse Event (%)
Renal	4.7	12.4†	3.3	10.4†
Hypotension	2.0	18.6††	1.7	14.8††
Hyperkalemia	1.1	36.9	0.3	27.1

†renal failure, renal failure acute, renal failure chronic, renal impairment

††dizziness, dizziness postural, hypotension, orthostatic hypotension, presyncope, syncope

*A Serious Adverse Event (SAE) is defined as an event that: is fatal or life-threatening; results in persistent or significant disability/incapacity; constitutes a congenital anomaly/birth defect; requires inpatient hospitalization or prolongation of existing hospitalization; or is medically significant (i.e., an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes previously listed).

The striking similarity between the adverse event profile of aliskiren when used with ACE inhibitor or ARB therapy (**Table 2**) and that of ACE inhibitor/ARB combination therapy (**Table 1**) is not surprising, given that all three classes of drugs work on the RAAS pathway. However, it is unclear why no benefit was seen with combination therapy in this non-standardized trial, given that other non-standardized trials of ACE inhibitor/ARB combination therapy did show clinical benefit over monotherapy (though benefits were not seen in the standardized trials). Nevertheless, the decision by Novartis to voluntarily withdraw Valturna, a combination of aliskiren and valsartan, attests to the severity of the danger of combination RAAS suppression.[40]

Given this recognized danger, the action taken by the FDA in April 2012 on aliskiren and ACE inhibitor/ARB products was insufficient. Inexplicably, the (non-black box) warning regarding this interaction was only placed on aliskiren-containing products and not on ACE inhibitor/ARB labels. Furthermore, the FDA failed to request the immediate withdrawal of Valturna, instead allowing the company to continue to market the dangerous therapy for three months following the safety communication.

E. Label Discussion

There are currently 10 different ACE inhibitors and eight different ARBs available on the U.S. market (**Tables 3 and 4**). Aliskiren is the only direct renin inhibitor on the market today. The labels of only one of the 10 ACE inhibitors (ramipril[41]), four of the eight ARBs (telmisartan,[42] valsartan,[43] candesartan,[44] and losartan[45]), and aliskiren[46] mention ACE inhibitor/ARB/aliskiren combination therapy at all (and none with a black box warning). The labels of these six drugs include the following information concerning concomitant use of the three medication classes:

(1) The telmisartan label contains a summary of ONTARGET and a recommendation not to use telmisartan with ramipril or any ACE inhibitor. The label also includes a paragraph summarizing a pharmacokinetic interaction between ramipril and telmisartan. Concomitant administration of these two drugs leads to higher serum concentrations of ramipril and lower concentrations of telmisartan, potentially increasing the risk of angioedema and other ACE inhibitor-specific adverse effects beyond the already-increased adverse effects described in ONTARGET.

The label does not include a full listing of the adverse events (renal impairment, hypotension, syncope, and hyperkalemia) experienced at higher rates by patients taking combination therapy compared with those on monotherapy in ONTARGET, mentioning only "acute renal failure." It also fails to list the full primary outcome (death, doubling of serum creatinine, or dialysis) that occurred at higher rates in the combination-therapy group, again only referring to "acute renal failure."

(2) The valsartan label contains a lengthy summary of the VALIANT trial along with the conclusion that there was "no evidence that ... [combination therapy] ... was of value." The label also summarizes the Val-HeFT trial, concluding that "there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor," including this statement under the Indications and Usage section. However, the label completely fails to mention the harms of combination therapy relative to monotherapy, including drug discontinuation, hypotension, and renal dysfunction, that were experienced at higher rates in the combination-therapy group in both the VALIANT and Val-HeFT trials. Consequently, unlike the telmisartan label, there is no explicit recommendation warning against combining ACE inhibitor therapy with valsartan.

(3) The candesartan label states within the Indications and Usage section that, when used with an ACE inhibitor, candesartan confers an additive benefit on reducing cardiovascular death and heart-failure hospitalizations in patients with heart failure relative to an ACE inhibitor alone. Listed deeper within the label is the basis for this claim — the **non-standardized** CHARM-Added study — along with the acknowledgment that the dose of ACE inhibitor used and the degree of benefit on these outcomes are unrelated. By contrast, the label completely fails to mention the **standardized** RESOLVD study, which showed no added clinical benefit of candesartan therapy on these outcomes when standardized doses of an ACE inhibitor were used. Although RESOLVD may have been underpowered to detect significant differences in clinical outcomes, CHARM-Added was similarly incapable of rigorously comparing combination therapy with ACE inhibitor monotherapy due to its non-standardized study design. Finally, the candesartan label includes mention of the risk of hyperkalemia with concomitant ACE inhibitor use, but does not include other adverse events, such as creatinine increases and hypotension, seen at higher rates with combination therapy in CHARM-Added.

(4) The losartan label warns of the adverse effects of dual blockade of the renin-angiotensin-aldosterone system: "Dual blockade of the renin-angiotensin-aldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function, and electrolytes in patients on COZAAR and ACE inhibitors." However, no specific trials, such as ONTARGET, are mentioned.

(5) The only ACE inhibitor label to include mention of combination therapy is ramipril. The ramipril label contains a summary of the ONTARGET study followed by a recommendation not to use ramipril and telmisartan together. There is no mention of contraindications to concomitant use with the other seven ARBs or potential class-wide effects. While the ramipril label, unlike that of telmisartan, does include the complete

primary outcome (death, doubling of serum creatinine, or dialysis) observed at higher rates in the combination-therapy group in ONTARGET, it does not include the hypotensive symptoms and syncope that were also found at higher rates in the combination-therapy group. Inexplicably, there is no mention of the pharmacokinetic interaction with telmisartan that is mentioned in the telmisartan label.

(6) The aliskiren label includes a contraindication to the concomitant use of aliskiren and any ACE inhibitor or ARB in patients with diabetes, in addition to advising against such combination use in patients with moderate renal impairment. A brief summary of the ALTITUDE trial listing the risks of ACE inhibitor/ARB and aliskiren combination use is also presented.

Table 3. ACE Inhibitors Available in the U.S. (several ACE inhibitors are also marketed in combination with other medications)

Generic Name	Brand Name
benazepril	LOTENSIN
captopril	CAPOTEN
enalapril	VASOTEC
fosinopril	MONOPRIL
lisinopril	PRINIVIL, ZESTRIL
moexipril	UNIVASC
perindopril	ACEON
quinapril	ACCUPRIL
ramipril	ALTACE
trandolapril	MAVIK

Table 4. ARBs Available in the U.S. (several ARBs are also marketed in combination with other medications)

Generic Name	Brand Name
azilsartan	EDARBI
candesartan	ATACAND
eprosartan	TEVETEN
irbesartan	AVAPRO
losartan	COZAAR
olmesartan	BENICAR
telmisartan	MICARDIS
valsartan	DIOVAN

F. Conclusion

It is clear that ACE inhibitor and ARB therapies represent breakthrough treatments for patients with CKD and CHF, but only when used individually. The combining of ACE inhibitor and ARB therapy to treat CKD and CHF is based on the theoretical additive benefit of shutting down the RAAS system at two different locations. Consistent with this hypothesis, surrogate biomarkers such as urinary albumin concentration and SBP/DBP do seem to improve with combination use relative to monotherapy. However, as is often the case with surrogate markers, these improvements do not translate into real clinical benefits for the patients most often treated with ACE inhibitor/ARB combination therapy. In fact, **there is no patient population thus far studied in standardized trials in which ACE inhibitor/ARB combination therapy confers added clinical benefits.** By contrast, virtually all patient populations studied – in both standardized and non-standardized trials – incur added harms with combination therapy, including an increase in serious and life-threatening adverse effects. Therefore, a black box warning advising health care providers of these risks is essential.

As ACE inhibitors and ARBs have been proven equivalent in preventing progression of both CHF and CKD, optimal titration of one or the other monotherapy is preferable to introducing a new class of drugs with its own unique side effect profile. To this end, the FDA should request that manufacturers include within the labels specific instructions on optimal titration of ACE inhibitor/ARB monotherapy as an alternative to combination therapy for patients failing to respond to usual doses of either drug.

Furthermore, the combination of aliskiren with either ACE inhibitor or ARB therapy is clearly as dangerous as ACE inhibitor/ARB combination treatment, with no added clinical benefit. Therefore, the action taken by the FDA in response to the recent findings from the ALTITUDE trial is inadequate and must be supplemented with the recommended course of action below.

III. SUMMARY OF PETITION REQUESTS

For the reasons stated above, we hereby petition the FDA, pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352, and 21 C.F.R. §§ 10.30 and 201.56, to immediately require the following:

(1) The addition of a black box warning to the label for all medications containing ACE inhibitors, ARBs, and aliskiren indicating that the three drug classes, when used in any combination (an ACE inhibitor with an ARB, or either drug with aliskiren), present an increased risk of renal failure, symptomatic hypotension, and hyperkalemia, with no countervailing clinical benefit compared with any of the drug classes used alone. We suggest the following wording for the requested black box warning:

> **In several large, long-term studies, taking angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), or aliskiren together, in any combination, has been shown to result in an increased risk of kidney dysfunction, low blood pressure, and high blood potassium levels. These side effects are potentially life-threatening. Taking these medications in combination is no more beneficial than taking the drugs individually.**
>
> **Therefore, the combined use of ACE inhibitors [corresponding drug name, if ACE inhibitor], ARBs [corresponding drug name, if ARB], and aliskiren should be avoided in all patients. Any patient necessitating combination therapy after careful consideration should have renal function, blood pressure, and electrolytes regularly monitored.**

(2) Combination therapy is currently addressed, wholly inadequately, in the labels of aliskiren and only five (ramipril, telmisartan, valsartan, candesartan, and losartan) of the 18 ACE inhibitor/ARB drugs. Given that the mechanism underlying the adverse effect profile of these specific combinations is common to drugs in all three classes, there is no reason to believe that the adverse risk-benefit profile of combination therapy is not class-wide. Therefore, all 18 ACE inhibitor/ARB drugs, in addition to aliskiren, should carry this black box warning.

(3) The mandatory distribution of FDA-approved patient Medication Guides for all medications containing ACE inhibitors, ARBs, and aliskiren, with a warning about the above-mentioned increased risk of renal failure, symptomatic hypotension, and hyperkalemia, with no added benefit over monotherapy. These guides should be dispensed prior to the administration of the first dose of these medications.

(4) The distribution by all manufacturers of these drugs of a "Dear Doctor" letter alerting physicians and other health care professionals to this warning, with instructions on optimal titration of ACE inhibitor, ARB, and aliskiren monotherapy as an alternative to combination therapy.

(5) The immediate removal of the following assertion in the Indications and Usage section of the candesartan label: "Atacand [candesartan] also has an added effect on these outcomes [of reducing cardiovascular death and heart-failure hospitalizations] when used with an ACE inhibitor." This is based on the non-standardized CHARM-Added trial, and the label fails to include any mention of the standardized RESOLVD trial that showed **no added benefit** of combination therapy with candesartan on these same outcomes in patients taking standardized doses of enalapril.

IV. ENVIRONMENTAL IMPACT STATEMENT

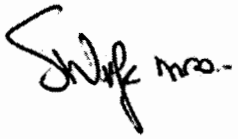
Nothing requested in this petition will have an impact on the environment.

V. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Sammy Almashat, M.D., M.P.H.
Researcher
Public Citizen's Health Research Group



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