The implications of a growing evidence base for drug use in elderly patients. Part 2. ACE inhibitors and angiotensin receptor blockers in heart failure and high cardiovascular risk patients

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Traditionally, angiotensin converting enzyme (ACE) inhibitors have been used for the management of patients with congestive cardiac failure. Studies performed over the last decade have demonstrated that (1) angiotensin receptor blockers (ARBs) are as effective as ACE inhibitors in reducing morbidity and mortality in cardiac failure; and (2) inhibition of the renin-angiotensin system provides beneficial effects in patients at high cardiovascular risk without cardiac failure. This review focuses on the applicability of the results of the main trials with ACE inhibitors and ARBs to the elderly population.

ACE inhibitors

Heart failure

A meta-analysis of 32 randomized clinical trials has demonstrated the effectiveness of angiotensin converting enzyme (ACE) inhibitors for reducing morbidity and mortality in patients with heart failure [1]. The benefits

of ACE inhibitors were similar in older and younger patients (odds ratio 0.79 in patients >80 years and 0.71 in patients ≤60 years, respectively).

One of these trials enrolled predominantly elderly patients [2]. The CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) study randomly

Figure 1

Age distribution of trials on ACE inhibitors in elderly patients. M mean age; SD standard deviation; Max maximum age; CCF congestive cardiac failure; HCR high cardiovascular risk

assigned patients with New York Heart Association (NYHA) class IV heart failure to enalapril or placebo (Figure 1 and Table 1). The group receiving enalapril had a significant reduction in mortality at 6 months and 1 year [2]. Treatment discontinuation rates were slightly higher in the enalapril group (17% vs. 14%). This difference was due to the higher incidence of hypotension in the enalapril group (5% vs. 0). A retrospective cohort study of very old patients (mean age 85 years) demonstrated that patients receiving ACE inhibitors had a 10% reduction in mortality compared with patients taking digoxin, as well as a lower rate of functional decline [3].

The SAVE (Survival and Ventricular Enlargement Trial) study investigated whether captopril reduced morbidity and mortality in patients with postmyocardial infarction left ventricular dysfunction vs. placebo (Figure 1 and Table 1) [4]. All-cause mortality was significantly reduced in the captopril group (absolute risk reduction (ARR) 4.2%, $P = 0.019$). The benefit was greater in patients ≥ 65 years (ARR 8.2%) [4]. Treatment discontinuation rates were slightly, but not significantly, higher

with captopril (3.5% in the captopril group vs. 2.7% in the placebo group).

In the AIRE (Acute Infarction Ramipril Efficacy) study, patients with clinical evidence of heart failure were randomized to ramipril or placebo (Figure 1 and Table 1) [5]. All-cause mortality was significantly lower in the ramipril group. The benefit was greater in patients > 65 years although the exact data have not been published. Incidence of syncope (ramipril 2.4%, placebo 1.7%), hypotension (ramipril 4.2%, placebo 2.3%), and renal failure (ramipril 1.5%, placebo 1.2%) were not significantly different between the two treatment groups [5].

In the GISSI-3 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) study, patients with acute myocardial infarction received lisinopril vs. placebo within the first 24 h (Figure 1 and Table 1) [6]. Lisinopril treatment was associated with lower 6-week all-cause mortality and reduced rates of a combined end-

Table 1
Clinical trials of ACE inhibitors in heart failure including elderly patients

Study	Agents	Follow-up	Elderly participants	Women	Inclusion criteria	Primary outcome measures	Incidence in active group	Incidence in placebo group	ARR	P value
CONSENSUS [2]	Enalapril 40 mg vs. placebo	6 months	NA	29.5%	CHF NYHA IV	All-cause mortality	36.2%	52.4%	16.2%	$P = 0.001$
SOLVD [18]	Enalapril 20 mg vs. placebo	37.4 months	NA	11.5%	CHF NYHA I-II with LVD	All-cause mortality	14.8%	15.8%	1.0%	$P = 0.30$
SAVE [4]	Captopril 150 mg vs. placebo	3.5 years	>70 years (15.0%)	17.5%	Post MI with LVD	All-cause and CV mortality	20.4%	24.6%	4.2%	$P = 0.019$
TRACE [7]	Trandolapril 4 mg vs. placebo	2–4.2 years	≥65 years (64.1%)	28.5%	Post MI with LVD	All-cause mortality	34.7%	42.3%	7.6%	$P = 0.001$
AIRE [5]	Ramipril 2.5–10 mg vs. placebo	15 months	NA	26.4%	Post MI with CHF	All-cause mortality	16.9%	22.6%	5.7%	$P = 0.002$
GISSI-3 [6]	Lisinopril 5–10 mg vs. placebo	6 weeks	>70 years (27.0%)	22.2%	Post MI + CHF	All-cause mortality and LVD	6.3%	7.1%	0.8%	$P = 0.03$
ISIS-4 [8]	Captopril 6.25–100 mg vs. placebo	5 weeks	>70 years (28.0%)	25.8%	Post MI + CHF	All-cause mortality	7.2%	7.7%	0.5%	$P = 0.02$

CHF congestive heart failure; NYHA New York Heart Association; LVD left ventricular dysfunction; MI myocardial infarction; CV cardiovascular; NA not available; ARR absolute risk reduction.

point of death and late-onset heart failure (ARR 1.4%, $P = 0.009$). Similar effects on the combined end-point were observed in patients >70 years (ARR 3.5%, $P = 0.0039$). Lisinopril treatment was associated with increased incidence of persistent hypotension (absolute risk increase (ARI) 5.3%) and renal dysfunction (ARI 1.3%). This, however, did not result in increased mortality or severe renal failure [6].

In the TRACE (Trandolapril Cardiac Evaluation Study Group) study, patients with left ventricular dysfunction postmyocardial infarction were randomized to trandolapril or placebo [7]. Patients treated with trandolapril had lower all-cause mortality (ARR 7.6%; ARR 7.2% in patients ≥ 65 years) [7]. Treatment with trandolapril was associated with an increased incidence of cough (ARI 12.9%, $P < 0.001$), hypotension (ARI 8.9%, $P < 0.001$) and renal dysfunction (ARI 2.9%, $p = 0.06$).

The ISIS-4 (Fourth International Study of Infarct Survival) study investigated the effects of captopril vs. placebo in patients up to 24 h following acute myocardial infarction (Figure 1 and Table 1) [8]. Treatment with captopril was associated with a significant reduction in 5-week mortality. The benefit was maintained after 1 year. Subgroup analysis revealed that there was no benefit imparted by captopril in patients ≥ 70 years (ARR -0.1%). Moreover, captopril treatment was associated with increased risk of severe hypotension necessitating termination of study treatment (ARI 5.2%, $P < 0.0001$), dizziness (ARI 0.15%, $P < 0.01$), and renal dysfunction (ARI 0.51%, $P < 0.001$) [8].

High-risk patients without heart failure

The STOP-2 (Swedish Trial in Old Patients with Hypertension) study investigated the effects of diuretics and β -adrenoceptor blockers vs. ACE-inhibitors and calcium channel blockers in elderly hypertensive patients (Figure 1, Table 2) [9]. The effects of ACE inhibitors on blood pressure and cardiovascular mortality were similar to the comparators. Except for dry cough, proportions of patients reporting common adverse events with ACE inhibitors were not significantly different when compared with the other drug classes [9].

In the HOPE (Heart Outcomes Prevention Evaluation Study Investigators) study, patients ≥ 55 years with vascular disease or diabetes plus one other cardiovascular risk factor but no heart failure were randomized to ramipril or placebo (Figure 1, Table 2) [10]. Ramipril reduced the composite end-point of myocardial infarction, stroke, or cardiovascular death [10]. More patients in the ramipril group discontinued treatment because of cough (7.3% vs. 1.8%) and hypotension (1.9% vs. 1.5%).

The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) trial investigated the effects of perindopril, with or without the diuretic indapamide, on recurrent stroke in patients with a previous cerebrovascular event (Figure 1, Table 2) [11]. The combination therapy significantly reduced the risk of recurrent stroke. Active treatment was associated with an increased incidence of cough and hypotension.

The EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease) study enrolled patients with coronary artery disease to investigate the effects of perindopril vs. placebo on a composite end-point of cardiovascular death, myocardial infarction, or cardiac arrest (Figure 1 and Table 2) [12]. Patients receiving perindopril had fewer cardiovascular events (ARR 1.9%) [12]. Sub-group analysis of patients >65 years showed similar results (ARR 2.2%) [12]. Treatment discontinuation rates with perindopril were not significantly different from placebo (22.8% vs. 20.7%).

The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study assessed the effects of lisinopril vs. amlodipine vs. chlorthalidone on the risk of coronary heart disease in hypertensive subjects with at least one other coronary heart disease risk factor (Figure 1 and Table 2) [13]. There was no significant difference in the primary outcome across the different drug treatments. Adverse events during lisinopril treatment were similar to the other groups, apart from a higher incidence of angioedema.

In the ANBP2 (Second Australian National Blood Pressure Study) study, elderly hypertensive patients were randomized to ACE-inhibitor or diuretic-based therapy (Figure 1 and Table 2) [14]. Although the antihypertensive effect was similar, there was a significant reduction in all-cause mortality or cardiovascular events in patients receiving ACE inhibitors [14]. No data have been provided on safety and tolerability.

Discussion

Several trials, published during the late 1980s and early 1990s, have clearly demonstrated the effectiveness of ACE inhibitors in elderly patients with heart failure and left ventricular dysfunction. Beneficial effects have been observed in patients up to 95 years of age (Figure 1). Disappointingly, only a proportion of elderly patients with stable heart failure receive ACE inhibitors and those who are treated often receive inappropriately low doses [15–17]. Caution is recommended with the use of these drugs and their dose up-titration in the acute post-myocardial infarction phase because of the risk of hypotension. This is probably due to the extreme sensi-

Table 2
Clinical trials of ACE-inhibitors in patients at high cardiovascular risk, without heart failure, including elderly patients

Study	Agents	Follow-up	Elderly participants	Women	Inclusion criteria	Primary outcome measures	Incidence in active group	Result of primary outcome Incidence in placebo group	ARR P value
STOP-2 [9]	Enalapril 10 mg or lisinopril 10 mg vs. diuretics or β -blockers	4 years	70–74 years (41.0%) 75–79 years (37.0%) 80–84 years (22.0%)	66.8%	HT + other CV risk factor	CVD mortality	20.5% (ACE inhibitors)	19.8% (β -blockers and thiazides)	–0.7% $P = 0.89$
HOPE [10]	Ramipril 10 mg vs. placebo	5 years	≥ 65 years (55.1%)	26.7%	CVD or DM plus one other CV risk factor	Composite end-point of MI, stroke, or CV death	14.0%	17.8%	3.8% $P < 0.001$
PROGRESS [11]	Perindopril 4 mg $\pm$ indapamide 2–2.5 mg vs. placebo	3.9 years	NA	30.3%	Previous stroke or TIA within 5 years	Total stroke	10.0%	13.7%	3.7% $P < 0.0001$
ALLHAT [13]	Lisinopril 10–40 mg vs. chlorthalidone 12.5–25 mg vs. amlodipine 2.5–10 mg	4.9 years	≥ 65 years (57.5%)	46.9%	HT plus at least one other CV risk factor	Combined fatal CHD or nonfatal MI	11.4%	11.5% (chlorthalidone)	0.1% $P = 0.81$
EUROPA [12]	Perindopril 8 mg vs. placebo	4.2 years	> 65 years (31.3%)	14.5%	CHD	Composite end-point of CV death, MI, or cardiac arrest	8.0%	9.9%	1.9% $P = 0.0003$
ANBP2 [14]	ACE-inhibitor vs. diuretic-based therapy	4.1 years	65–84 years (70.0%) 65–74 years (30.0%)	51.0%	HT and no CV events within 6 months	CV events or all-cause death	22.8%	24.2%	1.4% $P = 0.05$

HT hypertension; CVD cardiovascular disease; DM diabetes mellitus; TIA transient ischaemic attack; CHD coronary heart disease; MI myocardial infarction; CV cardiovascular; NA not available; ARR absolute risk reduction.

tivity of these patients to even minimal changes in cardiac afterload.

The benefits of ACE inhibitors in elderly patients with asymptomatic left ventricular systolic dysfunction are controversial. The mean age of patients in the SOLVD (Study Of Left Ventricular Dysfunction) study was 59 years and patients ≥ 80 years were excluded (Table 1) [18]. Enalapril had no effects on mortality over 3 years [18]. Several placebo-controlled randomized trials are currently studying the effects of ACE inhibitors on outcome in patients with heart failure and preserved left ventricular function. In one of these studies, the mean age of patients is 82 years and comorbidity is high [19]. These studies will ascertain whether the theoretical arguments and circumstantial evidence in favour of ACE inhibitors in this group of patients can be applied.

Numerous large-scale randomized controlled clinical trials have provided strong evidence for the effectiveness of ACE inhibitors in patients without congestive heart failure and different degrees of cardiovascular risk.

These studies show that ACE inhibitors are beneficial and relatively well tolerated up to the age of 90 years. Notably, the HOPE study included patients up to the age of 110 years (Figure 1) [10].

Angiotensin receptor blockers

Heart failure

An increasing body of evidence supports the use of angiotensin receptor blockers (ARBs) in the treatment of elderly patients with congestive heart failure who are intolerant to, or in addition to, ACE inhibitors. The ELITE (Evaluation of Losartan In The Elderly) and ELITE II studies evaluated losartan vs. captopril in patients ≥ 65 years with symptomatic congestive heart failure (Figure 2 and Table 3) [20, 21]. Although losartan was not superior in reducing morbidity and mortality, it was better tolerated than captopril. Only 9.7% of patients in ELITE II discontinued losartan treatment because of adverse events compared with 14.7% in the captopril group ($P < 0.001$) [20, 21].

Figure 2

Age distribution of trials on ARBs in elderly patients. M mean age; SD standard deviation; Max maximum age; CCF: congestive cardiac failure; HCR high cardiovascular risk

Table 3

Clinical trials of angiotensin receptor blockers in heart failure including elderly patients

Study	Agents and daily dose	Follow-up	Elderly participants	Women	Inclusion criteria	Primary outcome measures	Incidence in active group	Major results Incidence in placebo group	ARR P value
ELITE [20]	Losartan 50 mg vs. captopril 150 mg	0.9 years	>65years ≥70years (70.0%)	30.5%	CHF NYHA II-IV	Incidence of renal failure	10.5%	10.5% (captopril)	0% P = 0.63
ELITE II [21]	Losartan 50 mg vs. captopril 150 mg	1.5 years	≥60years ≥70years (57.6%)	30.6%	CHF NYHA II-IV	All-cause mortality	17.7%	15.9% (captopril)	-1.8% P = 0.16
Val-HeFT [22]	Valsartan 320 mg vs. placebo	2.2 years	≥65years (46.9%)	20.0%	CHF NYHA II-IV	Mortality or combined mortality and morbidity (cardiac arrest, hospitalization for CHF, or morbidity use of inotropes or vasodilators for ≥ 4 h without hospitalization)	28.8%	32.1%	3.3% P = 0.009
CHARM-Added [23]	Candesartan 32 mg vs. placebo	3.4 years	≥70years (17.9%)	21.3%	CHF NYHA II-IV	Composite end-point of CV death or hospitalization for CHF	37.9%	42.3%	4.4% P = 0.011
CHARM-Alternative [26]	Candesartan 32 mg vs. placebo	2.8 years	≥70years (23.2%)	31.8%	CHF NYHA II-IV and ACEI intolerance	Composite end-point of CV death or hospitalization for CHF	33.0%	40.0%	7.0% P < 0.0001
CHARM-preserved [27]	Candesartan 32 mg vs. placebo	3 years	≥70years (26.7%)	40.1%	CHF NYHA II-IV	Composite end-point of CV death or hospitalization for CHF	22.0%	24.2%	2.2% P = 0.12
OPTIMAAL [29]	Losartan 50 mg vs. captopril 150 mg	2.7 years	65–75years (33.6%) ≥75years (26.8%)	28.8%	Acute MI and CHF	All-cause mortality	18.1%	16.3% (captopril)	-1.8% P = 0.07
VALIANT [24]	Valsartan 320 mg vs. captopril 150 mg vs. both	2.1 years	≥65years (53.0%)	30.9%	Acute MI and CHF	All-cause mortality	16.8%	16.9% (captopril)	0.1% P = 0.62

CV cardiovascular; MI myocardial infarction; CHF congestive heart failure; NYHA New York Heart Association; ACEI angiotensin converting enzyme inhibitors; ARR absolute risk reduction.

In the Val-HeFT (Valsartan Heart Failure Trial) study, patients with congestive heart failure were randomized to valsartan or placebo plus standard background therapy (Figure 2 and Table 3) [22]. Compared with placebo, valsartan reduced morbidity and mortality and produced significant improvements in NYHA class ($P < 0.001$), ejection fraction ($P = 0.001$), signs and symptoms of heart failure ($P < 0.01$), and quality of life ($P = 0.005$) [22]. The beneficial effects of valsartan in patients ≥ 65 years were similar to those observed in younger patients [22]. An unexpected result of Val-HeFT was that the outcome was worse in patients receiving the combination of β -adrenoceptor blockers, ACE inhibitors, and valsartan [22]. This result was not confirmed in subsequent trials [23, 24]. Further analysis of Val-HeFT results according to age has shown beneficial effects on morbidity and mortality, neurohormonal activity, left ventricular function, and quality of life in both elderly and young patients [25].

The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) study assessed the effects of candesartan *vs.* placebo in three distinct populations (Figure 2 and Table 3): patients with left ventricular ejection fraction $\leq 40\%$ who were receiving an ACE inhibitor (CHARM-Added) [23] or not receiving an ACE inhibitor because of previous intolerance (CHARM-Alternative) [26], and patients with left ventricular ejection fraction $> 40\%$ (CHARM-Preserved) [27]. The primary outcome for the overall program was all-cause mortality, and for all three component trials it was cardiovascular death or hospital admissions for heart failure. The overall results showed a greater benefit with candesartan for all-cause mortality (ARR 2%, $P = 0.055$) [28]. Of note, the beneficial effects of candesartan were more evident in patients ≥ 65 years (ARR 1.3% in patients < 65 years, ARR 6.4% in patients $\geq 65 < 75$ years, and ARR 6.6% in patients ≥ 75 years) [28]. Candesartan treatment was associated with an increased risk of hypotension (3.5% *vs.* 1.7%, $P < 0.0001$), hyperkalaemia (2.2% *vs.* 0.6%, $P < 0.0001$), and increase in serum creatinine (6.2% *vs.* 3.0%, $P < 0.0001$). In the CHARM-Added trial, the addition of candesartan to therapy with an ACE inhibitor decreased the risk of cardiovascular death and hospital admission for heart failure [23]. In contrast to Val-HeFT, the beneficial effect of candesartan was observed also in patients receiving ACE inhibitors and β -adrenoceptor blockers [23]. In CHARM-Alternative there was a 24% risk reduction in cardiovascular mortality or hospital admission for heart failure with candesartan [26]. Finally, in CHARM-Preserved, candesartan did not have a significant impact on the composite end-point of car-

diovascular death or hospitalization for heart failure. However, it significantly reduced hospitalization particularly when patients were admitted at least once (ARR 3.3%, $P = 0.017$) [27].

ARBs are also effective in patients with left ventricular dysfunction postmyocardial infarction. In this setting, there is a significant and prolonged activation of the renin-angiotensin-aldosterone system which contributes to cardiac and vascular remodelling. The OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) study investigated the effects of losartan *vs.* captopril in clinically stable patients shortly after a myocardial infarction complicated by heart failure [29]. Patients were randomized within 10 days of symptom onset (Figure 2, Table 3). There was no significant difference in all-cause mortality between captopril and losartan, although losartan was better tolerated [29]. Sub-analysis of patients > 65 years yielded similar results [29].

More recently in the VALIANT (Valsartan in Acute Myocardial Infarction) trial, patients with acute myocardial infarction complicated by left ventricular dysfunction, heart failure, or both, were randomized to valsartan, captopril, or a combination of both (Figure 2 and Table 3) [24]. The effects of valsartan and captopril on all-cause mortality were comparable [24]. The hazard ratio for death in the valsartan group compared with the captopril group was 1.00 (97.5% CI 0.90, 1.11; $P = 0.98$), whereas the hazard ratio for death in the valsartan plus captopril group compared with the captopril mono-therapy group was 0.98 (97.5% CI 0.89, 1.09; $P = 0.73$) [24]. The subgroup analysis in patients ≥ 65 years yielded similar results [24]. Furthermore, about 70% of patients were taking a β -adrenoceptor blocker but no increased risk was observed in patients receiving triple neurohormonal blockade (*i.e.* β -adrenoceptor blocker, ACE inhibitor and ARB) [24].

High-risk patients without heart failure

The antihypertensive efficacy of ARBs is similar to that of ACE inhibitors and other antihypertensive drugs [30]. Results of a recent major clinical trial established the benefits of ARBs in high-risk hypertensive patients with left ventricular hypertrophy (LIFE, Losartan Intervention For Endpoint Study) [31]. Patients were treated with losartan or atenolol (Figure 2 and Table 4) [31]. Losartan was significantly superior to atenolol in preventing cardiovascular morbidity and death. Moreover, losartan produced a greater reduction of left ventricular hypertrophy, despite similar blood pressure reductions, and was better tolerated [31]. The effects of losartan on regression of left ventricular hypertrophy in patients

Table 4
Clinical trials of angiotensin receptor blockers in patients at high cardiovascular risk, without heart failure, including elderly patients

Study	Agents and daily dose	Follow-up	Elderly participants	Women	Inclusion criteria	Primary outcome measures	Major results		
							Incidence in placebo group	Incidence in active group	ARR P-value
LIFE [31]	Losartan 100 mg vs. atenolol 100 mg	4.8 years	55–80 years	54.0%	HT + LVH	Composite end-point of CV death, MI, or stroke	11.0%	12.8% (atenolol)	1.8% $P = 0.021$
SCOPE [33]	Candesartan 16 mg vs. placebo	3.7 years	70–89 years ≥80 years (21.3%)	64.5%	HT	Composite end-point of CV death, nonfatal MI, and nonfatal stroke	9.8%	10.9%	1.1% $P = 0.19$
VALUE [35]	Valsartan 80–160 mg vs. amlodipine 5–10 mg	4.2 years	NA	42.4%	HT and high CV risk	Cardiac event	10.6%	10.4% (amlodipine)	–0.2% $P = 0.49$

HT hypertension; LVH: left ventricular hypertrophy; CV cardiovascular; MI myocardial infarction; NA not available; ARR absolute risk reduction.

≥65 years were similar to those in patients <65 years [32].

In the SCOPE (Study on Cognition and Prognosis in the Elderly) study, elderly hypertensive patients were assigned to candesartan or placebo with open-label active antihypertensive therapy added as needed (Figure 2 and Table 4) [33]. The study was designed to assess whether candesartan-based treatment significantly reduced the rate of major cardiovascular events (cardiovascular deaths, nonfatal myocardial infarction, and nonfatal stroke). Despite a more effective blood pressure reduction in the candesartan group (21.7/10.8 vs. 18.5/9.2 mmHg), there was no significant difference in the primary endpoint. Candesartan was well tolerated. Subgroup analysis documented a significant reduction in nonfatal strokes and all strokes, particularly when the subgroup of patients with isolated systolic hypertension was analysed (ARR 1.9%, $P = 0.050$) [34].

Finally, the VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) study compared the effects of valsartan vs. amlodipine on the risk of future cardiac events in hypertensive patients at high cardiovascular risk (Figure 2 and Table 4) [35]. The main end-point did not differ between the treatment groups. Oedema (32.9% vs. 14.9%, $P < 0.0001$) and hypokalaemia (6.2% vs. 3.5%, $P < 0.0001$) were more common with amlodipine. By contrast, dizziness (16.5% vs. 14.3%, $P < 0.0001$), headache (14.7% vs. 12.5%, $P < 0.0001$), and diarrhoea (8.8% vs. 6.8%, $P < 0.0001$) occurred more frequently with valsartan [35].

Discussion

The available evidence supports the use of ARBs in elderly patients, particularly in the presence of symptomatic congestive heart failure and left ventricular dysfunction. Studies published in the last 5 years show beneficial effects in patients up to the age of 95 years (Figure 2). Combined treatment with ACE inhibitors might provide additional benefit, as demonstrated in the CHARM-Added study [23], suggesting that the role of these drugs is not limited to heart failure patients who are intolerant to ACE inhibitors.

In hypertensive elderly patients without heart failure, the use of ARBs, albeit well tolerated, has not shown significant additional benefits over other classes of antihypertensive drugs. The results of the LIFE study, demonstrating superiority of losartan over atenolol, might have been affected by the poor choice of the comparator [36]. Nevertheless, some benefit in stroke prevention has been shown in this group, although these data have been obtained from *posthoc* analysis [34]. Angiotensin receptor blockers were generally tolerated although a slight

increase in the risk of hypotension and renal failure with hyperkalaemia was observed in most studies.

Conclusions

The available evidence supports the use of ACE inhibitors and ARBs for the treatment of congestive heart failure in elderly patients up to the age of 95 years. These agents are generally well tolerated, particularly in ambulatory patients with stable heart failure, as long as renal function is carefully monitored and the concomitant use of nephrotoxic drugs is avoided. An increasing body of evidence supports the use of these agents in high cardiovascular risk patients without heart failure.

Despite these promising data, further evidence is required to demonstrate the efficacy of both ACE inhibitors and ARBs in old-old individuals and patients with asymptomatic left ventricular dysfunction. Moreover, research is needed to ascertain the additional benefit of maximal doses of both drug classes and the applicability of the results obtained in controlled large clinical trials to frail institutionalized patients suffering from multiple comorbidities.

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