1. Introduction

The most common risk factors for heart failure (HF) are hypertension and antecedent myocardial infarction (MI). Following first MI, more than 18% of those 65 years or older will develop HF during the subsequent 5 years, and once HF develops the 5-year mortality rate approaches 50%[1]. Angiotensin II (Ang II), the main effector peptide of the renin–angiotensin aldosterone system (RAAS), plays a key role in the pathogenesis of HF, largely through its effects on the Ang II type 1 (AT1) receptor[2].

Angiotensin receptor blockers (ARBs) are selective for the AT1 receptors and thus attenuate the deleterious effects of Ang II. The American College of Cardiology/American Heart Association (ACC/AHA) recommend ARBs as an alternative to an angiotensin-converting enzyme inhibitor (ACEI) in those intolerant if they have clinical or radiological signs of HF and/or a left ventricular ejection fraction (LVEF) less than or equal to 0.40 following acute MI[3]. Similarly, the Heart Failure Society of America (HFSA) recommends to use ARBs more liberally, as an alternative to an ACEI in ACEI intolerant and tolerant patients with HF with or without MI[4]. These are wide class recommendations that are extended to the...
eight US FDA-approved agents despite clinical trial data limited to three agents in patients with HF.

Seven randomized controlled clinical trials (RCTs) have compared three ARBs (losartan, candesartan, and valsartan) versus placebo or the prototype ACEI, captopril (Table 1) [5]. An additional RCT and a study of registry data have examined dose-dependent effects (Table 2). Since trial data are limited, if the goal is to approach pharmacotherapy in an evidence-based manner, drug and dose should reflect RCT evidence.

Valsartan's clinical trial data demonstrate mortality equivalence to captopril in the post-MI population when a mean daily dose of 247 mg is used in the management of new onset HF. Additional evidence supports valsartan use in combination with ACEIs to reduce hospitalizations for all-cause chronic HF [6,7]. Subsequently, US labeling clearly delineates indication according to RCT results [8]. In contrast, the European Medicines Agency’s Committee for Medicinal Products for Human Use has extrapolated from the data, extending valsartan’s indication to clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (1/2 – 10 days) MI [9].

This article discusses the basic chemistry, pharmacokinetic, and pharmacodynamics data for valsartan. It also reviews and synthesizes the current evidence regarding the use of valsartan and other ARBs in the post-MI HF population. It compares and contrasts the valsartan data with that of losartan and candesartan in this and other populations. Finally, this article also discusses the putative pleotropic effects of valsartan.

2. Chemical characteristics

Valsartan (Box 1), also referred to as CGP 48933, is a non-peptide, orally active, Ang II receptor blocker (ARB) which is highly selective for the AT1 receptor. Its empirical formula is C24H29N5O3. It is a white to practically white microcrystalline powder. It is soluble in methanol and slightly soluble in water. In a buffered solution, the solubility is increased since a di-anion salt is formed. Stable solutions can be prepared in aqueous buffers of neutral pH. An extemporaneous compound (4 mg/mL) can be prepared using Ora-Plus® oral suspending vehicle and Ora-Sweet SF® oral sweetening vehicle. In the US, valsartan is available in tablet form in doses of 40, 80, 160, and 320 mg. It is not available as an intravenous formulation [8,10].

Valsartan lacks activity at alpha1-, alpha2-, and beta1-adrenergic receptors, histamine1, substance P, GABA-A and -B, muscarinic, serotonin1 and serotonin2, and calcium channels [10]. It has a higher binding affinity at the AT1 receptor than losartan, but a lower binding affinity than the remainder of agents in the ARB class. With AT1 receptor blockade in vascular smooth muscle and the adrenal gland, the effects of Ang II, including vasoconstriction, sympathetic nerve activation, aldosterone secretion and cellular proliferation are decreased [11]. Since valsartan has a 20,000-fold greater affinity for the AT1 receptor than losartan, the AT2 receptor may be secondarily exposed to higher concentrations of Ang II via the RAAS feedback loop. Although AT2 receptor function remains uncertain, elevated Ang II concentrations may contribute to vasodilation and anti-cell proliferation [8,11].

3. Pharmacodynamic and pleotropic properties of valsartan

Cardiovascular pharmacodynamic properties in humans with HF have been reviewed previously and include a regression in ventricular remodeling and improved left ventricular ejection fraction, reduction in plasma brain natriuretic peptide and
## Table 1. Multicenter RCT Examining ARBs Versus Standard of Care ACEIs In Chronic Heart Failure or Post-MI Heart Failure.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Condition</th>
<th>Date</th>
<th>N</th>
<th>Location of Trial</th>
<th>Key Differences in Inclusion</th>
<th>Mean Age</th>
<th>Follow up (months)</th>
<th>Treatment Arms</th>
<th>ARB vs. placebo</th>
<th>ARB Dose, Initial</th>
<th>ARB target dose</th>
<th>Primary Endpoint(s)</th>
<th>Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM-Added</td>
<td>Heart Failure, NYHA II-IV</td>
<td>2003</td>
<td>2548</td>
<td>26 countries, including the US (23%), 618 sites</td>
<td>Required background ACEI</td>
<td>64</td>
<td>41</td>
<td>2</td>
<td>Candesartan</td>
<td>4 - 8 mg daily</td>
<td>32 mg daily</td>
<td>CV mortality or hospitalization for HF mortality, irrespective of cause and morbidity (2) mortality, irrespective of cause</td>
<td>HR 0.85 (adjusted value; P = 0.010)</td>
<td>Note: spironolactone use (17%)</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>Heart Failure, NYHA II-IV</td>
<td>2001</td>
<td>5010</td>
<td>26 countries, including the US (56%), 302 sites</td>
<td>Background ACEI use acceptable (93%)</td>
<td>62.7</td>
<td>23</td>
<td>2</td>
<td>Valsartan</td>
<td>40 mg BID</td>
<td>160 mg BID</td>
<td>CV mortality or hospitalization for HF mortality, irrespective of cause and morbidity (2) mortality, irrespective of cause</td>
<td>RR 0.87 (95% CI 0.77-0.97; p = 0.009)</td>
<td>(2) RR 1.02 (95% CI 0.88-1.18; p = 0.80)</td>
</tr>
</tbody>
</table>

**Control Drug (ACEI) – captopril (using initial doses of 6.25 mg TID and target doses of 50 mg TID).**

ACS: Acute Coronary Syndrome; ARB: Angiotensin Receptor Blocker; N: Sample size; RCT: Randomized controlled trial.
### Table 1. Multicenter RCT Examining ARBs Versus Standard of Care ACEIs In Chronic Heart Failure or Post-MI Heart Failure (continued).

#### Chronic heart failure trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Condition</th>
<th>Date</th>
<th>N</th>
<th>Location of Trial</th>
<th>Key Differences in Inclusion</th>
<th>Mean Age</th>
<th>Follow up (months)</th>
<th>Treatment Arms</th>
<th>ARB Dose, Initial</th>
<th>ARB target dose</th>
<th>Primary Endpoint(s)</th>
<th>Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE II</td>
<td>Heart failure, NYHA II-IV</td>
<td>2000</td>
<td>3152</td>
<td>46 countries, including the US, 289 centers</td>
<td>Most ACEI/ARB naïve (77%)</td>
<td>71</td>
<td>18</td>
<td>Losartan vs. placebo</td>
<td>12.5 mg</td>
<td>50 mg</td>
<td>All-cause mortality</td>
<td>NS (HR 1.13 [95% CI 0.95-1.35], p = 0.16)</td>
<td>Noninferiority not evaluated</td>
</tr>
</tbody>
</table>

#### Post-AMI trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Condition</th>
<th>Date</th>
<th>N</th>
<th>Location of Trial</th>
<th>Key Differences in Inclusion</th>
<th>Mean Age</th>
<th>Follow up Duration (months)</th>
<th>No. Treatment Arms</th>
<th>ARB (vs. active comparison)</th>
<th>ARB Dose, Initial</th>
<th>ARB target dose</th>
<th>Primary Endpoint</th>
<th>Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIMAAL Post MI Heart Failure</td>
<td>2002</td>
<td>5477</td>
<td>7 Western European/Scandinavian countries, 329 sites</td>
<td>HF or documented LVSD not required if an anterior MI present ACEI/ARB naïve</td>
<td>67.4</td>
<td>40</td>
<td>2 Losartan vs. captopril</td>
<td>12.5 mg daily</td>
<td>50 mg daily</td>
<td>Mortality, irrespective of cause</td>
<td>RR 1.13, 95% CI 0.99-1.28 (p = 0.07)</td>
<td>Losartan better tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VALIANT Post MI Heart Failure</td>
<td>2003</td>
<td>14703</td>
<td>24 countries including the US, 931 sites</td>
<td>ACC/AHA Stage B or C heart failure Prior ACEI/ARB use acceptable</td>
<td>64.8</td>
<td>24.7</td>
<td>3 Valsartan vs. captopril</td>
<td>20 mg BID</td>
<td>160 mg BID</td>
<td>80 mg BID</td>
<td>Mortality, irrespective of cause</td>
<td>Non-inferior, Valsartan not superior to captopril</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS: Acute Coronary Syndrome; ARB: Angiotensin Receptor Blocker; N: Sample size; RCT: Randomized controlled trial.
<table>
<thead>
<tr>
<th>Author</th>
<th>Condition</th>
<th>Date Published</th>
<th>N</th>
<th>Location of Study</th>
<th>Study Design</th>
<th>Mean Age</th>
<th>Follow-up Period</th>
<th>ARB study drug #1</th>
<th>ARB study drug #2</th>
<th>Primary Endpoint</th>
<th>Result</th>
<th>Secondary results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svanstrom</td>
<td>Chronic Heart Failure</td>
<td>2012</td>
<td>6479</td>
<td>Denmark</td>
<td>Registry based cohort study</td>
<td>72</td>
<td>Person-years: 19491 Median treatment duration: yrs candesartan 1.8 yrs losartan</td>
<td>Losartan (n = 4397)</td>
<td>Candesartan</td>
<td>All Cause Mortality</td>
<td>HR 1.10 (95% CI 0.96-1.25) using propensity score adjustment. Dose tertile subanalysis suggested high dose candesartan (16 - 32 mg) and losartan (100 mg) offered similar mortality risk; whereas low and moderate doses of losartan and candesartan were associated with increased mortality.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Konstam (HEAAL)</td>
<td>Heart Failure, NYHA II-IV</td>
<td>2009</td>
<td>3846</td>
<td>30 countries, including the US, 255 sites</td>
<td>Prospective randomized controlled trial</td>
<td>56.4 months</td>
<td>Losartan 50 mg</td>
<td>Losartan 150 mg</td>
<td>Composite mortality and HF hospitalization</td>
<td>HR 0.90 (0.82-0.99) (p = 0.027)</td>
<td>Dose ranging study of same drug ACEI intolerant patients and prior ARB use acceptable Losartan 150 mg associated with higher rates of hyperkalemia, hypotension, and renal impairment.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
aldosterone, and an improvement in pulmonary capillary wedge pressure, cardiac output, and systemic vascular resistance [12]. Pleotropic activity may also contribute to valsartan’s efficacy (Table 3) [33-35] in HF. Although available data are mainly derived from patients with hypertension, it is likely relevant to cardiovascular protection in patients with HF. Valsartan modulates tumor necrosis factor-α, interleukin-6, reactive oxygen species, tissue plasminogen activator, and monocyte chemotactic protein-1. Whereas telmisartan has significant peroxisome proliferator-activated receptor-alpha and gamma (PPAR-α and PPAR-γ) activity as recently reviewed, valsartan lacks these pleotrophic effects [26-28].

Valsartan exhibits a positive dose response for blood pressure across the dosing range of 20 – 320 mg [29,30]. With doses of 160 – 320 mg, systolic blood pressure reduces modestly by 13.7 – 14.5 mmHg [31]. In comparison, amlopine was more efficacious than valsartan 80 – 160 mg daily in reducing blood pressure (difference of 4.0/2.1 mmHg) in the first month of treatment of the VALUE trial [32]. However, a post hoc analysis using serial median matching for systolic blood pressure control (and other relevant clinical factors) for 5006 pairs demonstrated that valsartan offered the benefit of fewer hospitalizations for heart failure, a benefit beyond equivalent blood pressure attainment [33].

4. Pharmacokinetics and metabolism

Valsartan is currently delivered as a tablet formulation, although most oral pharmacokinetic data were obtained using valsartan administered as capsules or a phosphate buffered solution, the latter is notably an impracticable dosage [34,35]. The pharmacokinetic data for comparator ARBs are found in Table 4 [8,39-52].

Following oral administration, absorption of valsartan occurs and is characterized by two sequential first-order phases [34,38,53]. Oral bioavailability is 24% [34]. Although food can reduce absorption 46%, valsartan may be administered with or without food [8,10].

Valsartan does not appreciably accumulate in plasma with repeated administration [57]. In healthy controls, mean peak plasma concentrations (Cmax) are reached in 2 h (Tmax), whereas for HF patients there is a slight delay to 2.5 – 3 h [34,38]. Additionally, the Cmax value observed in HF is two times higher than values obtained in healthy subjects following the same 80 mg dose (Table 5). The Cmax increases fourfold when the valsartan dose is increased from 20 to 160 mg and the relationship between the AUC and Cmax and the dose of valsartan is linear [38].

Valsartan is extensively bound to plasma proteins (85 – 99%), mainly albumin (92%); therefore, it is not removed from the plasma by hemodialysis [54]. The estimated volume of distribution (17L) at steady state is less than the body water suggesting it does not extensively distribute into tissues [8,34].

Valsartan is minimally metabolized (20%) and is pharmacologically active in the unchanged form [8,34,35]. The enzymes primarily responsible for metabolism do not seem to be cytochrome (CYP) P450 isoenzymes, although CYP2C9 metabolism may be involved in the formation of the M-1 metabolite (CGP 71580), veleryl-4-hydroxy-valsartan [8,35].

The majority of drug excretion occurs within 12 h of dosing through non-renal routes (86%) [34,35]. As the main route of elimination is biliary, impairment of the hepatobiliary transport functions have a marked impact on the clearance of valsartan [55]. Valsartan’s pronounced biliary excretion suggests active involvement of an anion transporting system in the liver [35]. Subsequently, a genetic polymorphism (*1b allele) in the organic anion transporting polypeptide (OATP) 1B1 has been shown to slightly reduce valsartan’s AUC [56].

Valsartan pharmacokinetics are not altered by ethnicity (e.g., Japanese versus Caucasians) [36]. Although mean systemic exposure is higher in elderly (mean age 76) than young (mean age 23) patients this does not warrant an initial dose adjustment [53]. The pharmacokinetic differences that occur in HF or mild-severe renal dysfunction also do not suggest dose adjustment is necessary [12].

5. Valsartan dose and dosing interval selection

Use of adequate doses and dosing intervals are relevant for the treatment of HF as these patients significantly benefit from maximum blockade of the RAAS. In a repeated dose administration study of 16 normotensive subjects, valsartan produced a dose-dependent blockade of the AT1 receptor. Administration of valsartan 80 mg and losartan 50 mg once daily offered comparable, yet partial, blockade of the AT1 receptor as measured at peak, defined as 4 h post dose on day 8 of therapy. When the valsartan dose was further increased to 160 – 320 mg once daily, AT1 blockade was sustained and comparable to irbesartan 150 mg at peak, although trough valsartan AT1 blockade remained significantly lower [57].

Since there was a trend toward increased mortality with use of losartan 50 mg versus captopril in ELITE II, partial AT1 receptor blockade with low dose therapy was thought to be the likely contributor [58]. A comparison of low (50 mg) versus high (150 mg) dose losartan was completed to explore the relationship between losartan dose and clinical outcomes in 3846 patients with NYHA class II – IV chronic HF. Over a median 4.7-year follow-up interval, high-dose losartan statistically improved the combined morbidity-mortality endpoint, with each component of the endpoint directionally contributing [59]. More recently, a study of registry data conducted by Svanström also demonstrated that low doses of losartan and candesartan are associated with increased mortality in HF compared to high-dose therapies (Table 2) [60].

A multicenter RCT with an intended enrollment of 1116 patients with LV dysfunction following first episode of ST
Table 3. Pleotropic Effects of Valsartan in Humans.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prognostic Role in HF</th>
<th>Effect of Valsartan</th>
<th>Cohort(s) Studied</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>Helpful when used with other biomarkers (e.g., brain natriuretic peptide, troponin)</td>
<td>Reduces</td>
<td>In normal, stage 2 hypertension (HTN) (however, effect neutralized by adjunctive hydrochlorothiazide), hypertensive patients with metabolic syndrome, and heart failure (not currently on ACEIs) subjects</td>
<td>Not a cytokine, produced by the liver in response to IL-6</td>
</tr>
<tr>
<td>Tumor Necrosis Factor (alpha) (TNF-α)</td>
<td>Association with increased mortality</td>
<td>Reduces</td>
<td>HTN</td>
<td>Inflammatory biomarker</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6)</td>
<td>Association with increased mortality</td>
<td>Reduces</td>
<td>HTN</td>
<td>Inflammatory biomarker</td>
</tr>
<tr>
<td>Reactive Oxygen Species (ROS)</td>
<td>Association with myocardial remodeling</td>
<td>Reduces</td>
<td>Normal and HTN subjects</td>
<td>Oxidative stress biomarker</td>
</tr>
<tr>
<td>Tissue plasminogen activator antigen (t-PA [antigen])</td>
<td>Association with HF-related deaths or hospitalizations</td>
<td>Reduces</td>
<td>HTN subjects</td>
<td>Hemostatic biomarker</td>
</tr>
<tr>
<td>Monocyte chemotactic protein-1 (MCP-1)</td>
<td>Association with remodeling in the subacute phase of MI</td>
<td>Reduces</td>
<td>HTN subjects with hyperlipidemia</td>
<td></td>
</tr>
</tbody>
</table>

6. ARB clinical efficacy in post-myocardial infarction heart failure and chronic heart failure populations

Valsartan heart failure trial (Val-HeFT)

6.1 Valsartan heart failure trial (Val-HeFT)

In 1997, a randomized, placebo-controlled, double-blind, 2×2 factorial-group trial was initiated to demonstrate the efficacy of valsartan in HF with left ventricular systolic dysfunction (LVEF < 0.40) and LVDD > 2.7 cm, or at least 3 months duration on the co-primary endpoint of mortality and a combined end-point of mortality-morbidity. Following a 2-week, randomization period, patients were stratified by ACEI (any), beta blocker (β-blocker, any), and random assignment to 160 mg twice daily or placebo. During the treatment phase, the primary endpoint in patients on ACEI was a composite of all-cause mortality and non-fatal myocardial infarction, and the primary endpoint in patients not on ACEI was a composite of all-cause mortality and hospitalization for HF. Study drug tampering was limited to 1 mg twice daily and the dose was doubled every 2 weeks until the target dose of 160 mg was achieved. Study drug tampering 3 times weekly, 1 mg twice daily, and the dose was doubled every 2 weeks until the target dose of 160 mg was achieved. Study drug tampering was limited to 1 mg twice daily and the dose was doubled every 2 weeks until the target dose of 160 mg was achieved. Study drug tampering was limited to 1 mg twice daily and the dose was doubled every 2 weeks until the target dose of 160 mg was achieved.

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**Table 4. Key PK Differences Between Other ARBs.**

<table>
<thead>
<tr>
<th>ARB generic name (Brand)</th>
<th>Dose</th>
<th>Metabolism by CYP P450</th>
<th>Active metabolites</th>
<th>Cmax</th>
<th>Tmax (h)</th>
<th>AUC</th>
<th>Effect of Food on AUC</th>
<th>F (%)</th>
<th>Vd</th>
<th>Renal Excretion</th>
<th>ppb</th>
<th>Hepatic impairment</th>
<th>Renal Impairment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan potassium*</td>
<td>50 mg</td>
<td>3A4, 2C9, 2C10*</td>
<td>E3174</td>
<td>0.29 mcg/mL (parent)</td>
<td>1.5-2.5 (parent)</td>
<td>0.48 mcg h/L (parent)</td>
<td>32.6</td>
<td>34.4L</td>
<td>0.18 mcg·h/L</td>
<td>≥90%</td>
<td>Use lower starting dose in general cirrhosis increases sensitivity to RAAS axis interruption</td>
<td>No dosing adjustment</td>
<td>E3174 is 10-40x more potent than parent compound; responsible for efficacy</td>
<td></td>
</tr>
<tr>
<td>Irbesartan (Avapro)</td>
<td>300 mg</td>
<td>2C9 (3A4 negligible)</td>
<td>minimal</td>
<td>3.3 mg/L</td>
<td>2</td>
<td>11</td>
<td>19.8 mcg h/L</td>
<td>60-80</td>
<td>53-93</td>
<td>0.18 mcg·h/L</td>
<td>90%</td>
<td>No dosage adjustment is necessary in mild to severe renal impairment unless also volume depleted</td>
<td>Use lower starting dose in severe renal impairment</td>
<td>Following oral administration, rapidly hydrolyzed during gastrointestinal absorption to losartan</td>
</tr>
<tr>
<td>Candesartan cilexetil (Atacand)</td>
<td>16 mg</td>
<td>None</td>
<td>No</td>
<td>119.2 ng/mL</td>
<td>4</td>
<td>9</td>
<td>849 mcg h/L</td>
<td>none</td>
<td>15</td>
<td>0.13L/kg</td>
<td>99%</td>
<td>Use lower starting dose in moderate hepatic impairment</td>
<td>Use lower starting dose in severe renal impairment</td>
<td>Following oral administration, rapidly hydrolyzed during gastrointestinal absorption to candesartan</td>
</tr>
<tr>
<td>Telmisartan (Micardis)</td>
<td>120 mg</td>
<td>None</td>
<td>No</td>
<td>1046 ng/mL</td>
<td>1</td>
<td>19.2</td>
<td>4321 ng h/mL</td>
<td>minor</td>
<td>50</td>
<td>500L</td>
<td>Not applicable</td>
<td>&lt;99%</td>
<td>Avoid in obstructive biliary disease, cholestasis or severe hepatic impairment</td>
<td>No dosing adjustment</td>
</tr>
<tr>
<td>Eprosartan (Teveten)</td>
<td>300-600 mg</td>
<td>None</td>
<td>No</td>
<td>1273 ng/mL</td>
<td>1-2</td>
<td>20</td>
<td>4887 mg h/mL</td>
<td>by 15%</td>
<td>13</td>
<td>308L</td>
<td>1.8-2.4L/hr</td>
<td>98%</td>
<td>No dosage adjustment</td>
<td>Do not exceed 600 mg/day in moderate or severe renal impairment</td>
</tr>
<tr>
<td>Olmesartan medoxomil (Benicar)</td>
<td>20 mg</td>
<td>None</td>
<td>Yes</td>
<td>0.51 ng/mL</td>
<td>1.7-2.5</td>
<td>10.6</td>
<td>2.68 mg h/L</td>
<td>minor</td>
<td>26</td>
<td>35L</td>
<td>0.42-0.92 L/hr</td>
<td>99.7%</td>
<td>Use lower starting dose in moderate hepatic impairment Not studied in severe hepatic impairment</td>
<td>Do not use in severe renal impairment; dose maximum in mild to moderate renal impairment: 20 mg</td>
</tr>
</tbody>
</table>

*ARB prototype

1. Once daily dosing x 7 days
2. Cmax, AUC provided for 400 mg dose, 1:2 for the 600 mg dose, with all other PK data provided for the 300 mg dose
3. Limited pharmacokinetic data have been published.

combination ACEI-ARB without a beta blocker (n = 3034, 60.6%) showed that valsartan's benefit was limited entirely to a reduction in morbidity, with no reduction in mortality. The morbidity benefit was most significant in patients on ACEI doses below the median (e.g., lisinopril 17.5–20.7 mg) [66]. One component of the morbidity endpoint, HF hospitalization rate, was significantly reduced by valsartan regardless of background ACEI dose.

An economic evaluation found that valsartan did not significantly reduce costs in the entire cohort. However, valsartan did reduce costs associated with HF-related hospitalizations for the total cohort and overall costs in patients not on an ACEI at baseline [67].

6.2 The valsartan in acute myocardial infarction (VALIANT) trial

In 1998, Merck and Novartis initiated active comparison studies to demonstrate the efficacy of losartan (in OPTIMAAL) and valsartan (in VALIANT), respectively, in reducing mortality following MI complicated by HF. VALIANT assessed valsartan's non-inferiority to captopril, on the primary endpoint of all-cause mortality in patients following acute MI with ACC/AHA Stage B or C HF [7,68]. VALIANT enrolled 2.5 times more patients than OPTIMAAL. Approximately 77% of subjects had clinical or radiological evidence of HF. In contrast to OPTIMAAL, prior use of an ACEI or ARB was not exclusion criterion; however, use of a non-study ACEI/ARB was prohibited within 12 h of randomization.

Initially patients received low doses of valsartan (20 mg twice daily), captopril (6.25 mg three times daily), or combination therapy (valsartan 20 mg twice daily plus captopril 6.25 mg three times daily) with plans to maximize doses by the 3-month visit. When used as monotherapy captopril was titrated to target doses of 50 mg twice daily, whereas valsartan were titrated to target doses of 50 mg twice daily and 160 mg twice daily, respectively. When used as combination therapy, the target captopril dose was reduced by 50% while the target valsartan dose was retained. Both the target and the mean achieved doses (247 and 117 mg for valsartan and captopril, respectively) were similar to those rigorously evaluated in prior HF trials [4]. Study guidance documents did not dictate other therapies; however, patients received other evidence-based therapies at expected rates (aspirin 91.4%, beta blockers 70.1%, and statins 34.4%) within 24 h of randomization.

Similar to OPTIMAAL, after the pre-specified primary non-inferiority analysis was performed, subsequent superiority testing was to be performed. The primary endpoint of all-cause mortality was similar (19.9%, 19.3%, and 19.5%) regardless of treatment group (valsartan, combination, and captopril groups, respectively). Valsartan was subsequently found to be non-inferior to captopril (p = 0.004) and per-protocol (p = 0.002) analyses for the primary endpoint (p = 0.009) for the primary endpoint. Study non-inferiority analysis was planned, subsequent superiority testing was to be performed. The primary endpoint of all-cause mortality was similar (19.9%, 19.5%, and 19.6%) regardless of treatment group (valsartan, combination, and captopril groups, respectively). Valsartan was subsequently found to be non-inferior to captopril (p = 0.004) and per-protocol (p = 0.002) analyses for the primary endpoint (p = 0.009) for the primary endpoint.

Concerning the pharmacokinetic properties of valsartan, limited pharmacokinetic data have been published. A limited pharmacokinetic study showed that valsartan did not reduce costs in the entire cohort. However, valsartan did reduce costs associated with HF-related hospitalizations for the total cohort and overall costs in patients not on an ACEI at baseline [67].

Table 4. Key PK Differences Between Other ARBs (continued).

| ARB generic name (Brand) | Dose | Metabolism by CYP P450 | Active metabolites | Cmax | Tmax (h) | T 1/2 (h) | AUC | Effect of Food on AUC | F (%) | Vd | Renal Excretion | ppb | Hepatic impairment | Renal Impairment | Comments
|--------------------------|------|------------------------|--------------------|-------|----------|-----------|-----|----------------------|-------|-----|-------------------|-----|-----------------|----------------|---------|
| Azilsartan medoxomil (Edarbi) | 20–320 mg | 2C9 | Yes | 1.5–3 | 2.6 | 11 | -- | -- | 60 | 16 L | 0.138 L/hr | > 99% | No dosage adjustment. Not studied in severe hepatic impairment. | No dosage adjustment. Following oral administration, rapidly hydrolyzed during gastrointestinal absorption to azilsartan. Retain medication in original manufacturer's container and protect from light and moisture.

*ARB prototype

1 Once daily dosing x 7 days

2 Cmax, AUC provided for 400 mg dose, 1/2 for the 600 mg dose, with all other PK data provided for the 300 mg dose

3 Limited pharmacokinetic data have been published.


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discontinuation rates at 1 year were 15.3%, 19%, and 16.8% of patients in the valsartan, combination valsartan-captopril, and the captopril groups, respectively. Discontinuation rates were more common with combination therapy (p = 0.007 for the comparison between the combination valsartan-captopril group versus captopril monotherapy).

A post hoc analysis explored the differential effects of drug selection on quality of life and resource utilization. There were no significant differences in rates of outpatient (e.g., outpatient visits, emergency department visits, rehabilitation center admission, and cardiovascular tests/procedures) or inpatient resource utilization between valsartan and captopril groups. Additionally, a health-related quality of life (EuroQol-5D) evaluation did not differ significantly between groups. Subsequently, use of less expensive captopril potentially offered an advantage, since study medication costs had the greatest effect on the incremental cost and drug selection did not affect quality of life. However, if a more expensive ACEI is selected (vs. captopril), the financial difference may become inconsequential [69]. As more generic ARBs enter the marketplace, cost may become even less germane.

### Table 5. Comparison of Valsartan 80 mg Pharmacokinetic Parameters in Human Subject Subgroups.

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>N</th>
<th>Dose</th>
<th>Cmax (mg/L)</th>
<th>Tmax</th>
<th>T 1/2</th>
<th>AUC(0-12h) (mg·h/L)</th>
<th>F (%)</th>
<th>Cl(L/h)</th>
<th>Vd (L)</th>
<th>Renal Excretion (L/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Males</td>
<td>12</td>
<td>80 mg x1 (capsule)</td>
<td>1.64</td>
<td>2.0</td>
<td>7.05</td>
<td>8.54</td>
<td>23</td>
<td>2</td>
<td>17</td>
<td>0.62</td>
<td>23</td>
</tr>
<tr>
<td>Prasad Heart Failure</td>
<td>18</td>
<td>80 mg BID (capsule)*</td>
<td>3.95</td>
<td>2.5</td>
<td>6.5</td>
<td>6.54</td>
<td>25.94</td>
<td>23</td>
<td>1.04</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>12</td>
<td>80 mg x1 (Capsule)</td>
<td>3.73</td>
<td>2.5</td>
<td>7.57</td>
<td>2.37</td>
<td>23.7</td>
<td>23</td>
<td>1.04</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>

*Following 7 days of treatment

### 7. Safety and tolerability of valsartan

ARBs are typically a well-tolerated therapeutic option for patients with ACEI-related angioedema and cough and possibly hypotension. Unfortunately, hyperkalemia and acute kidney injury risk may not be mitigated.

The risk of angioedema with either an ACEI or an ARB is considered to be uncommon. In OCTAVE, a large trial of 12,634 patients receiving enalapril, angioedema occurred at a rate of 0.68% [70]. A similar rate of angioedema developed in captopril users (n = 4,879) and resulted in a dose reduction in the VALIANT trial. In contrast, only 0.2% of valsartan recipients (n = 4,885) developed angioedema [7]. If angioedema occurs with ACEI use, it is acceptable to interchange to an ARB. The risk of recurrent angioedema following interchange to an ARB is considered to be acceptably low, with 10% at most developing a definite occurrence [71].

The rate of captopril-related cough resulting in a dose reduction was relatively low (5%) in the VALIANT study [7]. In contrast, Bangalore showed in a recent meta-analysis that the pooled weighted incidence of ACEI-associated cough in a sample of 23,559 enalapril recipients was 11.48% (95% confidence interval [CI], 9.54% to 13.41%) [72]. Similar rates of cough occurred for all ACEIs examined. Notably, ACEI-related cough appeared to occur at even higher rates in the HF cohort, a group in which the incidence of cough may be higher due to CHF, rather than RAAS blockade. It has been suggested by some to trial an alternative ACEI to see if the cough resolves; however, for those with a history of ACEI-induced cough they are 29 times more likely to develop a cough with an alternative ACEI compared
to those without this prior adverse event [73]. Fortunately, with interchange to an ARB, the recurrent cough rate is quite low (0.3%) [74].

Weakness, dizziness, or syncope may result from an excessive reduction in blood pressure. In a head-to-head comparison of ARB and ACEI therapy in the VA-LIANT trial, more patients receiving valsartan (18.2%) than captopril (11.9%) developed hypotension necessitating a dose reduction of assigned therapy (p < 0.05) [7]. The mechanism of hypotension is unclear, however, it may represent enhanced Ang II synthesis due to the lack of ACE inhibition coupled with the shunting to the AT2 receptor resulting in enhanced vasodilation. However, this is merely speculation. Subsequently, this suggests that interchange from an ACEI to an ARB for hypotension would result in a similar risk. However, the CHARM-ALTERNATIVE trial allowed patients (n = 143) with prior ACEI-related hypotension to receive candesartan with surprisingly good tolerability. Only 9.1% (13 out of 134 patients) with prior ACEI-related hypotension developed recurrent hypotension with [75].

Combination ACEI-ARB therapy is marked by an increase in adverse effects. In the VAL-HEFT trial in which 95% of patients received background ACEIs, adverse events leading to drug discontinuation were more common (p < 0.001) with valsartan (9.9%) than with placebo (7.2%). Adverse events leading to discontinuation in more than 1% of valsartan users included dizziness, hypotension, and renal impairment. Mean changes in pertinent labs included an increase in BUN of 5.9 mg/dL, Scr 0.18 mg/dL, and potassium of 0.12 mmol/l (all with p < 0.001) [6]. A meta-analysis of four randomized controlled trials of ARBs in LV dysfunction suggested that combination ARB-ACEI therapy was associated with a 2.2-fold greater risk of worsening renal function (defined as an increase in serum creatinine of > 0.5 mg/dL). These findings were affirmed in a non-HF population in On-Target/Transcend [76,77]. Combination therapy was also associated with a 4.9-fold greater risk of hyperkalemia (defined as a serum potassium of 5.5 meq/L or greater). Overall, the number needed to harm (NNH) for the measure of significant increase in medication discontinuance due to adverse effects was 25 and 71 for the chronic heart failure and acute MI with LV dysfunction cohorts, respectively [78].

Although combination ACEI-ARB poses tolerability issues, Pitt et al. demonstrated that the aldosterone antagonist, eplerenone, can be safely used in those receiving either an ARB or an ACEI with HF following MI. Safe use requires attention to baseline serum K and glomerular filtration rate (or creatinine clearance); the exclusion of patients with a serum K > 5 meq/L or serum creatinine > 2.5 mg/dL or creatinine clearance ≤ 30 ml/min; periodic monitoring of serum K; and adjustment of the dose of eplerenone according to serum K and changes in renal function [79].

Other common adverse effects during initial therapy (e.g., first 4 months of treatment) in chronic heart failure cohorts, occurring at an incidence of at least 2%, include diarrhea (5%), arthralgias (3%), fatigue (3%), back pain (3%), postural dizziness (2%), and orthostatic hypotension (2%). In the post-MI HF cohort, a rare side effect leading to drug discontinuation in 0.2% of patients was nonspecific rash. In post-marketing data, valsartan has been associated with alopecia and elevated liver enzymes and rarely hepatitis and thrombocytopenia [8].

8. Conclusion

The ARB Valsartan, in addition to being an effective antihypertensive, has clearly demonstrated benefit as an alternative in ACE-I intolerant patients with congestive heart failure and post-myocardial infarction [6,80]. In combination with ACE-inhibitor therapy, there is a morbidity benefit as evidenced by reduced hospitalization and QoL measures in patients with congestive heart failure. Due to the half-life and formulations, this drug is readily titratable and a wide variety of doses can be achieved due to the ability of the drug to be given both once or twice daily. Additionally due to its metabolism it does not require dose adjustment for heart failure, or based on renal function. The major dose-limiting side effects are uncommon and are hyperkalemia, decreased eGFR, and hypotension. Furthermore it has a very modest side-effect profile, and as a consequence is well tolerated.

9. Expert opinion

Novartis’s European patent on valsartan ended in 2011. The United States patent will expire in September of 2012 and in Japan, the patent expires in 2013. This creates the opportunity for generic valsartan to become available. If the drug can be manufactured inexpensively, this would be a boon to patients because it is a modestly more effective antihypertensive that is more easily titrated than losartan [81,82]. In addition, there are strong data to support its use as an alternative or adjunct to ACE-I therapy in patients with LV systolic dysfunction and/or congestive heart failure. The use of ARB adjunctive therapy has been limited in congestive heart failure and LV systolic dysfunction due to cost. Indeed, in addition to the studies that demonstrated decreased morbidity and improved quality of life, there were studies demonstrating that that despite these benefits, the benefits were not cost-effective. Cost-effectiveness, however, is not static. An appropriately priced generic can transform a previously cost-ineffective strategy into a cost-effective strategy. ACE inhibitors cost pennies a day while ARBs presently cost dollars per day. A significant drop in the cost of valsartan, brought about by efficiently produced generics, would have a significant impact on the post-MI population that would be seen for years to come.
Declaration of interest

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** The VALIANT trial, examining valsartan in the post-MI population.


* Trial examining the anti-hypertensive and anti-inflammatory properties of valsartan.


• A major pharmacodynamic study of blood pressure reduction with valsartan.


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**The effects of candesartan on CHF.**


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