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REVIEW ARTICLE

STEPS OF IDENTIFICATION, DESIGN AND VALIDATION OF CANDESARTAN CILEXETIL

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ABSTRACT

Candesartan (CV-11974) is the active compound of the prodrug candesartan cilexetil (TCV-116) used in treatment of hypertension by selective blockade of Angiotensin II receptors and thus inhibits the effect of renin-angiotensin-aldosteron system. Chemical modification of the hit compound (CV-11194) yielded the lead compound (CV-11974) which passed through series of in vitro and in vivo studies successfully. The preclinical studies of CV-11974 and its prodrug shown that it was safe and did not cause serious adverse effects therefore TCV-116 was eligible for clinical trials which was firstly done in healthy individuals then involved wider group of patients with different cardiovascular conditions.

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INTRODUCTION

Candesartan cilexetilbelongs to new class of anti-hypertensive drugs its action involves selective antagonism of type 1 angiotensin II receptors (Kirk 1999). Chemicallyc and esartan is anon peptide benzimidazole-7-carboxylic acid (Naka *et al*. 1999). Candesartan considered as a selective long acting potent angiotensin II blocker but have a low oral bioavailability therefore it is synthesized as an ester prodrug (Burnier and Brunner 2000). Renin- Angiotensin system, especially angiotensin II receptor has been shown to be involved in the pathological process of several cardiovascular diseases like essential hypertension, heart failure, hypertension secondary to renal disease and renal disorder associated with hyper albuminuria (Barreras and Gurk-Turner 2003) therefore Candesartanhas been shown to be effective in treatment of these diseases (De Rosa 2010). As compared to losartan candesartan shown to be more effective in lowering blood pressure with lesser side effects in randomized controlled trials (Zheng *et al.* 2011). Robert Tigerstedt and Per Bergman firstly identified renin in 1898 when they found that injection of saline extract of rabbit kidney in rabbits caused a slow raise in blood pressure (Fyhrquist and Saijonmaa 2008). Several years later H Goldblatt's group induced hypertension in dogs by constriction of one of the renal arteries, this process then explained in 1940 as it has been shown that this ischemia induced renin synthesis and thus angiotensin-II in the kidney (Burnier and Brunner 2000).

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Gavras *et al.* (1971) found that injecting of large doses of angiotensin into rabbits produce myocardial infarction and acute renal failure. Individuals with increased renin activity are at high risk of stroke or myocardial infarction (Burnier 2001). In renin angiotensin system the cleavage of angiotensinogen by renin represents the first step in this pathway lead to the formation of angiotensin I, inactive decapeptide, which will be then converted to angiotensin II (ANG-II) by the angiotensin converting enzyme (Burrnier 2001) therefore angiotensin play a key regulatory effect in cardiovascular disease (Ferrario and Schiavone 1989). Binding of ANG-II to ANG-II receptor type I trigger a series of physiological responses that affect arterial blood pressure including arterial contraction, increase cardiac contractility in kidney enhance reabsorption of sodium ion in proximal convoluted tubule and stimulates contraction of efferent arterioles (Wood *et al.*1996).

Target Identification

Two types of ANG-II has been identified in cultured neonatal rat cardiomyocytes, these cardiomyocytesexhibited two types of binding affinity towards I-125 ANG-IIhormone. The first one was with Kd1 = 0.65 nM; maximum binding-1= 245 fmol/mg of protein and the second was of Kd2 = 5.57 nM, maximum binding-2= 720 fmol/mg of protein. Both of these sites were considered to be specific because the binding of I-125 ANG-II was significantly inhibited by the ANG-II peptide analogs while the I-125 Sar-1 Leu-8 ANG-II antagonist showed a high binding affinity towards one class of these receptors 45,300 sites per cell (Rogers, Gaa and Allen 1986). Later on Allen *et al*. (1987) found that treating cultured

neonatal cardiomyocytes with ANG-II caused an increase in spontaneous beating frequency and cardiac contractility.

Target Validation

The evidence of involvement of angiotensin II receptor in sustaining high blood pressure explained by Brunner *et al*.(1973) as they found intravenous administration of the octapeptide competitive inhibitor Sar-1 Leu-8 ANG-II (Saralasin) to individuals with renovascular or hypertension due to pyelonephritis or malignant hypertension cause a rapid and persistent decrease in blood pressure to about normal values. Interestingly the over dose did not caused hypotension moreover blood pressure in individuals with low or normal renin level did not affected by this dose. Saralasin was the first peptide ANG-II antagonist used in human but because of its low oral bioavailability it is not used any more (Kubo *et al.* 1992).

Hit Identification: The first specific non peptide ANG-II inhibitor was an imidazole derivative synthesized by Furukawa *et al.* in 1980 (Morimoto and Ogihara 1994). Kubo *et al***.** (1993) synthesized several compounds (substituted 2-butyl benzimidazoles with biphenylyl moiety on position number-1) they found that introducing substituent on positions 4, 5 and 6 will decrease the binding affinity while substitution at position-7 produced an increase in binding affinity to a degree comparable to losartan (Dup753). Functional analysis found that the most important group for antagonist activity was carboxyl group. The substitution of Carboxyl group at position-7 was very important because the comparison between compounds that have carboxyl group at position 4, 5, 6 and 7 in ANG-II induced contraction rabbit aortic ring revealed that the compound with carboxyl at position-7 was more potent than other analogs besides in vivo studies shown that oral dose of benzimidazole 7-carboxylic acids in rats produced a sustained inhibition in response to ANG-II induced hypertension. Optimum activity obtained by substitution of a carboxyl or an ester group at position-7 Figures 1. Among several compounds prepared and tested in vivo and in vitro studies they found that (CV-11194) was the hit compound as they found the following:

- In Vitro studies CV-11194 inhibited I-125 ANG-II specific binding to bovine adrenal cortical membranes at a concentration comparable to that of losartan. Also the CV-11194 induced contraction of rabbit aortic ring more potent than that caused by losartan.
- In vivo studies shown that oral dose of CV-11194 to normotensive rats and dogs caused an inhibition in response to hypertension induced by ANG-II. Furthermore 10mg/Kg po dose of CV-11194 caused a complete inhibition in response to hypertension induced by ANG-II persisted for 7 hours while similar dose of losartan caused 55% inhibition and for a shorter period of time. In spontaneous hypertensive rats 0.3mg/kg of CV-11194 caused a significant decrease in blood pressure for 7 hours while 43mg/kg of losartan (Dup 753) required to produce similar effect.

Lead Identification and Optimization: To study the structure activity relationship Kubo *et al*.(1993) synthesized severalCV-11194 analogs {2-substituted-l-[(biphenyl-4-yl)methyll-1H-benzimidazole-7-carboxylic acids} from the intermediate compound 3-amino-2- [(biphenyl-4-yl)methyl]amino] benzoate. Most of these compounds had a high affinity to ANG-II receptors and exerted an inhibition in response to ANG-II induced pressor more potently than CV-11194 and losartan (Dup 753).

Structure activity relationship (SAR)*:* Substitution of ethoxy or ethyl group at position-2 gave best results in binding affinity and inhibition of response to angiotensin II induced pressor. Also the antagonistic potency was enhanced by the steric factors, electron effect and lipophilicity of these groups, moreover substitution of carboxyl group at position-7 and tetrazole group at position-2' were important for oral activity, potency and long duration of action thus according to these SAR the compound (CV-11974) considered to be the lead compound, Figure -2, as it madeCV-11974 to appear more potent than Dup 753 and other ethoxybenzimidazolesin vitro assays. It has been shown that CV-11974 inhibited I-125 ANG-II specific binding to bovine cortical membranes and antagonized ANG-II induced contraction of isolated rabbit aorta at lower concentration compared to other compounds Table-1.In Vivo studies confirmed superiority of CV-11974 as it showed:

- mg/kg oral dose of CV-11974 in normotensive conscious rats caused a potent, long acting and complete inhibition in response to ANG-II induced pressor.
- 0.1-1 mg/kg I.V. doses of CV-11974 in spontaneous hypertensive rats caused a significant dose-dependent inhibition in blood pressure and was more potent than that caused by the active metabolite of Dup753 (Exp 3174).
- 1 mg/kg single I.V. dose of CV-11974 caused a reduction of about 50 mmHg in the mean arterial blood pressure and the effect persisted for more than 24 hours. However the basal heart rate did not altered at these doses.

AlthoughCV-11974 had these successful properties however its oral bioavailability was low, less than 5% in animals; therefore the carboxyl group on position-7 was esterified to yield an ester prod rug TCV-116 (Naka and Kubo 1999, Delacrétaz *et al.* 1995) Figure-3.

Pre-clinical studies: Examination of CV-11974 and its ester prod rug TCV-116 in rats using losartan (Dpu 753) and its active metabolite EXP 3174 as reference compounds shown that CV-11974 (IV dose) inhibited the response to angiotensin II induced pressor12 times more potent than EXP 3174,ID50=0.033mg/kg. While inhibition by TCV-116(oral dose) was 48 times more potent than Dup 753, ID50=0.069mk/kg (Shibouta *et al.* 1993). Mizuno *et al.* 1992 showed that daily oral dose of 1mg/Kg for 2 weeks to spontaneous hypertensive rats produced a significant increase in plasma levels of renin, ANG-I and II whereas aldosterone plasma level was reduced to about 70% and blood pressure was also significantly reduced. Affinity studies shown that specific binding of I-125 (sal-1 leu-8) ANG-II to ANG-II type I receptors in rabbit aorta membrane was significantly inhibited by CV-11974, Dup 753 and EXP 3174 but not but not affected by ANG-II type II antagonist PD123177. These results suggests that CV-11974 specific to ANG-II type I receptor as the affinity of CV-11974 for these receptors was 80 times higher than Dup 753 and 10 times more than EXP 3174 (Masakuni *et al*. 1993).

Table 1. Comparison of binding affinity aortic rabbit contraction and % inhibition in pressor response between different ethoxybenzimidazoles compounds data obtained from Kubo *et al.* (1993)

Compound	Carboxyl gp. Position	Receptor binding IC50 x 10^{-7} M	Aortic contraction IC50x 10^{-10}M	% inhibition in pressor response	
				3 hours	7 hours
35a	4	450	1310	22	5
35b	5	130	1910	4	4
35c	6	9.3	19	50	34
26b (CV-11974)	7	1.1	2	100	100

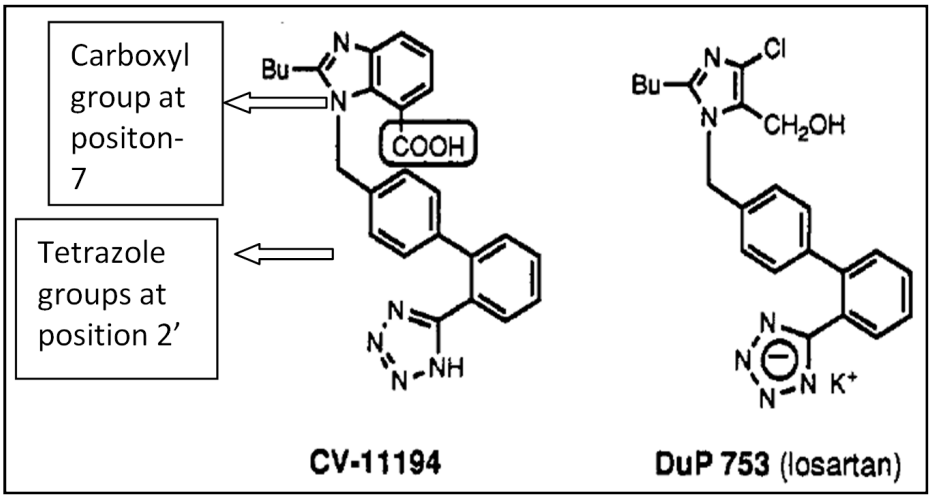

Figure 1. by Kubo *et al.* (1993) chemical structures of the Hit 2-butyl-1-[[2'-(1 *H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid (CV-11194)and losartan (DuP753)

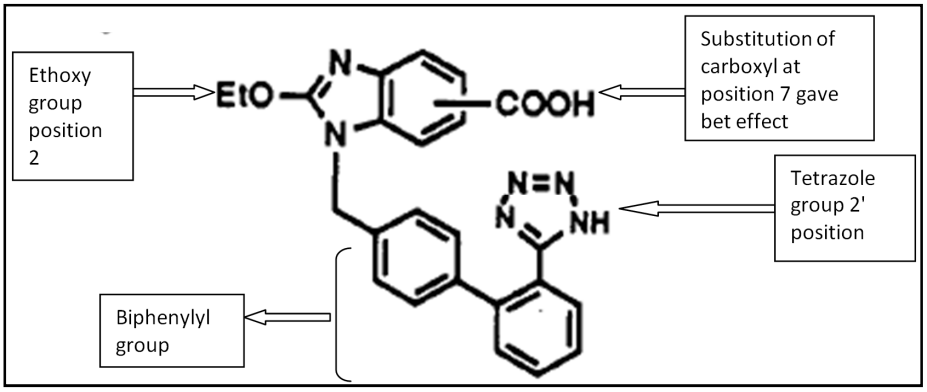

Figure 2. Kubo *et al.* (1993) Chemical structure of the lead compounds 35 a-c. In which substitution of carboxyl at position 7 yielded the lead compound 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylic acid (CV-11974)

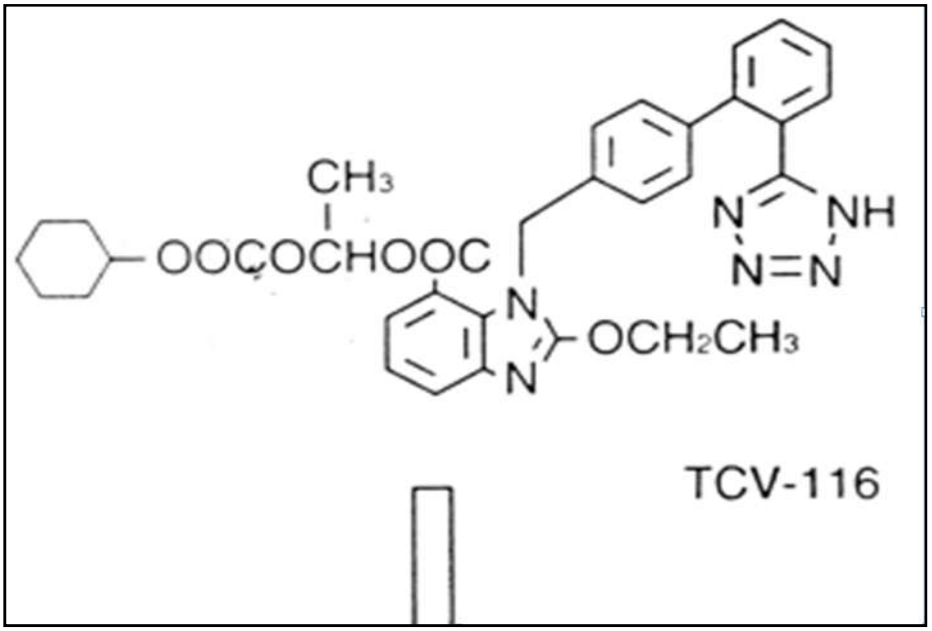

Figure 3. By Delacrétaz *et al.* (1995) chemical structure of the ester prodrug (candesartan cilexetil)

Moreover Nishikawa *et al*. (1997) shown that 0.1mk/kg for 10 weeks candesartan reduced the incidence of stroke in stroke-prone spontaneous hypertensive rats without affecting blood pressure. The most interesting fact was that higher doses 1-10 mg/kg produced similar effects besides giving a reduction in left ventricular hypertrophy and blood pressure and prevented nephroseclerosis.

Pharmacokinetic properties (PK)*:* PK studies by (Nishikawa *et al*. 1997) shown that candesartan PK was linear in both rats and dogs in dose ranging from1-100mg/kg.

Absorption*:* Candesartancilexetil absorbed from small intestine after oral administration of radio labeled ^{14}C-candesartan cilexetil to rat and dogs. During absorption the prod rug hydrolyzed rapidly to candesartan however the bioavailability was low in both species in rats was 5% while in dogs was 19-28%. In rats the Peak plasma concentration was Cmax=0.28µg/ml and achieved after tmax=2.3 hours while in dogs0.012µg/ml with tmax=1.3 hours. The observed half-life in both species was $t_{1/2}$ = 4 hours. It has been shown that ^{14}C-candesartan was highly distributed through the body and concentrated in highly vascularized organs of rats.

Metabolism*:* The metabolic pathway of Candesartan involves glucourindation and conversion to the inactive form CV-15959.Candesartan and its metabolite showed a high degree of protein binding in both species and cross placenta and were detected in the milk of female rats Figure-4.

Elimination*:* Candesartan and its metabolites mainly excreted through liver with feces in rats and dogs.

Effect on metabolizing enzymes*:* Repeated doses of candesartan in rats did not produced considerable drug accumulation and did not affect drug metabolizing enzymes.

Toxicological studies

Nishikawa *et al*. 1997 found that following single oral dose of candesartan 2000mg/kg in dogs; mice or rats did not produced acute lethal toxicity. However high doses of candesartan for 4 weeks to rats and dogs decreased heart weight and erythrocytes parameters but increased plasma nitrogen levels, in the other hand histopathological studies shown hypertrophy of juxtaglomerular cells, atrophy of adrenal zonaglomerulosa, and basophilic renal tubular epithelium. Nevertheless, these effects were thought to be related to high doses and the pharmacological action of candesartan. Furthermore candesartan did not affect fertility in rats and had no teratogenic effect in rats, mice or rabbits. However administration of candesartan to pregnant female rat in the last period of gestation till the weaning caused hydronephrosis in the offspring's kidney.

Carcinogenicity*:* It has been shown that candesartan did not have oncogenic or carcinogenic effects.

Cough: Interestingly candesartan was unlike enalapril asdid not affect citric acid or capsaicin- induced cough in guinea pigs and did not producebradykinin induced extravasations of plasma to bronchi or trachea.

Clinical Trials

Delacrétaz *et al*. (1995) conducted double blinded study in which 23 individuals received oral dose of either TCV-116(1, 2 and 4) orplacebo for 8 days double.

Table 2. observed pharmacokinetic parameters of candesartan on days 1 and 8. Transformation time is the time required for transformation of prodrug TCV-116 to active metabolite CV-11974. Mean residence time was calculated as (AUCM/AUC)-MAT where AUCM is the area under the curve of the very first concentration vs. time, MAT mean transformation time

PK Parameter	Day 1	Day 8
Time required to achieve peak plasma conc. Tmax/hours	3.5	6
Half-life /Hours	3.5	4
Apparent Clearance $L.h^{-1}.Kg^{-1}$	0.25	0.2
Transformation time /hours	1.2	1.3
Mean residence time/ hours	8.1	9.7

Table 3. % of serious adverse effects reported in candesartan and placebo groups during the Trial of preventing hypertension (TROPHY)

Adverse effect	Candesartan group % n=14	Placebo group % n=23
Cardiovascular	0.3	6
Cancer	1	0.8
Endocrine	0.5	0
Peripheral nerve	0.5	0
infections	0.5	1
Liver dysfunction	0.3	0.3
vascular	0.3	0
Psychiatric	0.3	0
Reproductive and breast	0	0.3
Ear disorders	0	0.3
Musculoskeletal and connective tissue	0.3	0.8
General disorder	0.8	0.3
Hepatobiliary	0	0.5
GIT	1	0.5

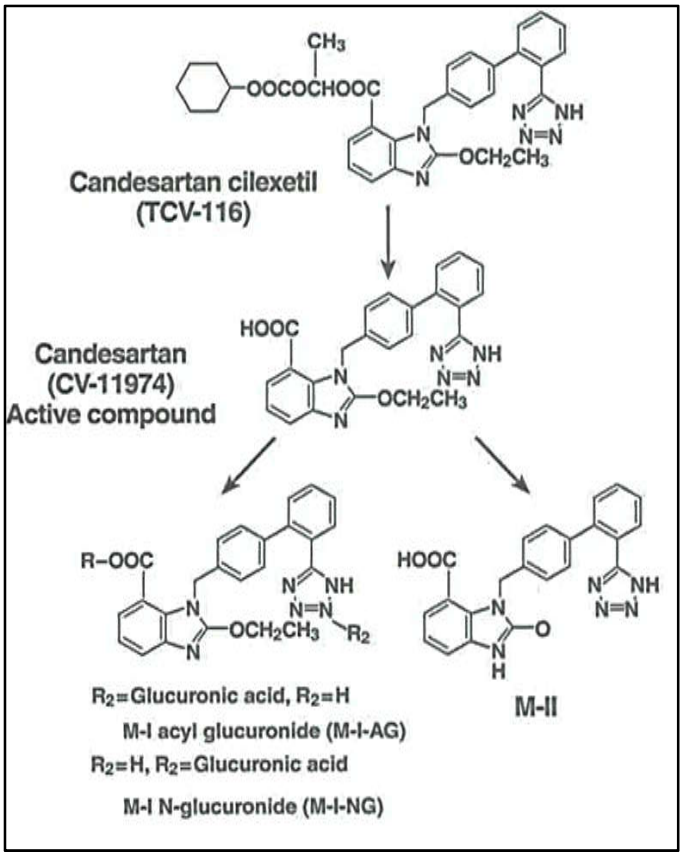

Figure 4 Nishikawa *et al.* (1997) metabolic pathway of candesartan cilexetil, in which candesartan cilexetil metabolized to its active form candesartan which will be then bio-transformed to glucuronide conjugates and the inactive form CV-15959

Table 4. Clinical trials involved use of candesartan in different fields. Where CHARM study: Candesartan in heart failure: Assessment of reduction in Mortality, SECRET study = The Study on Evaluation of Candesartan cilexetil after Renal Transplantation, SCOPE study = The Study on Cognition and Prognosis in the Elderly, ACCESS study = The Acute Candesartan Cilexetil therapy in Stroke Survivors, SCAST study = Candesartan for treatment of acute stroke, DIRECT study = Diabetic Retinopathy Candesartan Trials, CASE-J study = The Candesartan Antihypertensive Survival Evaluation in Japan, J-RHYTHM II study = The Japanese Rhythm management trial II for atrial fibrillation. All data obtained from the corresponding authors mentioned in researchers column

Trial	Researchers	Patients involved	Treatment	Outcome
CHARM-added	McMurray *et al.*(2003)	N=2548 CHF with LVEF < 40%	32 mg Candesartan+ACE inhibitors vs. ACE inhibitors	Candesartan reduced mortality and morbidity as compared with ACE inhibitors
CHARM-Alternative	Granger *et al.* (2003)	N=2028 CHF with LVEF <40%+ ACE-inhibitors intolerance	32 mg candesartan vs. placebo	Candesartan reduced mortality and hospitalization of those patients
CHARM-preserved	Yusuf *et al.* (2003)	N=3023 CHF with LVEF>40 %	32mg candesartan vs. placebo	Candesartan reduced mortality and hospitalization of those patients
CALM II	Knudsen *et al.* (2008)	N=75 hypertensive with type I or II diabetes	16 mg candesartan +20 mg lisinopril	Candesartan reduced pulse pressure when with combined with lisinopril
Elasticity of large and small arteries	Shargorodsky *et al.* (2008)	n=69 hypertensive+ diabetes	32mg candesartan vs. 6 mg vs. other antihypertensive drug	High dose of candesartan highly improve arterial elasticity compared to lower dose and other antihypertensive agents
SECRET	Philipp *et al*.(2010)	N=700 hypertensive +kidney transplant	4-16 mg candesartan vs. placebo	Candesartan was safe & tolerable and reduced blood pressure and proteinuria
Stage 4-5 chronic kidney disease	Tamura *et al*.(2008)	N=13 stage4-5 chronic kidney disease with blood pressure 140/90	Candesartan vs. Dugs other than angiotensin II receptor antagonists	Candesartan was safe as no adverse effect occurred and significantly reduced proteinuria and improved renal outcome after 3 years
Stage-1 chronic kidney disease	Rossing*et al.*(2003)	N=23 hypertensive +type II diabetic nephropaathy	8, 16 or 32 mg of Candesartan vs. placebo	Dose of 16 mg candesartan was optimum and provided renoprtective effect and reduced albuminuria.
SCOPE	Skoog *et al.* (2005)	N=4964 elderly hypertensive	Candesartan vs. placebo	Candesartan was well tolerated and reduced blood pressure and non-fatal stroke but did not affect cognitive function
ACCESS	Schrader *et al.(*2003)	N=399 hypertensive stroke survivors	4,8 16 mg candesartan vs placebo	Candesartan was safe and reduced hypotension-induced cardiovascular and cerebrovascular events
SCAST	Sandset *et al.* (2011)	N=2029 hypertensive+ acute stroke	Candesartan vs. placebo	Candesartan decreased blood pressure which produce negative consequences on the patients
DIRECT prevent-1 and DIRECT protect-1 of retinopathy	Chaturvedi *et al.* (2008)	Prevent-1:n=1421 normotensive type -I diabetic no retinopathy, no albuminuria Protect -1:n=1905 normotensive with diabetic type-I retinopathy, no albuminuria	16 and 32 mg candesartan vs. placebo	Incidence of retinopathy was reduced by candesartan however no improvement in retinopathy progression was seen
DIRECT protect-2	Sjølie *et al.* (2008)	N=1905 normotensive type II diabetes with mild to moderate severe retinopathy no albuminuria	16 and 32 mg candesartan vs. placebo	Retinopathy might be improved by candesartan treatment
CASE-J	Nakao *et al.* (2010) Ogihara *et al*. (2008)	N=4728 hypertensive with or without obesity	Candesartan vs. amlodipine	New-onset diabetes was more effectively prevented by candesartan in both patient categories and reduce cardiovascular mortality in obese diabetic patients
Migraine prophylaxis	Tronvik *et al.* (2003)	N=30 patients with migraine	16 mg candesartan vs. placebo	Candesartan was tolerable and gave effective prophylaxis against migraine
J-RHYTHM II	Yamashita *et al.* (2011)	N=318 hypertensive with paroxysmal atrial fibrillation	Candesartan vs. amlodipine	Candesartan reduced frequency of paroxysmal atrial fibrillation but was not better than amlodipine

Efficacy of TCV-116t was examined by repeated ANG-II bolus doses on days 1, 4 and 8. 4 individuals received TCV-116 8 mg orally in a single blind fashion. It has been shown that candesartan treatment did not produce any significant adverse effects as no changes in ECG, laboratory routine test or blood cell count.PK studies showed that only CV-11974 appeared in plasma after 1 hour, PK results shown in Table-2. Candesartan inhibited the response to ANG-II in doses dependentmanner and peak inhibitory effect was reached in 4 to 8 hours after drug administration and persisted for 24 hours on day-1. Surprisingly 4 mg on day 1 reduced the response to ANG-II to 41% of baseline response while on day 8 it was 21%. For the individuals treated with 8mg the response was reduced to 22 and 16 %.Therefore candesartan considered to be well tolerated, potent, orally active long acting ANG-II antagonist. Julius *et al*. (2006) conducted a randomized double blinded trail of preventing hypertension (TROPHY) using candesartan. Involvement criteria were no previous hypertension treatment and systolic blood pressure 130-139 mmHg and diastolic ≤ 89 mmHg or with systolic ≤ 139 mmHg and the diastolic 85-89 mmHg at repeated visits. First2 years involved Candesartan group n=391(16 mg once daily) and placebo group (n=381) then followed by 2 years placebo. In the first 2 years Candesartan was effective in preventing hypertension as only 53 individuals developed hypertension while placebo group was 154 individuals. After 4 years 240 and 208 participants in placebo and candesartan groups respectively had developed hypertension. Interestingly serious adverse effects had been reported In 14 participants (candesartan group) and 23 participants (placebo group) Table-3. It has been shown that Candesartan effectively managed hypertension in 702 individuals with or without diabetes as the systolic, diastolic and pulse blood pressure was significantly reduced compared to baseline readings in the 3 groups (Féghali *et al*. 2007). However there were comparable effects between Candesartan, telmisartan and valsartan in reduction of diastolic

blood pressure in 308 hypertensive patients with type II diabetes (Ozaki *et al*. 2010). Recently Grosso *et al.*(2010) showed that candesartan is more effective than losartan in reduction systolic and diastolic blood pressure in hypertensive patients but no difference between the 2 drugs in treatment of heart failure however candesartan treatment cost much more than losartan.

CHARM study*:* Candesartan in heart failure: Assessment of reduction in Mortality,

SECRET study= The Study on Evaluation of Candesartan cilexetil after Renal Transplantation,

SCOPE study= The Study on Cognition and Prognosis in the Elderly,

ACCESS study= The Acute Candesartan Cilexetil therapy in Stroke Survivors,

SCAST study= Candesartan for treatment of acute stroke,

DIRECT study =Diabetic Retinopathy Candesartan Trials,

CASE-J study= The Candesartan Antihypertensive Survival Evaluation in Japan,

J**-RHYTHM II study**= The Japanese Rhythm management trial II for atrial fibrillation. All data obtained from the corresponding authors mentioned in researchers column.

Conclusion

In conclusion from the aforementioned data about candesartan cilexetil it has been shown that it was a safe, effective and potent angiotensin II type I receptor antagonists and it was superior in its efficacy to other members of Angiotensin II receptor antagonists and other antihypertensive agents in management of hypertension as it did not produce cough, or first dos hypotension like angiotensin converting enzyme inhibitors. Several studies shown that candesartan reduced mortality and morbidity in heart failure patients and diabetic patients with nephropathy and even gave prophylaxis against migraine. Over all resultant candesartan was successful drug even though its cost much more than losartan.

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