IS CAPTOPRIL (CAPOTEN) THE PREFERRED ACE INHIBITOR IN THE MANAGEMENT OF THE POST MYOCARDIAL INFARCTION PATIENT?

The use of customized relational databases with the capacity to rapidly mine data and generate new teachings for the ACE inhibitor captopril

PRELIMINARY DRAFT

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SELECTED CLINICAL DATA IN SUPPORT OF CAPOTEN'S EFFICACY IN ATHEROSCLEROSIS

Acknowledgements

IS CAPOTEN THE PREFERED ACE INHIBITOR IN THE MANAGEMENT OF THE POST MYOCARDIAL INFARCTION PATIENT?

SUMMARY

In 2004, workers at the Institute for Vascular Signaling at the Johann Wolfgang Goethe University in Frankfurt am Main made a remarkable discovery. They reported for the first time that binding of an angiotensin I (Ang I)–converting enzyme (ACE) inhibitor to ACE, in addition to inhibiting the conversion of Ang I to Ang II was also associated with a sequence of events that resulted in the increased expression of intracellular ACE. This "outside-to inside" signaling effect has been observed in several cell types, that importantly include the monocyte/macrophage, and *in vivo*. In the absence of further insights, these new findings must be viewed as paradoxical. That is, a therapeutic goal of the administration of an ACE inhibitor is to inhibit the formation by ACE of Ang II. However, as these workers discover, binding of the inhibitor to ACE (with inhibition of formation of Ang II) activates and induces the synthesis of new ACE. This new ACE will mature and be transported to the cell membrane and will functionally replace ACE that has been inhibited by the administration of the ACE inhibitor, resulting in the additional generation of Ang II; in turn when located in its transmembrane position, the "replacement ACE" will likely be inhibited, but only to be replaced by more ACE, and so on.

At least in the context of atherosclerosis it is difficult to envisage that the ACE inhibitor-induced synthesis of new ACE is beneficial. Indeed, it can be more reasonably argued that in the treatment of the post myocardial infarct (MI) patient, this paradoxical effect limits the efficacy of ACE inhibitor therapy.

Within the physiological pH range, it is the ionization of the carboxylic acid group of Capoten that is pH-dependent, with no ionization or protonation of either the sulfhydryl or amide groups. The acidic extracellular environment of the surface-connected compartments (SCCs) of the infiltrated macrophage within the atherosclerotic lesion represents a critical determinant of the disposition and

effects of Capoten. Importantly, and in accord with expectation, lipophilicity, represented as log D values, measured using octanol-water partitioning within the pH range 1-7 covaries with the pH-dependent ratio of unionized:ionized Capoten.

Within this report, direct comparisons are made between Capoten and the ACE inhibitors, lisinopril, enalaprilat (the active form of the prodrug, enalapril) and ceronapril; this selection was based purely on the availability of comparable data. These data show that by contrast with Capoten, each of these inhibitors have several ionizable and/or protonable groups with pKa values, that when examined mathematically, allow the conclusion that throughout the physiological pH range they will exist as lipid-insoluble and membrane-impermeant species. In the context of the reasoning and published evidence presented within this document, and according to the well-established and well-tested tenets of the pH-partition hypothesis, it can be argued that the efficacy of each of these inhibitors in managing the post MI patient will be compromised and accordingly limited by the paradoxical and positively-reinforced signaling induced upon binding to extracellular ACE that results in newly-synthesized ACE.

Taken together, the available evidence supports the new proposal that the atherosclerosis plaque macrophage is a deep compartment for the accumulation of Capoten but not other ACE inhibitors, that because of their complex physico-chemical propeties are unable to accumulate within the intracellular compartment of the atherosclerosis infiltrated macrophage, and as a result they cannot inhibit the paradoxical formation of newly-synthesized ACE, induced by binding to extracellular transmembrane ACE. *A priori* Capoten surmounts the paradoxical effects of binding at extracellular ACE since it is able to accumulate within the infiltrated atherosclerosis macrophage and inhibit newly-formed ACE. This novel feature differentiates Capoten, and on this basis it is arguably the inhibitor of choice in the management of the post MI patient.

Introduction

Angiotensin I (Ang I)–converting enzyme (kininase II, dipeptidyl carboxypeptidase I, EC 3.4.15.1) (ACE), is a zinc metallopeptidase that catalyses hydrolysis of peptide substrates at two catalytic domains, described respectively as the C-terminal domain and the N-terminal domain. Whereas the decapeptide, angiotensin I (Ang I) is cleaved with similar kinetics by the two catalytic domains, resulting in formation of the vasoactive octapeptide, angiotensin II, hydrolysis of the haemoregulatory peptide, N-acetyl-Ser-Asp-Lys-Pro (Ac-SDKP) (an inhibitor of bone marrow proliferation) is catalyzed almost exclusively by the N-terminal catalytic domain of ACE. Various reports indicate that Ac-SDKP exerts anti-fibrotic effects, and it has been proposed that the anti-fibrotic effects of ACE inhibitors are in some part mediated by preventing degradation of endogenous Ac-SDKP with a resultant increase in levels of Ac-SDKP in plasma and tissue.

N-terminal and C-terminal catalytic domains of ACE

The ACE protein is a single polypeptide chain, composed of two separate and independent catalytic domains. These domains, containing the zinc-binding site motif are described as the NH_2-terminal (N-terminal) and COOH-terminal (C-terminal) domain, respectively.

Isoenzymes of ACE

There are two isoenzymes of ACE called somatic and testis ACE. The larger somatic isoform is the enzyme expressed in somatic tissues, and it is this form that is composed of two catalytic domains. The testis isoform is composed of only one catalytic domain, identical to that of the C-domain of the somatic isoform.

In more recent times, an homolog of ACE, designated as ACE2, has been isolated. ACE2 converts Ang I to the nonapeptide, Ang 1-9 and Ang II to the heptapeptide, Ang 1-7.

ACE is a transmembrane polypeptide

Both forms of ACE are located at the cell surface where they hydrolyze circulating peptides. Known as an ectoenzyme, ACE is anchored to the plasma membrane with the N-terminal facing the extracellular domain (Fig 1).

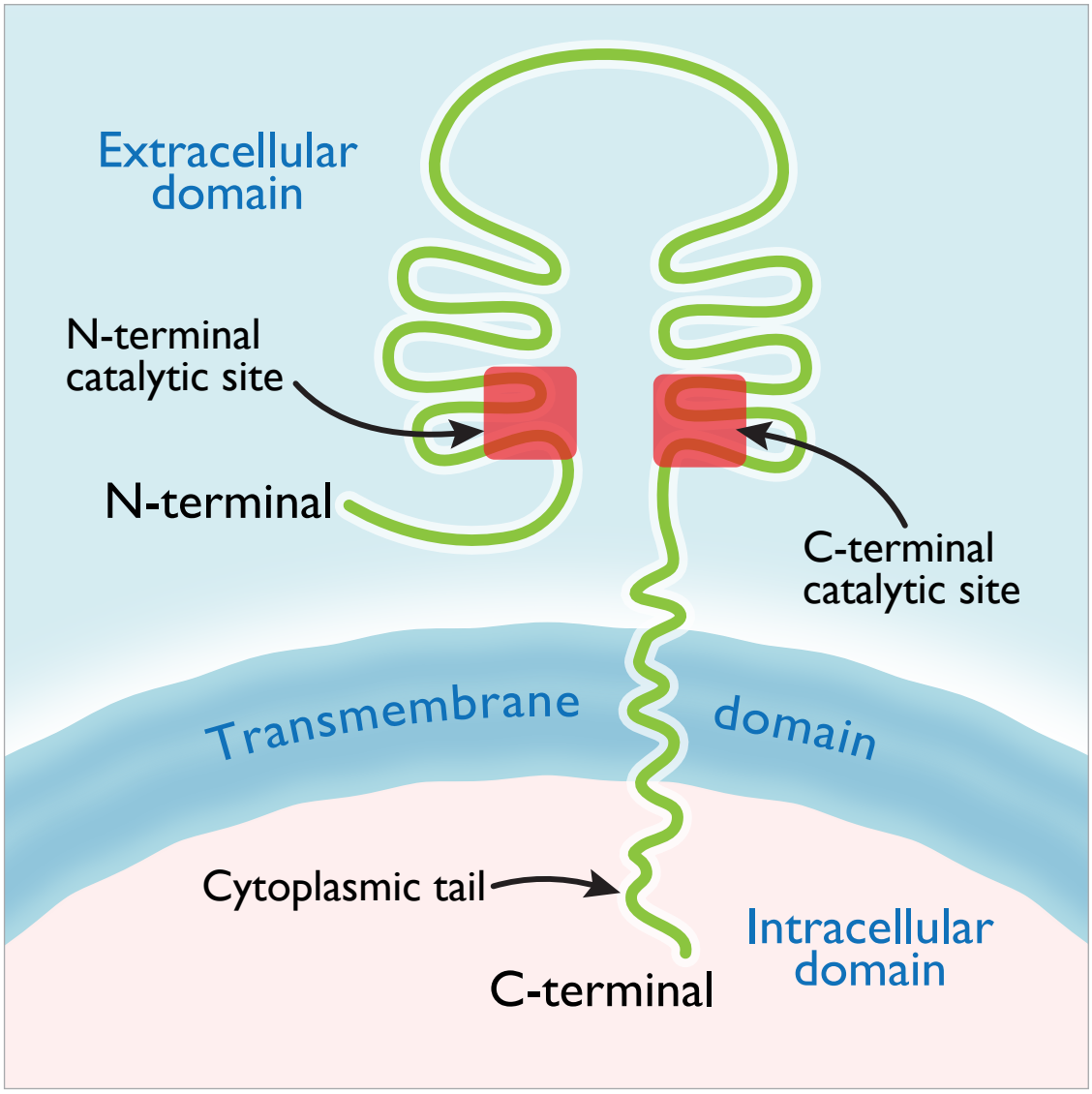


Figure 1: Schematic representation of ACE anchored within the cell membrane.

Soluble ACE

Despite the fact that ACE is expressed as a transmembrane polypeptide, a soluble form of ACE is found in plasma, seminal fluids and other body fluids.

This soluble form is derived from the membrane-bound form through the action of a so-called ACE secretase that cleaves the enzyme between Arg^{1203} and Ser^{1204} on the extracellular side of the transmembrane domain to generate a C-terminal truncated, soluble, or plasma form of the enzyme. Soluble ACE in healthy subjects arises essentially from the endothelium, but in disease states, it can be found in other biological fluids including cerebrospinal and bronchoalveolar fluids.

Tissue ACE

Both isoenzymes of ACE are expressed in humans. The somatic form is particularly abundant on the endothelial surface of lung vessels, and is also expressed in all other endothelial cells types as well as in some smooth muscle cells, cardiomyocytes, monocytes/macrophages, T lymphocytes, and adipocytes. The smaller germinal form is found exclusively in testis.

SIGNAL TRANSDUCTION BY ACE

A therapeutic paradox....*whereby the treatment induces the synthesis of the pathological mediator that it was designed to inhibit*

In 2004, Kohlstedt and coworkers (*Circ Res 2004 94(1) 60-7*) reported the remarkable finding that binding of an ACE inhibitor to ACE, in addition to inhibiting the conversion of Ang I to Ang II was also associated with a sequence of events that resulted in the increased expression of ACE.

More detail

These workers reported that binding of an ACE inhibitor activated a phosphorylation signaling cascade that enabled communication with the nucleus, resulting in an increase in the synthesis of ACE.

Phosphorylation is the addition of a phosphate (PO_4^{3-}) group to a protein or other organic molecule. Reversible phosphorylation of proteins is an important regulatory mechanism that occurs in both prokaryotic and eukaryotic organisms. Enzymes called kinases (phosphorylation) and phosphatases (dephosphorylation) are involved in this process. Reversible phosphorylation results in a conformational change in the structure in many enzymes and receptors, causing them to become activated or deactivated.

What did Kohlstedt et al discover?

The science….

It's well documented that the short cytoplasmic tail of somatic ACE contains between three and five serine residues. Specifically, in the cytoplasmic tail of human somatic ACE, the residue Ser^{1270} is located in a highly conserved thirteen amino acid sequence at the extreme C-terminal end of the polypeptide (Fig 2). Before their remarkable report in 2004, the same group had earlier observed that in endothelial cells, Ser^{1270} is phosphorylated by the kinase CK2. The basal phosphorylation of ACE by CK2 stabilizes its localization in the plasma membrane because the mutation of this site and the inhibition of CK2 both enhance the cleavage/secretion of the enzyme (*Circ Res 2002 91(8) 749-56*).

However, in their 2004 publication they report for the first time that the CK2-dependent phosphorylation of Ser^{1270} is a necessary prelude for the activation of a signaling cascade.

Using ACE immunoprecipitated from ACE-overexpressing cells as well as an affinity column composed of a peptide corresponding to the cytoplasmic tail of ACE, they observed that the kinases, mitogen-activated protein kinase kinase 7 (MAPKK7) and c-Jun N-terminal kinase (JNK) were also found to associate with the intracellular domain of the human enzyme. From these early observations they conclude that ACE phosphorylation is an essential step in the ACE signaling cascade, and the CK2-dependent phosphorylation of Ser^{1270} is required for the activation of ACE-associated JNK.

The increase in JNK activity results in the translocation of phosphorylated c-Jun to the nucleus, an enhanced binding of the activator protein-1 (AP-1) transcription factor to DNA followed by the increased expression of the ACE and cyclooxygenase-2 (COX-2) genes (A simplified version of this signaling cascade is shown in figure 2).

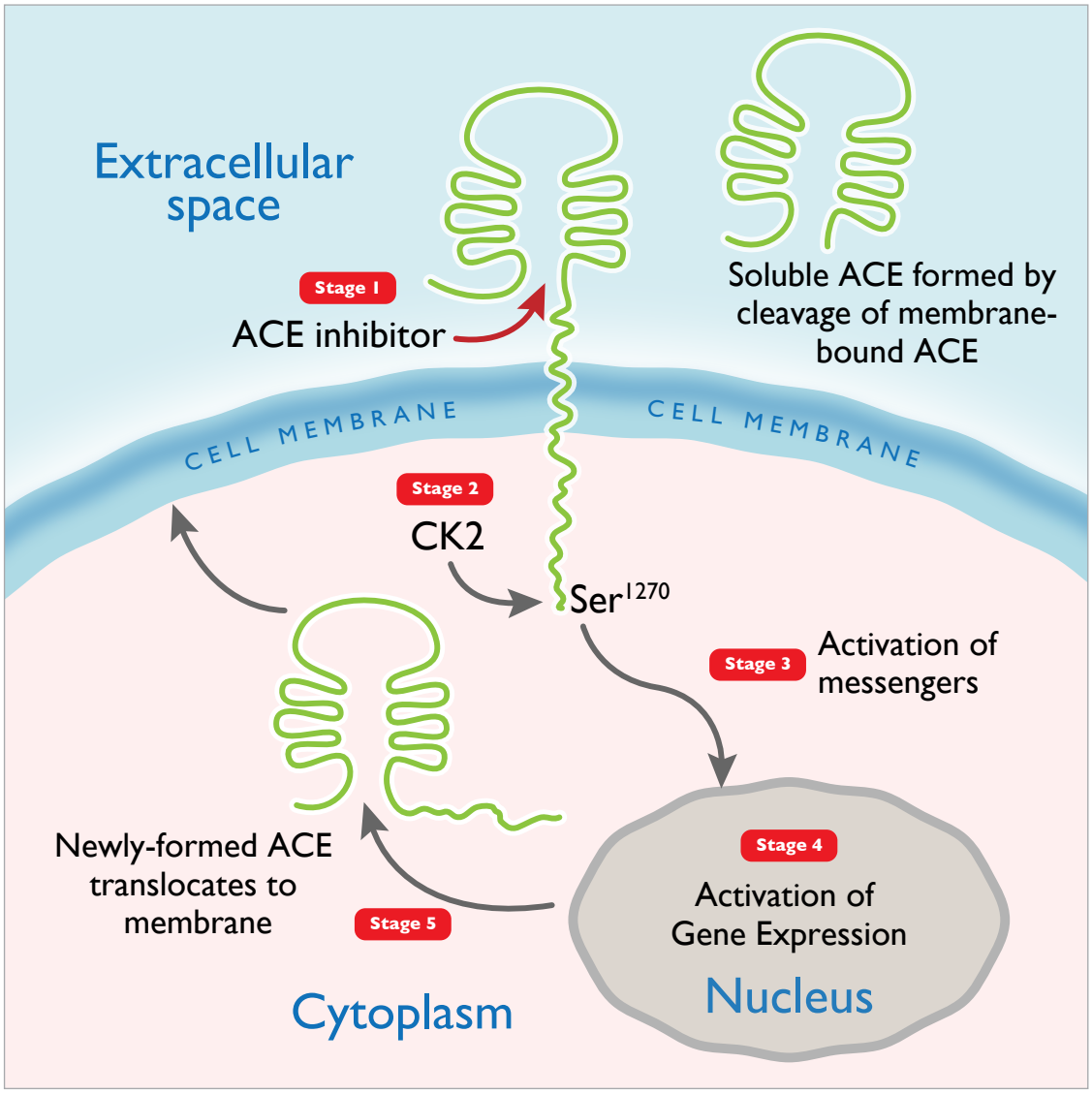


Figure 2: The discovery of an ACE signaling pathway generates a new hypothesis for a paradoxical effect of ACE inhibitors. An ACE inhibitor binds to extracellular transmembrane-bound ACE and inhibits the conversion of Ang I to Ang II. However, new findings reveal that binding of the inhibitor also activates an intracellular signal that is initiated by activation of the ACE-associated kinase, CK2, which phosphorylates the serine residue, Ser1270 in the cytoplasmic tail of the transmembrane-bound ACE. Sequential activation of other kinases results in an accumulation of the phosphorylated transcription factor, c-jun within the nucleus. In turn, this results in the increased expression of the ACE gene with subsequent synthesis of the gene product, ACE. Thus, paradoxically the ACE inhibitor activates the synthesis of new ACE.

Why does binding of an inhibitor to transmembrane ACE activate signaling?

At this time, there is no answer to this question. Indeed, the report by Kohlstedt and coworkers raises many other questions, to which there are few answers. In reviewing their findings, Kohlstedt et al (*Circ Res 2004 94(1) 60-7*) add that it is tempting to claim that the signaling via ACE that is initiated by the binding of an ACE inhibitor is protective/beneficial to vascular cell function and or the development of cardiovascular disease. However, they stress that such a view is speculation because the end point identified in their present study, *viz* an increase in the expression of ACE itself, could also be expected to have deleterious effects by leading to the enhanced generation of angiotensin II.

Importantly, on the basis of the available evidence, it is only the transmembrane-located ACE that is involved in signaling. That is, binding to intracellular ACE by an inhibitor (if the inhibitor can enter the cell) will not result in any additional signaling (*Personal Communication July 2011: Fleming, Ingrid; Professor of Physiology, Institute for Vascular Signaling, Goethe-Universität, Frankfurt am Main, Germany….a member of Kohlstedt's group).*

In summary, and in the absence of further insights, the remarkable findings by Kohlstedt et al must be viewed as paradoxical. That is, a therapeutic goal of the administration of an ACE inhibitor is to inhibit the formation by ACE of Ang II. However, as these workers show in endothelial cells, and later in monocytes/ macrophages (*Personal Communication July 2011: Fleming, Ingrid; Professor of Physiology, Institute for Vascular Signaling, Goethe-Universität, Frankfurt am Main, Germany….a member of Kohlstedt's group; Gershome, Cynthia; Dissertation: Molecular Mechanisms of the Intracellular Signal Transduction by the Angiotensin-Converting Enzyme, Goethe-Universität, Frankfurt am Main, Germany*) and adipocytes (*Mol Pharmacol 2009 75(3) 685-92*), and *in vivo* (mouse lung) (*Circ Res 2004 94(1) 60-7)* binding of the inhibitor to ACE (with inhibition of formation of Ang II) activates the synthesis of new ACE. This new ACE will mature and be transported to the cell membrane (J Biol Chem 1994 269(3) 2125-2130; J Biol Chem 2000 275(30) 23253-23258; Biochem 1996 316(Pt 1) 259-264) and will replace ACE that has been inhibited by the

administration of an ACE inhibitor, resulting in the additional generation of Ang II. At least in the context of atherosclerosis it is difficult to envisage that the ACE inhibitor-activated synthesis of new ACE is beneficial; indeed, it can be more reasonably argued that this paradoxical effect limits the efficacy of ACE inhibitor therapy to attenuate the formation of Ang II, in the treatment of the post myocardial infarction (MI) patient.

As discussed later, the physicochemical character of Capoten allows the proposal that it can inhibit both extracellular and intracellular ACE.

THE MACROPHAGE IN THE PATHOGENESIS OF ATHEROSCLEROSIS

Introduction

Atherosclerosis underlies the leading cause of death in industrialized societies and is likely soon to attain this status worldwide. It is a chronic disease that remains asymptomatic for decades. Atherosclerotic plaques can be separated into two broad categories, stable and unstable (also called vulnerable). While the pathophysiology of atherosclerotic lesions is very complicated generally, stable atherosclerotic plaques, which tend to be asymptomatic, are rich in extracellular matrix and smooth muscle cells, whereas unstable plaques are rich in macrophages and foam cells. Additionally, in unstable plaques the extracellular matrix separating the lesion from the arterial lumen (also known as the fibrous cap) is usually weak and prone to rupture. Rupture of the fibrous cap, exposes thrombogenic material, such as collagen to the circulation and eventually induces thrombus formation in the lumen. Upon formation, intraluminal thrombi can occlude arteries outright (i.e. coronary occlusion), but more often they detach, move into the circulation and eventually occlude smaller downstream branches causing thromboembolism. Apart from thromboembolism, chronically expanding atherosclerotic lesions can cause complete closure of the lumen.

Accumulation of lipoprotein assemblies and recruitment of blood-borne monocytes

Careful morphological and functional studies of the early stages of atherosclerosis in human and animal models indicate that the key initiating step is subendothelial accumulation of apolipoprotein-containing lipoproteins (apo-LPs). The key early inflammatory response to retained apo-LPs, which may be enhanced by oxidative modification of the lipoproteins, is activation of overlying endothelial cells in a manner that leads to recruitment of blood-borne monocytes. Monocytes then become firmly adhered to lesional endothelial cells through the interaction of monocyte integrins (receptors that mediate attachment between cells and the surrounding tissues) with endothelial cell ligands. Platelet aggregation on endothelium overlying atherosclerotic lesions may also promote monocyte-endothelial interactions by activating NF-kB (Nuclear Factor kappa-light-chain-enhancer of activated B cells**)** signaling and expression of adhesion molecules and by depositing platelet-derived chemokines on activated endothelium.

Finally, firm adhesion of monocytes is followed by their entry into the subendothelial space (diapedesis), leading to the formation of the classical established lesion depicted in figure 3.

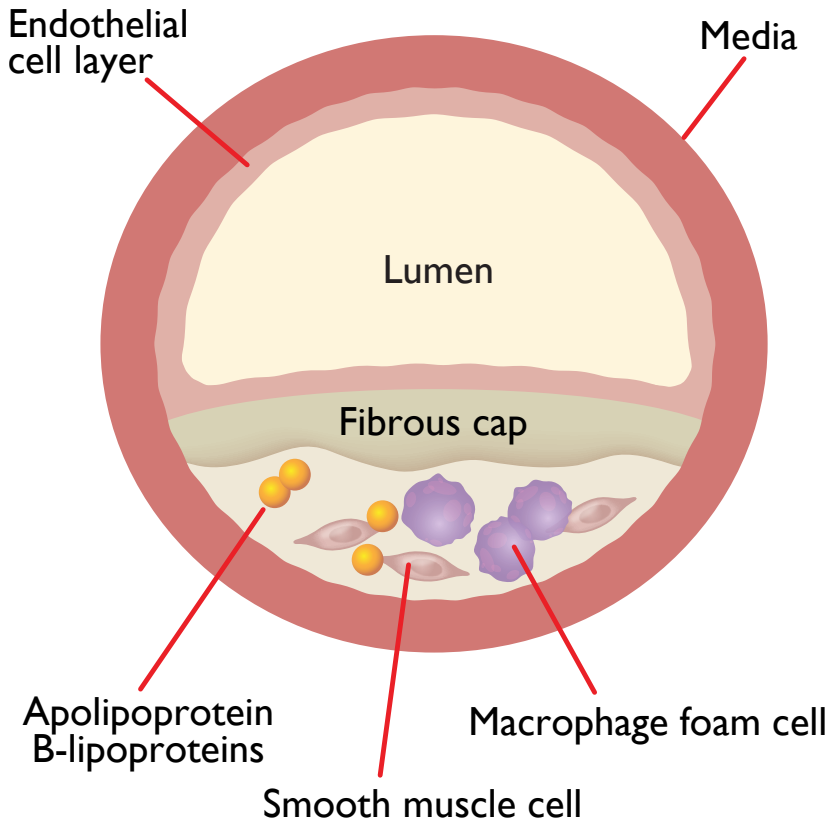


Figure 3: An established Atherosclerotic Lesion. The accumulation of apolipoprotein B-lipoproteins within the matrix beneath the endothelial cell layer of the arterial lumen leads to the recruitment of monocytes. Macrophages derived from these recruited monocytes participate in a maladaptive, non-resolving inflammatory response that expands the subendothelial layer due to the accumulation of cells, lipid and matrix.

Differentiation of the monocyte into a macrophage

Foam cells

Driven by macrophage colony-stimulating factor and probably other differentiation factors, the majority of monocytes in early atherosclerotic lesions become cells with macrophage and/or dendritic cell-like features. Even at very early stages of atherogenesis, many macrophages and dendritic-like cells have membrane-bound lipid droplets in the cytoplasm. These lipid-loaded cells are called “foam cells,” and their formation begins when phagocytes ingest and process apo-LPs.

INCREASED EXPRESSION AND CO-LOCALIZATION OF ACE, ANGIOTENSIN II AND AT1 RECEPTORS IN ATHEROSCLEROTIC HUMAN CORONARY ARTERIES

Ang II is produced locally by infiltrated macrophages and smooth muscle cells during the development and progression of human coronary atherosclerosis

The development and progression of human coronary artery atherosclerosis are dependent on multiple factors, including genetics, life style, and the imbalance of pro-atherosclerotic and anti-atherosclerotic humoral influences. Many vasoactive hormones, growth factors and cytokines promote while others counteract the development and progression of coronary atherosclerosis. Angiotensin II (Ang II) is now well recognized as one of most important vasoactive pro-atherosclerotic factors.

As discussed elsewhere within this document, early atherosclerotic lesions commonly involve infiltration and/or migration of macrophages into the vessel wall, where increased expression of ACE has been reported in macrophages and vascular smooth muscle cells in atherosclerotic plaques of human coronary arteries. These studies therefore suggest that local formation of Ang II is increased at the injured sites and occupies an important role in the development of human coronary atherosclerosis.

Expression of ACE and AT1 (Ang II receptor type I) receptors in inflammatory macrophages have been demonstrated to accumulate in early and advanced atherosclerotic lesions, thus implying an unspecified but important role for interactions between Ang II and macrophages. Ang II has been shown to increase macrophage-induced oxidation of low density lipoprotein or peroxide production via the AT1 receptor (*Atherosclerosis 1995 115(2) 201-215*) or via a lipoxygenase-dependent pathway (*J Vasc Res 1997 34(6) 436-446*). Furthermore, stimulation of peroxide production or induction of inducible nitric oxide synthase (iNOS) expression in accumulated macrophages by Ang II via the AT1 receptor has also been reported. In keeping with this context, it is not surprising to note that Ang II promotes atherosclerotic lesions and aneurysms

in apolipoprotein E-deficiency mice (apolipoprotein E promotes the regression of atherosclerosis) (J *Clin Invest 2000 105(11) 1605-1612*; *J Clin Invest* 2000 105(11) 1525-1526).

Upon review of the available evidence, Ohishi et al (*Int J Physiol Pathophysiol Pharmacol 2010 2(2) 111-124*) recently conclude that Ang II and macrophages interact to promote atherosclerosis via multiple mechanisms related to cell contraction and proliferation, and synthesis and/or release of cytokines, elastase, collagenase and free radicals. They add that over-expression or formation of Ang II in infiltrated microphages and migrated smooth muscle cells plays an important role in the development and progression of human coronary atherosclerosis.

Studies in atherosclerotic human coronary arteries

In human studies, Ohishi et al (*J Hypertens 1997 15(11) 1295-1302; Circulation 1997 96(10) 3328-3337; J Hypertens 1999 17(4) 547-553*) and other investigators (*Atherosclerosis 1997 130(1-2) 203-213; Circulation 1996 94(11) 2756-2767*) have demonstrated increased ACE expression in accumulated macrophages of early atherosclerotic lesions and atheromatous plaques. Because ACE is commonly expressed in the endothelium and adventitia but not in medial smooth muscle cells of normal coronary artery, increased ACE expression in accumulated macrophages and smooth muscle cells adjacent to atherosclerotic plaques strongly suggests an increase in local formation of Ang II at these cellular sites. Using quantitative *in vitro* autoradiography Ohishi et al (*Int J Physiol Pathophysiol Pharmacol 2010 2(2) 111-124)* was able to demonstrate increased ACE binding as a marker of ACE activity in early and advanced atherosclerotic plaques, where ACE co-localized with macrophages and smooth muscle cells. These data are consistent with their earlier studies in which Ang II immunostaining was identified in macrophages and smooth muscle cells of human coronary hypercellular lesions and atheromatous plaques (J Hypertens 1999 17(4) 547-553), thus providing further support to the concept that Ang II is produced locally in infiltrated macrophages and smooth muscle cells during the development and progression of human coronary atherosclerosis.

PROGRESSION OF CORONARY ARTERY ATHEROSCLEROSIS AFTER ACUTE MYOCARDIAL INFARCTION

The post MI patient

Prior MI is evidence of established coronary artery disease (CAD), and multiple coronary lesions are very often observed in such patients. The presence of lesions in the coronary arteries affects flow characteristics, which become turbulent and favour the disruption of atherosclerotic plaques. Turbulent flow may accelerate the atherosclerotic progression of early lesions at the "fatty-streak" stage, which are very often present in patients with acute coronary syndromes, but rarely visible on angiography (*J Am Coll Cardiol 2001 37(5) 1284-1288*). There are compelling reasons to believe that during acute coronary syndromes several mechanisms influence the stability of coronary plaques within the whole coronary tree. The systemic inflammatory response is increased, as reflected by elevated levels of C-reactive and amyloid protein, and inflammation of the fibrous cap is one of the major reasons for their instability (*N Engl J Med 1994 331(7) 417-424*). Normal endothelial function is distorted, which promotes thrombosis and vasoconstriction and may lead to plaque rupture or intraplaque haemorrhage, causing sudden and rapid progression of the lesion (*J Am Coll Cardiol 2006 47(8 Suppl) C7-12*). These mechanisms may be additionally enhanced by endogenous catecholamines, which intensify vasoconstriction and sheer stress (*Am J Cardiol 1990 66(19) 1368-1372; N Engl J Med 1985 313(21) 1315-1322*).

Multifocal plaque instability was confirmed in angiographic, intravascular and ultrasound, and angioscopic studies. Goldstein et al (*N Engl J Med 2000 343(13) 915-922*) found more than one unstable plaque, as assessed by angiography, in 39.5% of patients with acute MI. In an intravascular and ultrasound study conducted by Riouful et al (*Circulation 2002 106(7) 804-808*), 79% of patients had more than one unstable lesion. Similar findings were reported by Asakura et al (J Am Coll Cardiol 2001 37(5) 1284-1288), who examined patients with angioscopy one month after acute MI. Unstable plaques were found in 95% of non-infarct-related segments.

The concept of multifocal plaque instability may be the explanation for the rapid progression of lesions over a period of one month, as observed by Guazzi et al (*Circulation 1997 96(4) 1145-1151*), who found progression in 38% of lesions and 70% of patients after acute MI, compared with 2.5% and 9%, respectively, in matched patients with CAD. In stable CAD, Waters et al (*Circulation 1990 82(6) 1940-1953; 1993 87(4) 1067-1075*) found progression in 42% of patients and 11.2% of lesions over a period of two years, and Lichtlen et al (*Circulation 1993 86(3) 828-838*) found such progression in 56% and 10.2% of patients and lesions, respectively, on angiography conducted three years after inclusion within their study.

More recently, Hawranek et al (*J Invasive Cardiol 2010 22(5) 209-215*) assessed the progression of atherosclerosis in 186 post MI patients. After exclusion of patients not suitable for quantitative coronary angiography analysis, the final group was comprised of 154 patients. Twelve months after MI, they identified disease progression in 9.7% of preexisting coronary lesions, and 62 new lesions were found. Progression of atherosclerosis involved 60.3% of the patients which the authors remark is a finding that is somewhat less than in Guazzi's report (see above), but more than that observed in stable coronary disease.

INTRODUCTION TO CAPOTEN

Historical Perspective

In the 1960s, the Brazilian Scientist, Sergio Ferreira joined John Vane's group in the UK, who were actively engaged in the study of hypertension. Ferreira brought with him an extract described as *bradykinin potentiating factor* (BPF) that was derived from the venom of the Brazilian viper *Bothrops jararaca*. Ferreira had already established that BPF potentiated the actions of bradykinin, probably by inhibiting the enzyme that inactivated it. At Vane's request, BPF was tested on angiotensin converting enzyme (ACE) and found to be a potent inhibitor. This led to Vane's strong interest in ACE and its inhibition as a means of treating hypertension.

Involvement of Squibb

During the late 1960s and early 1970s, Vane was also a consultant to E. R. Squibb and Sons in New Brunswick. Vane presented to the Squibb research staff the concept that ACE is a major regulator of blood pressure. At that time, ACE was known to play a role in so-called "malignant hypertension" (a life-threatening, rapid escalation of blood pressure). Since this condition represents only about 5% of hypertensive disease and effective medications were available for that indication, it was not considered to be a viable commercial target. However, Vane's careful analysis of the probable role of the ACE system in so-called "essential hypertension" was attractive to the Squibb research staff since, if he was correct, it would give the Company an opportunity to enter the cardiovascular field, in which it clearly wanted to be represented but had no good drug candidates in the pipeline. Embarking on a major research program aimed at the ACE system was no simple undertaking thirty years ago, since the majority of clinical experts in the field at the time did not believe that ACE played a significant role in essential hypertension. Charles G. Smith, VP for R&D at Squibb contacted a dozen clinical experts to ask about their willingness to study a drug that inhibited ACE, and only two expressed any interest. John Laragh, then a professor at Columbia University Medical School, expressed considerable interest.

It must be emphasized that Vane's laboratory observations were made studying peptides from viper snake venom *in vitro*. Peptides are not absorbed when taken by mouth and must be injected to be effective in the animal body. Injection is not the preferred route of administration for the treatment of hypertension. In the early 1970s, no laboratory had succeeded in converting a peptide to a form that could be absorbed orally, but Squibb's concept was to "test the hypothesis" by investigating the snake venom peptide by injection and, if activity was demonstrated, then to tackle the problem of making an orally-available form of the drug. Although Squibb scientists (especially David Cushman and Miguel Ondetti) eventually succeeded in accomplishing this unlikely feat, there was no road map for them to follow. Smith was not infrequently asked how R&D could justify spending the Company's hard earned money studying an injectable peptide that cost one million dollars per kilo to synthesize, for a drug that only Vane and Laragh had any confidence might work.

Clinical Evaluation

The most critical clinical test to be performed was to demonstrate, as had been done in animals, that the peptide would block the conversion of angiotensin I to II. In such an experiment, angiotensin I or II is injected into an animal and both make the blood pressure rise. When the snake venom peptide was injected before the angiotensin, the blood pressure increased after angiotensin II but not after angiotensin I, as should be the case if ACE is inhibited in the body. When Squibb applied to the U.S. Food and Drug Administration (FDA) for permission to conduct this experiment in the United States, the FDA refused since angiotensin I was not marketed in the United States (although angiotensin II was approved). As a result, Vane arranged to have the first clinical test performed in the U.K. When the predicted inhibition of ACE was demonstrated in human beings in this landmark United Kingdom study, the FDA allowed Squibb to proceed in the United States using patients with essential hypertension.

John Laragh, a strong supporter of the ACE concept, performed the initial clinical trial in the United States. As Smith recalls, he treated seventeen patients with essential hypertension and the blood pressure came down in fourteen. This finding was followed by the development by Squibb of an orally-active form of the drug. Over the next decade, Squibb invested heavily in developing, testing and formulating and producing Capoten.

Approval of Capoten

Capoten gained FDA approval on April 6, 1981. Captopril (trade name Capoten) was Squibb's first billion dollar drug and it opened a new approach for the treatment of this serious disease. The drug became a generic medicine in the U.S. in February 1996.

Simple chemistry but very powerful pharmacology

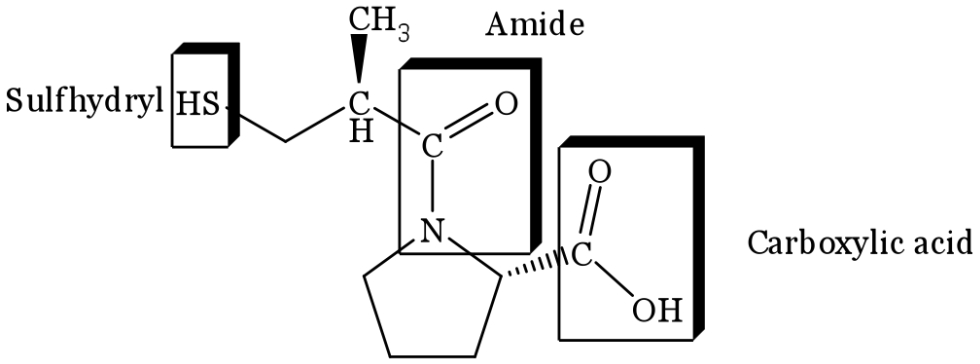
Capoten (Chemistry Diagram 1) is an angiotensin I-converting enzyme (ACE) inhibitor, and is the smallest molecule within this class, as the data published by Remko (Chem Pap 2007 61(2) 133-141) clearly illustrate (Table 1). The small molecular size of Capoten is compatible with rapid permeability of the unionized moiety across a lipid bilayer (lipophilicity as measured in octanol:water is comparable with that of aspirin).

Compound	Polar Surface Area	Molecular Volume	Molecular Weight
Captopril	57.6	195.6	217
Enalapril	95.9	356.7	376
Enalaprilat	106.9	322.4	348
Perindopril	95.9	358.3	368
Perindoprilat	106.9	323.9	340
Lisinopril	132.9	384.4	405
Ramipril	95.9	396.4	416
Ramiprilat	106.9	362.0	388
Trandolapril	95.9	413.2	430
Trandolaprilat	106.9	378.8	402
Quinalapril	95.9	411.4	438
Quinalaprilat	106.9	377.0	410
Fosinopril	110.2	538.7	564
Fosinoprilat	94.9	409.6	435
Benazepril	95.9	394.7	424
Benazeprilat	106.9	360.4	396
Cilazapril	99.2	392.5	417
Cilazaprilat	110.2	358.8	389

Table 1: Capoten is the smallest ACE inhibitor

Capoten has three functional groups (as defined by basic principals of chemistry), no protonable groups (within the physiological pH range), and only one ionizable group (COOH) (within the physiological pH range)

Three functional groups characterize the chemistry of Capoten. These groups are described by the terms, sulfhydryl (sometimes incorrectly described as a thiol), amide and carboxylic acid. Understanding a molecule's basic chemistry enables important insights in the molecule's pharmacology. One of the most important parameters of a molecule's chemistry is a constant known as pKa (sometimes the "a" in pKa is written as a subscript).



Chemistry Diagram 1: Capoten has three functional groups

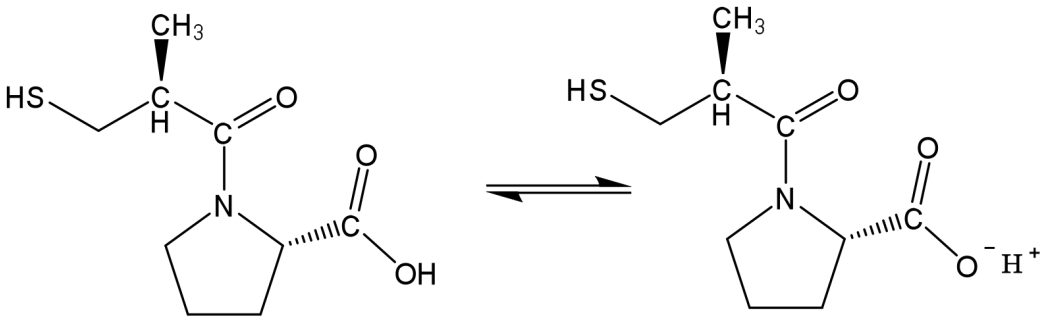
Each functional group is characterized by a pKa value

Each functional group is characterized by a pKa value that provides invaluable information about whether a molecule, when used as a drug, can exert an effect at the target site. For example, the carboxylic acid group (COOH) exists in a dynamic equilibrium in aqueous solution:

$$R\text{-}COOH \rightleftharpoons R\text{-}COO^- \; H^+$$

The group ionizes (dissociates) to liberate the carboxylate anion that is negatively charged, and a hydrogen ion (proton) that carries a positive charge.

The extent of dissociation can be determined by the pKa value. For Capoten the pKa value of the carboxylic acid group is about 3.7 (Range 3.45-5.45 with median value of 3.7 for a non-symmetric distribution). By definition of what pKa represents, this means that when pKa=pH (ie 3.7), the molar ratio of the unionised form (COOH) to the ionized (COO^-) is unity. That is, there is 50% COOH and 50% COO^-. The pH-dependent ionization (dissociation) is represented below (Chemistry Diagram 2).



Chemistry Diagram 2: The aqueous ionization equilibrium of Capoten

What happens to the above equilibrium when the pH is below the pKa value?

Since pH is a measure of the concentration of hydrogen ions (H^+), then in a high hydrogen ion concentration (low pH), the above equilibrium between unionized Capoten (R-COOH) and ionized Capoten ($R\text{-}COO^-$) shifts to the left. That is, the amount of R-COOH increases as the amount of $R\text{-}COO^-$ decreases. This is evident from the relationship if the above equilibrium is viewed as a system in which the increase in H^+ represents an increase in pressure that can only be reduced if the H^+ ions are consumed by $R\text{-}COO^-$ with the result that the equilibrium shifts to the left.

And what happens when the pH is greater than the pKa value?

At a pH above the pKa of 3.7, that is with less H^+ ions as neutrality is approached (ie pH 7), and beyond into an alkaline environment (pH>7), the equilibrium

shifts to the right in response to the reduced H^+ ion pressure. That is, the amount of $R\text{-}COO^-$ increases as amount of R-COOH decreases.

More on Capoten's carboxylic acid group

The published literature provides a range of values for the pKa of Capoten with the value of 3.7 being frequently cited (*Sigma-Aldrich Product Information; The Merck Index, 12th Edition, Entry #1817*). The values that are available are:

3.45 3.50 3.52 3.60 3.615 3.685 3.70 3.90 4.30 4.50 4.51 5.45

The distribution of these values is non-symmetric and the median value is 3.7 (3.69).

Using a relationship known as the Henderson-Hasselbach equation, for Capoten it is not difficult to calculate the ratio of unionized Capoten to ionized Capoten at different pH values. Before pursuing these calculations it should be emphasized that the amide group of Capoten is neutral throughout the physiological range. That is, it does not ionize and it does not attract any hydrogen ions, H^+. The sulfhydryl (sulphydryl) (HS) group of Capoten has a pKa value of about 9.8 (this is the most frequently reported value) and throughout the physiological pH range will remain unionized. That is, we can calculate that at pH 7.4 for example, HS exists as >99.99% unionized. Below pH 7.4 we can consider HS to exist as 100% as the unionized form. Also, within the physiological pH range the sulfhydryl group does not attract hydrogen ions. That is, it does not become positively-charged. Indeed, in general terms a sulfydryl group is extremely resistant to protonation (binding hydrogen ions), and in the laboratory, protonation of an aliphatic sulfhydryl group can usually only be achieved at remarkably low pH levels (likely negative values) using concentrated sulphuric acid.

Does the ratio of unionized:ionized Capoten at different pH values determine Capoten's clinical effects and distinguish this molecule from other ACE inhibitors?

Technical note: Uncertainty exists in the determination of a pKa value for the carboxylic acid group of Capoten

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The Capoten disulphide prodrug reservoir

Following oral administration of Capoten, circulating Capoten exists as protein-bound disulphide dimers, cysteine-Capoten disulphide and mixed disulphides. It has been proposed that these disulphide species act as a reservoir prodrug for the release of the "active" monomeric sulphydryl form.

It has been reasoned that captopril undergoes *cis-trans* isomerization within the time scale of minutes, and that captopril is oxidized spontaneously at its sulfhydryl group after dissolution in water to form its disulfide within the time scale of hours. The disulfide can probably exist as three conformational isomers in *cis-cis*, *cis-trans*, and *trans-trans* combinations.

It is well-established that proline-containing peptides exist as an equilibrium mixture of *cis* and *trans* isomers with respect to the proline amino group. On this basis, using NMR spectra Rabenstein and Isab confirm that captopril exists as two isomers across the amide bond (*Anal Chem 1982 54(3) 526-529*).

Under experimental laboratory conditions they show that the carboxylic acid group of the *trans* isomer is less acidic than that of the *cis* isomer by 0.66 pKa units, and the proportion of captopril in the *trans* form decreases from 0.86 to 0.58 upon titration of its carboxylic acid group. Again, under experimental laboratory conditions it has been proposed that intramolecular hydrogen bonding exists between the carbonyl oxygen of the amide group and the carboxylic acid proton (H^+) in the *trans* isomer.

In moving toward the physiological relevance of the above findings, using a novel combinatorial approach that exploits solution NMR, flexible docking calculations, mutagenesis, and enzymatic studies, Tzakos et al (*Bioorganic & Medicinal Chem Letts 2006 16(19) 5084-5087*) provide evidence that an equimolar ratio of the *cis* and *trans* states of captopril exists in solution and that the ACE enzyme selects only the *trans* state of the inhibitor.

From all of the above, it may be argued that differences in methodologies may reflect uncertainty in the determination of a value of pKa for the carboxylic acid group of captopril.

Using the Henderson-Hasselbach equation to determine the ratio unionized:ionized Capoten at different pH values

From the above discussion, within the physiological pH range, it is the ionization of the carboxylic acid group of Capoten that is affected by pH, with no ionization or protonation of either the sulfhydryl or amide groups. Since there is some uncertainty in the value of the carboxylic acid group pKa, calculations were performed for the two highest values (5.45, 4.51), the median (3.7) and the lowest value (3.45).

The calculated ratios of unionized:ionized Capoten using different pKa values within the pH range 3-7 are shown in figure 4.

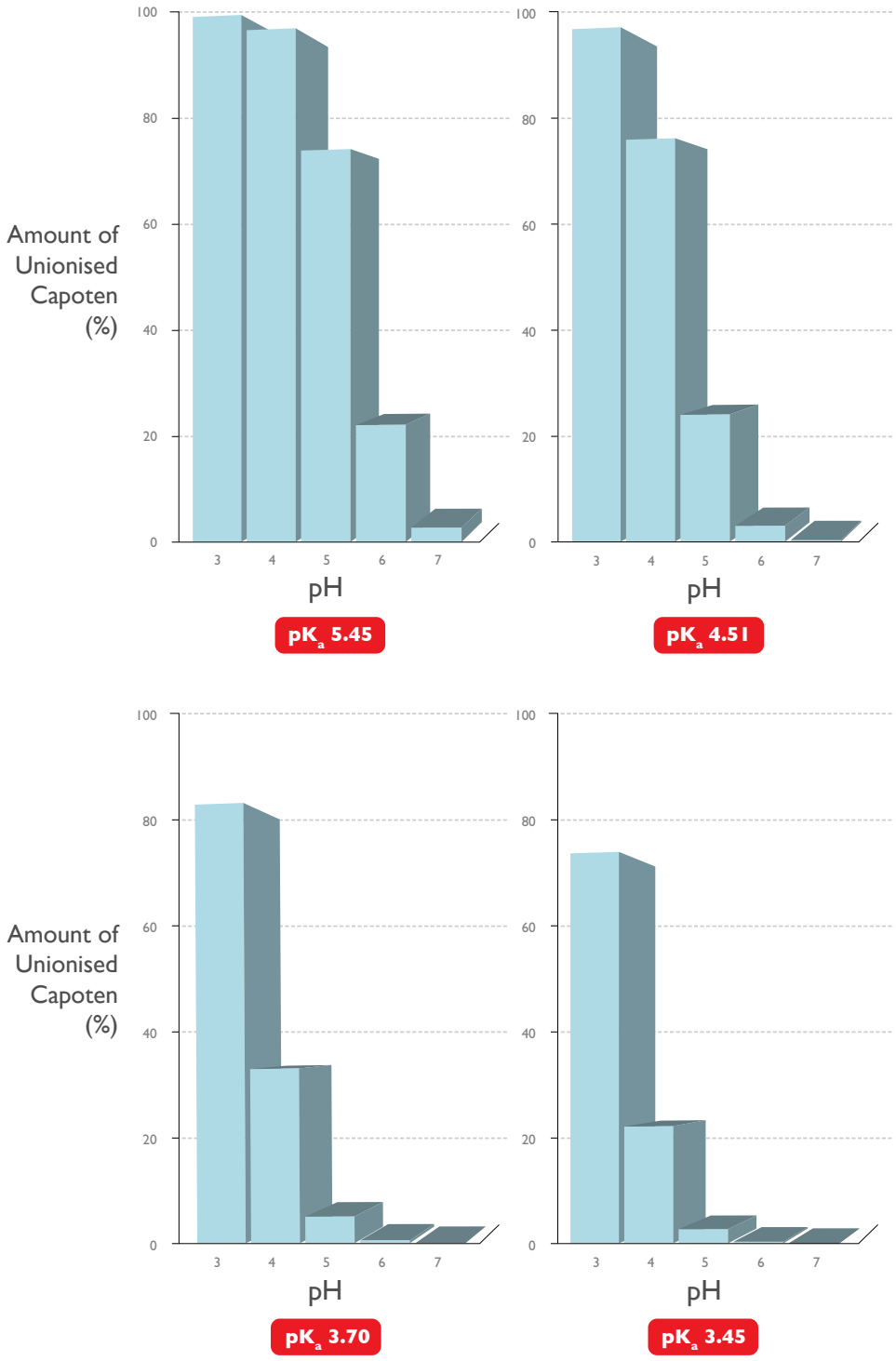
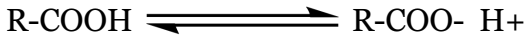


Figure 4: Within the acidic pH range (3.0-6.0) of the extracellular domain of the infiltrated macrophages of the atherosclerotic lesion, the formation of the lipid-soluble membrane-permeable unionized form of Capoten is inversely related to pH. The pH-dependent amount of unionized Capoten (%) is shown at four different pKa values for the carboxylic/carboxylate moiety of Capoten, for which a total of twelve pKa values were discovered within the available published literature. The pKa values of 5.45 and 4.51 are the first and second highest values, and the pKa value of 3.45 is the lowest value that was found, respectively. The pKa value of 3.70 is the median value (the distribution is non-symmetric).

Octanol-water distribution coefficient (Log D) of Capoten

Figure 5 shows that lipophilicity, represented as log D values, measured using octanol-water partitioning within the pH range 1-7 (*Pharmaceutical Res 1992 9(11) 1480-1486*) covaries with the ratio of unionized:ionized Capoten shown in the four illustrations within figure 4. This close correspondence is entirely consistent with a leftward shift in the equilibrium (See also Chemistry Diagram 2):



That is, as hydrogen ion concentration increases (pH falls to lower values) there is a proportional increase in the amount of the lipid-soluble and membrane-permeant unionized form of Capoten (ie R-COOH).

Conversely, as the data also show, as pH rises (reducing hydrogen ion concentration) the equilibrium shifts to the right with an increase in the lipid-insoluble and membrane-impermaent species of Capoten (ie $R\text{-}COO^-$).

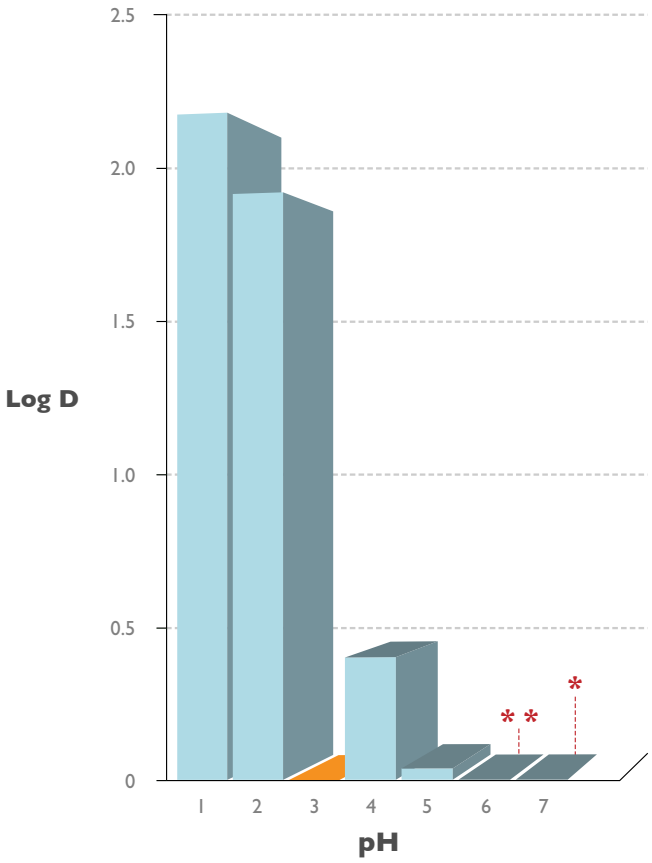


Figure 5: Octanol-water distribution coefficients (Log D) of Capoten at different pHvalues. As pH decreases the increase in distribution coefficient (spanning two orders of magnitude) reflects the pH-dependent formation of the lipid-soluble and membrane-permeant unionized form of Capoten. For comparative purposes, all Log D vs pH data shown within this report are represented using the same scale on the vertical axis. Data adapted from Pharm Res 1992 9(11) 1480-1486.

ND no data
* 0.004
** 0.007

Capoten can accumulate within the atherosclerotic macrophage by ion-trapping

The acidic extracellular environment of the surface-connected compartments (SCCs) (discussed in detail below) of the infiltrated macrophage within the atherosclerotic lesion represents a critical determinant of the disposition and effects of Capoten (Fig 6).

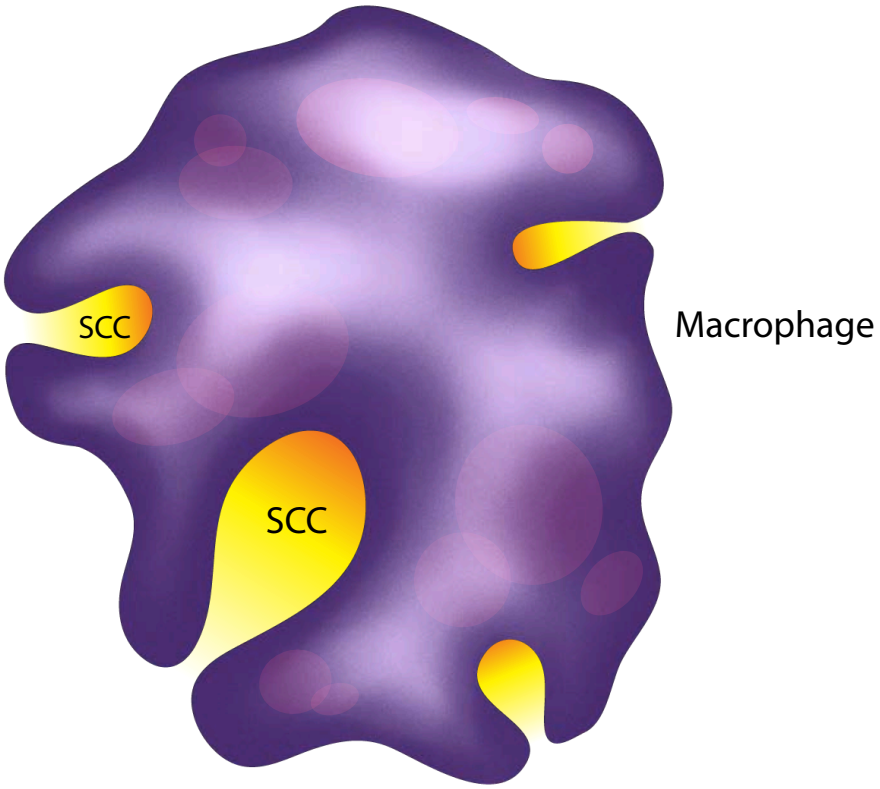


Figure 6: Infiltrated macrophages within the atherosclerosis plaque form invaginations in the cell membrane that are described as surface-connected compartments (SCCs). The extracellular space within these compartments is acidic with pH levels falling to below 4.0.

The extracellular environment of the macrophage within the atherosclerotic lesion, will favour an increase in the unionized (undissociated) form of Capoten:

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

That is, with a decrease in pH (increase in proton pressure), the above

equilibrium shifts to the left (See McCormack and Brune Arch Toxicol 1987 60 261-269 for further details, clinical relevance and detailed bibliography on the phenomenon of ion-trapping), and the lipophilic, membrane-permeable R-COOH species can now transfer across the cell membrane into the intracellular compartment of the macrophage. Within the higher pH (ie less acidity of the intracellular mileu), with a reduced proton pressure the above equilibrium now shifts to the right. That is, at the higher intracellular pH of about 7.2, R-COOH dissociates into the ionized, and impermeable ("trapped"), $R\text{-}COO^-$ species (Fig 7).

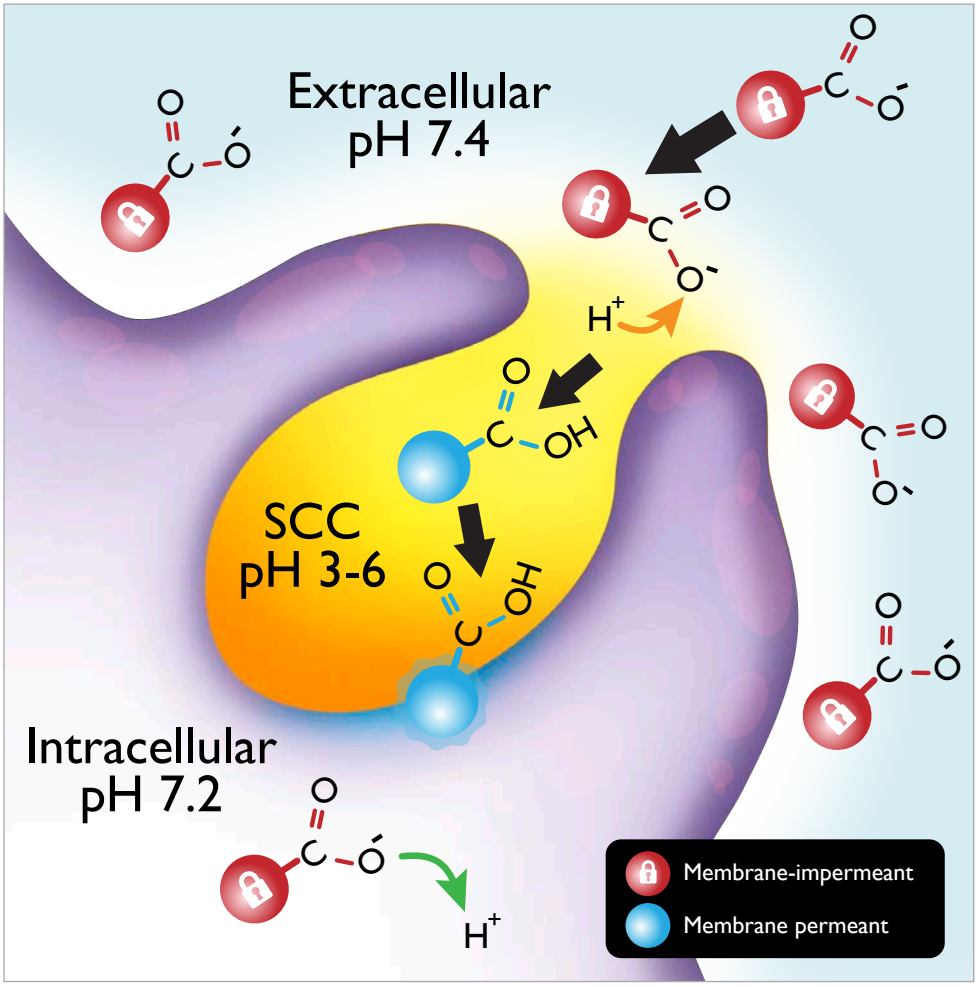


Figure 7: Within plasma at pH 7.4, Capoten is ionized (negatively-charged) and in this form it cannot cross the plaque macrophage cell membrane. However, within the highly acidic surface-connected compartments (SCCs), the greater hydrogen ion concentration (up to 10,000X that at plasma pH) converts ionized Capoten into the lipid-soluble membrane-permeable unionized (no charge) form. Within the intracellular compartment at pH 7.2, Capoten once more becomes ionized. Since the ionized form cannot pass back into the plasma, Capoten becomes "ion-trapped". In this setting the plaque macrophage represents a deep compartment for the accumulation of Capoten.

The difference in pH between the extracellular SCC (3-6) and the intracellular (7.2) environments consequently represents a gradient for the transfer of Capoten into the macrophage. For a pH-dependent ionizable drug, such as Capoten, the phenomenon known as "ion-trapping" is an important mechanism that will enable effective concentrations of Capoten to accumulate within the atherosclerosis macrophage. Restated, the infiltrated macrophage of atherosclerosis represents a deep compartment for the accumulation of Capoten, but not other ACE inhibitors.

Capoten stands apart from other ACE inhibitors

A priori Capoten surmounts the paradoxical effects of binding at extracellular ACE since it is able to accumulate within the infiltrated atherosclerosis macrophage and inhibit newly-formed ACE that is a direct result of Capoten binding at transmembrane ACE (Fig 8). This novel feature differentiates Capoten, and on this basis it is arguably the inhibitor of choice in the management of the post MI patient.

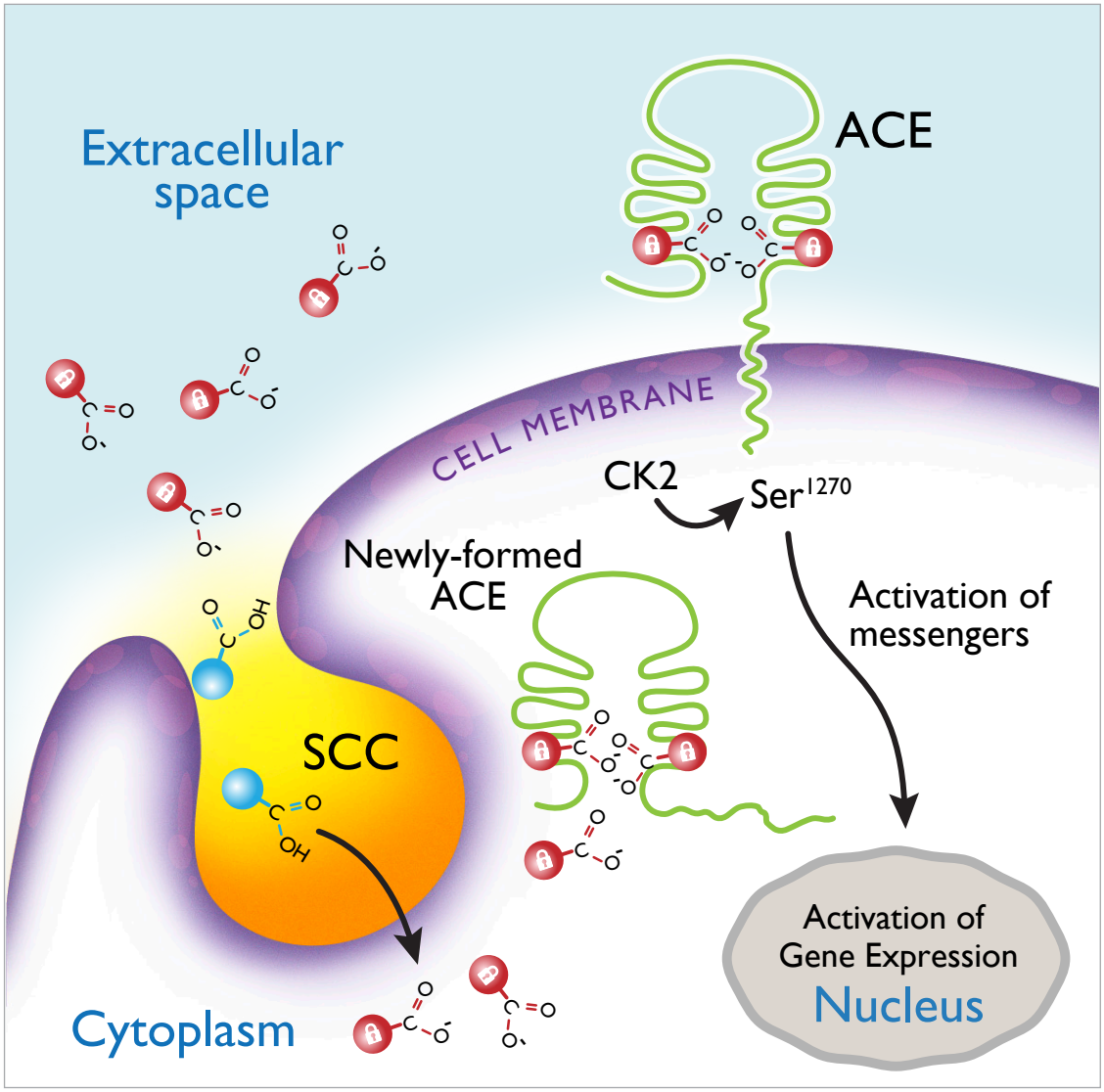
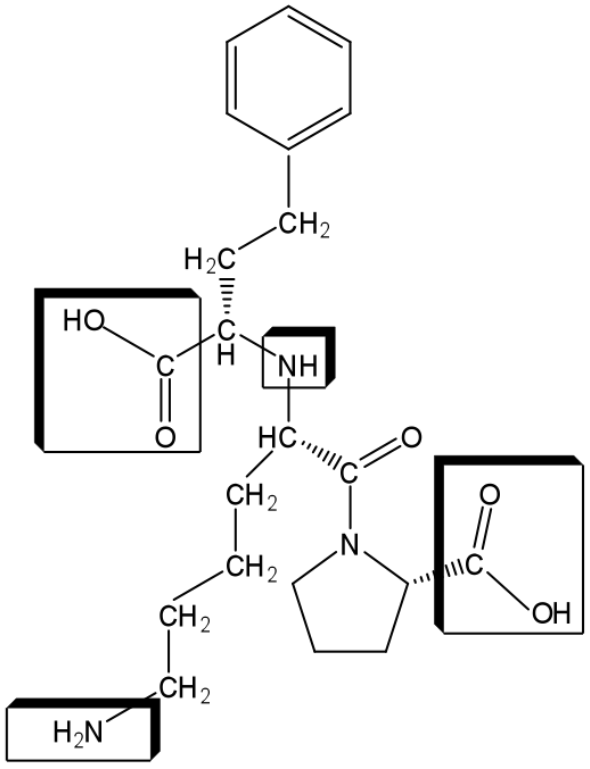


Figure 8: Capoten is a dual-acting bioresponsive (ie the molecule changes in response to a biological stimulus) ACE inhibitor, and can be distinguished from ACE inhibitors that remain charged throughout the physiological pH range. Within the acidic environment of the surface-connected compartments (SCCs) of the atherosclerosis macrophage, Capoten is converted into the lipid-soluble membrane-permeant unionized form enabling accumulation within the intracellular compartment by the phenomenon known as "ion-trapping". Consequently, Capoten is able to block the newly-formed ACE that is generated when transmembrane ACE is inhibited. The dual-action of Capoten means that this signal-induced newly-formed ACE cannot functionally replace the blocked transmembrane ACE.

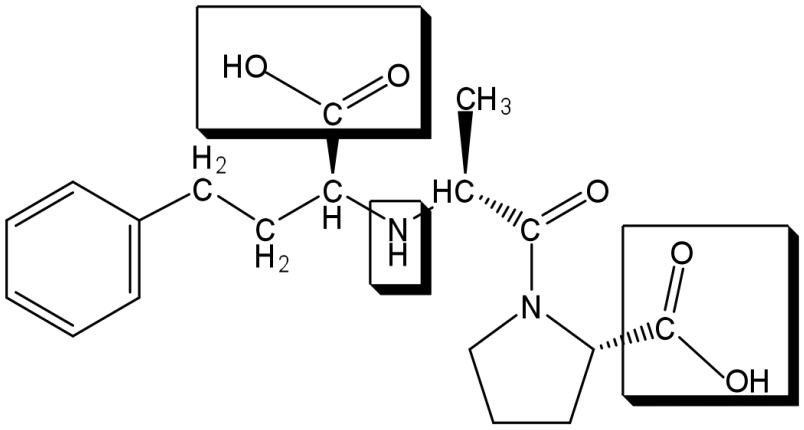
Other ACE inhibitors have multiple ionizable and/ or protonatable functional groups and within the physiological pH range they can be described as lipid-insoluble and membrane-impermeant

A priori, Lisinopril, enalaprilat and ceronapril cannot inhibit intracellular ACE

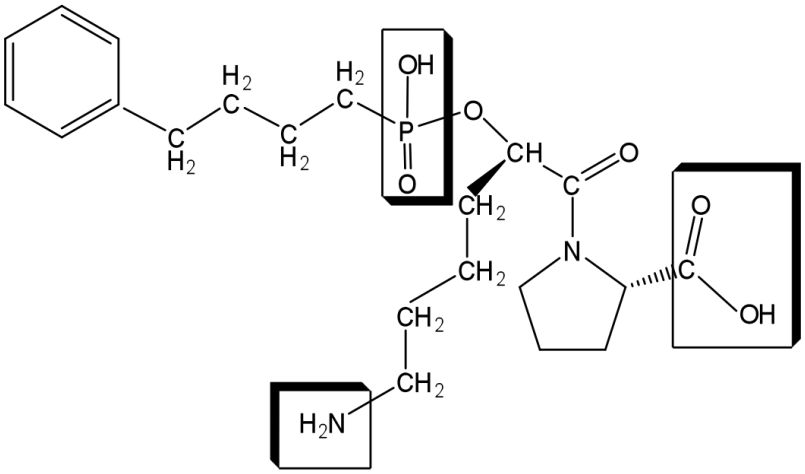
Given the available data for these ACE inhibitors (*Pharmaceutical Res 1992 9(11) 1480-1486*), chemistry diagrams 3, 4 and 5 show that each of these inhibitors have several ionizable and/protonable groups with pKa values that allow the conclusion that within the physiological pH range they will exist as lipid-insoluble and membrane-impermeant species. In the context of the reasoning and published evidence presented within this document, it can be argued that the relative efficacy of each of these inhibitors in managing the post MI patient will be limited by the paradoxical signaling induced upon binding to extracellular ACE that results in newly-synthesized ACE. By contrast, for Capoten the available evidence and reasoning herein suggests that Capoten's efficacy will not be limited.



Chemistry Diagram 3: Lisinopril has two ionizable groups and two protonable groups



Chemistry Diagram 4: Enalaprilat has two ionisable groups and one protonable group



Chemistry Diagram 5: Ceronapril has two ionizable groups and one protonable group

Octanol-water distribution coefficient (Log D) of lisinopril, enalaprilat and ceronapril

By contrast with figure 5 for Capoten, the log D data for lisinopril, enalaprilat and ceronapril (*Pharmaceutical Res 1992 9(11) 1480-1486*) shown in figures 9, 10 and 11 respectively, are entirely consistent with the presence of lipid-insoluble and membrane-impermeable forms that are predicted to exist according to the several pKa values for each drug.

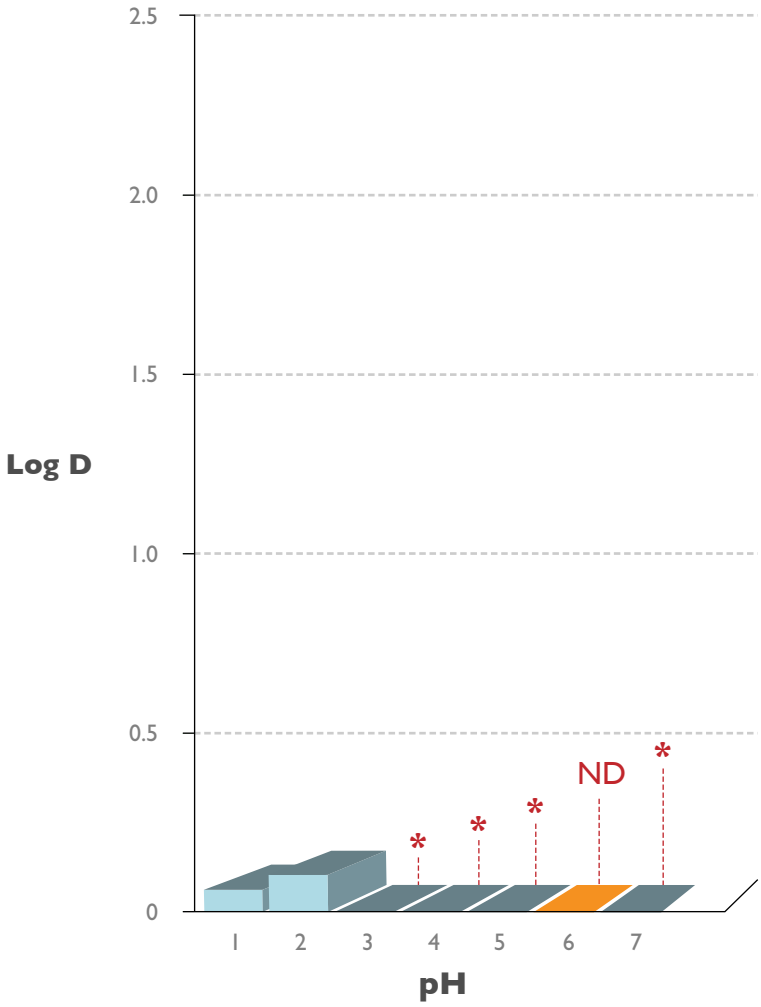


Figure 9: Octanol-water distribution coefficients (Log D) of lisinopril at different pH values. The low distribution coefficient of lisinopril at all pH levels reflects the multiple charges on the molecule throughout the physiological pH range. For comparative purposes, all Log D vs pH data shown within this report are represented using the same scale on the vertical axis. Data adapted from Pharm Res 1992 9(11) 1480-1486.

NDno data
*<0.001

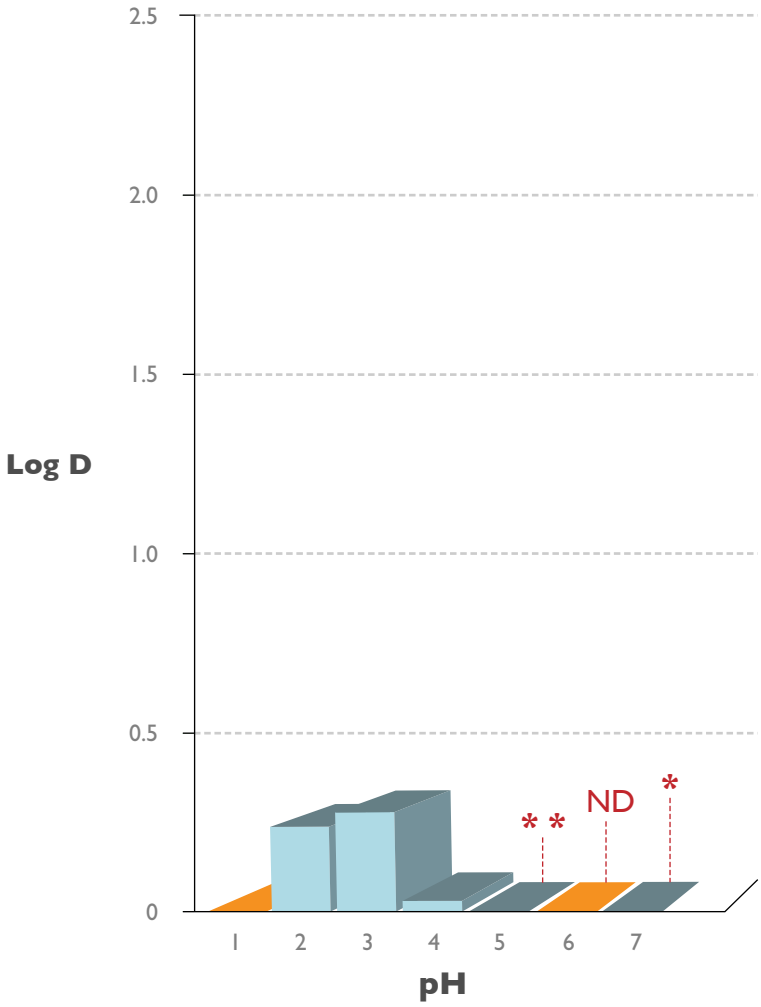


Figure 10: Octanol-water distribution coefficients (Log D) of enalaprilat (the active form of the prodrug enalapril) at different pH values. The low distribution coefficient of enalaprilat at all pH levels reflects the multiple charges on the molecule throughout the physiological pH range. For comparative purposes, all Log D vs pH data shown within this report are represented using the same scale on the vertical axis. Data adapted from Pharm Res 1992 9(11) 1480-1486.

ND no data
* <0.001
**0.0024

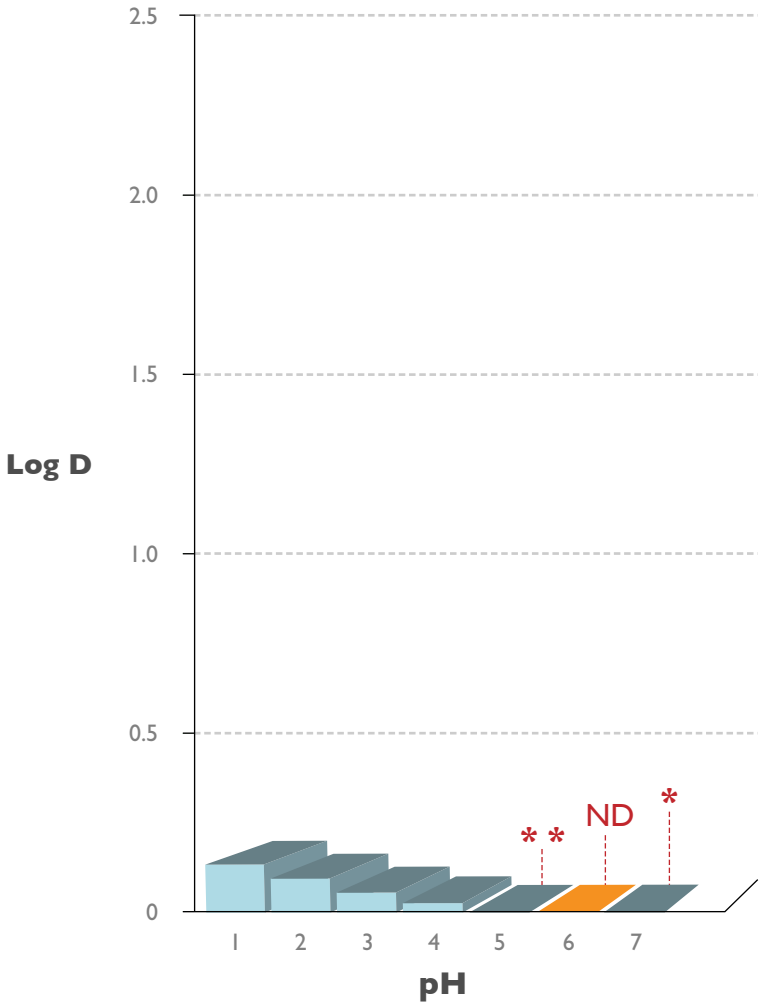


Figure 11: Octanol-water distribution coefficients (Log D) of ceronapril at different pH conditions. The low distribution coefficient of ceronapril at all pH levels reflects the multiple charges on the molecule throughout the physiological pH range. For comparative purposes, all Log D vs pH data shown within this report are represented using the same scale on the vertical axis. Data adapted from Pharm Res 1992 9(11) 1480-1486.

NDno data
*<0.001
** 0.002

MACROPHAGES CREATE AN ACIDIC EXTRACELLULAR HYDROLYTIC COMPARTMENT

The atherosclerosis plaque macrophage is a deep compartment for the accumulation of Capoten but not other ACE inhibitors

Recruitment of monocytes into developing lesions and accumulation of non-motile foam cells are integral to atherosclerotic plaque formation. A critical step in foam cell formation is the uptake of cholesterol from subendothelial lipoproteins. Although most studies model this interaction by incubating macrophages with monomeric lipoproteins, macrophages *in vivo* encounter lipoproteins that are aggregated. The physical features of the lipoproteins require distinctive mechanisms for their uptake.

Specialized surface-connected compartments (SCCs) are highly acidic

The specialized cellular processes involved in the interaction of macrophages with matrix-retained and aggregated low density lipoproteins (agLDL) have been partially characterized. Macrophages internalize agLDL by patocytosis, a non-scavenger receptor-mediated pathway. The agLDL is sequestered in deep invaginations at the cell surface, termed surface-connected compartment (SCCs) (The SCC is illustrated in figure 6). The membrane of the SCC is continuous with the cell surface for prolonged periods of time.

Haka et al (Mol Biol Chem 2009 20(23) 4932-4940) further investigated the role of SCCs in atherosclerosis and showed that macrophages create an extracellular and significantly acidic hydrolytic compartment in which agLDL are digested. They demonstrate delivery of lysosomal contents to these specialized compartments and their acidification by vacuolar ATPase, enabling aggregate catabolism by lysosomal acid hydrolases. They observed transient sealing of portions of the compartments, allowing formation of an “extracellular” proton gradient. The most acidic pH value they report is 5.0. An increase in free cholesterol is observed in aggregates contained in these compartments.

Thus, they show that cholesteryl ester hydrolysis can occur extracellularly in a specialized compartment. They conclude that a detailed understanding of these processes is essential for developing strategies to prevent atherosclerosis.

The macrophage has the capacity to elaborate extracellular pH values around 3.0

Silver at al (*Exp Cell Res 1988 175(2) 266-276*) showed that osteoclasts (a cell type that can be derived from the monocyte/macrophage lineage) and activated macrophages in culture generate an acidic microenvironment specifically in the attachment zone between the cell and the base of the culture dish. Measurements using pH microelectrodes revealed that osteoclasts, when firmly attached, could achieve a pH fall of about 1 unit min^{-1} to a limit value of pH 3.0 or less. Activated macrophages produced a slower fall of 0.5-2 pH units h^{-1} and a limit value of pH 3.6-3.7 was generally detected. They add that the method of activation was relatively unimportant, but where macrophages formed clumps the pH effect was reinforced.

Other references that discuss more generally the role of acidity and atherosclerosis:

J Lipid res 2008 49 782-789; Monteiro http.//www.infarctcombat.org; FEBS Letters 1998 434 317-321; FEBS Letters 1994 338 122-126;Atherosclerosis 2002 164 27-35; Atherosclerosis 1997 129 149-157;Arterioscler Thromb Vasc Biol 2010 30 1766-1772;

Capoten has access to the atherosclerosis macrophage via the vasa vasorum

Vasa vasorum are microscopic vessels that perfuse the walls of macroscopic arteries and veins. Numerous observations over the years underpin the speculation that vasa vasorum play a significant role in arterial disease. For instance, atheromatous plaques tend to form in arteries that normally have vasa vasorum, when there is damage to the outer adventitia or when vasa vasorum are ligated.

Vasa Vasorum as an Essential Factor for Progression of Atherosclerosis

Strong support for an active role by vasa vasorum is provided by Moulton et al (*Circulation 1999 99 1726-32; Proc Natl Acad Sci USA 2003 100 4736-41*) who demonstrated that inhibiting vasa vasorum neovascularization is strongly associated with a reduced lesion progression in apoE-deficient mice. In that study, it was also demonstrated that inhibition of plaque angiogenesis may have beneficial effects on plaque stability. The reduction in plaque progression was mainly attributed to the decreased influx on macrophages into the plaque, supporting the role of the vasa vasorum in the early stages of plaque development.

Thus, there exists in humans (but less likely in animals) an intense vasa vasorum with origins in the adventitia of the coronary arteries. That is, circulating Capoten has unhindered access to the macrophage population that infiltrates the plaque.

The lack of a vasa vasorum in plaques of small animals raises numerous issues on the use of data from animals; arguably, animal data would lack sensitivity to detect the effects of Capoten. Likely, this is a covariate that will not have been considered by many investigators.

SELECTED ANIMAL DATA IN SUPPORT OF CAPOTEN'S EFFICACY IN ATHEROSCLEROSIS

J Cardiovasc Pharmacol. 1990;15 Suppl 5:S65-72.
Effects of captopril on atherosclerosis in cynomolgus monkeys.
Aberg G, Ferrer P.

Source
Department of Pharmacology, Squibb Institute for Medical Research, Bristol-Myers Squibb Company, Princeton, New Jersey 08543-4000.

Abstract

A study was performed to investigate if oral dosing of captopril could influence the development of atherosclerosis in cholesterol-fed cynomolgus monkeys. Twenty-four monkeys were divided into four groups: (a) a control group given a normal monkey diet and placebo medication; (b) a high cholesterol group given a high cholesterol diet and placebo medication; (c) a low-dose captopril group given the cholesterol diet and 25 mg/kg of captopril twice daily; and (d) a high-dose captopril group given the cholesterol diet and 50 mg/kg of captopril twice daily. The doses of captopril used in this study did not change the levels of total serum cholesterol, high-density lipoprotein (HDL), or triglycerides. The total cholesterol/HDL ratio was also unaffected by captopril. The animals were killed after 6 months of treatment. The progression of atherosclerosis was assessed by gross pathology, histopathology, and biochemical methods. The results showed a significantly reduced progression of arterial lesions in monkeys given captopril; the effects of captopril were most evident in the coronary arteries, which were practically free from atherosclerosis in captopril-treated animals.

SELECTED CLINICAL DATA IN SUPPORT OF CAPOTEN'S EFFICACY IN ATHEROSCLEROSIS

The scientific journal FACTA UNIVERSITATIS
Series: Medicine and Biology Vol.6, No 1, 1999 pp. 69 – 72
Editor of Series: Vladisav Stefanović

LONG-TERM EFFECT OF CAPTOPRIL ON PLASMA LIPIDS IN ACUTE MYOCARDIAL INFARCTION: POSSIBLE MECHANISM OF ANTIATHEROSCLEROTICAL EFFECT OF ACE INHIBITION

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[3] Institute for Medical Statistics, Belgrade, Yugoslavia

Summary

It is known that ACE inhibitors have beneficial effects on the left ventricular function and cardiovascular events after myocardial infarction. Also, it is important that ACE inhibitors are lipid neutral, with no deleterious effects on the lipid status. The lipid status could influence progression of atherosclerosis and coronary artery related events. There is no reported long-term clinical study of ACE inhibitor treatment in and after acute myocardial infarction on a lipid status. In the placebo-controlled open label randomized study, 104 patients with acute myocardial infarction were observed for a period of seven years: 52 patients with standard therapy (con group) and 52 patients with captopril therapy (cap group), 6.25 mg the first 12 h after the onset of AMI, followed by 6.25 mg to 25 mg two times daily. No differences were observed between the groups at baseline. The seven years period was reached by 80 patients; in the captopril group, there were less patients with cardiovascular events ($p<0.05$), less patients with clinical signs of heart failure, less mortality, and higher levels ($p<0.02$) of HDL cholesterol. Despite the small group of patients ($n=52$), statistically significant increase in HDL cholesterol values and less pronounced mortality and morbidity during the entire period of seven years were observed in the cap group.

Acknowledgements: McCormack Limited acknowledges the expertise of Rick Lecoat of Shark Attack Limited, a UK-based Design Studio (www.sharkattack.co.uk), in the design and preparation of figures 1-11 and in the final assembly and construction of the completed document.