Dilatrend® PRODUCT MONOGRAPH

Comprehensive β_1-, β_2- and α_1-blocking Agent with Ancillary Properties

Indicated for Hypertension, Coronary Heart Disease, Chronic Heart Failure

CARVEDILOL

Dilatrend®

One life, one heart, multiple protection.

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- Comprehensive β_1-, β_2- and α_1-blocking agent, with ancillary properties
- Excellent efficacy and tolerability across the cardiovascular continuum: from hypertension to coronary artery disease to chronic heart failure
- Largest evidence base of any β-blocker across the full spectrum of CHF
- On Dilatrend®, fewer patients need to be treated to save one life compared with conventional β_1 selective β-blockers
- Offers clear metabolic advantages over conventional β_1-selective β-blockers
- Very well tolerated, with fewer side effects than other cardiovascular agents
- As a result of Dilatrend®'s mode of action and unique pharmacological profile, patients receiving Dilatrend will live longer and better lives
- COMET provides definitive evidence that Dilatrend is the β-blocking agent of choice in CHF

2. Cardiovascular Disease: a Major Healthcare Issue

Burden of disease

Cardiovascular disease is a significant burden, not just because of the often severely debilitating effects on patients, but also due to the costs to the health-care system and society in terms of hospitalisation and loss of productivity. In its many forms, cardiovascular disease is the most frequently reported cause of death in the Western world. The incidence and prevalence of cardiovascular disease world-wide is likely to continue to increase as people live longer and have greater access to improved secondary care.[1] Chronic heart failure (CHF) especially has become more important over the years due to the ageing of the population; it is the single most frequent reason for medical admission in people aged > 65 years.[2] It is estimated that approximately 10-15% of all hospital admissions are caused or complicated by CHF alone.[2, 3]

The cardiovascular continuum

The aetiology of cardiovascular disease is complex, but the disease can be thought of as a continuum. This continuum begins with the effects of various risk factors on the cardiovascular system, e.g. hypertension, smoking, dyslipidaemia, and glucose disorders like type 2 diabetes mellitus;[4, 5] however, the endpoint of the continuum is severe CHF (Figure 1).

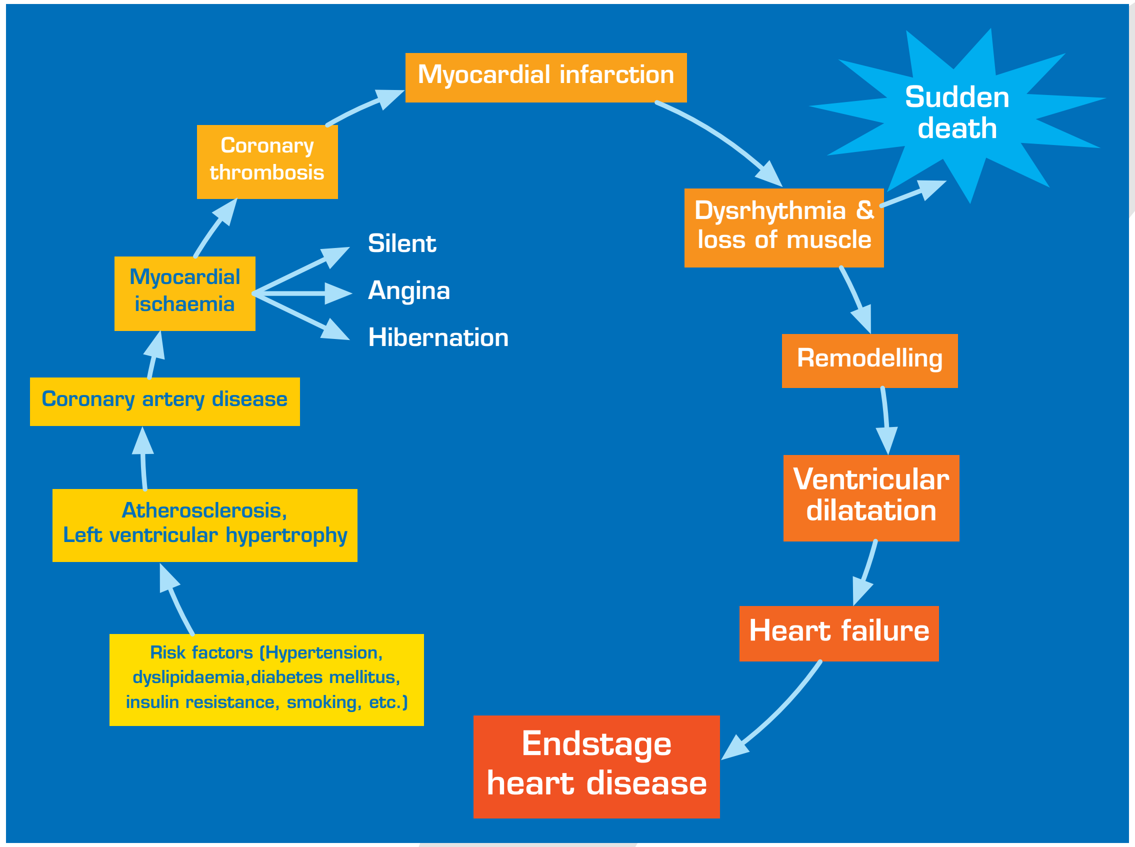


Figure 1: The cardiovascular continuum

Hypertension is a primary predisposing risk factor in the cardiovascular continuum, leading to the development of coronary artery disease (CAD), myocardial infarction (MI) and CHF.

In hypertensive patients this risk increases if other factors are also present, including: smoking; type 2 diabetes mellitus; dyslipidaemia; obesity; left ventricular (LV) hypertrophy and remodelling, and endothelial dysfunction.

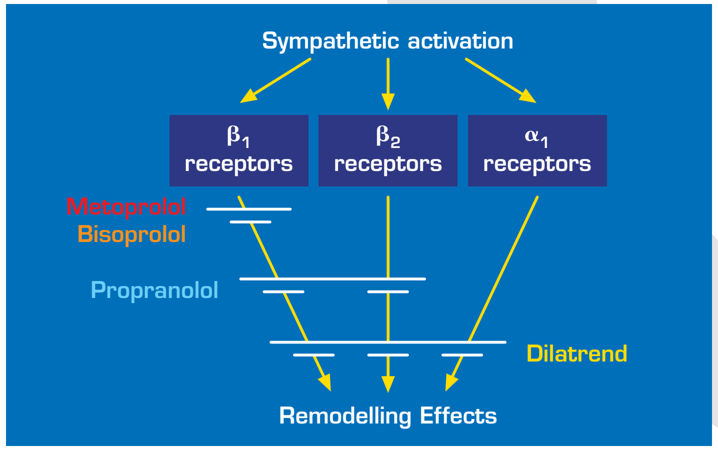


Figure 2: Antiadrenergic therapy with β-blockade: Dilatrend® provides comprehensive adrenergic inhibition, unlike other β-blocking agents.

3. The Sympathetic Nervous System: a Major Role in Cardiovascular Disease

Sympathetic activation

Cardiovascular disease is a significant burden on patients and on healthcare resources, and is likely to increase worldwide as the population lives longer. The disease represents a continuum from hypertension and other concomitant risk factors leading to MI, CHF and death.

Activation of the sympathetic nervous system plays a major role in cardiovascular disease. Sympathetic stimulation releases norepinephrine, constricts blood vessels and increases heart rate, contractility, blood pressure and rate of metabolism. Progression through the cardiovascular continuum is characterised by neurohormonal activation represented by adrenergic activation and renin-angiotensin-aldosterone system over-activity.
This is a compensatory response to the reduced cardiac output and systemic blood pressure which accompany systolic LV dysfunction. Chronically increased levels of norepinephrine and angiotensin II can damage the heart and affect peripheral circulation and fluid balance, leading to adverse clinical outcomes and further progression of disease.

The adverse effects of sympathetic activation are caused by the increase in norepinephrine levels, which activate the β_1, β_2 and α_1 adrenergic receptors. Myocyte growth is affected by all three receptors, but the inotropic and chronotropic responses of the heart, and the cytotoxic effects of norepinephrine, are mediated through the β_1 and β_2 receptors.[6, 7]

In CHF, chronic sympathetic overactivation changes the cellular adrenergic pathway and leads to down-regulation of myocardial β_1 adrenergic receptor density,[8] leading to a greater proportion of β_2 receptors. Over time, signal transduction of β receptors is altered by selective β_1-blockers, leading to up-regulation of β_1 adrenergic receptors in CHF patients, compensating for the reduced receptor activation caused by the initial receptor inhibition.[6]

Stimulation of the sympathetic nervous system also greatly affects the body's haemodynamic and fluid balance. Initiation of therapy with conventional β_1-selective β-blockers may be associated with increased fluid retention, resulting in oedema and reduced urinary volume; stabilisation with an appropriate diuretic regimen is therefore recommended before therapy begins. However, in cardiovascular disease, particularly CHF, management of fluid balance is highly complex, involving a number of factors. Insufficient or over-aggressive diuresis can result in inappropriate ventricular filling and low cardiac output, which may further activate the sympathetic nervous system in order to maintain circulation.

Progression through the cardiovascular continuum is characterised by chronic neurohormonal activation, characterised by increasing levels of norepinephrine. Chronically elevated levels of norepinephrine have deleterious effects on the heart and circulation, which are mediated by β_1, β_2 and α_1 receptors.

4. Properties of an Ideal β-Blocking Agent

An ideal β-blocking agent to treat cardiovascular disorders should have several key properties:

Comprehensive adrenergic blockade

Since the adverse effects of chronically elevated norepinephrine plasma levels are mediated through β_1, β_2 and α_1 receptors, an ideal β-blocking agent should not only selectively block one single receptor (e.g. the β_1 receptor), but ideally block all three receptors in order to provide maximal protection of the heart and circulation.

Effective, with established safety across the cardiovascular continuum

The agent should demonstrate superior efficacy, tolerability and safety across the entire cardiovascular continuum, from hypertension and CAD through to CHF.

Saves lives

It should demonstrate a significant reduction in the mortality and morbidity of patients with cardiovascular diseases. The healthcare burden should also be reduced, with fewer, shorter hospitalisation episodes. In addition, the patients' quality of life should be improved.

Good tolerability/safety profile

Tolerability is extremely important; the agent should have as few side effects as possible, and any adverse effects should be minor or transient.

Easy to use

An ideal agent should be easy to use both for the physicians and the patients; the dosing schedule should be practical and simple. It should possess the ability to be used in all patient populations with a proven efficacy at low dosing ranges, and should have a good safety profile when administered on its own or in combination with other therapies.

No adverse metabolic effects

Many patients have concomitant metabolic disorders such as diabetes or lipid disorders. An ideal antiadrenergic agent should have at least no adverse, or, ideally, beneficial effects on these metabolic disorders.

Other beneficial effects

Protection against the adverse effects of oxygen free radicals on the circulation and the heart as well as antiproliferative effects to prevent the progression of atherosclerosis and the development of LV hypertrophy are desirable throughout the spectrum of cardiovascular diseases.

5. Dilatrend®: a Unique Mode of Action

Dilatrend® has a unique mode of action, blocking β_1, β_2 and α_1 receptors. In addition, Dilatrend® possesses antioxidative and antiproliferative properties, as shown by cardio- and vasoprotective effects independent of α- and β-blockade.[9, 10, 11, 12]

Comprehensive adrenergic blockade

Combined β_1 and β_2 blockade

Dilatrend® **blocks β_1 and β_2 adrenergic receptors equally**,[13] and displays **no intrinsic sympathetic activity** (ISA).[13, 14, 15, 16]

The combined β_1 and β_2 antagonist properties of Dilatrend® have been well established in both *in vitro* and *in vivo* studies.[17] A lack of ISA is of major importance because of potential effects on mortality; neither lipophilicity nor β_1 selectivity appear to be important contributors to mortality effects.[18]

In failing hearts, as β_1 receptors are typically down-regulated, while β_2 receptors are up-regulated, combined β_1/β_2 receptor blockade should offer significant advantages over selective β_1 blockade. In clinical[19] and preclinical studies,[15, 20] cardiac β_1 receptors were not up-regulated in CHF when treated with Dilatrend®, as they were with selective β_1-blocker therapy. However, the impact of these findings remains to be elucidated.

The reduction in heart rate due to Dilatrend®'s β-blocking activity is more pronounced when the sympathetic tone is high, such as in CHF. Also, the increased heart rate caused by exercise or emotional stress is inhibited to a greater degree than resting heart rate; the actual expected reduction by Dilatrend® is from 5-15 bpm, depending on the conditions. In hypertensive patients, Dilatrend® at equipotent doses reduces the heart rate somewhat less than selective β_1-blockers,[21, 22] because Dilatrend®'s vasodilatory effect contributes significantly to overall blood pressure reduction.

α_1 blockade: peripheral vasodilation

Dilatrend® blocks α_1 adrenergic receptors, located on both coronary and peripheral vascular smooth muscle cells, inducing a vasodilatory effect. The α-blocking properties of Dilatrend® are approximately 10 times weaker than its β-blocking effects.[13, 17, 23]

Dilatrend®'s α_1 antagonistic effects also result in increased renal perfusion.[24] Moreover, the peripheral vasodilation provided by α_1 blockade facilitates the up-titration process in CHF by off-loading the left ventricle, thus reducing the tendency for fluid retention. Unlike metoprolol, Dilatrend® reduces systemic arterial resistance in hypertensive patients (Figure 3).[25]

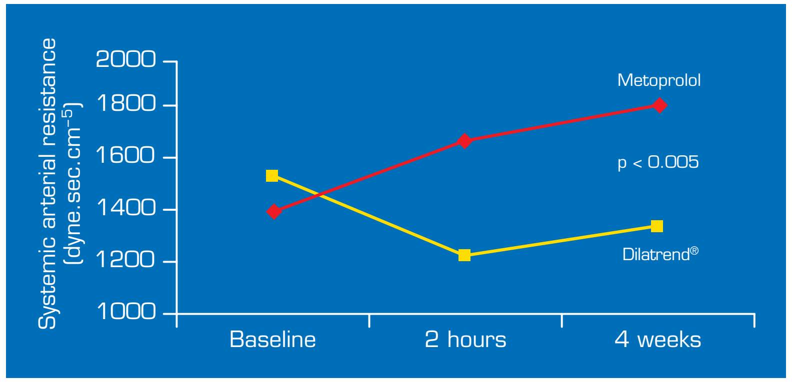


Figure 3: Dilatrend® reduced systemic arterial resistance following 4 weeks of therapy. This improvement was significantly better than metoprolol ($p < 0.005$).

Dilatrend® blocks both β_1 and β_2 receptors equally, reducing blood pressure and heart rate, and has no intrinsic sympathomimetic activity. Importantly, Dilatrend® also blocks α_1 receptors, inducing a dose-dependent vasodilatory effect that increases renal perfusion and eases up-titration in CHF.

No significant α_2 adrenergic receptor activity is displayed by Dilatrend®;[26, 27, 28] however, some evidence for calcium antagonist activity in higher doses has been found in isolated vessel preparations.[29, 30]

Haemodynamic effects

Dilatrend® has **beneficial and balanced haemodynamic effects** as a result of its combined α- and β-receptor antagonistic activity. The resulting effects are therefore very different from those of conventional β_1-selective β-blockers. The vasodilatory activity offsets the peripheral vasoconstriction and increase in total peripheral resistance (TPR) typically seen with selective β_1-blockade.

Some form of haemodynamic impairment, e.g. increased TPR, which underlies arterial hypertension, characterises many cardiovascular diseases. Increased TPR is also a typical feature of CHF, along with reduced stroke volume and decreased LV ejection fraction (EF). In contrast to conventional β_1-selective β-blockers, Dilatrend® reduces TPR.

Therefore, Dilatrend® does not compromise the blood supply to distinct organs and vascular beds such as kidneys, skeletal muscle, forearms, legs, skin, brain or carotid artery.[31, 32, 33, 34, 35, 36, 37] This is particularly true for renal blood flow.[38, 39]

Dilatrend® has consistently demonstrated maintenance of stroke volume (SV) and reduction of TPR, unlike conventional β_1-selective β-blockers, which generally reduce cardiac output and increase TPR. The fact that hypertensive patients treated with Dilatrend® only rarely experience the typical side-effects associated with conventional β_1-selective β-blockers, such as cold extremities [40] or early fatigue during physical activity,[41] may be due to the drug's beneficial haemodynamic effects.

A study measuring the physiological performance revealed that Dilatrend® did not affect maximal workload, time to reach it, or behavioural measures of perceived exertion.[42]

In patients with coronary artery disease, acute administration of Dilatrend® reduced the pulmonary capillary wedge pressure under exercise, in comparison with propranolol.[43]

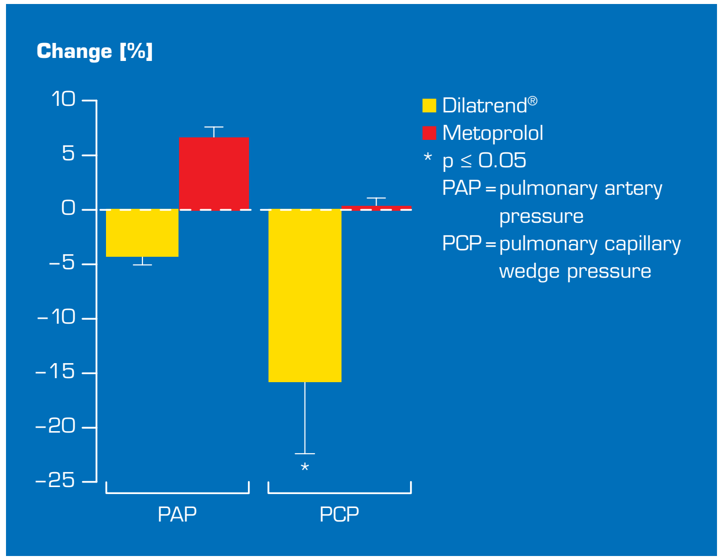


Figure 4: Acute reduction in preload induced by the oral administration of either Dilatrend® or metoprolol in patients with idiopathic dilated cardiomyopathy.[47]

Left ventricular filling pressures (reflected by pulmonary artery pressure, pulmonary capillary wedge pressure) and afterload (TPR) were also significantly reduced by Dilatrend® in patients with CHF.[19, 44, 45, 46, 47, 48, 49] The conventional β_1-selective β-blocker metoprolol, however, tended to increase pre- and afterload (Figure 4). The differences were more marked in acute as opposed to chronic administration.[19,47] Unloading of the heart in CHF patients is particularly important during the initiation of β-adrenergic therapy in order to offset the negative inotropic effects. Data from a CHF study have shown that Dilatrend®, but not metoprolol, improves renal haemodynamics in CHF patients.[24]

> Dilatrend® improves the haemodynamic imbalance typically seen in hypertension and chronic heart failure. The increase in peripheral vascular resistance characteristically seen in these diseases is counteracted by the vasodilating effects of Dilatrend®.

Other effects (independent of β-blocking activity)

Dilatrend® is a **potent antioxidant** and can reduce or inhibit the production of free oxygen radicals, further arresting the progression of cardiovascular disease. There is growing evidence that 'oxidative stress', an imbalance away from endogenous defence mechanisms towards production of reactive oxygen radicals, plays an important role in the progression of cardiovascular disease by damaging cellular components, leading to impaired organ function. These processes occur particularly during ischaemia and reperfusion. Many of these reactive oxygen radicals have been assumed to be important in the progression of atherosclerotic processes and the development of CHF.[50, 51, 52, 53, 54] Substances that reduce the production of these free radicals, or act as scavengers of them, may therefore arrest or slow the progression of cardiovascular disease.

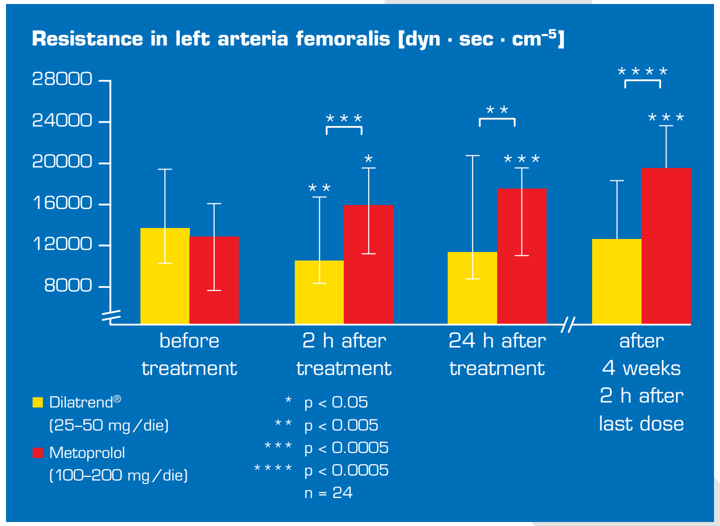


Figure 5: Resistance of the left femoral artery in 24 patients before and during treatment with either Dilatrend® or metoprolol.[36]

The antioxidant effect of Dilatrend® is not mediated by β-adrenergic receptors. This is demonstrated by the fact that both enantiomers have the same antioxidative potency, whereas only the L-enantiomer mediates the agent's β-antagonistic properties.[23, 55] Furthermore, BM 91.0228, a Dilatrend® metabolite that lacks β-antagonistic activity, is an even more potent antioxidant than the parent compound.[9, 56, 57, 58]

Dilatrend®'s antioxidant properties are linked to the carbazol moiety of the molecule. The clinical significance of Dilatrend®'s antioxidant properties have been outlined in trials.[59, 60, 61, 62]

Dilatrend® also prevents cell damage by inhibition of lipid peroxidation,[63, 64] and Dilatrend®'s capacity to protect against major organ damage by oxidative stress has been demonstrated in several investigations.[65, 66, 67, 68, 69, 70,71, 72, 73] The drug's influence on the New York Heart Association (NYHA) class (a functional and therapeutic classification for prescription of physical activity for cardiac patients), quality of life score and LV EF has been investigated in CHF patients in parallel with oxidative stress indices.[74] The correlation observed suggests that Dilatrend®'s antioxidant properties may contribute to its clinical benefits.

Dilatrend® also appears to act as an **anti-apoptotic agent**. Apoptosis is considered to be the major cause of cardiac muscle death in ischaemia and reperfusion and may contribute significantly to the progression of cardiovascular disease.[75, 76, 77] Evidence for Dilatrend®'s reduction of oxidative stress and apoptosis in CHF patients has been elucidated from clinical data from investigations using *ex vivo* techniques.[77]

Dilatrend® is a **potent antiproliferative agent**, primarily on vascular smooth muscle cells, which contribute greatly to the formation of atherosclerotic plaques. The agent inhibits vascular smooth muscle cell proliferation in the low micromolar range. This inhibitory effect is much less pronounced with propranolol, and is not observed with celiprolol, sotalol or labetalol.[78] Dilatrend® also exhibits a more pronounced antiproliferative effect than other β-blockers on human vascular smooth muscle cells generated from saphenous vein and restenotic lesions.[79]

Mitogen-induced mesangial cell proliferation in the glomerula, which may have a role in the progression of renal failure, as well as proliferation of human fibroblasts, is also inhibited by Dilatrend®.[12, 80] This observation may explain some of Dilatrend®'s renal protective effects, observed in other investigations.

In a rat model of percutaneous transluminal coronary angioplasty (PTCA), Dilatrend® inhibited neointima formation after carotid ballooning by 84%.[81] Prevention of restenosis after coronary atherectomy, however, was not demonstrated in a double-blind, controlled clinical trial.[82]

Dilatrend® possesses strong antioxidative properties, reducing the amount of free oxygen radicals in the oxidative stress that occurs during ischaemia and perfusion. Anti-apoptotic effects are also evident. In experimental models, Dilatrend® possesses strong antiproliferative properties on vascular smooth muscle cells, which may slow down progression within the cardiovascular continuum.

6. Dilatrend®: Excellent Efficacy and Safety across the Cardiovascular Continuum

(i) Highly Effective in Arterial Hypertension

Dilatrend® **effectively lowers blood pressure** in hypertensive patients, with positive effects on the overall cardiovascular risk profile. Hypertension is one of the most critical risk factors associated with the development of cardiovascular and cerebrovascular disease. Chronic high blood pressure predisposes towards MI, stroke, CHF, LV hypertrophy and renal failure. Concomitant risk factors, such as type 2 diabetes mellitus and dyslipidaemia can contribute to the progression of these events, so effective antihypertensive therapy should not only lower the blood pressure, but should work to prevent these concomitant factors, or should at least have a neutral effect on them. In studies with various antihypertensive agents, the reduction of blood pressure reduces the incidence of stroke by about 40%; the incidence of MI and CHF, however, is reduced by about 20% in comparison.[83] This suggests that concomitant risk factors may be more important in the overall risk for cardiac events. Some of these risk factors are negatively influenced by conventional β_1-selective β-blockers.

Dilatrend® is a highly effective antihypertensive agent, lowering blood pressure without the negative effects (e.g. decrease in peripheral perfusion) associated with conventional β_1-selective β-blockers.

Rapid onset of antihypertensive action

Dilatrend® has a **rapid onset of antihypertensive action** compared with conventional β_1-selective β-blockers. Reduction in blood pressure in hypertensive patients has been noted immediately following the drug's first administration.[31, 84, 85, 86, 92] The peak effect of each dose following a single administration occurs at about 2 to 4 hours, and the cumulative maximum antihypertensive effect is achieved within a few weeks of the initiation of therapy (Figure 6).

Additionally, there is no evidence that Dilatrend®'s hypotensive effect attenuates with chronic treatment (> 3 months). Consequently, there is no evidence of tachyphylaxis or the development of tolerance.[22, 41, 60, 87]

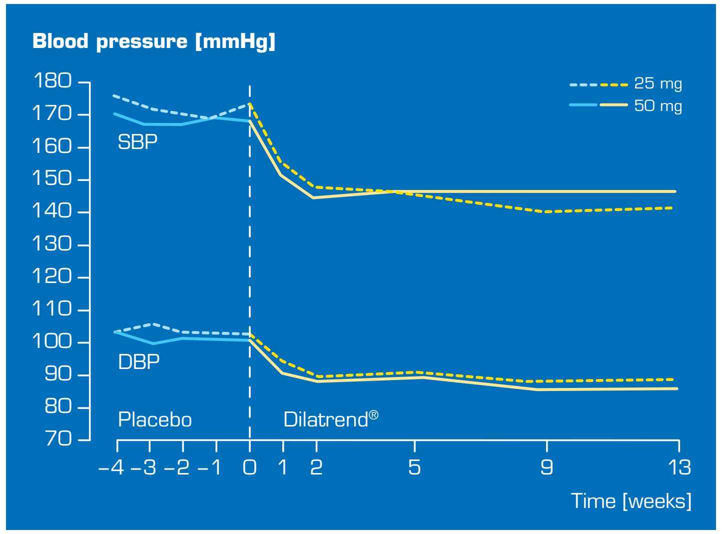


Figure 6: Reduction in mean systolic and diastolic blood pressure in patients with essential hypertension under therapy with Dilatrend® 25 mg or 50 mg once daily.[101]

24-hour control with preservation of circadian rhythm

Dilatrend® **preserves and maintains the physiological circadian rhythm** of blood pressure during therapy (Figure 7).[22, 85, 88, 89, 90] Blood pressure monitoring at trough drug levels (24 hours after administration of the last dose) consistently show that blood pressure is still reduced at this time. Dilatrend® also reduced patients' heart rate equally effectively at night as well as during the day.[92] This 24 hour regulation of blood pressure ensures control even at times associated with increased risk of cardiovascular events. A once-daily dosing schedule is therefore recommended and has been approved by most health authorities.

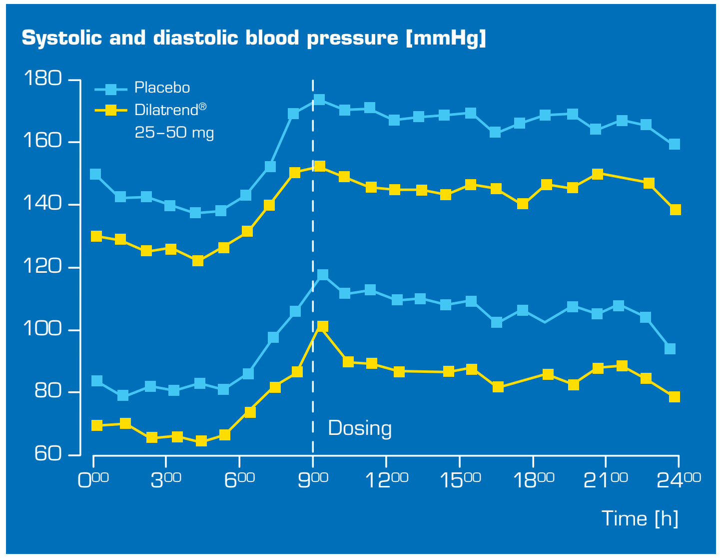


Figure 7: Effects of Dilatrend® on the 24-hour blood pressure profile as compared to placebo.[88]

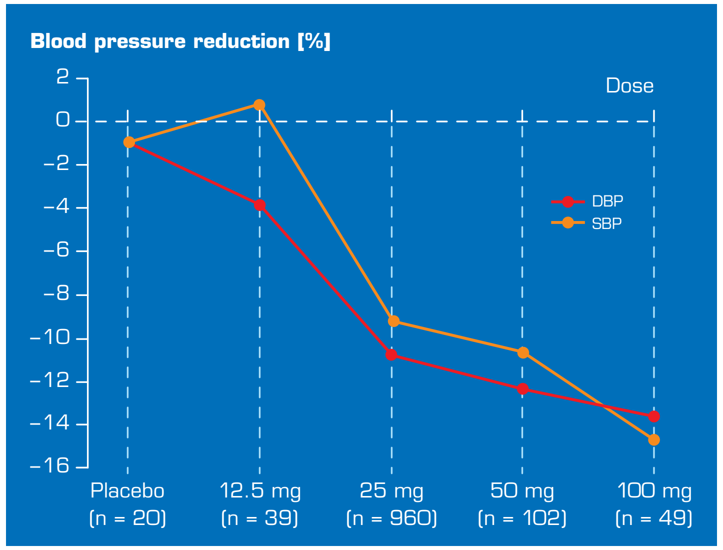


Figure 8: Dose response curve of the reduction in systolic and diastolic blood pressure induced by Dilatrend® (once daily). (Results of a meta-analysis of 36 studies comprising a total number of 1,170 hypertensive patients).[91]

Dilatrend®'s antihypertensive effect is sustained over 24 hours with once-daily dosing, and circadian rhythm is preserved.

Dose-dependent efficacy

Dilatrend® exerts **dose-dependent antihypertensive efficacy**.[85] A meta-analysis of 36 Dilatrend® studies demonstrated a clear dose-response effect between 25 mg and 100 mg (Figure 8).[91] The meta-analysis also revealed that systolic and diastolic blood pressures were both reduced to the same extent. Initiation of Dilatrend® at 12.5 mg once daily for 2-3 days, progressing to 25 mg once daily, is recommended; the lower dose may be sufficient to control hypertension in some patients during chronic treatment, particularly in the elderly.

A dose of 25 mg Dilatrend® once daily is sufficient for control of hypertension in most patients. This was confirmed by a multicentre study in 3,328 patients; of the patients who received 25 mg Dilatrend®, 75% had adequately controlled blood pressure.[93] Two other post-marketing surveillance studies revealed similar results,[94, 95] and there were no obvious differences in efficacy and tolerability between younger and elderly patients.[93, 96]

Clinical trials in Japan have revealed that lower doses (normally 10 mg once daily) may be appropriate for the treatment of Japanese hypertensive patients.[33, 97, 98, 99, 100]

> The recommended Dilatrend® dose of 25 mg once a day controls blood pressure in the majority of patients.

High responder rates

Therapy with Dilatrend® shows consistently high response rates. Responder rates of over 80% have been reported with once daily doses of 25 mg Dilatrend®;[101] similar rates have been confirmed in a number of studies with various patient populations.[86, 102, 103, 104, 105] There is no evidence that the responder rate is age-dependent.[93,96] Dilatrend® has been favourably compared to other β-blockers.

In 8 of 20 patients enrolled in a comparison between Dilatrend® and metoprolol, 200 mg/day metoprolol did not sufficiently reduce blood pressure,[106] but after switching to Dilatrend® the patients responded with a further reduction in blood pressure.

Effective control of blood pressure during exercise

Dilatrend® **effectively controls blood pressure**, reduces the increased heart rate induced by exercise, and also inhibits the increase in systolic blood pressure (Figure 9).[90, 92, 106, 107, 108, 109, 110] The exercise capacity of hypertensive patients has also been observed to increase over time with Dilatrend® therapy.[108]

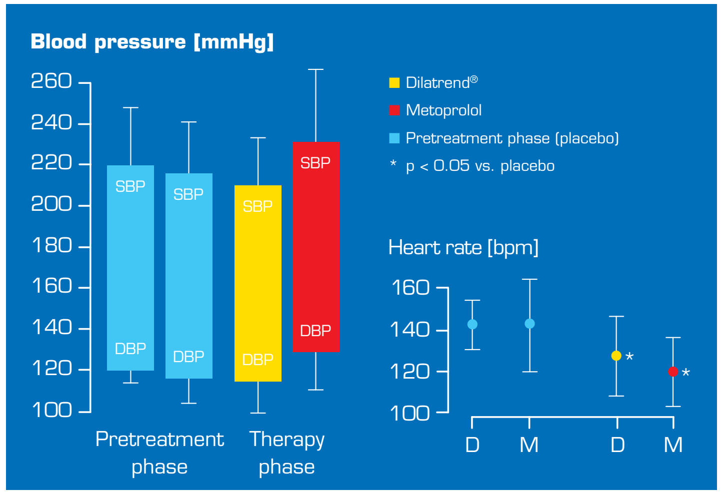


Figure 9: Effect of Dilatrend® and metoprolol on trough systolic and diastolic blood pressure and heart rate during maximum work load.[90]

Effective, with good safety, in combination therapy

Dilatrend® is **effective, with a good safety profile when used in combination therapy** with other antihypertensive agents in instances where blood pressure cannot be adequately controlled by monotherapy. Addition of calcium antagonists or angiotensin-converting enzyme (ACE) inhibitors to Dilatrend® therapy should initially be by small doses, in order to prevent any undesirable first dose effects. The same is true when Dilatrend® is given to dehydrated patients or to those treated with high doses of diuretics. Complete down-titration of conventional β_1-selective β-blockers is not required when patients are switched from these to Dilatrend®.

> Response rates with Dilatrend® are high, and consistent across age groups. Dilatrend® is effective in counteracting the physiological effects of exercise and can be safely used in combination with other antihypertensive agents.

Advantages over other antihypertensive agents

Versus conventional β-Blockers

β-receptor blocking agents without ISA have an unequivocally proven benefit in primary prevention of cardiovascular complications in hypertension and, in particular, stroke. This has been established in a variety of epidemiological studies for diuretics and β-blockers, and has led the Food and Drug Administration (FDA), the European, and most National Societies for Hypertension to recommend β-blockers amongst first-line treatment.

Doctors have been hesitant to initiate conventional β-blockers because of their perceptions of tolerabiltiy, e. g. cold extremities, tiredness and fatigue, impairment of physical capacity and, in particular, unfavourable effects on haemodynamics and on lipid and glucose metabolism. It should be emphasised again that hypertension is characterised by an increase in peripheral vascular resistance which is not reversed by conventional β_1-selective β-blockers.

Dilatrend® is distinct from conventional β-blockers, because of its multiple adrenergic blockade leading to the reduction or elimination of side-effects such as:

- Increases in peripheral vascular resistance
- Cold extremities
- Negative influences on cardiac function (e.g. ejection fraction, cardiac output)
- Reductions in renal perfusion
- Negative influences on lipid disorders
- Negative influences on glucose metabolism such as insulin sensitivity
- Negative influences on physical capacity

The blood pressure-reducing effect of Dilatrend® was compared in a variety of clinical studies with conventional β-blockers. A considerable number of these studies were well-designed and well-controlled trials. In most of these studies Dilatrend® was compared with metoprolol or atenolol. In some other studies, propranolol, pindolol or labetalol were used as comparative compounds. In all these studies, Dilatrend® has been shown to be at least as effective as conventional β_1-selective β-blockers with respect to blood pressure reduction. In some studies, Dilatrend® decreased the blood pressure more effectively than the comparative medication. For example, Franz *et al.* (1992)[106] showed that patients whose blood pressure could not be sufficiently controlled by metoprolol reached normal values after switching over to Dilatrend®. Nevertheless, the hypotensive activity is not the major difference between Dilatrend® and conventional β-blockers. Therefore, two other studies will be discussed in more detail in order to show the difference between Dilatrend® and conventional β-blockers.[21, 90, 111, 112, 113]

Haemodynamic effects

Weber *et al.* (1996)[36] compared the haemodynamic effects of Dilatrend® and metoprolol in a controlled study of 24 patients with mild to moderate essential hypertension. Both compounds reduced blood pressure and heart rate equally and significantly. However, whereas metoprolol induced a decrease in cardiac output, this parameter remained unchanged with Dilatrend® treatment. In addition, along with the reduction of blood pressure, a decrease in systemic vascular resistance was calculated for Dilatrend®, whereas the systemic vascular resistance increased in the metoprolol group. The most striking difference was seen in local vascular resistance of the lower legs. Whereas metoprolol dramatically increased the vascular resistance in the skeletal muscles, such an effect was not observed with Dilatrend®. This may explain why patients feel exhausted during physical exercise when treated with conventional β-blockers, but not with Dilatrend® (note that physical capacity was not measured in this haemodynamic study).[22, 43, 53, 74, 104, 114, 115, 116, 117]

Versus ACE inhibitors/angiotensin receptor blockers

The big studies with ACE inhibitors cover, in particular, their benefits in the treatment of CHF (CONSENSUS I, SOLVD, SAVE) and post-myocardial infarction (AIRE). The benefits for patients with high cardiovascular risk has also been demonstrated (HOPE). Conclusions of a preventive effect on complications of hypertension (such as stroke) can be drawn, although only indirectly. However, ACE-inhibitors have not been shown to be effective as anti-anginal drugs. This is important as more than 30% of hypertensive patients also have stable coronary artery disease.

ACE inhibitors are given frequently to hypertensive patients with concomitant CHF. Neutrality on lipid and carbohydrate metabolism is a further asset of this therapeutic class.

But:

- ACE inhibitors have a low response rate of 50-60% if they are not used concomitantly with diuretics.
- A rather frequent side effect is the ACE-inhibitor-induced cough, which implies withdrawal from the drug when occurring.

Caution is advised in patients with higher grade renal impairment, because renal filtration under ACE inhibition can decrease spontaneously. This is of particular importance for those ACE inhibitors that are eliminated predominantly by the kidney. For these compounds, the dose must be adjusted to the renal function.

Dilatrend® has been compared with
1. Captopril [87]
2. Enalapril [41, 118]
3. Perindopril [119]

In all these well-controlled studies, the blood pressure response to Dilatrend® was at least as effective as with the ACE-inhibitors. Of special interest was that side-effects do not differ markedly. In particular, quality of life during the 5 months' hypertensive therapy was assessed by means of the Göteborg Quality of Life Questionnaire[41]. Except cough, which was significantly more frequent in the enalapril-treated patients, there were no significant differences in all other aspects, including sexual life and physical activity. Overall, patients maintained quality of life during treatment, indicating the favourable tolerability of both treatment regimens. The other comparative study focussed more on psychological aspects.[118] All three agents were well-tolerated. The data revealed that Dilatrend® reduced both 'state anxiety' and 'trait anxiety' more than the comparative drug. Importantly, Dilatrend® did not reduce the proportion of patients satisfied with their sexual life.

The study of Giugliano *et al.*[119] focussed on endothelial dysfunction observed in hypertensive patients. Indeed, both perindopril and Dilatrend® improved the endothelial function to nearly the same extent.[41, 87]

The value and position of angiotensin receptor blockers (ARBs) as first-line treatment in hypertension still needs to be established. Despite recently published data from the LIFE study the final position of ARBs needs to be established.[120]

Versus calcium antagonists

Calcium channel blockers (calcium antagonists) have a blood pressure-lowering effect due to their vasodilating activity. In particular, dihydropyridines - mostly used for the treatment of hypertension - have been shown to stimulate the neurohormonal system (reflex tachycardia, leg oedema). This effect is believed to be less pronounced with newer long-acting members of this class, but these side-effects are still evident in clinical practice.

Krönig *et al.* (1990)[86] compared Dilatrend® with nitrendipine in a double-blind controlled study in elderly patients. Similar effects on blood pressure reduction were observed during the 3 month treatment period (Figure 10). However, only Dilatrend® reduced the heart rate. Similar findings were observed in further well-conducted trials comparing Dilatrend® with nifedipine.[121, 122, 123, 124] Juttmann *et al.* (1992)[121] showed that the combination of Dilatrend® and nifedipine is more effective than either treatment alone. Overall, all the studies demonstrate that the antihypertensive efficacy of Dilatrend® at doses of 25-50 mg o.d. is comparable to that of nifedipine at 20 mg b.i.d. Only Dilatrend® reduced the heart rate, whereas nifedipine produced a slight increase in heart rate, at least at the beginning of therapy. This increase may have some impact on the long-term prognosis of patients.

In a comparative trial, Albergati *et al.* (1992)[122] showed that neither nifedipine nor Dilatrend® impaired glucose metabolism in patients. This was determined using glucose clearance in the blood after challenge with an oral dose of 75 g glucose.[86, 121, 122, 123, 124]

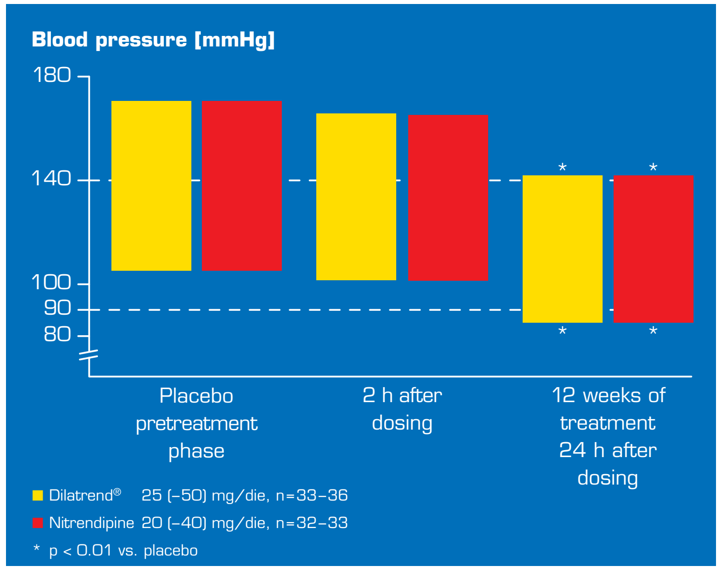


Figure 10: Systolic and diastolic blood pressure levels after short- and long-term (4-12 weeks) therapy with either Dilatrend® or nitrendipine. A doubling of the initial dose (25 mg Dilatrend ®once daily) was allowed after 4 weeks of treatment; after 12 weeks of treatment 88% and 84% of the patients of the Dilatrend® group or the nitrendipine group, respectively, received the initial dose.[86]

Versus diuretics

Diuretics and β-blockers have been shown in large-scale trials to reduce the risk of long-term complications. In particular, they are able to prevent stroke by about 40% and cardiac events by about 20%. They also reduce cardiovascular mortality rate. Even though the ARB losartan has recently been shown to have a higher preventive effect than atenolol,[120] there is currently no doubt that β-blockers and diuretics are first-line medications in the treatment of hypertension.

Also, diuretics are the first choice partner for all other antihypertensive agents, enhancing their activity.

Diuretics (in particular loop diuretics) have been employed widely for more than 30 years as basic medications for treatment in CHF and (in particular thiazides) in hypertension. Despite the development of newer agents for treating both conditions, diuretics continue to be utilised and are among the most commonly prescribed drugs in the world.

Dilatrend® displays comparable efficacy to other antihypertensive agents, with distinct advantages such as reduction of heart rate. Dilatrend® can be safely combined with other antihypertensive agents.

Effective and well-tolerated in patients with concomitant disorders

Impaired renal function

Dilatrend® is an effective and well-tolerated agent in patients with renal impairment, with no need for dose adjustment; this has been demonstrated in a number of studies.[38, 98, 114] It is cleared predominantly by hepatic metabolism, with minimal renal excretion. Its efficacy has also been shown in chronic renal failure, haemodialysis and post-renal transplant.[111, 125, 126, 127] In dialysis patients, Dilatrend® gradually reduces blood pressure both during dialysis itself and between periods of dialysis, with blood pressure lowering effects comparable to those in patients with normal renal function. In chronic treatment with Dilatrend®, the autoregulatory blood supply is preserved and glomerular filtration is unchanged (Figure 11).[32, 128]

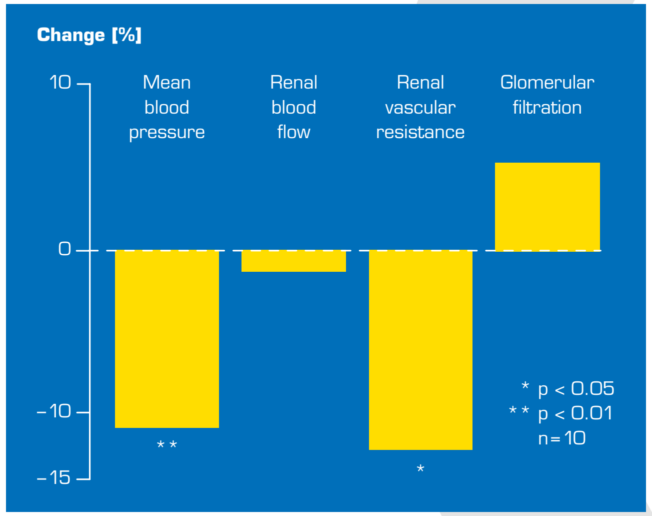


Figure 11: Effect of 50 mg Dilatrend® once daily on renal function in patients with essential hypertension. Measurements were obtained before the morning administration after 4 weeks of therapy.[32]

Treatment group	Dilatrend® monoth.	ACE monoth.	β Blocker monoth.	Ca Ant monoth.	Diuretic monoth.	Other monoth.
n	4014	592	586	470	165	173
MAU-pos. at baseline	1525 (38%)	221 (37.3%)	142 (24.2%)	159 (33.8%)	52 (31.5%)	45 (26%)
MAU-neg. after 3 months	975 (63.9%)	103 (46.6%)	75 (52.8%)	70 (44%)	29 (55.8%)	20 (44.4%)

MAU = microalbuminuria

Table 1: Effect of different antihypertensive drugs on microalbuminuria in non-diabetic hypertensive patients.[131]

Dilatrend® reduces microalbuminuria (MAU), an early marker of renal injury.[129] MAU is reduced by Dilatrend® in a greater proportion of hypertensive patients than by selective β_1-blockers.[40] Dilatrend® is at least as effective as ACE inhibitors or calcium antagonists (Table 1).[130, 131]

Dilatrend® is not eliminated during dialysis since it does not cross the dialysis membrane, most probably because of its high plasma protein binding. In a comparative trial in haemodialysed patients, Dilatrend® was better tolerated and reduced blood pressure more effectively than slow-release nifedipine.[132]

Following renal transplantation, Dilatrend® reduces blood pressure to normal values. Plasma concentrations of cyclosporin A were not increased by Dilatrend® at trough.[127]

Left ventricular hypertrophy

Dilatrend® is effective at lowering blood pressure in hypertensive patients with concomitant left ventricular hypertrophy (LVH) and results in regression of LVH, which is beyond the effect achieved by blood pressure reduction alone. LVH is a predisposing risk factor for further cardiovascular complications, such as arrhythmias and the development of CHF, in hypertensive patients. Various techniques have been used to assess LV mass, but the most consistent finding has been that both the thickness of the wall or the septum is reduced by 12-15% after about six months of treatment.[60, 110, 112, 133, 134]

The data obtained from hypertensive patients fit those generated from patients with coronary artery disease, where reduction of the end-systolic and end-diastolic volumes, prevention from cardiac remodelling or improvement of the spheric indices of patients with CHF have been observed. Treatment of patients suffering from hypertension and LVH for 10 months with Dilatrend® not only reduces blood pressure at rest and exercise and induced regression of LVH, but also significantly reduces supraventricular and ventricular arrhythmias, particularly tachycardic episodes.[110]

Diabetes

Dilatrend® is an effective and well-tolerated treatment for hypertensive patients with diabetes. It does not impair glucose metabolism, unlike conventional β_1-selective β-blockers. This is a result of the combined metabolic effects of β- and α_1-blockade.[115]

The metabolic effects of Dilatrend® have been investigated in a variety of clinical studies. In a study of hypertensive patients with type 2 diabetes mellitus, Dilatrend® had no adverse effects on fasting, postprandial glucose concentration or glycosylated haemoglobin A_1, and there was no need to adjust the dose of the anti-diabetic agents.[103]

Dilatrend® improves insulin sensitivity, unlike metoprolol (Figure 12).[116] Dilatrend® had no adverse effects on glucose tolerance or insulin sensitivity, as demonstrated by comparison with nifedipine in hypertensive patients with type 2 diabetes mellitus, where neither agent had any affect on glucose tolerance.[122] This was confirmed by a comparison study of Dilatrend® and metoprolol, which enrolled hypertensive prediabetic patients with impaired insulin sensitivity (syndrome X, Figure 12). After 3 months of treatment, significant differences favouring Dilatrend® were demonstrated, measured by normoglycemic hyperinsulinaemic clamp techniques.

Insulin resistance is also a frequent finding in CHF patients, even in the absence of diabetes mellitus. In a recently published prospective, randomised, double-blind study versus placebo, Dilatrend® was shown to have no negative impact on insulin sensitivity.[135]

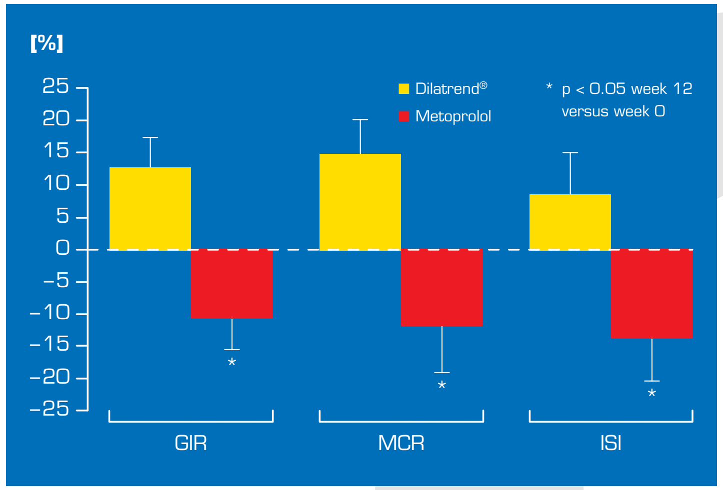


Figure 12: Relative changes in insulin sensitivity in the two treatment groups receiving Dilatrend® or metoprolol. Comparison of baseline versus follow-up at 12 weeks. (GIR = glucose infusion rate; MCR = metabolic clearance rate; ISI = insulin sensitivity index.)[116]

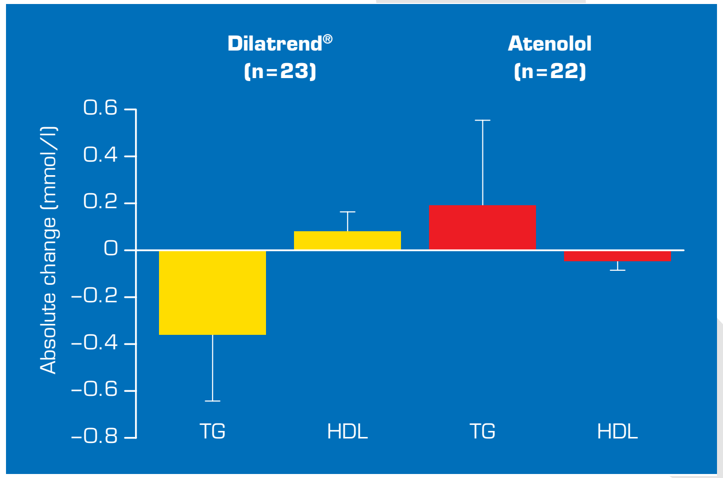


Figure 13: Effect of Dilatrend® and atenolol on lipids in diabetic patients with hypertension. (TG = triglycerides; HDL = high-density lipoproteins.)

Lipid disorders

Dilatrend® is effective and well-tolerated in hypertensive patients with impaired lipid metabolism. In contrast to other β-blockers, it does not adversely affect lipid metabolism, and even shows favourable effects on serum lipids over time (Figure 13). This reduces the incidence of LDL cholesterol deposition in arterial cell walls in atherosclerosis. In principle, beneficial results on insulin sensitivity and plasma lipid profile were observed in a double-blind controlled study of Dilatrend® versus atenolol. Dilatrend® increased the serum concentration of HDL cholesterol and reduced LDL cholesterol and triglycerides, whereas the conventional β_1 selective β-blocker atenolol had the opposite effects.[60]

In a double-blind study in hypertensive patients with CAD treated with Dilatrend®, atenolol or doxazosin, substantial differences were observed be-tween the blood lipid levels with Dilatrend® and atenolol (Table 2).[136] In a double-blind, controlled trial in patients with dyslipidaemia, both Dilatrend® and captopril showed favourable effects on serum lipids after 6 months of treatment (Figure 14).[87] Dilatrend® does not affect plasma concentrations of total cholesterol, its sub-fractions or triglycerides, as shown by a one-year open clinical trial[102] and a meta-analysis of 36 studies.[91] This is unlike the experiences with conventional β_1-selective β-blockers.[137] Other studies have also observed reductions in high concentrations of lipids and neutral effects on normolipemic individuals.[99,100]

The reason for Dilatrend®'s beneficial effect on the plasma lipid profile are its α_1-blocking properties as well as inhibition of α-lipase.[113]

	Dilatrend® pre	Dilatrend® post	Atenolol pre	Atenolol post
HDL cholesterol:				
> 40 mg/dl	49 ± 6	48 ± 8	50 ± 7	41 ± 6*
< 40 mg/dl	36 ± 4	37 ± 6	35 ± 6	30 ± 4*
Triglycerides:				
> 150 mg/dl	236 ± 42	224 ± 30	220 ± 18	224 ± 20*
< 150 mg/dl	121 ± 24	129 ± 13	124 ± 19	136 ± 18*

* p < 0.05 versus before treatment

Table 2: Effects of Dilatrend® and atenolol treatment on serum lipids in 78 hypertensive patients with ischaemic heart disease and stable angina during exercise, at baseline and after 6 months of treatment.[136]

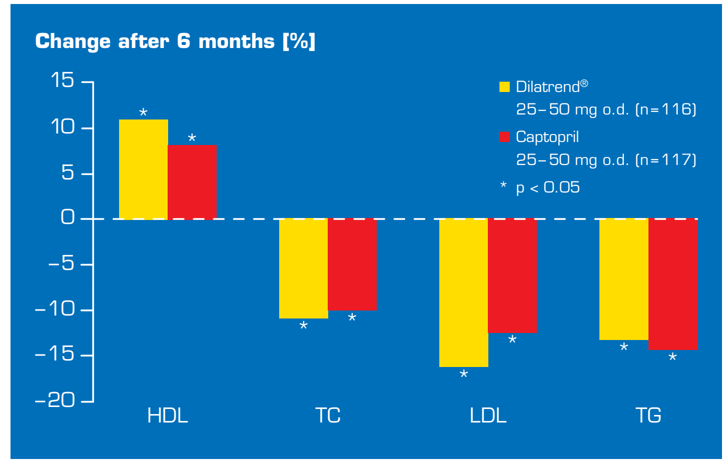


Figure 14: Influence of Dilatrend® (25-50 mg) or captopril (25-50 mg) on serum lipid concentrations in more than 220 patients with essential hypertension and dyslipoproteinaemia (HDL cholesterol < 40 mg/dl, total cholesterol (TC) 200-350 mg/dl, triglycerides (TG) 200-500 mg/dl). The serum lipid concentrations were determined at baseline (at the end of a 4-week placebo wash-out phase) and after 6 months of therapy. All patients received a standard diet at the onset of the placebo phase.[87]

Cerebrovascular ischaemia

Dilatrend® has no adverse effects on cerebral blood flow (CBF) in cerebrovascular ischaemia, displaying an excellent safety profile for hypertensive patients with this disorder. Cerebrovascular ischaemia is present in a significant number of hypertensive patients due to the progression of atherosclerosis and other reasons.

In a double-blind, crossover study in hypertensive patients, propranolol tended to decrease CBF, whereas Dilatrend® had no effect.[35] Also, Dilatrend® did not reduce CBF in hypertensive patients with no history of stroke.[34] CBF autoregulation was maintained; the flow reserve was shifted to lower pressure values according to the blood pressure-lowering effect of Dilatrend®. In elderly patients, Dilatrend® not only reduced blood pressure, but also increased carotid arterial flow (Figure 15).[33] There was also an improvement in haemorrheological parameters, such as the ability of erythrocytes to aggregate and deform. Dilatrend® also inhibits platelet aggregation[138] and increases the fibrinolytic index.[136]

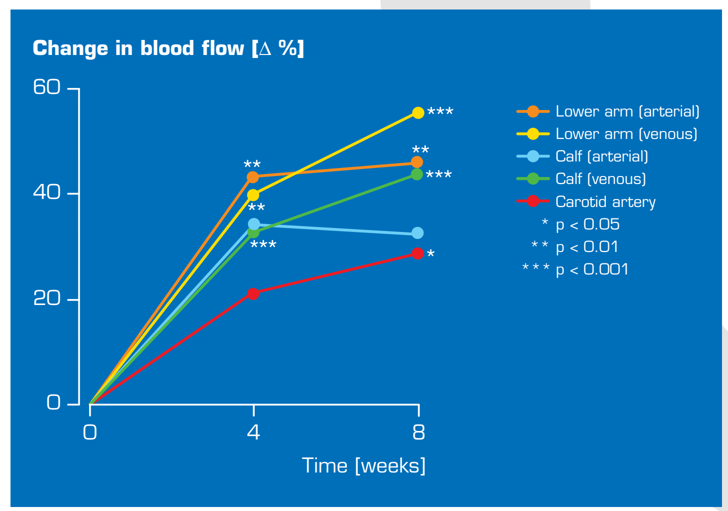


Figure 15: Increases in peripheral blood flow in the lower arm, calf and common carotid artery in 11 elderly Japanese hypertensive patients receiving Dilatrend®.[33]

Peripheral vascular disease

Dilatrend® improves lower limb perfusion in peripheral vascular disease, which is also a significant factor in a number of hypertensive patients. For example, in a study of hypertensive patients with peripheral occlusive vascular disease (stages II-III), Dilatrend® increased walking distance and improved the pulse leg/arm index of patients after 30 days of treatment.[139] However, Dilatrend® is not recommended for administration in advanced stages of peripheral arterial disease, due to limited experience with such patients.

Dilatrend® is effective and well tolerated in hypertensive patients with concomitant diseases:

- regression of left ventricular hypertrophy
- no adverse effects on glucose metabolism or insulin sensitivity in diabetes
- favourable effects on plasma lipid profile
- improvement of limb perfusion and walking distance in peripheral vascular disease
- no decrease in renal perfusion
- no need for dose adjustment in patients with impaired renal function
- reduction of microalbuminuria in hypertensive patients

Quality of life

Dilatrend® **improves quality of life parameters**, as demonstrated in two large, double-blind, controlled trials comparing Dilatrend® with enalapril.[41,118] The first study focused on psychological aspects of treatment with Dilatrend®, atenolol or enalapril. Regarding sexual function and activity, Dilatrend® compared favourably versus the ACE inhibitor enalapril as well as versus atenolol in both studies, and had no negative impact on sexual life and activity. The data showed that Dilatrend® reduced state anxiety and trait anxiety more than atenolol or enalapril, with no significant differences observed for any other factors.[118]

In the second study, using the Göteborg Quality of Life Questionnaire, no significant differences were found for the various quality of life factors between the two compounds, except cough, which was more frequent in the enalapril group. A similar pattern of changes in quality of life parameters was observed between the two groups, in line with the favourable tolerability of both treatment regimens.[41]

(ii) Effective in Coronary Artery Disease

Dilatrend® demonstrates **anti-ischaemic and anti-anginal efficacy** in patients with coronary artery disease, the 'second stage' of the cardiovascular continuum. Its combined β_1/β_2 receptor blocking properties and vasodilation by α_1 blockade reduce oxygen demand by reducing heart rate, myocardial contractility, myocardial wall tension and myocardial afterload (Table 3).

Many studies have investigated Dilatrend® in MI models, progression of atherosclerosis and organ protection, but clinical data on some of these aspects is limited. However, Dilatrend®'s well-documented antioxidant and antiproliferative qualities are likely to have some additional benefit in patients with coronary artery disease by slowing down the atherosclerotic processes.

Dilatrend® has, due to its comprehensive adrenergic blockade and antioxidant effects, superior efficacy in patients with coronary artery disease and chronic angina pectoris.

Effective in stable angina

Anti-anginal efficacy has been observed consistently in all the placebo-controlled trials and actively controlled trials as well as in daily practice.[46, 95, 140, 141, 142, 143, 144, 145]

Dilatrend®'s effect on silent myocardial ischaemia, particularly common in elderly and diabetic patients, has been evaluated in a placebo-controlled trial using 24-hour Holter monitoring.[142] Dilatrend®-treated patients experienced a significant reduction in the number and duration of ischaemic periods.

Property	Physiological effect(s)	Therapeutic effect(s)
β blockade	Reduction of heart rate	Reduction of myocardial oxygen demand
α blockade	Vasodilation Reduction of total peripheral resistance (long-term therapy)	Reduction of myocardial oxygen demand Reduction of peripheral resistance
Antioxidant effect	Prevention of ischaemic damage	Prevention of anginal attacks, prevention of adverse cardiac events in myocardial infarction
Antiproliferative effect	Slowing of atherosclerosis and coronary artery disease	Improvement of myocardial blood supply
Prevention of platelet aggregation and thrombosis	Prevention/relief of coronary artery obstruction	Improvement of myocardial blood supply; reduction of myocardial ischaemia; prevention of adverse cardiac events in myocardial infarction

Table 3: Pharmacological properties of Dilatrend and relationship to therapeutic efficacy in coronary artery disease.

(See CHRISTMAS Trial, p43.)

Dose-dependent anti-anginal efficacy

Dilatrend® exerts a dose-dependent anti-anginal effect that was first demonstrated as early as 1985.[143] This has since been confirmed in a number of subsequent clinical investigations.

Dilatrend®'s anti-ischaemic and anti-anginal effects have been investigated in a number of trials, where standard methods for anti-anginal efficacy were used in most cases: standard exercise tests; total exercise time (TET); time to onset of angina; and, time to 1 mm-ST-segment depression. These evaluations were made before and after treatment. In addition, the double product (systolic blood pressure x heart rate) was determined as an estimate of the myocardial oxygen consumption. The number of anginal episodes (analysed by ECG Holter monitoring, or by a diary) and consumption of acute nitrates were occasionally monitored as a measure of the long-term anti-anginal effects.

Dose-response relationship studies have shown that 50-100 mg b.i.d. Dilatrend® exerts anti-anginal effects.[144, 145] Three smaller doses (12.5, 25 and 50 mg b.i.d.) were used to assess the dose-response relationship for Dilatrend®'s anti-anginal effects in comparison with placebo. Dose-dependent activity was observed on the basis of exercise capacity, number of angina-free days, and number of angina attacks. The medium and high doses of Dilatrend® demonstrated significant anti-anginal efficacy, whereas the low dose did not. There were no significant differences in side-effects between the Dilatrend® and placebo-treated patients, except for dizziness and hypotension; the side effects were not dose-dependent.[145]

The doses required for anti-anginal efficacy are somewhat higher than those required for antihypertensive efficacy. This is because, unlike in hypertension, the α_1-blockade only contributes to Dilatrend®'s anti-anginal efficacy to a small extent, and the combined β_1/β_2 blockade is the key contributor to its anti-ischaemic and anti-anginal efficacy. The same deduction can be made from the results of a controlled study in hypertensive patients with concomitant coronary artery disease treated with Dilatrend®, the β-blocker atenolol or the α_1 antagonist doxazosin. All three compounds induced a similar blood pressure response, but anti-anginal activity was only observed with Dilatrend® and atenolol, not with doxazosin.[136]

Dilatrend®'s efficacy in stable angina is dose-dependent, without dose-dependent side effects.

Advantages over other anti-anginal agents

Dilatrend® has **advantages over other agents in the treatment of stable angina**. It has been investigated in comparison with other anti-anginal drugs in a variety of clinical trials, many of which have been referred to in a review article.[146]

Versus conventional β_1-selective β-blockers

Dilatrend® is at least as effective as conventional β_1 selective β-blockers in stable angina, and generally lower doses of Dilatrend® are required to have the same effect. A large, multicentre, double-blind, randomised trial compared the efficacy and safety of Dilatrend® (25 or 50 mg b.i.d.) with metoprolol (50 or 100 mg b.i.d.) in patients with stable angina.[147] Good anti-anginal efficacy was demonstrated by both drugs, with no difference in efficacy and safety between younger and elderly patients (≥ 65 years). The lower and higher doses were equally well tolerated. However, Dilatrend® appeared to show a superior anti-ischaemic efficacy to metoprolol, reflected by a greater improvement in time to 1 mm-ST-segment depression. The reduction in pressure-rate product at peak exercise was also greater with Dilatrend® than with metoprolol.

The anti-anginal efficacy of Dilatrend® in comparison with atenolol was also investigated in 12 patients with stable effort angina and a positive stress test. After single administration, 50 mg Dilatrend® exerted approximately the same anti-ischaemic and anti-anginal efficacy as 50 mg atenolol.[148]

Patients with chronic stable angina were treated over a period of 6 months with either Dilatrend® (25 mg b.i.d.) or a combination of propranolol (80 mg b.i.d.) and slow-release isosorbide dinitrate (20 mg b.i.d.).[149] Dilatrend® was significantly more effective at trough, even though the propranolol/isosorbide dinitrate combination appeared to be slightly more effective on the first day of treatment. This may possibly be due to the development of tolerance to the organic nitrate.

Dilatrend® (50 mg/day) was compared to atenolol (100 mg/day) in a 6 month study in patients with co-existing hypertension and chronic stable angina.[146] Both agents reduced blood pressure and the number of ischaemic episodes, and increased the time to 1 mm-ST-segment depression.

Versus calcium antagonists

Dilatrend® also displays greater efficacy than calcium antagonists in the treatment of stable angina. In a multicentre, double-blind, controlled study using 25 mg b.i.d. Dilatrend® and 120 mg t.i.d. verapamil in the treatment of chronic stable angina,[150] both compounds increased TET (total exercise time), time to angina and time to 1mm-ST-segment depression in a similar manner. At peak exercise, however, Dilatrend® reduced heart rate, systolic pressure and the double product more significantly than verapamil, suggesting that during exercise, Dilatrend® reduces cardiac stress to a greater extent. Dilatrend® reduced heart rate, premature ventricular beats and ischaemic episodes more than verapamil, as revealed by Holter monitoring. Both treatments were well tolerated, but there were fewer serious adverse events with Dilatrend® than with verapamil.

Comparison of 25 mg b.i.d. Dilatrend® with slow release nifedipine (20 mg t.i.d.) in a double-blind controlled trial showed a similar anti-anginal efficacy for both compounds, but Dilatrend® reduced the double product to a greater degree. Dilatrend®-treated patients also experienced less frequent adverse events, particularly those concerned with vasodilation.[151]

Dilatrend®'s effects have also been assessed in comparison with diltiazem in silent myocardial ischaemia. The study involved patients with coronary artery disease and end-stage renal failure maintained on haemodialysis, and 48-hour Holter monitoring was used for assessment. Both compounds reduced the number of systematic ischaemic episodes, but Dilatrend® was superior in the reduction of silent myocardial ischaemia, in terms of both the number and duration of episodes.[152]

Versus isosorbide dinitrate

Dilatrend® is at least as effective as organic nitrates in stable angina, and offers benefits in terms of better tolerability.[153] In comparison with slow-release isosorbide dinitrate (ISDN), Dilatrend® tended to exhibit superior effects, demonstrated by TET and time to angina assessed in exercise tests. The number of anginal attacks and the level of nitrate consumption was similar for both compounds, but treatment with Dilatrend® was associated with fewer adverse events; in particular, there was a lack of induction of headaches (the most frequently reported side-effect of nitrates). Patients could switch to a combination of both drugs after 12 weeks for a further 3-month period. This resulted in an additional increase in TET, with a further reduction in the rate of side-effects.

Dilatrend® offers, due to its comprehensive mode of action, clear advantages over other anti-anginal agents in stable angina: it is as equally effective as conventional β_1-selective β-blockers, but is more effective at lower doses during exercise than calcium antagonists, and better tolerated than organic nitrates.

Reduces ischaemic burden in unstable angina

Dilatrend® is **effective, with good safety, in the treatment of unstable angina**, and significantly improves the ischaemic burden on the heart. Dilatrend® has been evaluated in 116 patients, hospitalised due to acute unstable angina, in a double-blind, placebo-controlled trial.[113, 154] Holter monitoring was used during the 48-hour treatment in the coronary care unit. Dilatrend® effectively reduced heart rate and blood pressure, percentage of patients with repetitive ischaemic episodes, total number of ischaemic episodes, and total duration of ischaemia, all of which indicate an improvement in ischaemic burden (Figure 16). There was no significant difference in the incidence of side-effects between the Dilatrend®-treated and placebo-treated patients. In a hospital coronary care setting, therefore, Dilatrend® may be useful as adjunctive therapy in patients with unstable angina; however, Dilatrend® has not yet been approved for this indication.

Dilatrend® is effective at reducing the ischaemic burden in unstable angina, and is well tolerated in these patients.

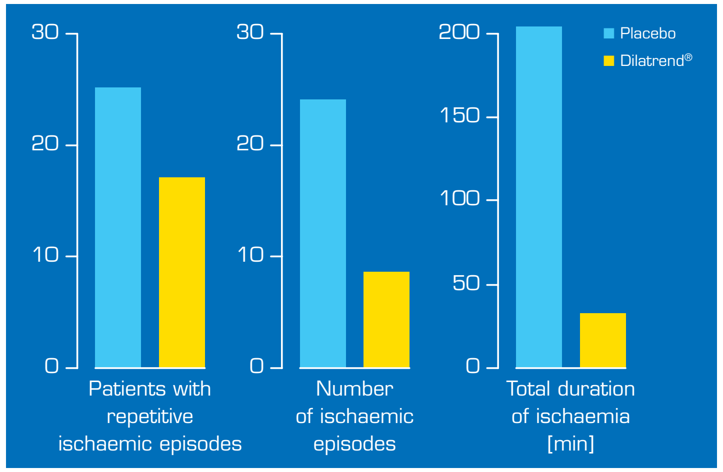


Figure 16: Effects of Dilatrend® on the percentage of patients experiencing repetitive ischaemic episodes, the number of ischaemic episodes and the total duration of ischaemia in patients with unstable angina monitored over 48 hours.[154]

The CHAPS trial – effects of Dilatrend® in acute myocardial infarction

Dilatrend® is **effective and well-tolerated in the treatment of acute MI**; its ability to reduce the size of the infarcted area or areas at risk of infarction has been consistently demonstrated in a variety of experimental models, supported by findings in clinical trials. Its efficacy has consistently proved to be greater than that obtained with conventional β_1-selective β-blockers.
Dilatrend® is effective and well-tolerated in acute MI in a clinical setting, protecting against early and progressive LV remodelling, as demonstrated by the CHAPS trial (**C**arvedilol **H**eart **A**ttack **P**ilot **S**tudy).[155] This double-blind, placebo-controlled study enrolled 151 patients, who were randomised to receive either Dilatrend® (beginning with 2.5 mg iv) or placebo within 24 hours of onset of chest pain, in addition to standard therapy (including aspirin and heparin with or without thrombolysis). This was followed by oral Dilatrend® (6.25 mg b.i.d.) or matching placebo for 2 days. The Dilatrend® dose was then gradually increased and maintained at 12.5 or 15 mg b.i.d. for 6 months. The Dilatrend®-treated patients experienced a reduction in cardiac events (18 out of 77, compared to 31 out of 74 in the placebo group, $p < 0.02$). Dilatrend®-treated patients also experienced significantly fewer serious cardiac events than patients in the placebo group (Figure 17).
Dilatrend® reduced blood pressure and heart rate at rest and in exercise, increased stroke volume and improved diastolic filling of the left ventricle (all $p \leq 0.02$). The diastolic function of the heart was better preserved and the LV mass and wall thickness was reduced with Dilatrend®, which particularly favoured the geometry of the left ventricle in a subgroup of patients with reduced LV EF (< 45%).[156]

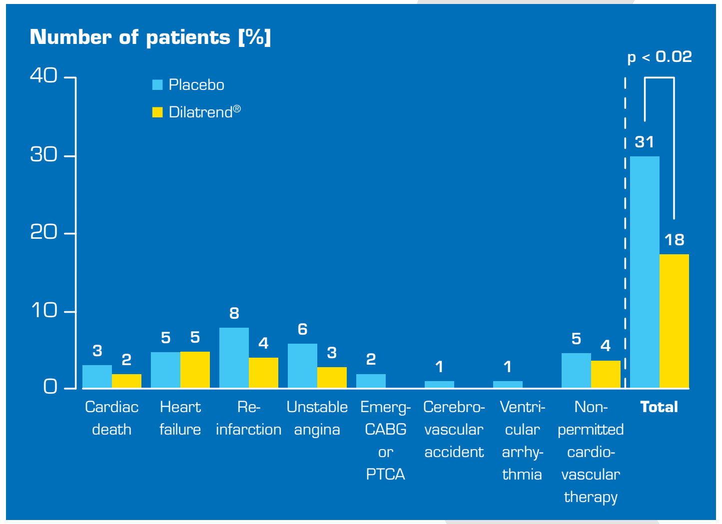


Figure 17: Effect of Dilatrend® on primary cardiovascular endpoints in the CHAPS trial.[155]

The CAPRICORN trial – effects of Dilatrend® post myocardial infarction

Dilatrend® is also effective and well-tolerated in the long-term treatment of post-MI patients. This was clearly demonstrated in the CAPRICORN (**Ca**rvedilol **P**ost Infa**r**ct Surv**i**val **Con**trol in LV Dysfunctio**n**) trial, an international multicentre, randomised, double-blind, placebo-controlled study in 1,959 patients with acute MI and proven LV dysfunction, all randomised within 21 days following the MI[157]. The trial assessed Dilatrend® in addition to standard therapy; about one third of patients were receiving diuretics, and 98% were receiving ACE inhibitors. The results showed a significant reduction in all-cause mortality by 23% (p = 0.031) (Figure 18) in the Dilatrend®-treated patients. Importantly, this impressive result was shown on top of the effects of ACE inhibitors and reperfusion therapy. The reduction in all-cause mortality was accompanied by a 41% reduction in recurrent non-fatal MI (p = 0.014) (Figure 19) and a 26% reduction in sudden death. Dilatrend® treatment also reduced cardiovascular mortality by 25% (p = 0.024) and reduced cardiovascular mortality or non-fatal recurrent MI by 30% (p = 0.02). Dilatrend® was very well tolerated.

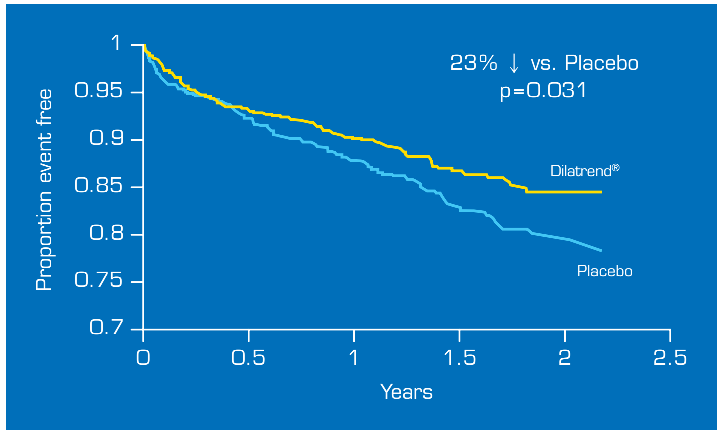


Figure 18: CAPRICORN primary endpoint – all-cause mortality. There was a 23% risk reduction for all-cause mortality in patients receiving Dilatrend® as compared to the placebo group.[157]

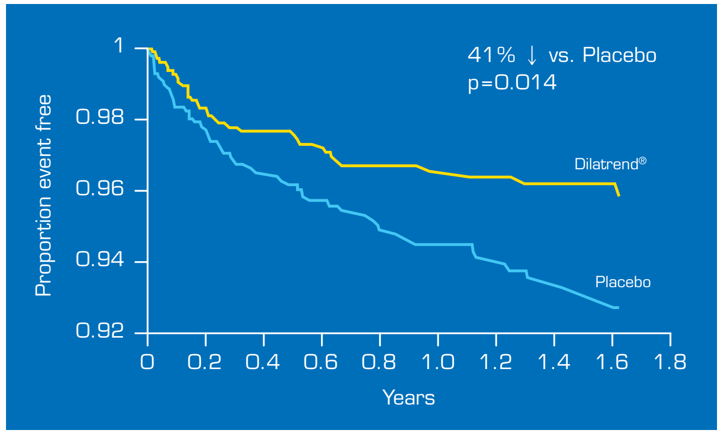


Figure 19: CAPRICORN additional analyses – recurrent non-fatal MI. There was 41% risk reduction of recurrent non-fatal myocardial infarction in patients receiving Dilatrend® as compared to patients receiving placebo.[157]

Reduces arrhythmias in coronary artery disease

Dilatrend® **significantly reduces the incidence of ventricular arrhythmias**, ventricular premature contractions (VPCs) and ventricular tachycardia. In a double-blind comparison study in patients with coronary artery disease, Dilatrend®-treated patients experienced a more pronounced reduction in VPCs than verapamil-treated patients.[150]

In a study of 168 patients, Dilatrend®'s benefits in reducing the number of complex non-sustained ventricular arrhythmias (Lown class III, IV or V) was assessed compared with placebo.[132] Patients with ischaemic or idiopathic dilated cardiomyopathy and complex ventricular arrhythmias were recruited to the trial. By the end of 3 months of treatment, EF significantly improved in all patients treated with Dilatrend®, with an improvement of +7.3% in both ischaemic and idiopathic patients by study end compared with baseline (p < 0.05). At 6 months, premature ventricular contractions and non-sustained ventricular tachycardia were significantly reduced in both ischaemic and idiopathic patients treated with Dilatrend® compared with baseline (p < 0.05 for all), an effect not seen with placebo.

In the Holter substudy of the CAPRICORN trial,[157, 158] Dilatrend® significantly reduced supraventricular and ventricular arrhythmias/fibrillation in patients with LV dysfunction post-acute myocardial infarction. These included a reduction in risk in all supraventricular arrhythmias of 52% (p = 0.0015) and a reduction in all ventricular arrhythmias of 63% (p < 0.001). The risk of ventricular arrhythmia/ventricular tachycardia was reduced by 76% (p < 0.001) (Figure 20). In CAPRICORN,[157] these results translated into an impressive 26% reduction in the risk of sudden death.

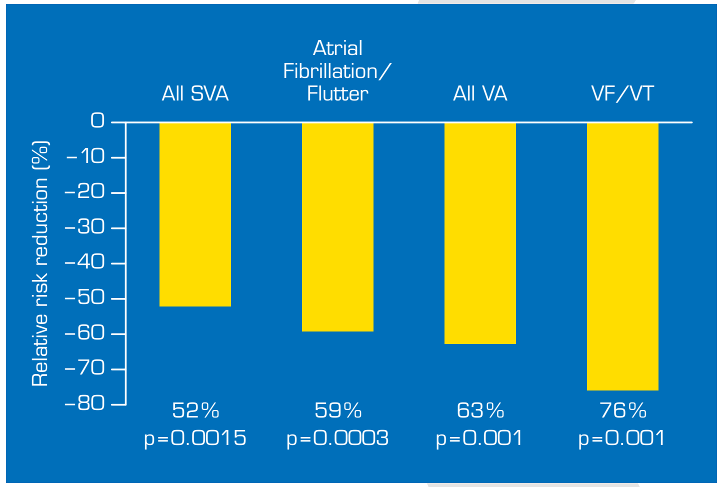


Figure 20: CAPRICORN – reduction in supraventricular and ventricular arrhythmias/fibrillation. (SVA = supraventricular arrhythmia; VA = ventricular arrhythmia; VF = ventricular flutter; VT = ventricular tachycardia.)[158]

(iii) Efficacy across the Entire Spectrum of CHF

Dilatrend® is **highly effective in mild, moderate and severe CHF**, a consequence of its unique comprehensive mechanisms of action; this has been demonstrated in several landmark trials. CHF is not just a haemodynamic problem characterised by impairment of myocardial contractility and an increase in pre-and afterload, but is also characterised by complex neurohormonal interactions.[159, 160, 161] Chronic overactivation of compensatory mechanisms aggravates the disease, leading to progressive worsening of LV function, symptoms, need for hospitalisations and, ultimately, early death. There is good evidence that high concentrations of catecholamines, typically found in individuals with CHF, are toxic to myocytes and disturb adrenergic signalling. Other processes are directly or indirectly involved, including: alterations in myocardial signal transduction;[162, 163] myocyte apoptosis;[77] and oxidative stress.[50, 53, 54, 164, 165, 166] Therefore, treatments based solely on the haemodynamic considerations do not offer long-term benefits to patients.

Besides their effects on β_1 and β_2 receptors, catecholamines also mediate many of the circulatory effects of α-receptors. These, in contrast to β_1 receptors, do not appear to be down-regulated in CHF.[163, 164, 167, 168]

However, the proportion of β_2 receptors that mediate the sympathetic activation is increased in CHF patients, which provides a pathophysiologic rationale for an agent which blocks both β_1 and β_2 receptors.

CHF is accompanied by early and progressive increases in circulating norepinephrine concentrations, which increase proportionally with the severity of the disease.[169, 170] Norepinephrine release from the heart, mediated by β_2-adrenoceptors, is increased in CHF patients (Figure 21). Dilatrend®'s inhibitory effect on norepinephrine release from the heart exposed to ischaemia has been demonstrated, but this effect is not shared by metoprolol or bisoprolol.[171]

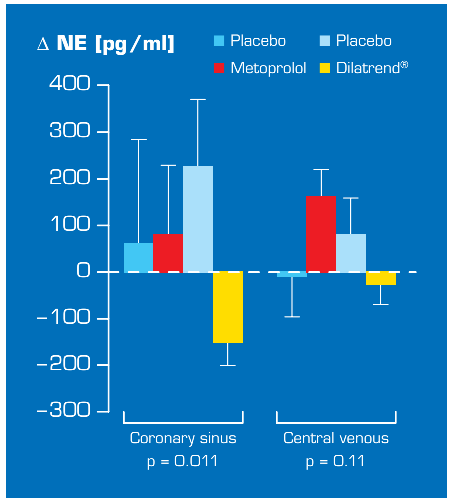


Figure 21: Changes in coronary sinus and central venous norepinephrine concentrations following administration of placebo, metoprolol or Dilatrend®.[19]

Results with Dilatrend® in patients with impaired myocardial function were reported as early as 1990,[44, 172] and showed that Dilatrend® improved haemodynamics, LV EF and the patients' exercise capacity. A variety of clinical studies have since been performed, covering all aspects of efficacy and safety. The results of these studies had a profound effect on the paradigm shift from the previous contraindication of β-blockers for CHF to current recommendations for their use in CHF, recognised by the release of new guidelines.[173, 174, 175] The majority of trials were placebo-controlled and enrolled patients who had been previously treated with standard CHF therapy.

Dilatrend® offers superior efficacy across the spectrum of mild, moderate and severe chronic heart failure.

Improves haemodynamics and symptoms

Dilatrend® **greatly improves the haemodynamic profile** in CHF patients, and significantly eases the symptoms of the condition. In a trial of 60 CHF patients (NYHA class II-IV), treated over 4 months by gradual increase of Dilatrend® dose from 3.125 mg to 25 or 50 mg b.i.d., EF and stroke-work index were significantly increased, while heart rate, pulmonary capillary wedge pressure and NYHA classification were all reduced (Figure 22).[49] In another trial of 40 CHF patients (NYHA class II-IV), also treated for a 4-month period, haemodynamic improvements were observed, in parallel with the improvement of sub-maximal exercise capacity and NYHA class, and the Frank-Starling curve, a measure of the increase in force enabling the heart to eject additional venous return, was shifted to the left and upwards.[48]

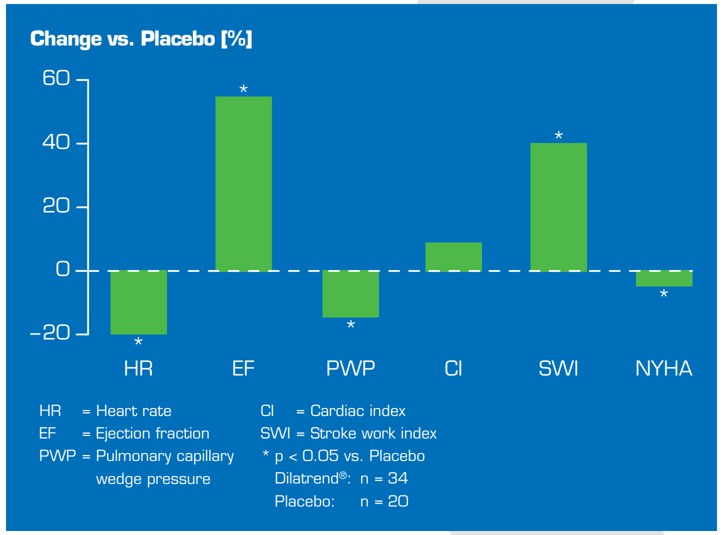


Figure 22: Influence of Dilatrend® on various haemodynamic parameters in CHF (ischaemic or non-ischaemic aetiology, NYHA class II-III) patients and an LV EF ≤35%.[49]

Haemodynamics and symptom score were also improved in 56 patients with severe CHF (NYHA class III-IV), with a significantly reduced risk of death or worsening of CHF.[176] Dilatrend® also significantly reduced ventricular tachycardia and fibrillation.

A large study in Australia and New Zealand assessed Dilatrend® in 415 patients with mild to moderate CHF due to coronary artery disease.[177, 178] Dilatrend® increased the EF and reduced the combined endpoint of mortality and/or hospitalisation rates by 26% during the mean observation period of 19 months. The results did not reach statistical significance due to the overall small event rate in the study population; however, echocardiographic results demonstrated a significant decrease in end-systolic and end-diastolic diameters, indicating a reversal of cardiac remodelling.[179]

Dilatrend® improves haemodynamic profiles in heart failure: it increases LV EF and cardiac output, reduces heart rate and pulmonary capillary wedge pressure, resulting in a significant functional improvement in NYHA class.

Significant reduction in morbidity and mortality

Dilatrend® **significantly improves survival** across the spectrum of symptomatic CHF. In addition, tolerability is excellent. Treatment with Dilatrend® not only improves symptoms but also significantly reduces the risk of death and hospitalisations in patients who are already receiving optimised standard treatment for CHF, comprising digoxin, diuretics and ACE inhibitors. Dilatrend® has been shown to improve survival in mild to moderate CHF (US Carvedilol Program) and in severe CHF (COPERNICUS trial).

Dilatrend® has been studied in more patients, in all aspects of CHF severity than any other drug in its class.

The US Carvedilol Program – effects of Dilatrend® in mild-to-moderate CHF

The US Carvedilol Program[180] enrolled 1,094 patients with mild, moderate or severe CHF. The patients were assigned to three different arms of the study according to disease severity, i.e. mild,[181] moderate[182] or severe CHF.[183] A fourth arm of the study was designed as a dose-ranging investigation to find the optimum Dilatrend® dose for the treatment of CHF (MOCHA study: **M**ulticentre **O**ral **C**arvedilol **H**eart failure **A**ssessment). The entire trial programme was arranged as a single study with the same inclusion and exclusion criteria, dosing titration, target doses, data evaluation, common safety committees and other factors.

The US Carvedilol Program was terminated prematurely for ethical reasons upon the recommendation of the Data and Safety Monitoring Board, based on the fact that Dilatrend® had a highly significant positive effect on survival of the patients with CHF. At the time the study was terminated, there was a 7.8% death rate among the 398 patients randomised to placebo (plus standard therapy), compared to 3.2% among the 696 Dilatrend®-treated patients, representing a highly significant ($p < 0.001$) reduction in risk of death of 65% (Figure 23). This mortality reduction was reflected by a reduction in sudden death and death from pump failure. Reduction in mortality was observed after an average of just 6.5 months of treatment. The effect was observed across all sub-populations, regardless of CHF aetiology, age, sex, and severity of symptoms, EF at baseline, etc. The effect of Dilatrend® on EF, mortality and hospitalisation was dose-dependent (Figure 24),[184] and already at a low dose (6.25 mg b.i.d.), a clear-cut and significant risk reduction was observed; at the highest dose (25 mg b.i.d.), a 93% reduction in risk profile was observed. These results provided the basis of a rationale for the current dose recommendations.

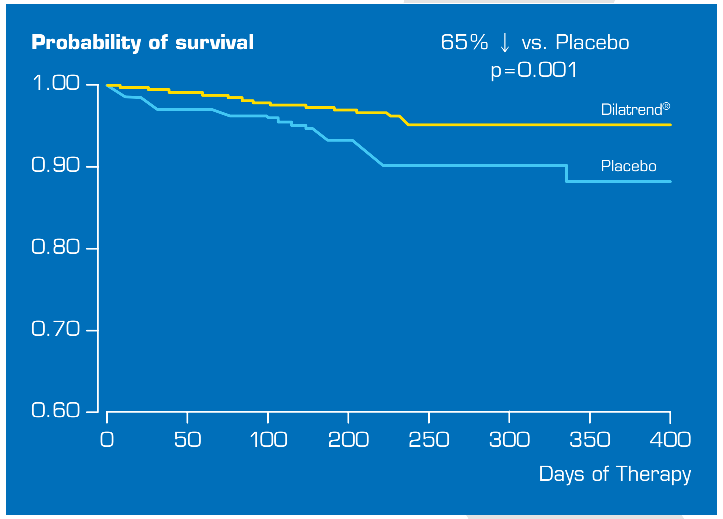


Figure 23: Results of the US Carvedilol Program: the Kaplan-Meier survival curves show a 65% risk reduction for death in patients receiving Dilatrend® compared to the placebo group. This difference was highly statistically significant ($p < 0.001$).[180]

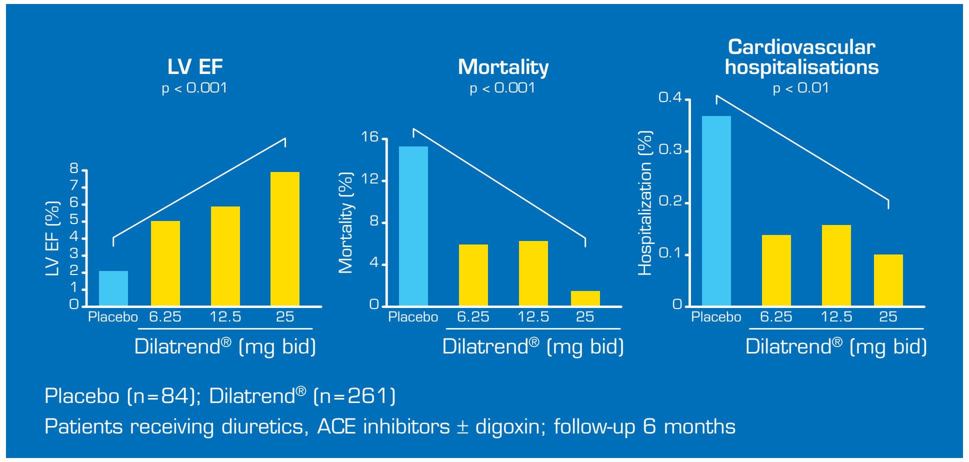


Figure 24: Dose-response effect of Dilatrend® on LV EF, mortality and cardiovascular hospitalisations. (LV EF = left ventricular ejection fraction.)[184]

Hospitalisations due to cardiovascular reasons were reduced in the whole study by 26% (p = 0.042), and the combined risk of death or cardiovascular hospitalisation was reduced by 38% (p = 0.0008) (Figure 25). The Kaplan-Meier curve for effects on patient prognosis began to diverge a few weeks after the initiation of treatment, and progressively split for the total time of treatment (up to 18 months) before early termination in the double-blind phase.[185] The same effect could be seen after study termination in patients who switched from placebo to Dilatrend® in open follow-up.[186]

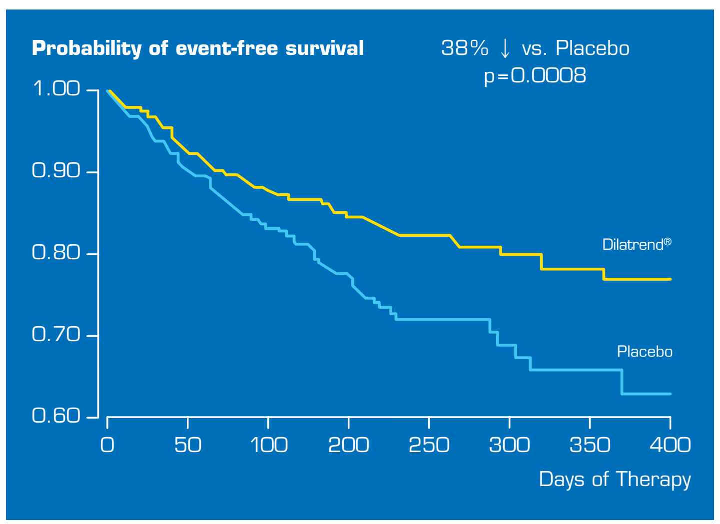


Figure 25: Results of the US Carvedilol Program: the Kaplan-Meier survival curves show a 38% lower risk of hospitalisation for cardiovascular reasons (event-free survival) for patients receiving Dilatrend® compared to the placebo group. This difference was statistically highly significant (p = 0.0008).[180]

Haemodynamic improvement was demonstrated by a significant reduction in pulmonary capillary wedge pressure and an increase in EF. Improvement in clinical symptoms was seen by a shift towards lower NYHA classes, paralleled by a considerably better global assessment of Dilatrend® by patients and physicians, compared to placebo (Figure 26). **Over 90% of patients tolerated Dilatrend®** during the challenge phase and the entire study. **There were fewer withdrawals due to adverse experiences in the Dilatrend®-treated patients than in the placebo group.**

In patients with mild-to-moderate chronic heart failure, Dilatrend® results in a highly significant reduction of mortality and hospitalisations.

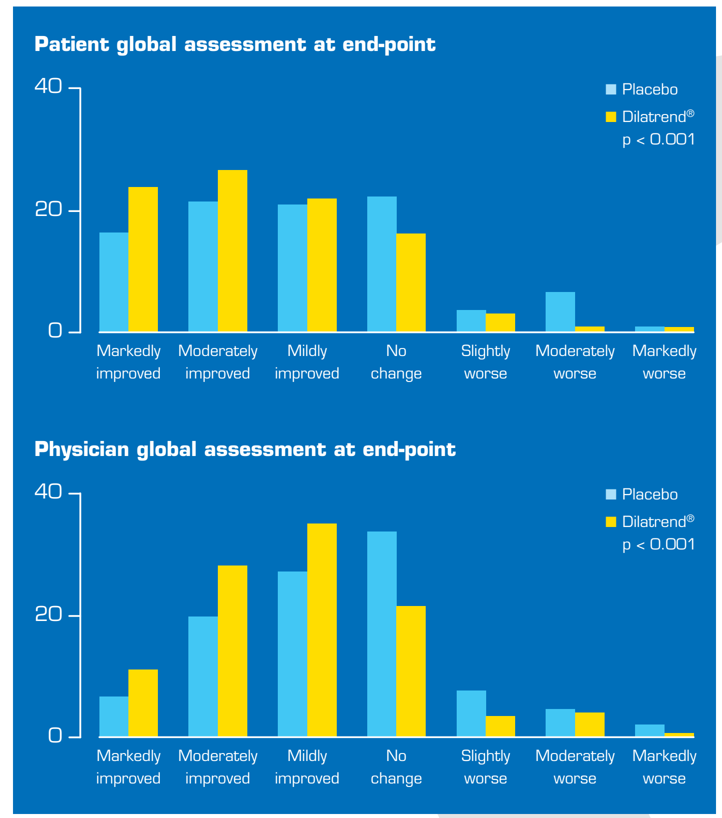


Figure 26: Patient and physician global assessment of Dilatrend® or placebo therapy in the US Carvedilol Program.[180]

The COPERNICUS trial – effects of Dilatrend® in severe CHF

Treatment with Dilatrend® leads to a **highly significant lower mortality rate** in patients with severe CHF, as demonstrated by primary results from the COPERNICUS (**C**arvedil**o**l **P**rosp**e**ctive **R**a**n**dom**i**sed **Cu**mulative **S**urvival) trial. This trial, which investigated the most severely ill population ever studied in a β-blocking trial in CHF, was designed to examine the effects of Dilatrend® on patients with severe CHF. This double-blind placebo-controlled prospective study enrolled 2,289 patients with symptoms of severe CHF (dyspnoea and/or fatigue at rest or on minimal exertion for at least 2 months and EF < 25%). The primary endpoint was all-cause mortality.[187]

The primary results of this landmark trial showed a highly significant reduction in all-cause mortality ($p = 0.00013$) for Dilatrend® treatment versus placebo. The risk of all-cause mortality was reduced by 35% in the Dilatrend®-treated patients (Figure 27), and death or hospitalisations for CHF were reduced by 31%. Dilatrend® was not only effective in the study population, but also in the most severely ill patients, i.e. those with recent or recurrent decompensation. The results of the COPERNICUS trial have substantial implications on public health; if 1,000 patients were treated with Dilatrend® for 1 year, approximately 70 lives would be saved.

The results of the COPERNICUS trial also amply demonstrated the safety and tolerability of Dilatrend®; the withdrawal rate of patients from Dilatrend® therapy was significantly lower than that from the placebo arm of the trial.

COPERNICUS is the first and only randomised, placebo-controlled trial demonstrating the benefit of a β-blocking agent in patients with severe chronic heart failure.

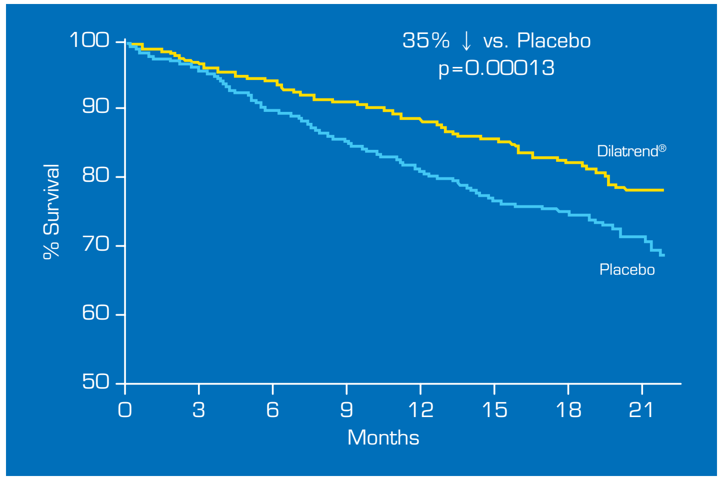


Figure 27: Results of the COPERNICUS trial: the Kaplan-Meier survival curves show a 35% risk reduction in all-cause mortality for patients receiving Dilatrend® compared to the placebo group. This difference was highly statistically significant ($p = 0.00013$).

Effective in all patient populations

Dilatrend® demonstrates **efficacy in all patient populations** in CHF; no specific sub-populations could be identified that do not benefit from Dilatrend® treatment, as discerned by analysis of sub-groups in the US Carvedilol Program. This is particularly true for the elderly, blacks, patients with atrial fibrillation and also for patients who are not receiving ACE inhibitor therapy, or not receiving concomitant treatment with amiodarone.[188, 189, 190, 191, 192] Diabetic patients have shown a worse prognosis than non-diabetic patients, but Dilatrend®'s effect on the mortality of these high-risk populations was even more pronounced.[186]

Dilatrend® can be used safely and effectively in severe CHF, provided that careful monitoring and up-titration are performed in order to avoid some of the potential side effects common in these patients at the beginning of therapy, such as dizziness, fatigue and worsening of symptoms.[193]

Examination of data from the ANZ study confirmed that Dilatrend® could be safely co-administered with amiodarone, with no increase in the rate of side effects.[188, 192]

Dilatrend® demonstrates efficacy across all stages of CHF and is well tolerated even at the late stages of the cardiovascular continuum.

Superior to metoprolol

Dilatrend® consistently demonstrates superior safety and efficacy to metoprolol in the treatment of severe CHF. Comparisons of the haemodynamic effects of Dilatrend® and metoprolol in short-term studies[47] and after 6-8 months treatment[19] have shown that Dilatrend® demonstrated an off-loading of the heart by a reduction in pulmonary wedge pressure, right atrial pressure and total peripheral resistance, whereas metoprolol did not. This effect may facilitate the initiation of β-blocker therapy in patients with impaired myocardial function. Two small, relatively short-term comparison studies showed a tendency towards a greater increase in EF with Dilatrend®; significant differences between other variables were not observed.[194, 195]

Patients with dilated cardiomyopathy who were not as well controlled as expected on previous state-of-the-art therapy, including 12 months with metoprolol, were enrolled in a double-blind, controlled study. The patients were then randomised, either continuing therapy with metoprolol or switching to Dilatrend®. After 12 months, the Dilatrend®-treated patients experienced an average increase in EF of 7 units, whereas a small reduction of about 1 unit was observed in the metoprolol-treated patients.[196] Dilatrend® also slightly reduced end-systolic and end-diastolic volumes, whereas metoprolol showed the opposite effects. Also, a reduction in arrhythmic episodes was observed in the Dilatrend®-treated patients. These differences bordered statistical significance.

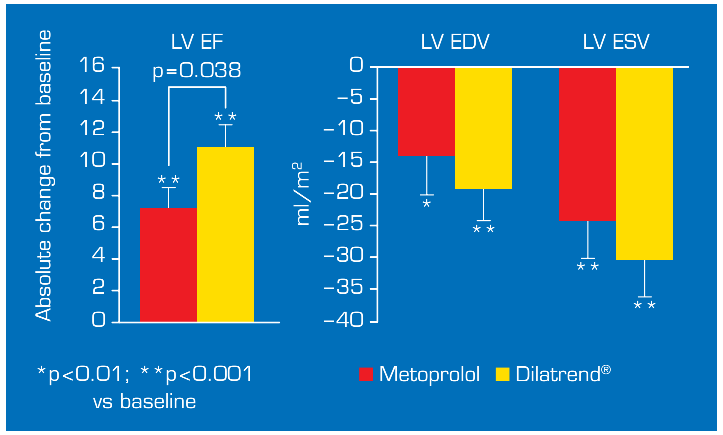


Figure 28: Following 13 to 15 months of therapy, Dilatrend® significantly improved LV EF, LV EDV, LV ESV from baseline and compared with metoprolol in 150 patients with CHF. (LV EF = left ventricular ejection fraction; LV EDV = left ventricular end diastolic volume; LV ESV = left ventricular end systolic volume.)[197]

A double-blind comparison trial was conducted with Dilatrend® and metoprolol in 150 patients with moderate to severe CHF (EF at baseline 20.6 ± 4.2%). After a year of treatment, Dilatrend® significantly increased EF more than metoprolol (mean 10.9% versus 7.2%). Left ventricular stroke volume index and stroke work index were also increased, but preload indices were more reduced in the Dilatrend® group. There were no major differences regarding sub-maximal exercise tolerance, improvement of symptoms or quality of life.[197] In a meta-analysis of all 19 randomised controlled trials of Dilatrend® or metoprolol (15 placebo controlled, 4 direct head-to-head comparisons) that measured LV EF before and after an average of 8.3 ± 0.1 months of treatment with 2,184 patients with CHF.

In the 15 placebo-controlled trials, mean EF increased significantly more in the Dilatrend® trials as compared to the metoprolol trials (placebo-corrected increases of +0.065 and +0.038, respectively, p = 0.0002). In the four active-controlled trials comparing metoprolol directly with Dilatrend®, the mean EF also increased significantly more in the Dilatrend® groups than in the metoprolol groups (+0.084 on Dilatrend® and +0.057 on metoprolol, p = 0.009) (Figure 29).[198]

COMET (see page 47) confirmed that comprehensive β_1-, β_2- and α_1- blockade with Dilatrend® is superior to that of a conventional β_1-selective blocker.

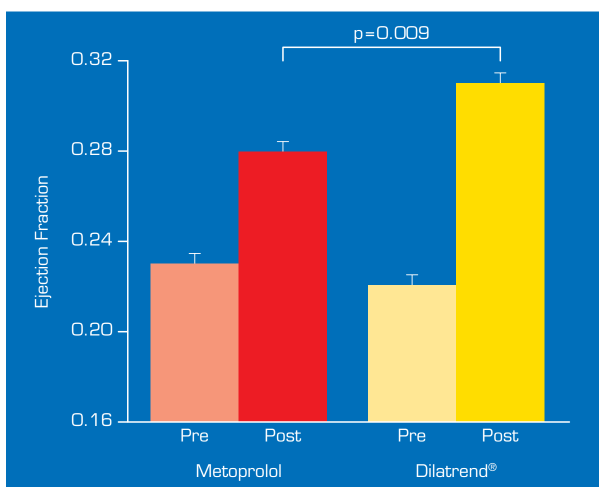


Figure 29: Mean values for LV EF pre and post treatment with metoprolol or Dilatrend® in 248 patients enrolled in 4 trials directly comparing the two treatments.[198]

The CHRISTMAS trial – effects of Dilatrend® in patients with myocardial hibernation

The CHRISTMAS (**C**arvedilol **H**ibernation **R**eversible **IS**chaemia **T**rial; **MA**rker of **S**uccess) trial was performed to determine whether the presence or absence of hibernating myocardium predicts the magnitude of improvement in LV EF following treatment with Dilatrend® (Figure 30).[199] Hibernation is a chronic extension of stunning (transient contractile dysfunction following overt or silent myocardial ischaemia lasting hours or days),[200] describing a prolonged down-regulation of contractile dysfunction that may last weeks, months or even years.

From baseline to a mean follow-up of 6 months, Dilatrend® treatment significantly improved EF by 3.2% (p = 0.0001) versus placebo. Highly significant improvements in LV EF were seen in patients with both hibernating and non-hibernating myocardium, increasing by 3.6% in hibernating myocardium (p = 0.0002) and by 2.4% in non-hibernating myocardium (p = 0.0113) (Figure 31). Patients with low baseline LV EF showed greater improvement in LV EF following Dilatrend® treatment. Similarly, patients with a large number of baseline hibernating segments showed a greater increase in LV EF with Dilatrend®.

The CHRISTMAS results show that pharmacotherapy with Dilatrend® is a valuable treatment option with a special benefit for CHF patients with ischaemic aetiology. Dilatrend® therapy significantly improves LV EF in these patients, regardless of the presence or absence of hibernating myocardium.[201]

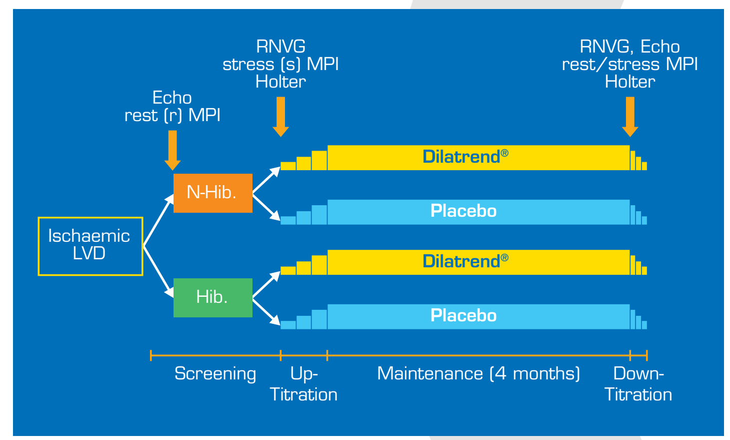


Figure 30: CHRISTMAS study design. (LVD = left ventricular dysfunction; Hib = patients with hibernating myocardium; MPI = myocardial perfusion imaging, at rest (r) or during stress (s); N-Hib = patients without hibernating myocardium; RNVG = radionuclide ventriculography.)[199]

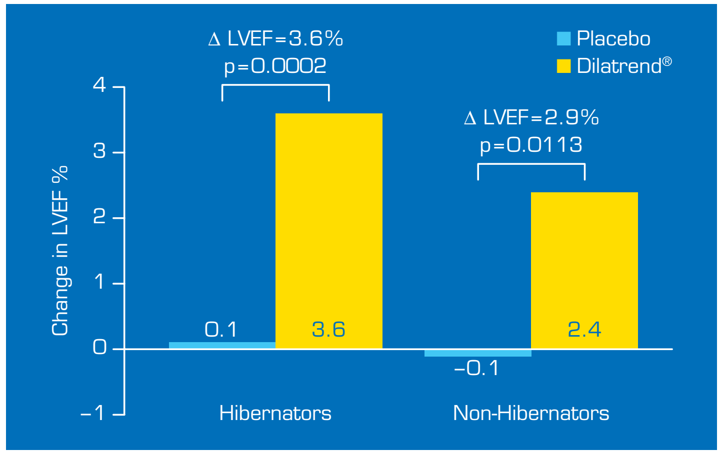


Figure 31: CHRISTMAS primary results. LV EF was assessed at baseline and study end. Patients with and without hibernating myocardium had a significantly improved LV function following Dilatrend® treatment compared with placebo at study end. (LV EF = left ventricular ejection fraction.)

The SWEDIC trial – effects of Dilatrend® in CHF patients with diastolic dysfunction

The SWEDIC (**SW**edish **E**valuation of **DI**astolic dysfunction in **C**HF) trial investigated the treatment potential of Dilatrend® in patients with diastolic dysfunction, based on the hypothesis that Dilatrend®'s unique pharmacological profile may be of special value in diastolic CHF (Figure 32). One hundred and thirteen patients with diastolic dysfunction and symptoms of CHF were enrolled into the study. All patients had normal LV systolic function, 32.6% were NYHA class I, 53.3% class II and 14.1% class III. After 6 months of treatment, the Dilatrend®-treated patients showed a statistically significant improvement in LV diastolic dysfunction as assessed by Doppler-echocardiography ($p = 0.046$).[202] In patients with diastolic dysfunction and symptoms of CHF, Dilatrend® therapy resulted in a significant improvement in diastolic function.

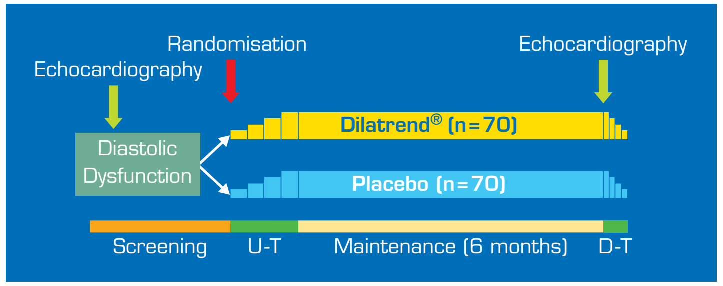


Figure 32: SWEDIC study design. (U-T = up-titration; D-T = down-titration.)

The CARMEN trial – Dilatrend® + ACE inhibition

CARMEN (**C**arvedilol **A**CE Inhibitor **R**emodelling **M**ild HF **E**valuatio**N**) is the first direct large-scale comparison of β blockade versus ACE inhibition on the effects of LV function in chronic heart failure CHF.[203, 204] The trial was designed as a controlled, prospective, double-blind, randomised trial to evaluate the remodelling effects of enalapril and Dilatrend®, in combination or alone, in patients with mild CHF (Figure 33).

mortality/all-cause hospitalisation over the study period.

CARMEN enrolled 572 patients with mild CHF from 65 centres in 13 European countries. Patients had to have a history of at least 2 months of symptoms of mild heart failure and EF ≤ 0.39 at baseline as assessed by echocardiography. Heart failure medication had to be unchanged for the 2 weeks

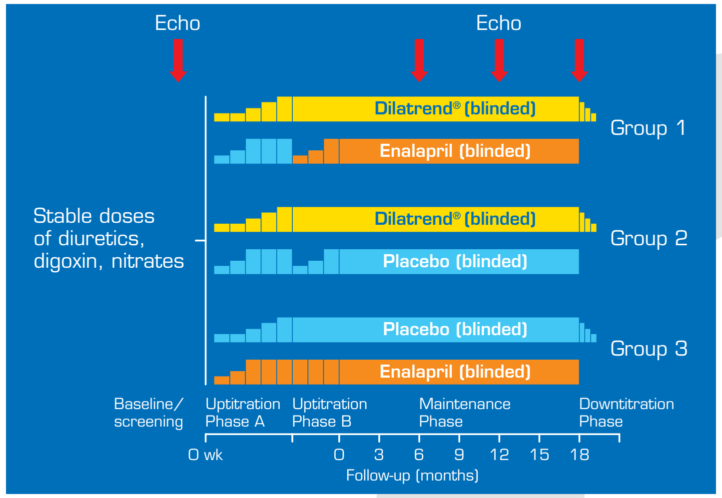


Figure 33: CARMEN study design.

The primary endpoint was the mean change in LV end-systolic volume index (LV ESVI) between baseline and follow-up at month 18 (end of the maintenance phase), between the combination of Dilatrend® and enalapril versus enalapril monotherapy and between Dilatrend® monotherapy versus enalapril monotherapy. Serial measurements of LV ESVI (biplane), as determined by transthoracic echocardiography, were used to assess treatment effects on cardiac remodelling. Major secondary endpoints were within-treatment comparisons in each arm for the primary parameter between baseline and month 18, as well as evaluating changes in LV EF, LV diastolic volumes and all-cause

prior to the baseline visit. Patients with symptoms at rest or unstable heart failure were excluded from the study.

The combination of Dilatrend® and enalapril resulted in a highly significant reduction of LV ESVI compared to enalapril alone ($p < 0.02$). This reversal of LV remodelling was seen as early as month six and was maintained over the whole treatment period. Although Dilatrend® monotherapy showed no significant difference versus enalapril monotherapy in reduction of LV ESVI, the substantial decrease in the Dilatrend® arm shows a clear trend favouring Dilatrend® (Figure 34).

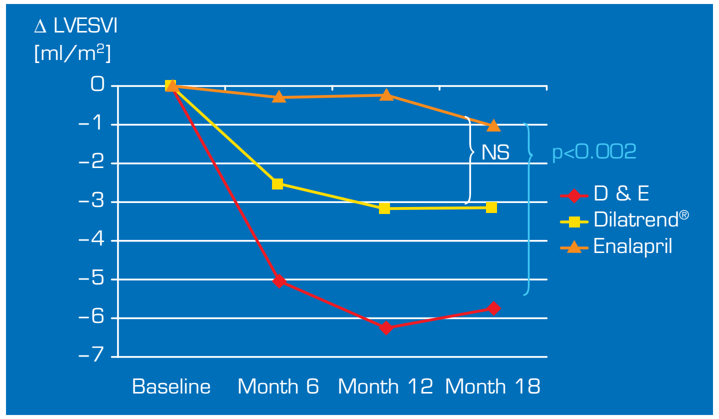


Figure 34:
CARMEN results: Mean changes from baseline in LV ESVI, comparison between treatments. (D = Dilatrend®; E = enalapril; LV ESVI = left ventricular end-systolic volume index.)

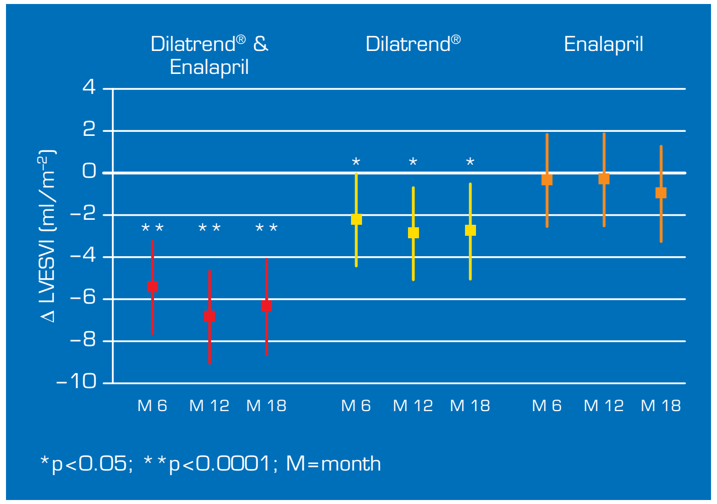


Figure 35: CARMEN results: Mean changes from baseline in LV ESVI, comparison within treatment arms in the ITT population. (LV ESVI = left ventricular end systolic volume index.)

Comparison of the three treatment arms showed a highly significant reduction in LV ESVI in patients treated with the combination of Dilatrend® and enalapril that was already present after 6 months of maintenance treatment, and maintained at 12 and 18 months ($p < 0.0001$). Notably, Dilatrend® monotherapy also significantly reversed LV remodelling ($p < 0.05$). The significant reduction in LV ESVI was also maintained over time. In contrast to the groups receiving Dilatrend®, no change from baseline could be seen in patients receiving enalapril monotherapy (Figure 35).

The results from CARMEN demonstrated that the combination of Dilatrend® and ACE inhibition resulted in a highly significant improvement in LV remodelling. Reversal of remodelling was seen in all patients receiving Dilatrend®, whether in combination with enalapril or as monotherapy, results that were not seen in patients receiving enalapril alone. In addition, a similar safety and tolerability profile was seen in all three treatment arms and, in contrast to common perception, there was no difference in tolerability between Dilatrend® and enalapril. Indeed, Dilatrend® was safely initiated before starting ACE inhibition. The results from CARMEN confirm the current treatment guidelines,[205, 206] and provide an immediate mandate for the earlier prescribing of ACE inhibition and Dilatrend® combination therapy in patients with mild CHF.

The CARMEN results indicate that the combination of Dilatrend® and ACE inhibition should be started early in mild CHF and not delayed until further disease progression.

The COMET trial

Large clinical trials in CHF have established mortality and morbidity benefits with the β-blocking agents Dilatrend® (carvedilol), metoprolol and bisoprolol.

However, there are important pharmacological distinctions between the recommended β-blocking agents. Metoprolol and bisoprolol are conventional β_1-selective β-blockers, while Dilatrend® provides comprehensive β_1-, β_2- and α_1-blockade with additional ancillary properties.[9, 10, 11, 12]

Small studies directly comparing effects on LV EF and LV volumes, demonstrated the clear advantages of Dilatrend® over metoprolol.[194, 195, 197, 233]

Similarly, a meta-analysis of placebo- or active-controlled studies concluded the same advantage of Dilatrend® over metoprolol on measures of LV EF.[198]

COMET was designed to answer the important question:

Do the pharmacological differences between Dilatrend® and a conventional β_1-selective β-blocker translate into significant survival benefits?

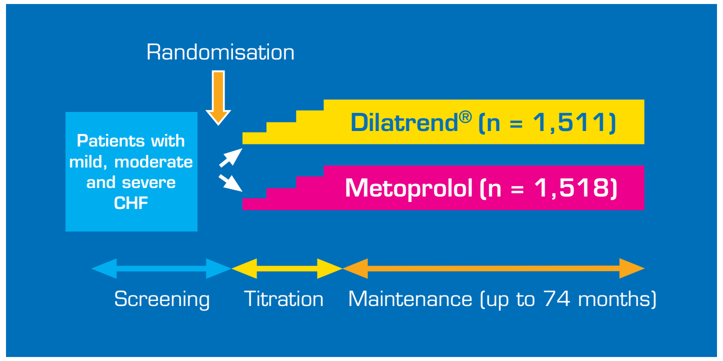


Figure 36:

COMET trial design

COMET Design and Study Population

COMET (**C**arvedilol **or M**etoprolol **E**uropean **T**rial) was a randomised double-blind, head to head comparison of Dilatrend® versus metoprolol in mild, moderate and severe CHF (Figure 36). Eligible patients were already receiving standard therapy for CHF including diuretics and ACE inhibitors. The study used an event driven design and continued until at least 1,020 fatal events occured.[220]

The mean study duration was 58 months and included over 14,000 patient years of follow up making COMET the longest and largest study of β-blockade in CHF.[234]

All-cause mortality and the combination of all-cause mortality and all-cause hospitalisations were the primary endpoints.

Primary Endpoints: All-cause Mortality

COMET demonstrated a highly significant 17% survival benefit (p=0.0017) for patients receiving Dilatrend® versus those on metoprolol (Figure 37).

The estimated median survival for patients receiving Dilatrend® was 8.0 years compared with 6.6 years for those receiving metoprolol. Thus Dilatrend® prolongs median survival by 1.4 years.

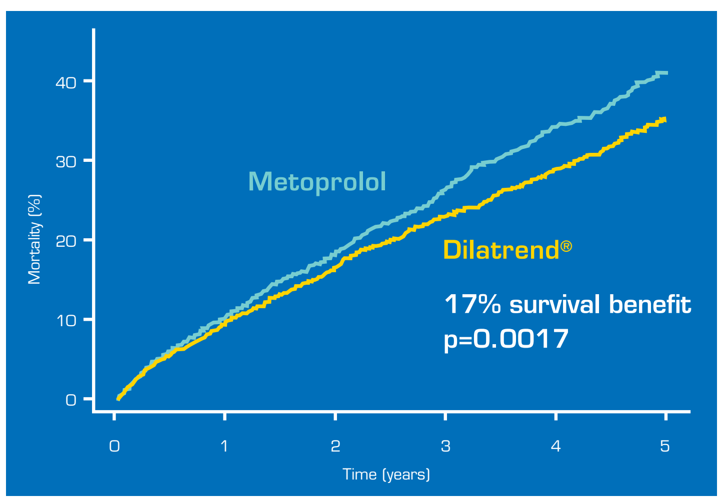


Figure 37: COMET primary mortality endpoint. Dilatrend® showed a highly significant 17% survival benefit (p=0.0017) over metoprolol

All-cause Mortality and All-cause Hospitalisations

The combined endpoint of all-cause mortality and all-cause hospitalisations (time to first event) showed a 6.3% advantage (p=0.12) for Dilatrend®. This illustrates that in COMET, the benefit of Dilatrend® over metoprolol was mainly driven by mortality. This was confirmed by the results for cardiovascular mortality in COMET (20% relative risk reduction p=0.0004, Dilatrend® versus metoprolol) and further emphasises the clear survival benefit of Dilatrend® over a conventional β_1-selective β-blocker.

Consistency across Subgroups

The survival benefit of Dilatrend® over metoprolol was consistent across all pre-defined subgroups (Figure 38).

Tolerability

The percentage of patients with adverse events or serious adverse events and the number of patients withdrawn from study medication was lower with Dilatrend®. This is particularly striking given the longer survival time and hence exposure to study medication for patients receiving Dilatrend®.

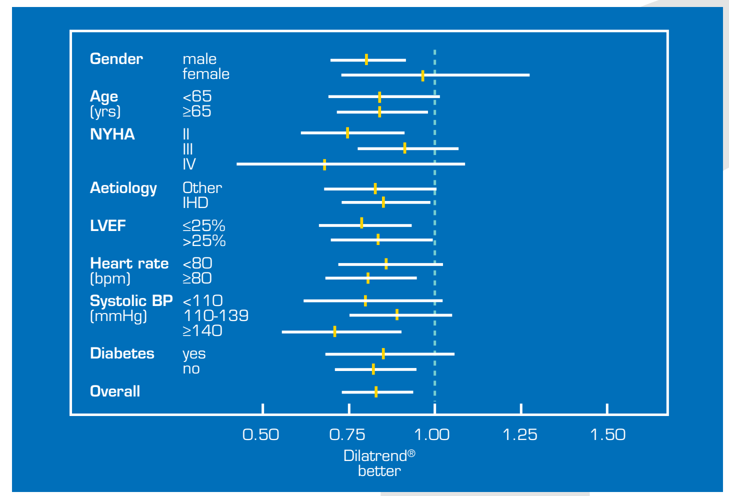


Figure 38: Pre-defined subgroups. The benefit of Dilatrend over metoprolol was consistent across all subgroubs studied in COMET

- COMET is the first ever head-to-head mortality study comparing two β-blocking agents in chronic heart failure
- With more than 14,000 patient years of follow up, COMET is the longest and largest study of β-blockade in chronic heart failure
- COMET demonstrates that Dilatrend® provides a highly significant 17% survival benefit (p=0.0017) over metoprolol
- COMET confirms that comprehensive β_1-, β_2- and α_1-blockade with Dilatrend® is superior to that of a conventional β_1-selective blocker
- COMET provides definitive evidence that Dilatrend® is the β-blocking agent of choice in chronic heart failure

7. Dilatrend®: Excellent Tolerability and Safety Profile

Agents such as β-blockers and α-blockers are associated with adverse events that are characterised as compensatory reactions to their haemodynamic effects. Mutual interaction of the combined therapeutic principles can in part neutralise these adverse events. [207] Vasodilation can induce a counter-regulatory increase in sympathetic activity, which may result in, for example, reflex tachycardia, and the renin-angiotensin system may be stimulated. This in turn increases the likelihood of sodium and, consequently, fluid retention.

- Because of its β-blocking activity, Dilatrend® counteracts the sympathetic reflex activation induced by its vasodilatory property. The antihypertensive effect of vasodilation remains undisturbed by the reflex activation of the sympathetic nervous system.

- Vasodilation simultaneously protects against some of the undesired effects of the β-blockade, such as Raynaud's phenomenon, reduced perfusion of the extremities, exhaustion and fatigue. Cardiodepression and bradycardia are almost completely non-existent. Thus, Dilatrend® induces a synergistic blood pressure reduction with neutralisation of negative effects of both principles.

Tolerability and safety in hypertensive patients

An important aspect, especially of antihypertensive drug treatment, is quality of life, which should at least not be negatively affected. The quality of life of hypertensive patients treated with either Dilatrend® or enalapril was compared in a study of 248 patients.[41] Neither treatment adversely affected patient quality of life, except for 12% of the enalapril patients who experienced discomfort from frequent cough, compared to none of the Dilatrend® patients.

Response rates (defined as DBP < 90 mm Hg or drop in DBP ≥ 10 mm Hg on treatment versus baseline) are approximately 80% with doses ≥ 25 mg o.d.[208] Overall, the percentage of hypertensive patients with at least one adverse event was lower under 25 mg doses of Dilatrend® (19.9%) than in the placebo group (26.9%); even the adverse events in the 50 mg Dilatrend® dosage group (26.4%) were virtually the same as the placebo events (Table 4).

Hypotensive reactions occurred only rarely and were most frequently observed after the first administration of the drug, generally at higher dosages. It can therefore be concluded that particular hypotensive side effect due to vasodilation (e.g. dizziness) may be avoided through a step-wise increase in dosing at the beginning phase of Dilatrend® treatment.

Reaction [%]	Dilatrend®		Placebo
	25 mg (n = 469)	50 mg (n = 794)	(n = 2275)
Dyspnoea	2.8	2.2	0.6
Asthenia	3.5	5.1	2.5
Dizziness	3.7	9.4	2.9
Dry mouth	0.9	0.1	0.1
Nausea	2.1	2.2	1.4
Chest pain	0.9	0.8	0.4
Diarrhoea	1.2	0.7	0.8
Somnolence	1.2	0.7	0.8
Abdominal pain	1.1	0.6	1.4
Malaise	1.7	1.1	0.5
Postural hypotension	0.6	0.8	1.8
Bradycardia	0.7	3.2	–
Hypotension	–	1.2	0.1
Peripheral perfusion disturbance	–	0.6	–
Dyspepsia	–	0.5	0.6
Headache	6.8	6.2	11.0
Percentage of patients with at least one adverse event	19.9	26.4	26.9

Table 4: Rate of adverse events reported for daily doses of 25 mg or 50 mg Dilatrend® (as a single, or twice-daily dose) in comparison to placebo. Events that were reported in less than 1% of Dilatrend®-treated patients and that were more frequent with placebo are not listed. (F. Hoffmann-La Roche, data on file.)

Tolerability and safety in patients with coronary artery disease

Dilatrend® was also shown to be well-tolerated in elderly patients and in patients with coronary artery disease.[44, 86, 96, 105]

The safety and tolerability of Dilatrend® and metoprolol were compared in younger and elderly patients with stable angina (Table 5).[147] This study was primarily designed to investigate the safety of 50 mg Dilatrend® in those patients who did not adequately respond to the 25 mg dose. The types and frequency of adverse events associated with active therapy were no different between Dilatrend® and metoprolol. Dizziness was the most frequent adverse event in both groups, but with no significant difference in the incidences (4.8% for Dilatrend® versus 5.0% for metoprolol). Similar results were observed for all the adverse events noted, especially with regard to the most frequent adverse events (bronchitis, asthenia and headache, which was the second most frequent event for metoprolol).

	Dilatrend® (n=248)		Metoprolol (n=120)	
	No. (with AE)	% (with AE)	No. (with AE)	% (with AE)
Dizziness	12	4.8	6	5.0
Bronchitis	9	3.6	3	2.5
Asthenia	8	3.2	3	2.5
Headache	8	3.2	4	3.3
Back pain	6	2.4	2	1.7
Gastro-enteritis	4	1.6	4	3.3
Sinusitis	4	1.6	1	0.8
Upper respiratory infection	3	1.2	4	3.3
Angina pectoris	2	0.8	–	–
Dyspepsia	2	0.8	–	–
Dyspnoea	2	0.8	–	–
Gastritis	2	0.8	–	–
Postural hypotension	2	0.8	–	–
Myocardial ischaemia	2	0.8	2	1.7
Nervousness	2	0.8	1	0.8
Diarrhoea	1	0.4	2	1.7
Malaise	1	0.4	1	0.8
Sum of AEs (%)	–	28.0	–	27.4

Table 5: Adverse events (AEs) profile of Dilatrend® and metoprolol patients with coronary artery disease (all AEs that occurred in at least 2 patients).

Tolerability and safety in patients with CHF

The safety profile of Dilatrend® in CHF patients has been well established and documented. The most relevant safety data in CHF come from two large-scale, double-blind, placebo controlled studies: the US Carvedilol Program investigating the safety and efficacy of Dilatrend® predominantly in patients with mild to moderate CHF,[180], and the COPERNICUS study investigating the safety and efficacy of Dilatrend® in severe CHF patients.[209] Interestingly, no major differences in Dilatrend®'s safety profiles were found between the two studies, although, due to the more severely affected study population in COPERNICUS, a higher rate of adverse events could have been expected (Table 6).

Symptoms of worsening heart failure such as dyspnoea, fatigue/asthenia and peripheral and generalised oedema were among the most frequently observed adverse events in both studies. Importantly, during initiation of study treatment, there was no increase in the incidence of worsening heart failure between Dilatrend® and placebo. During continued treatment, this incidence was higher in the placebo group.

In both studies the incidence of adverse events was initially slightly higher in the Dilatrend® group than in the placebo group, but this was reversed with continued treatment. This was mostly due to vasodilatory events, bradycardia, heart block and worsening heart failure, all reflecting the pharmacological profile of the drug. For those drug-specific adverse events the difference between Dilatrend® and placebo groups after 90 days was equalised (AV block), reduced (vasodilatory events) or even reversed (serious bradycardia).[210]

The adverse events occurring in > 2% of patients exposed to Dilatrend® from both trials (with frequency higher in the Dilatrend® than placebo group) were examined in order to compare the safety profile of Dilatrend® in the two trials. Using a programmed spreadsheet for risk estimations, study-specific relative risk estimates were prepared for each adverse event of interest, and then compared across studies. Overall, the safety profiles of events in the two trials were similar.

Four events – AV block, bradycardia, blurred vision and back pain – showed slight differences in relative risk. However, these differences did not reach statistical significance. The relative risk for back pain was higher in the COPERNICUS trial than in the US Carvedilol Program, while all of the other relative risks were higher in the US Carvedilol Program.

In conclusion, the adverse event profile of Dilatrend® in the two large-scale CHF studies were similar from both a clinical and statistical point of view, and consistent with the pharmacological profile of the drug.

Table 6a: Adverse events profile of Dilatrend® in mild-to-moderate and severe heart failure.

Adverse event profile of Dilatrend versus placebo in severe CHF†*	Placebo %	Dilatrend %	Adverse event profile of Dilatrend versus placebo in mild to moderate CHF‡*	Placebo %	Dilatrend %
Cardiovascular System			**Cardiovascular System**		
Heart failure	31.5	26.0	Heart failure	21.0	16.0
Hypotension	8.2	13.9	Hypotension	3.4	8.5
Bradycardia	2.7	10.3	Bradycardia	0.9	8.8
Syncope	5.0	7.6	Syncope	2.5	3.4
Hypertension	2.2	2.6	Hypertension	2.5	2.9
AV block first degree	1.6	2.3	AV block first degree	0.5	2.9
Angina pectoris	4.1	5.5	Angina pectoris	1.1	2.0
Chest pain	7.6	6.8	Aggravated chest pain	14.2	14.4
Respiratory System			**Respiratory System**		
Bronchitis	4.5	5.2	Bronchitis	4.3	5.4
Upper respiratory infection	12.6	13.6	Upper respiratory tract infection	17.6	18.3
Dyspnoea	11.0	11.2			
Cough increased	4.2	4.5	Pharyngitis	2.7	3.1
Lung disorder	3.2	4.0			
Metabolic and Nutritional Disorders			**Metabolic and Nutritional Disorders**		
Weight gain	10.7	11.7	Weight increase	6.9	9.7
Hyperglycaemia	3.3	4.5	Hyperglycaemia	7.8	12.2
Gout	2.7	3.5	Gout	6.2	6.3
Creatinine increased	1.4	2.9	NPN increased	4.6	5.8
Hyperkalaemia	1.9	3.3	BUN increased	4.6	6.0
			Hypercholesterolaemia	2.5	4.1
			Dehydration	1.6	2.1
			Hypervolaemia	0.9	2.0
Body as a Whole			**Body as a Whole**		
Asthenia	9.4	10.9	Fatigue	22.4	23.9
Back pain	1.4	2.9	Back pain	6.6	6.9
Generalised oedema	4.9	6.0	Oedema generalised	2.5	5.1
Pain in extremity	2.5	2.1	Pain	7.6	8.6
Accidental injury	2.0	1.7	Injury	5.5	5.9
Peripheral oedema	6.4	7.0	Oedema legs	0.2	2.2
			Oedema dependent	1.8	3.7
			Fever	2.3	3.1
			Drug level increased	3.7	5.1

Table 6b: Adverse events profile of Dilatrend® in mild-to-moderate and severe heart failure.

Adverse event profile of Dilatrend versus placebo in severe CHF†*	Placebo %	Dilatrend %	Adverse event profile of Dilatrend versus placebo in mild to moderate CHF‡*	Placebo %	Dilatrend %
Central Nervous System			**Central Nervous System**		
Dizziness	16.8	24.1	Dizziness	19.2	32.4
Headache	3.0	4.8	Headache	7.1	8.1
			Paraesthesia	1.8	2.0
Gastrointestinal			**Gastrointestinal**		
Diarrhoea	3.1	4.8	Diarrhoea	5.9	11.8
Nausea	3.3	3.8	Nausea	4.8	8.5
Abdominal pain	3.0	2.2	Abdominal pain	7.1	7.2
			Vomiting	4.3	6.3
Urinary System Disorders			**Urinary System Disorders**		
Urinary tract Infection	2.4	1.6	Urinary tract infection	2.7	3.1
Kidney function abnormal	2.3	2.1	Haematuria	2.1	2.9
Haematologic and Lymphatic System			**Haematologic and Lymphatic System**		
Anaemia	2.0	2.4	Thrombocytopenia	0.5	2.0
Musculo-skeletal System			**Musculo-skeletal System**		
Muscle cramps	1.2	2.0	Myalgia	2.7	3.4
			Arthralgia	4.8	6.4
Vision Disorders			**Vision Disorders**		
Blurred vision	2.2	2.8	Vision abnormal	1.8	5.0
Immunological System			**Immunological System**		
Infection	2.4	2.5	Infection	0.9	2.2
Endocrine Disorders			**Skin and Appendages Disorders**		
Diabetes mellitus	1.7	2.0	Sweating	2.1	2.9

† Data from the COPERNICUS study, adverse events listed by body system, incidence ≥ 2%, regardless of causality
‡ Data from the US carvedilol trial program, adverse events listed by body system, incidence > 2%, regardless of causality
* Only those adverse events were taken into consideration where the incidence was higher in the Dilatrend group versus placebo (exception was heart failure)
NPN = non-protein nitrogen
BUN = blood urea nitrogen

Tolerability and safety in combination with other drugs

The management of CHF, hypertension and coronary heart disease, for which Dilatrend® is indicated, often requires the administration of a combination of two or more medications. This means that there is potential for drug interactions to occur. Drug interactions are difficult to predict because of the high degree of inter-individual variability. Certain drug interactions may be avoided through knowledge, sound clinical judgement and/or drug level measurements (Figure 39).

- Several studies have shown good tolerability during co-administration of Dilatrend® with calcium channel blockers.[121]
- The safety and tolerability of co-administration with Dilatrend® and hydrochlorothiazide has been well documented in several studies in patients with essential hypertension.[211, 212, 213]
- The safety and tolerability of combination therapy with Dilatrend® and isosorbide dinitrate in patients with chronic stable coronary artery disease has also been demonstrated.[149]
- In the case of co-administration with anti-arrhythmics, however, as with conventional β_1-selective β-blockers, it is recommended that ECG and blood pressure should be monitored.
- Co-administration with Dilatrend® and digoxin may increase the digoxin concentration by about 15%, however there are several studies showing the benefit of this combination in CHF patients.[214, 215, 216] Regular monitoring of plasma digoxin levels is recommended when initiating, adjusting or discontinuing Dilatrend®.[217]
- Interaction between Dilatrend® and cyclosporin has been investigated in one study.[218] This study showed that there is a wide inter-individual variability in the cyclosporin dose adjustment required. The recommendation was that cyclosporin blood concentration be monitored closely after initiation of Dilatrend® therapy and the dose of cyclosporin adjusted as appropriate.
- Two studies have demonstrated that Dilatrend® does not decrease the insulin sensitivity in hypertensive and in CHF patients.[116,135] However, until further studies are performed, regular monitoring of blood glucose levels is recommended in type 2 diabetes mellitus patients taking insulin or oral hypoglycaemics.
- It has been shown that concomitant use of Dilatrend® with inducers and/or inhibitors of hepatic metabolism is well-tolerated.[219] One still has to consider that these co-medications may cause Dilatrend® serum levels to increase (inhibitors of mixed function oxidases, e.g. cimetidine) or decrease (inducers of mixed function oxidases, e.g. rifampicin). Therefore regular monitoring of blood pressure and heart rate is recommended in patients with these co-medications.

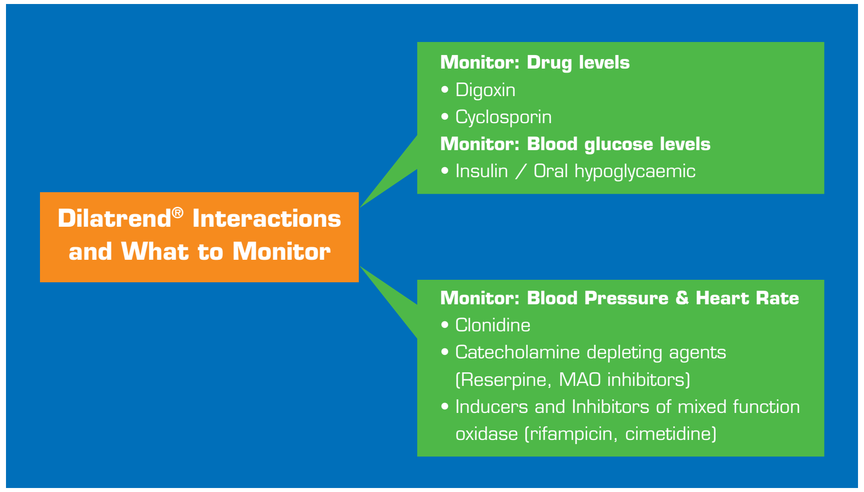


Figure 39: Dilatrend®: potential interactions and recommendations for monitoring.

8. Dilatrend®: Easy To Use

Dilatrend® has **consistently proven to be easy to use**, for both patients and physicians, with a good dosing schedule (once daily in hypertension, twice daily in chronic angina and CHF). It is effective, with a good safety profile, across the cardiovascular continuum, including patients with concomitant disorders. It is effective in all patient populations, regardless of age, gender, race or concomitant diseases, and can be safely used in combination with other agents.

The following section briefly illustrates how to use Dilatrend® for the treatment of patients with CHF. The recommendations follow the guidelines of leading societies such as the European Society of Cardiology,[205] the American College of Cardiology and the American Heart Association.[206]

Patients

Potential CHF patients for treatment with Dilatrend® should have none of the classical contraindications for β-blockade, and should be euvolaemic without symptoms of fluid retention. They should have been stable for at least 2 weeks regarding symptoms and basic medication, which must include standard optimised medication for CHF (at least diuretics and ACE inhibitors, possibly also digitalis glycosides). In patients with severe CHF, initiation of Dilatrend® therapy should be performed by a physician experienced in the treatment of CHF with β-blockade in all countries.

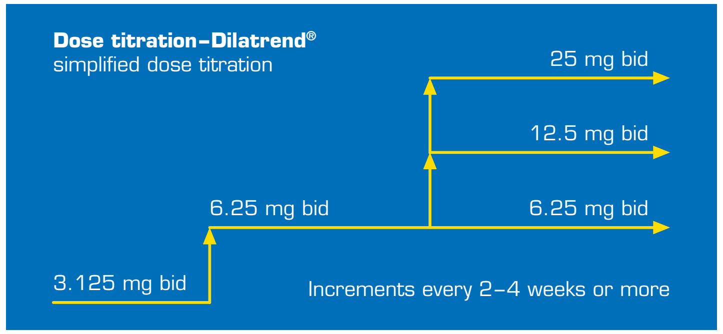


Figure 40: Initiation and up-titration of Dilatrend® therapy in CHF.

Dosing

Dilatrend® therapy is initiated with 3.125 mg twice daily, and medical supervision is recommended for the initial dose (Figure 40). Up-titration of Dilatrend® can then commence; the dose should be doubled every 2-4 weeks, with a target dose of 25 mg twice daily, or the highest tolerated doses (50 mg twice daily is recommended in patients with body weight > 85 kg).

Management

Any side effects that occur after initiation of therapy can be effectively managed. For example, symptoms of CHF, such as increasing dyspnoea and decreasing exercise capacity, can be managed in a number of ways. The dosage of concomitant therapy, e.g. diuretics and/or ACE inhibitors, can be increased. If necessary, the dose of Dilatrend® can be reduced, or the titration interval prolonged. Other possible causes should be sought, however, which may include thyroid malfunction, intercurrent infections, non-compliance of drug intake and excessive liquid intake or fluid retention.

For blood pressure reduction symptoms, e.g. hypotension or orthostatic dizziness, the diuretic dose can be reduced, as can the ACE inhibitor dose if necessary. If this is not successful, then the dose of Dilatrend® can be reduced, or the titration interval prolonged.

At signs of bradycardia, the dose of digitalis (and/or concomitant amiodarone therapy) should be checked and a reduced dose considered. Thereafter, Dilatrend® dose can be reduced by one titration step, or the titration interval can be prolonged. Dilatrend® should only be stopped if symptoms or haemodynamic compromise by bradycardia are observed.

If symptoms of bronchial obstruction occur, other possible causes should be sought, such as concurrent infections or subacute pulmonary oedema. The Dilatrend® dose should only be reduced or withdrawn in case of severe bronchial obstruction and after other possible causes of symptoms have been ruled out.

Maintenance

As with many drugs, Dilatrend®'s optimal therapeutic effect is obtained with high doses (e.g. 25 mg twice daily), but even lower doses have proven to be effective in terms of a significant reduction in mortality and hospitalisation rates,[184] and inhibiting the progression of CHF (Figure 24). Slow and careful titration is recommended in order to reach the target doses of 25 mg twice daily, respectively 50 mg twice daily over 85 kg.

The absolute contraindications for β-blockade should be strictly adhered to, and care should be taken that fluid retention does not occur. The patient should be referred to a hospital or a cardiologist experienced in the treatment of CHF as soon as problems occur that might indicate potential decompensation. Withdrawal of Dilatrend®, if necessary, should be performed gradually by down-titration. A potential worsening of CHF symptoms seen in some patients at the beginning should not be a reason for discontinuation of Dilatrend® therapy, and do not preclude later benefit.

9. Summary

Dilatrend® – the ideal β-blocking agent

The properties of Dilatrend®, and the data obtained from numerous experimental and clinical investigations, show that Dilatrend® easily fulfils the five key properties of an ideal β-blocking agent:

Comprehensive receptor blockade

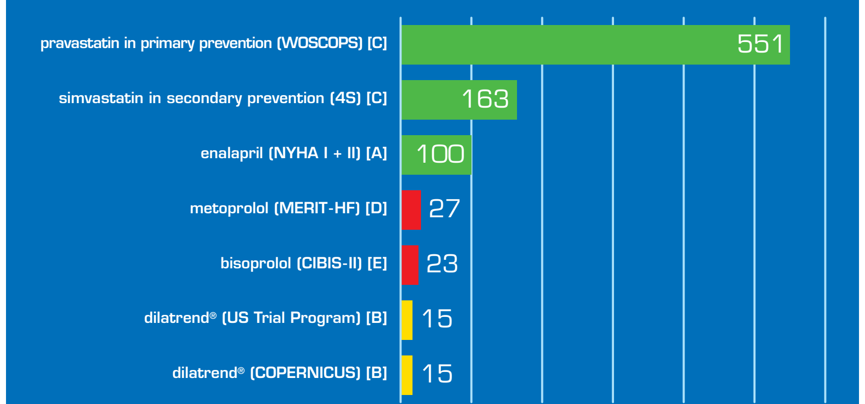
Dilatrend® is a potent antagonist of the β_1, β_2 and α_1 adrenergic receptors, with no intrinsic sympathetic activity, and is extremely effective in inhibiting chronic activation of the sympathetic nervous system.

Effective and well tolerated across the cardiovascular continuum

The results of many trials in hypertension, CAD, and the large database of the unique Dilatrend® clinical trial programme in CHF demonstrate that Dilatrend® is effective across the entire cardiovascular continuum.

Saves lives

Dilatrend®'s unique mode of action does transfer into saving lives. Compared to the conventional β_1-selective β-blockers metoprolol and bisoprolol, Dilatrend® saves more lives as fewer patients need to be treated (number needed to treat (NNT) to save one life (Figure 41).



[A] Bandolier. 17(1995);137.
[B] F. Hoffman-La Roche AG,data on file.
[C] Kumana CR, Cheung BMY, Lauder IJ. Gauging the impact of statins using number needed to treat. JAMA. 282 (1999); 1899-1901.
[D] Data calculated from MERIT-HF Study Group, Lancet. 353 (1999); 2001-2007
[E] calculated from CIBIS-II Investigators, The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. Lancet. 1999 (353); 9-13.

Figure 41: Number of patients needed to treat for one year to save one life. As compared to outcome studies with statins, ACE inhibitors or conventional β_1 selective β-blockers, significantly fewer patients need to be treated to save one life.

Evidence base

Largest evidence base of any β-blocker across the full spectrum of CHF.

Good tolerability/safety profile

Dilatrend® consistently demonstrates fewer, and less serious side-effects than other cardiovascular agents, and is extremely well tolerated. It has demonstrated safety and efficacy in all patient populations, and when used in combination with other agents.

Easy to use

Across the cardiovascular continuum, Dilatrend® has a practical and simple dosing schedule (once or twice daily), making it easy to use for patients and physicians.

Dilatrend® amply fulfils all the criteria of the ideal β-blocking agent.

10. Appendix: Chemistry, Toxicology, Pharmacokinetics

Chemistry

The International Non-proprietary Name (INN) of the active ingredient is carvedilol. The structural formula of carvedilol is shown in Figure 42.

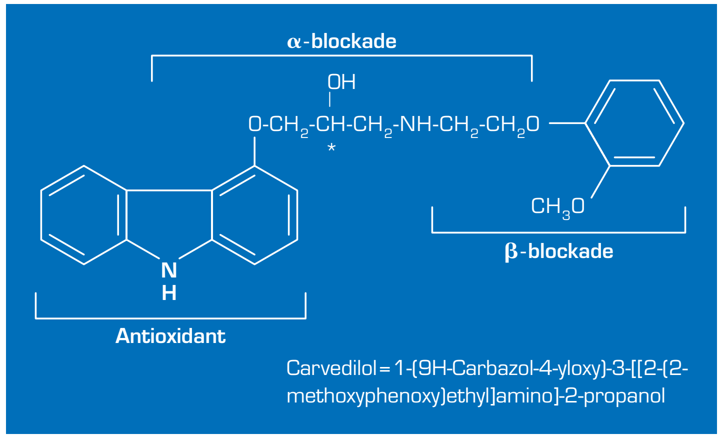


Figure 42: Structural formula of carvedilol: Carvedilol = 1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanolol.

Laboratory codes:	BM 14.190, SK&F 105517, Ro 205-2179/000; DQ-2466
Chemical name:	(±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxy)ethyl]amino]-2-propanol
Molecular formula:	$C_{24}H_{26}N_2O_4$
Molecular weight:	406.55

Carvedilol is a white to off-white crystalline powder and has low solubility in water (0.01 mg/ml). The apparent oct/water for carvedilol is 500. A pKa of 7.8 was obtained for the secondary amine group. Carvedilol is essentially nonhygroscopic. It is a racemic compound with an asymmetric centre at the secondary C-atom of the propanol side chain. The enantiomers have been characterised and investigated pharmacologically. R(+)-carvedilol and S(-)-carvedilol possess similar α_1-adrenoceptor blocking and antioxidative properties. Only the S(-)- enantiomer has β-adrenoceptor blocking activity.[55]

Plasma concentrations of carvedilol can be analysed using an HPLC method described by Reiff (1987).[221]

Toxicology

Acute toxicity

Mouse, female:

36 mg/kg i.v., 364 mg/kg i.p., > 8000 mg/kg p.o.

Mouse, male:

27 mg/kg i.v., 568 mg/kg i.p., > 8000 mg/kg p.o.

Rat, female:

25 mg/kg i.v., 769 mg/kg i.p., > 8000 mg/kg p.o.

Rat, male:

27 mg/kg i.v., 1244 mg/kg i.p., > 8000 mg/kg p.o.

Chronic toxicity

In chronic toxicological studies, the liver was identified to be the target organ. Increases in organ weight, biliary epithelial hyperplasia and liver cell hyperplasia were found. However, the doses required for showing these effects are at least 30 times higher than those for inducing β-adrenoceptor antagonism. No other evidence for substance-related toxic effects was observed in chronic toxicity studies carried out in rats (up to 18 months) and dogs (up to 12 months).

Carcinogenicity and mutagenicity

Carcinogenicity studies in rats and mice with dosages up to 75 mg/kg/day and 200 mg/kg/day, respectively (150 to 400 times the human dose), revealed no sign of carcinogenic effects. No mutagenic effects of carvedilol were seen *in vitro* or *in vivo*.

In studies investigating embryotoxicity of carvedilol in rats, doses of 60 mg/kg/day were slightly toxic and 300 mg/kg/day severely toxic for the pregnant animals. At the high dose of 300 mg/kg/day, embryotoxic and foetotoxic effects were observed in rats (increased numbers of resorptions, reduced numbers of successful matings, decrease in foetal weight). In rabbits, a dose of 75 mg/kg/day led to a slight increase in intra-uterine resorption. In studies investigating the peri- and postnatal toxicity in rats at 60 mg/kg/day, reduced foetal weight and delayed physical development of the F1 generation was observed. At the toxic dose of 300 mg/kg/day, adult rat fertility showed a prolonged mating time, reduced number of successful matings, significantly fewer corpora lutea, implants per dam and a decrease in foetal weight. It was shown in rats that carvedilol is excreted through the mother's milk. No experience has been gained for the use of carvedilol during pregnancy and lactation periods in women.

Pharmacokinetics

An overview of the pharmacokinetic profile of carvedilol has been published.[222] After oral administration, carvedilol is almost completely and rapidly absorbed from the gastrointestinal tract. Maximum plasma concentrations are reached within two hours after ingestion. After a single dose of 25 mg, concentrations of 50-100 ng/ml carvedilol are reached. There is a dose-linear kinetic pattern.[223] Due to first-pass metabolism in the liver, the absolute bioavailability is about 25% after oral administration. [224, 225, 226] In patients with impaired liver function, the bioavailability may be increased up to 80%.[227] Therefore, for patients with severely impaired liver function, either carvedilol should not be used or dose adjustment is needed.

The plasma protein binding is about 98%, but interactions due to displacement from protein binding were not found, even though those compounds are also highly protein-bound, such as phenprocoumon,[228] digitoxin, glibenclamide or warfarin. The volume of distribution is about 2 L/kg, indicating extensive extravascular tissue distribution. The plasma concentrations of the R(+)-enantiomer are 2 - 3 times higher than those of the L(-)-enantiomer, indicating stereo-specific metabolism.[225, 229] The total plasma concentrations vary considerably between the individuals, but there are small intra-individual variations with respect to total plasma concentrations and to those of the enantiomers.

Following oral administration, the elimination half-life is approximately 6 - 8 hours. In CHF patients, the half-life is increased slightly, resulting in some accumulation of carvedilol; however, this increase is not clinically relevant. The total plasma clearance is approximately 600 ml/min; only a small part is due to renal elimination (5 ml/min).

Carvedilol is extensively metabolised in the liver. Demethylation of the phenyl ring and hydroxylation on both ring systems and subsequent conjugation (e.g. glucuronidation) are the major routes of metabolism.[230] The P450 family seems to be involved in the metabolism of carvedilol, such as CYP2D6,[229] with the consequence that poor metabolisers of the debrisoquine type (< 10% in Caucasian population) may have increased carvedilol plasma concentrations. Also, various other members of the P450 family are involved in carvedilol's metabolism. Additionally, there are non-oxidative pathways of elimination. Therefore, the activation or blockade of one individual P450 enzyme has only limited influence of the disposition of carvedilol in an individual.[231]

Three of the metabolites have some β-blocking activities. Although these metabolites occur at most at 10 times lower concentrations than the parent compound, one of the metabolites may contribute to the β-blocking activity after oral administration of carvedilol. There is no evidence that any metabolite contributes to the α_1-adrenoceptor antagonism of carvedilol. The carbazol hydroxylated metabolites exhibit strong antioxidative properties.[56]

Due to primarily biliary excretion, about 60% of a single oral dose of carvedilol is excreted as metabolites via the liver. Only 1% is eliminated as unchanged compound via the kidneys. Therefore, accumulation in patients with impaired renal function does not occur; dose adjustment is not needed in those patients.[232] Even in haemodialysed patients, there are no altered pharmacokinetic patterns since carvedilol does not cross the dialysis membrane.[125, 126] There are no obvious differences in the pharmacokinetic variables between younger and elderly patients.[96]

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Carvedilol is marketed under the following trade names: Cardiol®, Coreg®, Coropres®, Dilatrend®, Dilbloc®, Dimitone®, Eucardic®, Kredex®.

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