Review

The mechanism of action of calcium channel blockers in the treatment of diabetic nephropathy

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Abstract

Three types of calcium channels have been identified voltage-sensitive, receptor operated (cardiac muscle and vascular smooth muscle) and stretch operated (in some blood vessels) channels. Using electrophysiological and pharmacological techniques, three different types of voltage-gated calcium channels have been identified, namely, L-type (for long lasting, large channels), T-type (for transient, tiny channels) and N-type (for neuronal, neither L nor T). Many compounds are known to have a calcium channel inhibitory effect. Calcium antagonists, based on the specificity of inhibition of the slow calcium current, can be classified into three groups: Group A: for 90 to 100 percent inhibition of calcium influx without change in the sodium current (verapamil, diltiazem and the dihydropyridines); Group B: for 50 to 70 percent inhibition of calcium influx current without change in the sodium current (bepridil, cinnarizine and pirenpanyline) and Group C: for agents exhibiting some inhibition of calcium influx (phenytoin, indomethacin and propranolol). There is now increasing evidence that, certain calcium channel blockers especially the dihydropyridines are more strongly associated with vasodilation of afferent arterioles than of efferent arterioles and also with increase intraglomerular pressure and albuminuria. Thus they have a beneficial effect in terms of reducing proteinuria and slowing the progression of diabetic renal failure.

Key words: Amlodipine, calcium channel blockers, diabetic nephropathy, diabetes mellitus, ischaemia

Pharmacoeconomics

By the year 2000, it is estimated that 85,000 individuals will enter into ESRD annually, incurring yearly medical expenditures of approximately US$50,000 per individual. ESRD patients are estimated to consume more than 10 times the health care resources of the average US citizen. Many studies have been performed to clarify the potential benefits of reducing DNP and ESRD in diabetic patients and have confirmed the cost-effectiveness of nephroprotective strategies in the diabetic population primarily through a reduction in ESRD related case costs.1,2

Calcium Channel Blockers

Calcium ions are vital in many biologic processes including a variety of enzymatic reactions, activation of excitable cells, coupling of electrical activation to cellular secretion, haemostasis and the metabolism of bone. Calcium antagonists are drugs whose pharmacologic actions are derived primarily from the blockage of calcium influx through calcium channels in excitable membranes. They affect the entry of calcium rather than its intracellular actions and are referred to by some authors as “Calcium Entry Blockers” to make their actions clearer. Since extracellular calcium concentration is approximately 10,000 times greater than its intracellular concentration in a resting smooth muscle, it is clear that small changes in the permeability of calcium across the plasma membrane could have a significant effect on cellular function. The calcium ion is an almost ubiquitous intracellular second messenger. This indicates the multiplicity of the effects associated with drug actions aimed at interfering with calcium ions. In view of the widespread involvement of intracellular calcium as a regulator of cell function, calcium antagonists have been shown to affect many different physiological processes, including secretion of hormones, muscle contraction, platelet function and neurotransmitter release. However, when given to man or experimental animals, their major effects are related to the heart and vascular smooth muscle and their other actions are relatively unimportant. This tissue specificity is critically important in practice. One important factor of this specificity is heterogenicity of calcium channels. Another factor that leads to physiological selectivity is the characteristic of many calcium antagonists that show properties of “use-dependence” i.e. blocking more effectively in those cells in which the calcium channels are most active. Many investigators also show “voltage dependent” blocking actions i.e., blocking more strongly when the membrane is depolarized; this may be partially responsible for the marked selectivity that some drugs show between different kinds of smooth muscles.3

Types of Calcium Channels

Three types of calcium channels have been identified-voltage-sensitive, receptor operated (cardiac muscle & vascular smooth muscle) and stretch operated (in some...
blood vessels) channels. The regulation of calcium ions depends on both the entry and exit of calcium across the plasma membrane and on the sequestration and release of calcium within the cell. At the membrane level, calcium entry into the cell occurs partly through voltage gated calcium channels (VGCCs) which open when the cell membrane is depolarized. VGCCs belong to a family of homologous proteins that also includes channels for sodium and potassium. In addition, there are believed to be receptor-operated calcium channels (ROCCs), which are coupled to excitatory receptors either directly or via G-proteins and open in response to receptor ligands, such as noradrenaline acting on alpha-adrenoceptor. In general, calcium channels are membrane-spanning, funnel-shaped glycoproteins that function like ion selective valves. They form a water-filled pore that open and close to permit calcium ions to move in the direction of its electrochemical concentration gradient. Each channel has outer and inner gates; the outer gates are specifically blocked by tetrodotoxin in fast channels and by calcium channel blockers in slow channels. The inner gates, particularly in slow channels, appear to be dependant on the phosphorylation state of the membrane. The position of a channel gate, which is a portion at or near the inner side of the gate, indicates whether the channel is in the closed or open state. Verapamil and diltiazem block slow channel conduction at the inner gate and possess some fast channel blocking activity as well.4

When conformational changes in the channel macromolecule occur, the activation and inactivation gates move into and out of an occluding position. This determines opening and closing of the channel pore. Calcium binding sites present in the pore ensure ion selectivity of the channels. Phosphorylation sites as well as drug and toxin binding sites of the channel macromolecule play important roles in the regulation of the channel. It should be emphasized that the exact macrostructure of the channel proteins, putative gates and other regulatory sites is unknown at this time.5

Though the direct evidence for ROCCs appears to be strong, they have so far eluded identification experimentally and some even doubt their existence. ROCCs do not appear to be targets for any of the known types of calcium antagonists which act only on VGCCs.6

Types of VGCCs
Using electrophysiological and pharmacological techniques, Tsien et al7 identified three different types of VGCCs which they called L-type (for long lasting, large channels), T-type (for transient, tiny channels) and N-type (for neuronal, neither L nor T). They are classified according to their activation and inactivation kinetics, their conductances, their ion specificity and their sensitivity to drug and toxin. Subsequently, high threshold VGCCs were found to exist in some neurons and were termed P-type channels (for purkinje cells).

There are several endogenous and exogenous modulators that inhibit calcium channels, including dependence of the tissue on external calcium ions, existence of calcium channel subtypes, voltage dependence of drug binding and effects, and frequency dependence of drug effects. All excitable tissues contain voltage dependent calcium channels and high affinity, reversible and stereospecific binding sites for calcium channel-inhibiting drugs. However, calcium antagonists do not affect every tissue equally.7

L-type channels
These are widely distributed in many tissues particularly in heart, smooth and skeletal muscles. They are highly sensitive to the dihydropyridines e.g. nifedipine, phenylalkylamines e.g. diltiazem. There appear to be diverse forms of the L-type channels (L1,2,3,4 isoforms) allowing tissue selectivity and diversity of function.5,9

N-type channels
These N-type channels generally seemed to be sensitive to W-contoxins and in certain instance may be coupled to transmitter release whereas selective antagonists of L-type channels do not normally modify neurotransmitter release. Like T but unlike L, N- channels, contribute to phasic currents and require strongly negative holding potentials for complete removal of inactivation. Like L but unlike T, N – current requires strong depolarization for activation and is relatively sensitive to the inorganic blockers cadmium.10

P-type channels
These were proposed by Llinas et al12 on the basis that, dihydropyridine and contoxin resistant currents present in cerebellar Purkinje and granule cells. The most selective toxin is funnel web spider venom. They may form a larger proportion of calcium channels in the brain. Although several calcium ion channels are known, all presently available CCBs act preferentially or solely on one of them, the L-channel.

History of calcium channel blockers
Calcium channel blocking drugs represent one of the more important clinical pharmacological advances of this decade. The discovery of calcium antagonism occurred by chance in November 1963 as a new principle of action of coronary drugs, when it was reported that two new compounds, later given the generic names verapamil and prenylamine, mimicked the cardiac effect of simple calcium withdrawal in that they diminished calcium dependent high energy phosphate utilization, contractile force and oxygen requirement of the beating.13

In 1969, the term calcium antagonists were given a novel drug designation. In an extensive search for other calcium antagonists, a considerable number of substances that also met these criteria were identified in 1975 e.g. nifedipine, nimodipine. In 1975, Japanese pharmacologists introduced diltiazem to this group.14

Fleckenstein15 stated that complete blockage of transmembrane calcium ions entry is incompatible with life and therefore the term calcium blockade should be avoided. However, the term calcium antagonist implies that calcium and its antagonists interact at specific receptors. This is
probably not the case, as their predominant action is to reduce calcium ions influx at specific sites including cell membrane. For these reasons, the term calcium channel blocking drug was preferred. Also, they were referred to by some authors as calcium entry blockers as their primary action is inhibition of the inward movement of calcium ions through voltage-dependent calcium channels at different sites.

Classification

Several thousand compounds are known to have a calcium channel inhibitory effect. Fleckenstein classified calcium antagonists, based on the specificity of inhibition of the slow calcium current, into: Group A: for 90 to 100 percent inhibition of calcium influx without change in the sodium current (verapamil, diltiazem and the dihydropyridines); Group B: for 50 to 70 percent inhibition of calcium influx current without change in the sodium current (bepridil, cinnarizine and prenylamine); Group C: for agents exhibiting some inhibition of calcium influx (phenytoin, indomethacin and propranolol).

Robertson and Robertson divided CCBs into three groups: Group I is the group that blocks VGCCs in the myocardium and arteries. This group was further subdivided into: Group IA, which consists of drugs that affect myocardium with no action on SA or AV nodes and includes dihydropyridines e.g. amlodipine, nifedipine and nicardipine and Group IB, which has additional action on SA and AV nodes and includes phenylalkylamines (verapamil, anipamilard and gallapamil), benzoiazepines (diltiazem). Group II drugs block calcium channels of peripheral arteries, but spare myocardium, and includes diphenylpiperazines, cinnarizine and flunarizine. Group III contains drugs which have action on calcium and fast sodium channels, having selective myocardial effect and includes bepridil, prenylamine and tiapamil.

Mechanism of action

The interaction of the calcium channel modulators with calcium channels is complex. Three distinct but allosterically interacting receptors exist for the three different chemical classes of drugs- 1-4 dihydropyridines (nifedipine-like drugs), phenylalkylamines (verapamil-like drugs) and benzoiazepines (diltiazem-like drugs). All these receptors are located on the VGCCs. The effects of calcium antagonists are membrane potential (voltage) dependent. The binding and effects of calcium antagonists are stereoselective. Generally, stereoisomers of the same compound produce qualitatively the same effects, with one stereoisomer being more effective than the other. In a few special situations, the stereoisomers produce opposite pharmacological effects. While the (R)-enantiomers of Bay, K-8644 and 202-791 (two recently synthesized experimental 1,4-dihydropyridine derivatives), act like calcium antagonists, the (S)-enantiomers are calcium agonists. It has been postulated that either conformational alterations occur in the receptors and/or separate binding sites exist for agonists and antagonists.

Rang et al. showed that CCBs exert their effect through either the production of a physical plug-like obstruction or distortion of the membrane through a nonspecific interaction with the membrane phospholipids, that surround and functionally modulate ion transport by channel proteins. However, it was found that dihydropyridines, which bind to alpha, subunit of the calcium channel, affect channel function in a complex way, not simply by physical plugging of the pore. This became clear when some dihydropyridines were found to bind to the same site but to act in the converse way, that is, to promote the opening of VGCCs.

Calcium antagonists exhibit different binding affinities. Depending on the membrane potential (voltage) and the frequency of channel opening, it is thought that calcium antagonists bind with highest affinity to channels in the inactivated state. The channels can exist in one of three distinct states; mode 0, 1, and 2. When a channel is in mode 0, it does not open in response to depolarization. In mode 1, depolarization produces a low opening probability and each opening is brief. In mode 2, depolarization produces a very high opening probability and single openings are prolonged. Under normal conditions, about 70% of the channels at any one moment exist in mode 1, with only 1% or less in mode 2. Each channel switches randomly and quite slowly between the three modes. Dihydropyridines of the antagonists type bind selectively to channel in mode 0, thus favouring this non-opening state.

It was found that only the L-type channels were sensitive to calcium channel-inhibiting drugs. Since the distribution of the channel subtypes differs in various tissues, drug sensitivity of the tissues is also different. In addition, even the L-type calcium channels are different in various tissues with respect to their affinities for calcium antagonists. CCBs bind to the receptors with higher affinity under depolarized rather than polarized conditions. The effects of one calcium antagonist should not be extrapolated to another of a different subtype because drugs belonging to different subtypes have different pharmacological effects.

CCBs and DNP

There is now increasing evidence that, certain CCBs especially DHPCCBs is more strongly associated with vasodilation of afferent arterioles than of efferent arterioles and also with increase intraglomerular pressure and albuminuria. Thus they have a beneficial effect in terms of reducing proteinuria and slowing the progression of diabetic renal failure. They are attributed nephroprotective capacity beyond their blood pressure lowering capacity, by decreasing production of lymphokines by the mesangial cells and decelerating disease progression. In addition, Luno et al. stated that non-dihydropyridine type also has been shown to have a beneficial effect on DNP, decreasing proteinuria and slowing progression of the disease.

Tarif and Bakris showed that, DHPCCBs effectively reduce arterial pressure but do not significantly affect proteinuria nor prevent development of glomerular scarring. Conversely, the non-DHPCCBs blunt both the rise in proteinuria as well as mesangial matrix expansion and subsequent glomerular scarring in diabetes. Additionally, the non-DHPCCBs markedly attenuate development of glomerular scarring in the remnant kidney model. The
primary reasons for these differences between subclasses of CCBs relate to a lack of the following attributes by DHPCCBs— they fail to reduce glomerular membrane permeability which is increased in DNP, they fail to affect the synthesis of certain key matrix proteins that perpetuate development of glomerular scarring (this effect may be due to the differential expression of calcium channels within the glomerular mesangium) and they totally abolish renal autoregulation in DNP, an effect not observed with non-DHPCCBs. Furthermore, additional putative mechanisms include, antagonizing of preglomerular vasoconstriction, the ability to retard renal growth, attenuation of mesangial entrapment of macromolecules and mitogenic effects of diverse growth factors, reduction of microalbuminuria, changing size selectivity of the glomerular membrane, hence changing its permeability resulting in reduction in proteinuria, and preservation of kidney function in diabetic patients with incipient DNP.23,24

In acute regimens, all CCBs do not appear to have the same effect in patients with DNP, they can lower acute proteinuria by lowering intraglomerular hydrostatic pressure, an effect that is due to preglomerular vasodilatation alone or pre-and post-glomerular effects. However, long-term studies are needed to consolidate the beneficial effects of CCBs in DNP.25

Only diltiazem and verapamil appear to be as consistently effective as ACE inhibitors in lowering protein excretion in diabetic patients. Furthermore, the antiproteinuric effects of verapamil and an ACE inhibitor may be additive. In one study of patients with type II diabetes, lisinopril or verapamil alone lowered protein excretion from 5.8 to 2.7 g/day. In comparison, using roughly one-half the dose of both drugs (mean of 16 mg of lisinopril and 187 mg of sustained release verapamil) had a much greater antiproteinuric effect. The low-dose combination regimen was also associated with fewer drug-induced side effects (such as constipation with verapamil and dizziness with lisinopril). A similar antiproteinuric advantage has been demonstrated with combination therapy with verapamil andtrandolapril. Studies in animals suggest that CCBs may minimize progressive glomerular injury independent of a reduction in the intraglomerular pressure, perhaps by reducing the associated glomerular hypertrophy. In humans, antiproteinuric effects with diltiazem may also be due to improved glomerular size selectivity. These observations on the potential benefit of CCBs are of uncertain relevance; their efficacy in the preservation of renal function in relation to ACE inhibitors has not yet been evaluated in humans.24

The United Kingdom Prospective Diabetes Study (UKPDS) found no difference in outcome between captopril and atenolol. In this trial, 758 patients with type II diabetes were randomized to aggressive blood pressure control with captopril or atenolol; patients who did not reach the target blood pressure were given other medications but not either of the two primary drugs. The attained blood pressure was similar in the two groups (144/82 mmHg) and at nine years follow up, there was no difference between the two groups in the frequency of microalbuminuria, progression to overt proteinuria or a doubling of the plasma creatinine concentration.26

Short-acting nifedipine has been associated with an increased cardiovascular risk but more recent studies have suggested that long-acting dihydropyridines are safe. However, a recent report from the Appropriate Blood Pressure Control in Diabetes (ABCD) trial raises a question about whether this applies to diabetics or not. The purpose of this trial of patients with type II diabetes was two-fold: to compare moderate with intensive control of the diastolic blood pressure (80 to 89 mmHg versus a target of 75 mmHg) and to compare first line therapy with enalapril and nisoldipine. In the subset of 470 patients who had hypertension at study entry, those treated with nisoldipine had a significantly higher incidence of fatal and non-fatal myocardial infarction (24 versus 4, risk ratio 7.0). Since there was no placebo group, it could not be determined with certainty whether the difference in coronary risk was due to the benefit of ACE inhibition or a deleterious effect of nisoldipine. The incidence of myocardial infarction in those treated with nisoldipine was similar to that seen in nontreated hypertensive diabetics.27

Long acting dihydropyridines have been associated with a higher rate of myocardial infarction than diabetic patients treated with an ACE inhibitor. Although it has been suggested that, this represents a beneficial effect of ACE inhibition rather than a deleterious effect of calcium channel blockade, there is no compelling reason to use a dihydropyridine in most patients with DNP since there is, at present, no evidence that they are renoprotective.28

The efficacy of the CCB, nitrendipine, in preventing renal and glomerular hypertrophy and increased urinary albumin excretion was studied in experimental diabetic rats, starting treatment at the onset of diabetes, and ending with the following conclusion: administration of nitrendipine to diabetic rats for 8 weeks had a significant inhibitory effect on renal and glomerular hypertrophy and showed a tendency towards a reduction in urinary albumin excretion without affecting metabolic control or systemic blood pressure.29

Suzuki and Saruta30 conducted a trial to study the effects of treating hypertension with a calcium antagonist, bendipine, on renal function and blood pressure in 58 patients (mean age: 71±9) with hypertension and chronic renal insufficiency (the level of creatinine ranging from 1.5 to 4.0 mg /d). The results of their trial gave some support to the idea that long acting calcium antagonists such as bendipine are renoprotective through reduction of systolic blood pressure in the elderly people with hypertension and chronic renal insufficiency. However, if systolic blood pressure were not reduced below 160 mmHg throughout a year, the substantial declines in renal function would be expected.

Shigihara et al.31 examined the effects of a combination therapy using ACE inhibitor plus a long acting CCB; amlodipine and compared them with the effect of an ACE inhibitor alone in thirty hypertensive, type II diabetic patients with microalbuminuria for 32 weeks of treatment. They conclude that, in hypertensive microalbuminuric type
II diabetic patients, the combination of an ACE inhibitor plus amlodipine resulted in a more pronounced decrease in blood pressure (diastolic blood pressure < 80 mmHg) and a greater reduction in urinary albumin excretion than did using an ACE inhibitor alone. This combination strategy should thus be a more effective tool for obtaining optimal blood pressure control in patients with DNP. This concept was also confirmed by Sheinfeld and Bakris. They recommended adding a second antihypertensive agent as an option if the target blood pressure is not achieved with a single agent, especially the combination of ACE inhibitor and CCB.

ACE Inhibitors and DNP

The most important factor in slowing the decline of renal function is aggressive treatment of hypertension, particularly with inclusion of Angiotensin Converting Enzyme Inhibitors (ACEIs). According to the guidelines of the sixth report of The Joint National Committee, 1997, on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, blood pressure above 135/85 mm Hg in a diabetic patient is abnormal. Treatment should be directed at lowering the systolic level to about 100 to 110 mm Hg.

With an aggressive treatment approach, the decline in renal function can be reduced to half of the decline seen without treatment (i.e. from 10% to 5% per year). In patients with type I diabetes, the decline can be further reduced to 2% per year (glomerular filtration rate, 0.2 ml/min per month) if ACE inhibitors are included in the antihypertensive regimen. In patients with type II diabetes, there is no evidence of any additional advantage of ACE inhibitors over other antihypertensive agents in slowing the decline in renal function. Besides reducing systemic hypertension, ACE inhibitors decrease intraglomerular hypertension by reversing vasoconstriction of efferent arterioles caused by angiotensin II. Other potential mechanisms of ACE inhibitors are the effects on the bradykinin-kallikrein system, resulting in decreased breakdown of and increased intrarenal levels of vasodilating prostaglandins and decreased intrarenal levels of the powerful growth factor angiotensin II.

The benefit of antihypertensive therapy with an ACE inhibitor in type I diabetes can be demonstrated early in the course of the disease when microalbuminuria is the only clinical manifestation. In one study, for example, the administration of an ACE inhibitor to normotensive type I diabetics with microalbuminuria decreased both albumin excretion and at two years, progression to overt DNP when compared to patients treated with placebo. A more pronounced benefit has been demonstrated in the largest study to date in type I diabetics who already had overt nephropathy. Four hundred and nine patients with overt proteinuria and a plasma creatinine concentration of 2.5 mg/dl were randomized to therapy with either captopril or placebo. At approximately four years of nearly equivalent blood pressure control, patients treated with captopril had a slower rate of increase in the plasma creatinine concentration and less likelihood of progression to end-stage renal disease or death. This benefit was limited to patients with a plasma creatinine concentration of 1.5 mg/dl, and in whom the rate of rise in the plasma creatinine concentration was reduced by over 50 percent from 1.4 mg/dl per year in the placebo group to 0.6 mg/dl per year with captopril. In comparison, no improvement could be demonstrated in the patients with a lower baseline plasma creatinine concentration because the rate of progression was very slow in this group, with the plasma creatinine concentration rising by only 0.1 to 0.2 mg/dl per year.

There has been much less information on the effect of ACE inhibitors in patients with type II diabetes although strict blood pressure control is clearly important. In terms of slowing the progression of protein excretion, ACE inhibitors are beneficial in both normotensive and hypertensive subjects. A study randomized 52 patients with type II diabetes, proteinuria and renal insufficiency to lisinopril, a non-dihydropyridine CCB (verapamil or diltiazem) or the beta-blocker atenolol. The following results were noted after a mean follow up of five years despite a similar reduction in blood pressure in each group. The yearly rate of loss of creatinine clearance was lower with lisinopril (1.06 ml/min per 1.73 m²) than with atenolol (-1.56 ml/min per 1.73 m²) than with atenolol (-3.48 ml/min per 1.73 m²). Therapy with lisinopril or a CCB resulted in a greater reduction in proteinuria (1.5 to 2 g/day) than with atenolol (0.4 g/day). This difference in antiproteinuric activity has been confirmed in other studies.

Both ACE inhibition and dietary protein restriction lower protein excretion in diabetic patients with microalbuminuria and in those with overt (dipstick-positive) renal disease. With ACE inhibition, the better the degree of blood pressure control, the greater the antiproteinuric effect. By comparison, the DHPCCBs (such as nifedipine, nitrrendipine and amlopidine) have a variable effect ranging from increased protein excretion to no effect to a fall in protein excretion in different studies.

The general aim with an ACE inhibitor in hypertensive diabetics is to reduce the diastolic pressure to 80 mmHg or below and, in those with more than 1 to 2 g of proteinuria per day, to 75 mmHg. Most patients require more than one drug to achieve this goal. One potential complication of antihypertensive therapy, particularly if intensive, is that, the fall in blood pressure may lead to a haemodynamically mediated decline in GFR in the first few months of treatment. It has been argued that therapy should not be altered if the change is small. The fall in GFR in this setting does not reflect structural injury.

The use of ACE inhibitors may have additional benefit in diabetics such as reducing the incidence of myocardial infarction and increasing insulin sensitivity, which modestly lowers the plasma glucose and haemoglobin A1C concentrations. However, patients occasionally treated with insulin or oral antidiabetic agents can develop episodes of severe hypoglycaemia. Diltiazem or verapamil can be used if administration of an ACE inhibitor is limited by side effects such as hyperkalaemia or persistent cough or if there is insufficient decline in blood pressure.
Clinical trials with ACE inhibitors have consistently demonstrated a decrease in the progression of renal disease in diabetic patients. The angiotensin II receptor blocker (ARB) losartan has been shown to reduce microalbuminuria to the same extent as the ACE inhibitor enalapril. The non-dihydropyridine CCBs- verapamil and diltiazem- have also been shown to decrease urinary albumin excretion. Clinical literature suggests that if monotherapy with an ACE inhibitor or ARB does not provide an adequate response, NDHPCCB should be added to the regimen. Finally, we can say, ACE inhibitors should be considered first line therapy for diabetic patients with nephropathy. Angiotensin II receptor blockers should be considered as an alternative for patients who are unable to tolerate an ACE inhibitor due to adverse effects. If blood pressure goals are not achieved with an ACE inhibitor or ARB, then the addition of an NDHPCCB should be considered.49

In summary diabetic nephropathy is considered a CRD, it is a major cause of illness and premature death in people with DM. Furthermore, it is considered the single most important cause of end-stage renal disease in the western world and accounts for more than a quarter of all end-stage renal disease.

References


