Summary: Calcium channel blockers are important drugs for the treatment of chronic stable angina. However, negative inotropic and dromotropic effects may limit their usefulness in patients with atrioventricular conduction abnormalities or left ventricular dysfunction. A new generation of calcium channel blockers will soon be available that have a more vascular selective action than currently available agents. Of the new agents, nicardipine has been most extensively studied. In experimental studies, nicardipine is more specific for vascular smooth muscle than for cardiac smooth muscle and for coronary than peripheral vasculature. In controlled trials, nicardipine exhibited efficacy and safety that was comparable to older calcium blockers or beta blockers. However, nicardipine was associated with minimal negative inotropic or dromotropic effects even in patients with existing left ventricular dysfunction. Thus, nicardipine may have an advantage over existing calcium channel blockers, especially in patients with underlying cardiac disease.

Key words: angina, calcium channel blockers, nicardipine

Introduction

In recent years, calcium channel blockers have become an important component of the medical therapy for angina pectoris. The efficacy and safety profiles of calcium channel blockers currently available, diltiazem, nifedi-
TABLE I Characteristics of some old and new calcium antagonists

<table>
<thead>
<tr>
<th></th>
<th>Systemic vasodilation</th>
<th>Myocardial depression</th>
<th>Blocks AV conduction</th>
<th>Vasoselectivity</th>
<th>Nonvascular smooth muscle side effects</th>
<th>Vasodilatory side effects</th>
<th>Safe for concomitant use with beta blockers</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<td>+ + +</td>
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</tr>
<tr>
<td>Verapamil</td>
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<td>+ + +</td>
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<td>0</td>
<td>+ + + b</td>
<td>+</td>
<td>0</td>
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<tr>
<td>Felodipine</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>+ ++</td>
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<td>0</td>
<td>+ + +</td>
<td>0</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Nisoldipine</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>+ + +</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>+ + +</td>
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<td>0</td>
<td>+ + +</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

*Values are based on a scale from 0 to 4 where 0 = least and 4 = most.

bParticularly constipation in the elderly.

Data not available.

tissue preparations, nicardipine was compared with diltiazem, nifedipine, and verapamil and found to have at least twice the specificity for vascular tissue versus papillary muscle than the other calcium blockers. In a separate study, the relative specificity of nicardipine and nifedipine for vascular tissue was compared in isolated mesenteric and coronary artery tissue. Nicardipine exhibited two-fold greater specificity for coronary artery than for mesenteric artery while the effects of nifedipine were similar in both tissues.

The differential effects of nicardipine on the coronary and systemic circulation have been investigated in a number of studies of patients with coronary artery disease. In a study of 15 patients with coronary artery disease, intravenous nicardipine decreased both coronary and systemic resistance, but there was a greater percent change in coronary resistance in 10 of 14 patient. Accompanying the decrease in coronary vascular resistance was an increase in coronary blood flow ranging from 7% to 44% during rest, exercise, or atrial pacing.

In patients with angina, acute administration of nicardipine resulted in a larger increase in coronary blood flow (41%) and thus myocardial oxygen supply than in myocardial oxygen demand (18%). These changes are consistently observed in other studies where the increase in coronary blood flow, which reflects myocardial oxygen supply, exceeded the increase in myocardial oxygen demand (Fig. 1). Thus, in acute studies, nicardipine appears to increase the myocardial oxygen supply to demand ratio. Nicardipine might relieve myocardial ischemia entirely through its effects on myocardial oxygen demand. However, most studies show little to no reduction in hemodynamic indices of myocardial oxygen demand despite improvement in ischemia. These results add very strong support to the conclusion that the beneficial effects of nicardipine are related to improved blood flow. Furthermore, the lack of negative dromotropic effects has not been a limitation relative to prevention of ischemia.

In other studies, the favorable effects of nicardipine on myocardial oxygen utilization and metabolism have been demonstrated. Overall, nicardipine reduced myocardial lactate production during stress-induced ischemia and increased lactate extraction by the myocardium. These improvements in oxygen and lactate utilization should lead to reduced myocardial ischemia and improvement in ventricular function. Rousseau et al. demonstrated sustained improvement in myocardial metabolism in 35 patients treated with nicardipine or propranolol for one month. Although both drugs improved metabolic markers at rest, nicardipine was superior during pacing-induced tachycardia.

The relative specificity of nicardipine for vascular smooth muscle versus cardiac muscle and coronary vasculature versus peripheral vasculature leads to an
apparent lack of negative inotropic effects at clinically useful doses. In 12 patients with coronary artery disease, intracoronary administration of either nicardipine or nifedipine reduced peak positive dP/dt, but the reduction was significantly (p<.05) greater with nifedipine (Fig. 2). Nifedipine also increased left ventricular end-diastolic pressure (LVEDP) at one minute by 79% compared with 29% with nicardipine (p<.005). In trials of acute and chronic administration of nicardipine to patients with heart failure, nicardipine routinely increased cardiac index while decreasing systemic vascular resistance and LVEDP. Burlew et al.10 studied 10 patients with congestive heart failure (CHF) after a single 10 mg IV dose of nicardipine and following 9 days of oral therapy. Cardiac index increased by 45% during acute therapy and 28% during chronic therapy, while LVEDP decreased by 18% to 22%. Similar changes were observed in another study of 10 CHF patients. Cardiac index increased 49% at rest and 20% during exercise, and LVEDP decreased by 26% and 14% during the same time periods. There was no evidence of a negative inotropic or dmmotropic effect in either study. Thus, nicardipine as the prototype second-generation calcium channel blocker exhibits potent effects at select vascular sites with little detectable negative effect on cardiac function at clinically useful doses.

Efficacy of New Calcium Channel Blockers in Angina Pectoris

Of the new calcium channel blockers, only nicardipine has been extensively studied for the treatment of angina. In double-blind, randomized, placebo-controlled studies in patients with chronic stable angina, nicardipine significantly prolonged exercise duration and time to 1-mm ST-segment depression and improved subjective measures of angina. These beneficial effects were sustained in studies of up to six months’ duration. In studies comparing nicardipine with either calcium channel blockers or beta blockers,nicardipine exhibited similar efficacy and generally had a lower incidence of adverse events during treatment than did the comparative agents.

Placebo-Controlled Trials

Nicardipine was evaluated for the treatment of angina in three double-blind, randomized, placebo-controlled trials (Table II). All antianginal medications except sublingual nitroglycerin were withdrawn prior to these studies, and patients were treated with nicardipine 30–120 mg/day or placebo for 4 to 6 weeks. In all three studies, treadmill exercise time and time to 1-mm ST depression

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Dose (mg/day)</th>
<th>Duration (weeks)</th>
<th>Exercise time</th>
<th>1-mm ST depression</th>
<th>Angina frequency</th>
<th>Nitroglycerin consumption</th>
</tr>
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<tbody>
<tr>
<td>Khurmi et al.</td>
<td>20</td>
<td>SB</td>
<td>30 to 60</td>
<td>4</td>
<td>16 to 22(^b)</td>
<td>15 to 27(^b)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(1984) (12)</td>
<td>16</td>
<td>DB,CO</td>
<td>60</td>
<td>2</td>
<td>3(^b)</td>
<td>15(^b)</td>
<td>0</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>SB</td>
<td>90 to 120</td>
<td>4</td>
<td>28 to 35(^b)</td>
<td>50(^b)</td>
<td>-50</td>
<td>-20</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>open</td>
<td>90 to 120</td>
<td>18-26</td>
<td>73</td>
<td>44</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gheorghide</td>
<td>20</td>
<td>DB,R,CO</td>
<td>90 to 120</td>
<td>8</td>
<td>12-18(^b)</td>
<td>26-28(^b)</td>
<td>-68(^b)</td>
<td>-63(^b)</td>
</tr>
<tr>
<td>et al. (1985)</td>
<td>10(^a)</td>
<td>DB,R,CO</td>
<td>90 to 120</td>
<td>6</td>
<td>18(^b)</td>
<td>10</td>
<td>-</td>
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<tr>
<td>Scheidt et al.</td>
<td>56</td>
<td>DB,R,CO</td>
<td>90 to 120</td>
<td>6</td>
<td>8-9(^b)</td>
<td>12 to 21(^b)</td>
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</tr>
<tr>
<td>(1986) (14)</td>
<td>29(^a)</td>
<td>DB,R,CO</td>
<td>90 to 120</td>
<td>6</td>
<td>8(^b)</td>
<td>12</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

\(^a\)Patients were reentered into a second double-blind, crossover phase after 5 months of open-label nicardipine 90 to 120 mg/day.

\(^b\)Significantly different from placebo.

Abbreviations: SB = single-blind; DB = double-blind; R = randomized; CO = crossover.
were significantly (p<.01) prolonged by nicardipine. Angina frequency decreased by up to 68%, and sublingual nitroglycerin consumption decreased by up to 63%.

The response to nicardipine after 5 to 6 months of open label therapy was also evaluated in each of these studies. Khurmi et al.12 observed that exercise time increased by 73% and time to 1-mm ST depression increased by 44% compared with placebo in 11 patients who continued on nicardipine for 18-26 weeks. Gheorghiade et al.13 introduced a second double-blind, placebo-controlled, crossover phase after five months of open-label therapy with nicardipine. The initial 18% increase in exercise time with nicardipine was maintained during the second double-blind phase. It is interesting that no rebound of angina symptoms occurred with sudden withdrawal of nicardipine during the second double-blind phase. Scheidt et al.14 evaluated 29 patients with a second double-blind, crossover phase after 28 weeks of open-label therapy with nicardipine. The antianginal efficacy of nicardipine was maintained during the second controlled phase as evidenced by a significant (p< .01) increase in exercise time (8%) and a 12% increase in time to 1-mm ST depression.

**Comparative Trials**

Nicardipine was compared with the calcium blockers nifedipine and verapamil and with beta blockers for the treatment of angina in eight clinical studies (Tables III and IV). All were blinded, randomized trials of 2 to 9 weeks' duration. Overall, there was no significant difference between nicardipine and the comparative drugs when exercise time or time to 1-mm ST depression was measured.

In three studies, nicardipine 90 mg/day was compared with nifedipine 30-60 mg/day.15-17 Both drugs were significantly (p<.01) better than placebo for improving exercise time and time to ST depression, and there was no difference between the responses to nicardipine and nifedipine. With nicardipine, angina frequency decreased by 38% to 75%, and sublingual nitroglycerin consumption decreased by 31% to 76%. This was not significantly different from nifedipine.

Rodrigues et al.18 compared the effects of nicardipine 90 mg/day and verapamil 360 mg/day in 22 patients with chronic angina. After 8 weeks, both drugs had significantly (p<.01) increased exercise time and time to 1-mm ST depression. However, verapamil also significantly (p = .001) decreased both resting and peak exercise heart rate compared with placebo, while nicardipine increased heart rate.

Several calcium blockers and propranolol were compared with placebo in a series of double-blind randomized trials.19 Exercise time and time to ST depression were significantly increased by all drugs. However, the heart rate response varied considerably with each drug; nicardipine increased heart rate by 17%, while diltiazem, verapamil, and propranolol decreased heart rate by 8% to 28% (Fig. 3).

Nicardipine was compared with the beta blockers atenolol and propranolol in three separate studies.20-22 In a double-blind comparison with propranolol 120 mg/day,

### Table III Comparative studies of nicardipine versus other calcium blockers in patients with chronic stable angina

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Dose (mg/day)</th>
<th>Duration (weeks)</th>
<th>Exercise time</th>
<th>1-mm ST depression</th>
<th>Angina frequency</th>
<th>Nitroglycerin consumption</th>
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</thead>
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<td>-31</td>
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<td>DiPasquale et al. (1984)</td>
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<tr>
<td>Khurmi and Raftery (1987)</td>
<td>16</td>
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<td>NC 120</td>
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<td>40a</td>
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<td>-</td>
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<td></td>
<td>37</td>
<td>D 360</td>
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<td></td>
<td>73</td>
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<tr>
<td></td>
<td>78</td>
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<td></td>
<td></td>
<td>73</td>
<td>68a</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*aSignificant difference from placebo.

b1.5 ST depression.

cMedian.

*Abbreviations: SB = single-blind; DB = double-blind; R = randomized; CO = crossover; P = placebo; Pa = parallel; NC = nicardipine; NF = nifedipine; V = verapamil; D = diltiazem.*
nicardipine 90 mg/day significantly (p<.01) improved exercise time, ST depression, angina frequency and was comparable to propranolol. However, propranolol caused significant reductions in heart rate and peak rate-pressure product. In addition, there were significant increases in maximal workload and angina threshold with nicardipine but not propranolol.

In contrast, Bjerle et al. observed no improvement in exercise time or ST depression with either nicardipine or propranolol compared with placebo. This may have been due to the high exercise capacity in their patient population; patients exercised for over 8 min before the onset of angina. Despite the lack of improvement in exercise performance, nicardipine produced a significant increase in the rate-pressure product. The authors suggested that an increased double product results in an increased dilatation of coronary arteries to compensate for higher myocardial oxygen demand.

Finally, nicardipine 90 mg/day was compared with atenolol 100 mg/day in 40 patients with chronic angina. Both drugs significantly (p<.01) improved exercise performance and decreased angina frequency. The double product at maximum workload decreased on atenolol but was unchanged on nicardipine.

Nicardipine was also evaluated for the treatment of angina at rest. Seventeen patients with angina at rest were treated with nicardipine 90-160 mg/day or placebo during a double-blind randomized trial. Fourteen patients had failed previous therapy with nitrates and other calcium channel blockers. The average optimal dose of nicardipine was 89 mg/day. There was significant (p<.05) decrease in angina frequency from 2.11 attacks/day with placebo versus 0.47/day with nicardipine. There was a similar decrease in sublingual nitroglycerin consumption. The number of ischemic ST-segment episodes on ambulatory monitoring decreased from 51 with placebo to 15 with nicardipine. Thus, nicardipine was effective for the prevention of rest angina.

The frequency of adverse events during nicardipine therapy in angina patients has generally been similar to that during placebo or the comparative drug treatment. This is most evident in the findings of long-term studies. Khurmi et al. reported that only 2 of 19 patients withdrew from a short-term study while on nicardipine. All 11 patients who entered an open-label study completed 18 weeks of therapy; one patient reported pedal edema and dyspnea during this period. Scheidt et al. observed study-related adverse events in 19 patients on nicardipine.

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**TABLE IV** Comparative placebo-controlled trials of nicardipine versus beta blockers in patients with chronic stable angina

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Dose (mg/day)</th>
<th>Duration (weeks)</th>
<th>Exercise time</th>
<th>1-mm ST depression</th>
<th>Angina frequency</th>
<th>Nitroglycerin consumption</th>
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<td>4</td>
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<td>Logan et al. (1986) (21)</td>
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<td>NC 90</td>
<td>8</td>
<td>13a</td>
<td>39a</td>
<td>-26a,b</td>
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<td>NC 120</td>
<td>2-4</td>
<td>35a</td>
<td>40a</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a Significant difference from placebo.

Abbreviations: NC = nicardipine; A = atenolol; P = propranolol; DB = double-blind; R = randomized; CO = crossover.

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**Fig. 3** Change in resting heart rate following therapy with nicardipine (NIC), diltiazem (DIL), nifedipine (NIF), verapamil (VER), and propranolol (PRO) in double-blind, randomized, placebo-controlled trials of patients with chronic stable angina pectoris. (Adapted from Ref. 19.)
versus 4 patients on placebo, but dizziness was the only symptom that occurred significantly (p< .01) more often in the nicardipine group. During the long-term phase, only 2 of 37 patients withdrew due to adverse events (gastric pain and fullness).

Of the other new calcium channel blockers, only nisoldipine has been investigated in patients with angina. The antianginal effects of nisoldipine and nifedipine were comparable in two trials, while a third study found that nisoldipine was superior to nifedipine when total exercise time and time to ST depression were measured.24

Impact of Negative Inotropic Effects on Therapeutic Response

An important consideration when selecting antianginal therapy is the potential for negative inotropic effects. Calcium channel blockers increase cardiac output and lower systemic vascular resistance during short-term administration in patients with existing left ventricular dysfunction.25 However, at least with nifedipine and felodipine, these effects are not translated into long-term improvements in symptoms or exercise tolerance.25 Despite improvements in ventricular performance in patients with mild left ventricular dysfunction, cardiac function often deteriorates during calcium blocker therapy in patients with severely depressed myocardial contractility.

The acute hemodynamic effects of nifedipine and nitroprusside were evaluated in nine patients with severe congestive heart failure.26 Both drugs increased cardiac index and improved other hemodynamic parameters. However, peak left ventricular dP/dt was significantly reduced by nifedipine but unchanged by nitroprusside. In another trial, nifedipine 10-50 mg was administered to 31 patients with New York Heart Association class III or IV heart failure and a mean ejection fraction of 0.17%.27 Although cardiac index improved by ≥15% in 20 patients, the remaining 11 patients had only minimal improvement (>15%) or a decrease in cardiac index, and 6 patients deteriorated on nifedipine therapy.

Recently, the results of a multicenter trial of diltiazem for reduction of mortality following myocardial infarction were reported.28 Overall, there were 11% fewer cardiac events (death or reinfarction) in the diltiazem group versus the placebo group. However, in subsets of patients with coronary angiograms showing significant coronary artery disease, the rate of cardiac events was higher in the diltiazem group than in the placebo group. The results suggest that new calcium channel blockers may be contraindicated or of limited usefulness in the presence of these conditions.

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Rational Selection of Calcium Channel Blockers for Antianginal Therapy

The efficacy of calcium channel blockers for chronic stable angina is well documented. These drugs, as a class, are an important addition to the currently available antianginal drugs. However, the impact of the cardiovascular effects of calcium channel blockers must be considered when selecting antianginal therapy. Patients with angina may have concomitant cardiac diseases, left ventricular dysfunction, or atrioventricular conduction abnormalities. Currently available calcium channel blockers may be contraindicated or of limited usefulness in the presence of these conditions.

The new generation calcium channel blockers have more specific pharmacologic actions than diltiazem, nifedipine, and verapamil. Thus, even in the patient with severe left ventricular dysfunction, further depression of myocardial contractility does not appear to occur, and in some cases, ventricular function may actually improve. This attribute suggests that new calcium channel blockers may be useful for the treatment of angina in patients with coexisting left ventricular dysfunction or borderline heart failure.

Of the new calcium channel blockers, nicardipine has been most extensively studied. In well-controlled clinical trials, nicardipine was comparable to other calcium blockers and to beta blockers for the treatment of angina, and adverse events were generally attributable to vasodilatory effects of the drug. However, nicardipine may have an advantage over existing calcium channel blockers because of the lack of contraindications to its use. Nicar-
dipine may be the first dehydropyridine available in both oral and intravenous dosage forms, which may simplify the transition from acute to maintenance therapy in patients with more severe forms of hypertension or angina. This may be especially important to the patient with preclinical or borderline heart failure or low-grade conduction abnormalities.

References