Amlodipine and Landmark Trials: A Review

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Abstract

High blood pressure is considered one of the major risk factors for heart disease. In addition to evidence of low heart disease and death with adequate control of blood pressure, antihypertensive treatment is still less effective in clinical practice. It is well documented that there is a decrease in cardiovascular events, such as stroke and MI, with potent therapies to combat high blood pressure. This, however, is generally believed to be the result of a phase. This review paper includes and focuses on evidence from clinical trials in support of amlodipine as a first-line anti-hypertensive agent, showing how its unique properties can provide better cardiovascular protection compared to other antihypertensive agents to prevent stroke and cardiovascular disease. Evidence from the many randomized controlled trials presented below shows that amlodipine has excellent efficacy and safety, as a first-rate anti-hypertensive agent not only to control BP but also to safely improve patient outcomes. Patients treated with this drug have benefited as they have fewer hospitals and lower rates of recovery. Its unique mechanism of action leads to a reduction in the development of atherosclerosis. In addition, amlodipine with effective BP control for 24 hours may also be helpful as an adjunct to the treatment of patients with renal impairment by reducing the progression of end-stage renal disease.

Introduction

Calcium channel blockers (CCBs), initially introduced over 3 decades ago for coronary heart disease (CHD), are now widely known and used for their efficacy in hypertension (HTN). Indications for use, besides HTN, also include angina, chronic stable angina or vasospastic angina1. Amlodipine has many unique qualities, it is a long-acting CCB, effective for 24 hours BP control, and causes minimal BP variability thus setting it apart from other agents in this class2. The current review aims to provide a detailed examination of the landmark trials of amlodipine and compare amlodipine with other antihypertensive agents with a particular focus on the ability to improve cardiovascular (CV) health and reduce adverse CV outcomes. The current review aims to examine the landmark trials of amlodipine and to compare it with other antihypertensive medications, and the beneficial impact on cardiovascular health and CV outcomes.

Clinical Indications, Pharmacodynamics, and Pharmacokinetics

Amlodipine, a dihydropyridine, is a third-generation calcium channel blocker (CCB) and a long-acting, lipophilic agent, that selectively inhibits calcium ion influx across cell membranes of
vascular smooth muscles cells and cardiac muscle cells, to cause a decrease in peripheral vascular resistance (PVR) and a reduction in blood pressure. This makes Amlodipine effective in the treatment of high blood pressure (BP)/HTN and angina. In addition, the usefulness of amlodipine in angina pectoris has been established by several randomised trials. Amlodipine is usually prescribed for once-daily dosing because of its long half-life, which makes for favourable patient compliance usually at a starting dose of 5 mg, with a maximum daily dose of 10 mg. Due to a gradual onset of action of Amlodipine, it causes no significant reflex neuroendocrine activation. There may be negative effects on carbohydrate and lipid mechanisms due to activation of reflex mechanisms, such as increased PVR or raised heart rate. The bioavailability of amlodipine is high, ranging from 60% to 80%; it undergoes hepatic metabolism and shows some impaired elimination in patients with liver cirrhosis, but no accumulation is seen in cases of renal failure. Unlike clonidine, discontinuation of amlodipine is not associated with any rebound hypertension, and BP usually returns to baseline over a week.

Role as Monotherapy in HTN

Several trials have evaluated the antihypertensive efficacy of amlodipine as monotherapy versus other agents like angiotensin receptor blockers (ARBs), diuretics and ACE inhibitors (ACEIs). Data from these trials suggest that amlodipine has good efficacy and safety as a first-line antihypertensive agent, not only for controlling BP, but also for safely improving patient outcomes, and these trials will be discussed below. The efficacy of amlodipine as an antihypertensive has been demonstrated by multiple double-blinded, placebo-controlled, randomised studies. These studies demonstrated that once-daily administration of amlodipine in patients with mild to moderate hypertension leads to statistically significant placebo-corrected reductions averaging about 13/7 mmHg in supine and 12/6 mmHg standing blood pressures, 24 hours post-dose. In addition, maintenance of blood pressure control over the 24-hour dosing interval was observed, with little difference in peak and trough effect. No tolerance to amlodipine occurred in patients studied for up to 1 year. Young and older patients showed similar effects on diastolic pressure, while the effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Coronary artery disease (CAD) was detected angiographically in 1991 patients. They were enrolled in the randomized trial, 'Comparison of Amlodipine versus Enalapril to Limit Occurrence of Thrombosis (CAMELOT), and was given either amlodipine (10 mg), enalapril (20 mg), or placebo, and was followed for over 2 years. To begin with, the baseline BP was low, with an average of 129/78. However, both amlodipine and enalapril groups showed similar lowering of BP, 4.8/2.5 and 4.9/2.4, respectively. A lower rate of cardiovascular events (primary outcome) occurred in patients on amlodipine as compared to those on enalapril or placebo (Figure 1). The study also showed that the normotensive patients (number treated =16) that were treated with amlodipine, had a decline in cardiovascular events, showed evidence of regression of atherosclerotic changes, had fewer hospitalizations, and had a significant decrease of non-fatal myocardial infarction by 26% and stroke or transient ischaemic attack by 50% (Figure 2).

Figure 1. Subject-specific computational fluid dynamic workflow for the aortic arch.

Figure 2. A comparison of individual components and secondary outcomes of the cardiovascular events in the three study arms. The coronary revascularization component was reduced the most in the amlodipine group (N=78), as compared to enalapril (N=95) and placebo (N=103). Hospitalization for angina was similarly reduced in the amlodipine group (N=51), as compared to enalapril (N=86) and placebo (N=84). The rate of revascularization after baseline PCI was significantly reduced in the amlodipine arm (N=27), as compared to the enalapril arm (N=42) and placebo (N=52). Adapted from Nissen et. al., JAMA 2004.
Some studies with ARBs versus amlodipine had established a beneficial role of CCBs on cardiac remodelling. Therefore, a trial was conducted on Japanese patients with mild-to-moderate HTN (J-ELAN) to study the effects of losartan (an ARB) versus amlodipine (a CCB) on LV dysfunction. The study by J-ELAN was done with 57 patients who had LVH and mild-to-moderate HTN and had them randomised to either losartan or amlodipine. The doses of these drugs were up titrated over 18 months. To achieve overall BP control, other anti-HTN drugs except the ones that affect LVH such as ACEIs, ARBs, other CCBs, or BBs were added to the regimen. Although both groups showed a similar reduction in BP, but the amlodipine group had a greater effect on carotid intimal-medial thickness (Figure 3). Additionally, the LV mass in both groups showed no significant difference (Figure 4). The role of amlodipine on LV remodelling was not inferior to ARBs, as the study suggested.

The ALLHAT (Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial) which enrolled over 33000 patients with HTN and one CHD risk factor, was one of the largest ever randomised trials of antihypertensive drugs. The objective of the ALLHAT trial was to determine if the incidence of CHD or other CV diseases is lower in patients treated with a diuretic, a CCB, or an ACEI. Patients were randomised to Lisonopril, Chlorthalidone, or Amlodipine with a mean follow-up of about 4.9 years. The primary outcome was considered to be a combined fatal CHD or nonfatal myocardial infarct, analysed by intent-to-treat. Combined CHD including primary outcomes, coronary vascularization or angina with hospitalisation, and combined CVD which included combined CHD, stroke, treated angina without hospitalisation, heart failure (HF), and peripheral vascular disease, and all-cause mortality and stroke as such, were all taken as secondary outcomes. The primary and secondary outcomes for all-cause mortality were almost similar among the various groups. The trial demonstrated that amlodipine can be recommended as a first-line agent in the treatment of HTN since it was neither superior nor inferior as compared to ACEIs or thiazide diuretics in managing HTN in patients with other comorbid conditions (Figure 5(a) and (b)). A study had shown that Nitric oxide (NO) production diminishes in patients with HTN. In a small study, exhaled NO was measured in seven untreated patients with essential hypertension to assess whether amlodipine influences NO. They detected higher levels of NO in the exhaled air after 2 months of amlodipine, suggesting an increased production of NO in the pulmonary circulation. Zhang and colleagues conducted a small study to measure the NO levels in hearts explanted and harvested during transplant. The previous studies had suggested that NO released from endothelial cells was a kinin-mediated mechanism. Kinins are usually degraded by ACE. As the ACEIs facilitate the accumulation of these compounds, it was the rationale behind enlisting ramiprilat for comparison. It was found that while amlodipine increased NO production in these failing hearts, it was almost similar to the NO production seen with ramiprilat. Therefore, it was suggested that increased NO production may be one of the beneficial effects of amlodipine in heart failure (HF), which is not a factor shared by other members of the CCB class. Amlodipine also has an anti-inflammatory and antioxidative role, making it a vasoprotective agent with benefits beyond its BP-lowering effects. These benefits...
may be due to an increase in endothelial NO synthase expression and inhibition of ACE. Amlodipine may thus be beneficial even for patients with high renin HTN.

The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial was a large randomized, double-blind, parallel-group comparison of therapy based on valsartan or amlodipine that enrolled 15245 patients, ≥ 50 years, who had hypertension (controlled or uncontrolled), and was at a greater risk for any CV events. The study aimed to test the benefits of valsartan as compared to amlodipine, in reducing CV morbidity and mortality in patients with hypertension, who were at a greater risk for CV events. In addition, this study also looked at the efficacy of amlodipine versus valsartan in attaining a BP goal of <140/90. The doses of amlodipine and valsartan were increased to 10 mg amlodipine and 160 mg valsartan, respectively. Two additional steps were taken, including the addition of hydrochlorothiazide (HCTZ), which was followed by addition of other agents except for ACEIs, ARBs or other CCBs. The results showed that both monotherapy groups improved their blood pressure in similar ways, with average blood pressures in the 130s/80s for both, although the effects of the amlodipine-based regimen were more obvious, especially in the early stages. In comparison to amlodipine, valsartan caused a substantial increase (19 percent, p=0.02) in total MI (fatal and nonfatal). Although some have questioned the results because of amlodipine’s faster BP lowering early on, the Kaplan-Meier MI curves showed that as BP became similar between the two groups (as the trial progressed), the curves continued to diverge, implying that amlodipine versus valsartan has a BP-independent beneficial effect on MI.

Combination Therapy

The Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT) was a prospective, randomized, open-label trial with a blinded endpoint and a double-blind 2 × 2 factorial component. People with HTN in the UK, Ireland, and Nordic countries (n=19 342) were randomly assigned to the blood pressure-lowering arm (BPLA). ASCOT tested the primary hypothesis that amlodipine (with perindopril as required) would be more effective in preventing coronary heart disease than the β-blocker atenolol (with or without a diuretic). Reductions in the primary composite endpoint of the BPLA—which included non-fatal myocardial infarction and fatal coronary heart disease—along with significant reductions in fatal and non-fatal stroke, total cardiovascular events and procedures, all-cause mortality, and incident diabetes with amlodipine-based treatment over atenolol, led to the BPLA arm being prematurely stopped after 5.5 years.

ASCOT Legacy, involved long-term follow up of the 8,580 patients from the original trial who were from the United Kingdom. In addition to high blood pressure, the patients enrolled, had three or more CVD risk factors without any previous history of a CV event. This was the first study that reported the long-term benefits of lipid-lowering and blood pressure-lowering therapies on cardiovascular health.

Over the median follow-up of 15.7 years, patients with hypertension and no previous coronary events showed the long-term benefits of antihypertensive and lipid-lowering treatment with a calcium channel blocker-based regimen and lipid-lowering with a statin. Of interest here, is to note that assignment to amlodipine-based treatment (with perindopril added as required) was associated with fewer stroke deaths throughout the follow-up.

Long-term follow-up of trials in patients with hypertension where active treatment was compared with placebo, and where blood pressure differences were associated with substantial reductions in cardiovascular events, a carryover effect was seen in the post-trial period along with on average 9% long-term reductions in mortality in the groups previously receiving active treatment.

Overall, findings from the ASCOT Legacy strongly suggest that antihypertensive treatment and lipid-lowering interventions are associated with long-term benefits for cardiovascular outcomes.
Effects in Documented Coronary Artery Disease

The role of calcium regulation in the pathogenesis of atherosclerotic plaque formation resulted in several mechanisms being proposed to account for amloidipine’s potential benefit in atherosclerosis. The lipophilic nature and the chemical structure of amloidipine have been shown to prevent oxidative damage by free radicals in ‘In Vivo’ and ‘In Vitro’ studies. The oxidative stress is countered by inhibiting the formation of free radicals by donation of protons by amloidipine to the lipid peroxide molecules, thereby protecting the lipid bilayer of the cell membrane. The packing of phospholipid molecules becomes disarrayed in atherogenesis, resulting in swelling of the lipid bilayer, which promotes smooth muscle proliferation and atheroma development. Enhancement of NO production is in atherogenesis, resulting in swelling of the lipid bilayer, thereby protecting the lipid bilayer of the cell membrane.

Amloidipine is also known to upregulate the expression of interleukins, which have antiproliferative effects as well as favourable effects on extracellular matrix remodelling. The Prospective Randomised Evaluation of the Vascular Effects of Norvasc (PREVENT) trial was a pivotal trial that assessed amloidipine’s role in atherosclerosis. PREVENT was a multicentre, randomised, placebo-controlled, double-blinded study that evaluated the development and progression of atherosclerosis in 825 patients with angiographically documented CAD. The PREVENT study also used carotid intima medial thickness (CIMT) measurements to analyse the progression of carotid atherosclerosis. Patients were randomized to amloidipine (5–10 mg once daily) or placebo and were followed over 3 years. The primary endpoint was a change in mean coronary luminal diameter in segments with a baseline of 30% stenosis as assessed by quantitative coronary angiography over 36 months since it has been proposed that acute coronary syndrome does not usually result from more stable plaques but rather rupture of minimal lesions. Amloidipine has no influence on the risk of all-cause mortality or major CV events, according to PREVENT data, and it does not affect the development or progression of CAD lesions. There was, nevertheless, a statistically significant influence on carotid artery atherosclerosis progression (p=0.007). Because of the low event rates (i.e., 2% per year for MI), this trial had poor statistical power to detect a treatment difference in mortality and serious morbidity rates. There were fewer incidents in the amloidipine group when major and other reported vascular events/procedures were combined (raising the power to determine an effect). Amloidipine also showed a reduction in the incidences of unstable angina and coronary revascularization, which is equivalent to results from beta-blockers, nitrates, and lipid-lowering medications. These effects were not seen in angiographic studies with nifedipine or nicardipine. When the event rates for unstable angina and coronary revascularization were closely examined, the authors of PREVENT found that these curves diverged extremely early (in the first year). Although amloidipine may not have shown a significant effect in the prevention or progression of the early atherosclerotic lesion, it has been found to have a beneficial role by lowering several hospitalizations for angina and coronary revascularizations.

The randomised trial Coronary Angioplasty Amlodipine Restenosis Study (CAPARES) was undertaken to evaluate the effect of amloidipine on restenosis and clinical outcomes in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). In this prospective, double-blind trial, 635 patients were randomised to 10 mg of amloidipine or placebo. Pre-treatment with amloidipine started two weeks before PTCA and continued until four months after PTCA. The primary angiographic endpoint was the loss in minimal lumen diameter (MLD) from post-PTCA to follow-up, as assessed by quantitative coronary angiography (QCA). Clinical endpoints were death, myocardial infarction, coronary artery bypass graft surgery, and repeat PTCA (major adverse clinical events).

Angioplasty was performed in 585 patients (92.1%); 91 patients (15.6%) had coronary stents implanted. Angiography was performed for QCA analysis as a follow-up for 236 patients in the amloidipine group and 215 patients in the placebo group (per-protocol). The mean loss in minimal luminal diameter (MLD) was 0.30 ± 0.45 mm in the amloidipine group versus 0.29 ± 0.49 mm in the placebo group (p = 0.84). The study showed that the requirement for a repeat PTCA was significantly lower in the amloidipine versus the placebo group (10 [3.1%] vs. 23 patients [7.3%], p = 0.02, relative risk ratio (RR): 0.45, 95% confidence interval [CI]: 0.22 to 0.91), and the composite incidence of clinical events (30 [9.4%] vs. 46 patients [14.5%], p = 0.049, RR: 0.65, CI: 0.43 to 0.99) in the duration of four months of the follow-up (intention-to-treat analysis).

Amlodipine therapy starting two weeks before PTCA does not reduce luminal loss, but patients on amloidipine had a reduced incidence of PTCA and the composite major adverse clinical events were significantly reduced during the four-month follow-up period after PTCA.

Amlodipine exerts its beneficial effects outside of calcium channel blockade for HTN management. While many of these trials show non-superiority of amloidipine to other agents in preventing CAD. However, it can be safely used in patients with CAD for the management of HTN.

The CAMELOT trial enrolled 1318 patients with CAD documented recently by angiography, who did not show left main coronary disease and did not have evidence of heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89%...
with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomised to double-blind treatment with either amlodipine (5–10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anticoagulants (40%), and diuretics (32%), but excluded other calcium channel blockers. The mean duration of follow-up was 19 months. The primary endpoint was the time of the first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease. The total occurrence of first events for amlodipine and placebo groups was 110 (16.6%) and 151 (23.1%), respectively, for a hazard ratio of 0.691 (95% CI: 0.540–0.884, p = 0.003). The primary endpoint is summarized in Table 1. For a large part, the outcome of this study was derived from the prevention of angina related hospitalisations and the prevention of procedures for revascularization. Effects in various prespecified subgroups are shown in Table 2. The CAMELOT conducted an angiographic substudy on 274 subjects using intravascular ultrasound, to study the effect of amlodipine and placebo on atheroma volume in the coronary artery, and no significant difference was found in the two arms.

The significant composite endpoint and the clinical outcomes from the composites of the primary endpoints are summarized in Table 1 below. There was not much difference seen between the effects of amlodipine and placebo on the outcomes for the other primary endpoint features like death related to a CV event, resuscitated cardiac arrest, myocardial infarction, hospitalisation related to heart failure, stroke or TIA, or peripheral vascular disease.

Role in Renoprotection

Hypertension is one of the leading causes of end-stage renal disease (ESRD), and blood pressure levels are known to correlate with renal disease progression. Therefore, stringent BP control is necessary to prevent renal disease progression and to reduce cardiovascular risk in hypertensive patients with chronic kidney disease (CKD). There is considerable clinical evidence to suggest that inhibitors of the renin-angiotensin system (RAS), ACEIs and ARBs have an apparent renoprotective effect. However, adequate BP control can seldom be achieved with only one RAS inhibitor. A combination of two to three antihypertensive drugs is required to decrease BP to target levels, especially in patients with kidney disease.

<table>
<thead>
<tr>
<th>Clinical outcomes N (%)</th>
<th>Amlodipine (N=663)</th>
<th>Placebo (N=665)</th>
<th>Risk reduction (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite CV endpoint</td>
<td>110 (16.6)</td>
<td>151 (23.1)</td>
<td>31% (0.003)</td>
</tr>
<tr>
<td>Hospitalization for angina*</td>
<td>51 (7.7)</td>
<td>84 (12.8)</td>
<td>42% (0.002)</td>
</tr>
<tr>
<td>Coronary revascularization*</td>
<td>78 (11.8)</td>
<td>103 (15.7)</td>
<td>27% (0.033)</td>
</tr>
</tbody>
</table>

Note: Adapted from Nissen et. al., JAMA 2004.

Table 2. Adverse cardiovascular events in various prespecified subgroups in the CAMELOT study.

<table>
<thead>
<tr>
<th>2-Year Event Rates</th>
<th>Amlodipine</th>
<th>Placebo</th>
<th>Relative Risk Reduction</th>
<th>Significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No/Total (%)</td>
<td></td>
<td></td>
<td>(% (Is P&lt;0.05), P Value)</td>
<td></td>
</tr>
<tr>
<td>Lipid Lowering Therapy</td>
<td>Amlodipine</td>
<td>Placebo</td>
<td>(Is P&lt;0.05), P Value)</td>
<td></td>
</tr>
<tr>
<td>Treated with statin</td>
<td>93/551</td>
<td>135/552</td>
<td>33.9</td>
<td>Yes (0.002)</td>
</tr>
<tr>
<td>Not treated with statin</td>
<td>17/112</td>
<td>16/103</td>
<td>4.1</td>
<td>No (0.91)</td>
</tr>
<tr>
<td>Age, years</td>
<td>Less than 65</td>
<td>84/487</td>
<td>21.9</td>
<td>22.9</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>88/506</td>
<td>23</td>
<td>26.8</td>
</tr>
<tr>
<td>Female</td>
<td>22/157</td>
<td>41/177</td>
<td>23.2</td>
<td>42.8</td>
</tr>
<tr>
<td>Sitting Systolic Blood Pressure</td>
<td>Less than Mean</td>
<td>51/340</td>
<td>21.4</td>
<td>32.2</td>
</tr>
<tr>
<td>Mean</td>
<td>59/323</td>
<td>73/205</td>
<td>24.7</td>
<td>29.6</td>
</tr>
<tr>
<td>All Patients</td>
<td>110/663</td>
<td>151/655</td>
<td>23.1</td>
<td>30.9</td>
</tr>
</tbody>
</table>

Note: Adapted from Nissen et. al., JAMA 2004.
Amlodipine is an excellent first-line antihypertensive drug with a wide range of pharmacological advantages spanning from blood pressure control to antianginal and antiatherosclerotic properties. Amlodipine is a long-acting dihydropyridine CCB, has a long half-life at 30 to 50 hours thus effective for 24 hours BP control, and causes no BP variability. This is safe and well-tolerated, often used in combination therapy or as a monotherapy for hypertension. Amlodipine has been demonstrated to be highly successful for the treatment of HTN and stable angina in the studies described in this publication, as evidenced by fewer hospitalizations for unstable angina and revascularization in randomized controlled trials. Amlodipine shows robust reductions on CV endpoints (especially stroke) but does not alter the prognosis in HF. Its unique abilities to prevent activation of counter-regulatory mechanisms, to delay the progression of atherosclerosis, to impart antioxidant properties and to increase NO production are all beneficial actions. The preference in the management of HTN is inclining more towards dual or triple combination therapy and a patient profiling approach is required as the number of comorbid states increases. Amlodipine is a superior option from amongst the wide variety of antihypertensive agents, not only for controlling BP but also for safely improving patient CV outcomes.

Conclusion

Amlodipine is an excellent first-line antihypertensive drug with a wide range of pharmacological advantages spanning from blood pressure control to antianginal and antiatherosclerotic properties. Amlodipine is a long-acting dihydropyridine CCB, has a long half-life at 30 to 50 hours thus effective for 24 hours BP control, and causes no BP variability. This is safe and well-tolerated, often used in combination therapy or as a monotherapy for hypertension. Amlodipine has been demonstrated to be highly successful for the treatment of HTN and stable angina in the studies described in this publication, as evidenced by fewer hospitalizations for unstable angina and revascularization in randomized controlled trials. Amlodipine shows robust reductions on CV endpoints (especially stroke) but does not alter the prognosis in HF. Its unique abilities to prevent activation of counter-regulatory mechanisms, to delay the progression of atherosclerosis, to impart antioxidant properties and to increase NO production are all beneficial actions. The preference in the management of HTN is inclining more towards dual or triple combination therapy and a patient profiling approach is required as the number of comorbid states increases. Amlodipine is a superior option from amongst the wide variety of antihypertensive agents, not only for controlling BP but also for safely improving patient CV outcomes.

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Conflict of Interest

MYK and KG are full-time employees of Dr. Reddy’s laboratories, SS, AO, and PJ are members of the advisory board for Dr. Reddy’s laboratories.

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