Angiotensin Converting Enzyme Inhibitors Attenuate Ischemic Brain Metabolism in Hypertensive Brain Rats

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Background and Purpose: Angiotensin converting enzyme (ACE) inhibitors are expected to modulate neuronal activities. The present study was designed to examine the beneficial effects of ACE inhibitors on microcirculation and metabolism in the ischemic brain.

Methods: Cerebral ischemia was developed for 60 minutes in spontaneously hypertensive rats (SHR, n=35) by bilateral carotid artery occlusion. ACE inhibitors (0.1 or 10 mg/kg SQ 29,852 or captopril) were intravenously injected 15 minutes before cerebral ischemia. Cerebral blood flow to the parietal cortex was measured with the H2 clearance technique. Lactate, pyruvate, and ATP in the brain were estimated by the enzymatic method.

Results: Before cerebral ischemia, high doses of both SQ 29,852 and captopril significantly decreased mean arterial pressure by 15 to 25 mm Hg and reduced cerebral vascular resistance by 13% to 17% of the resting values. Cerebral blood flow and arterial pressure during ischemia were not altered by these ACE inhibitors. After 60 minutes of cerebral ischemia, tissue lactate in vehicle-treated SHR increased 6.6-fold and ATP decreased to 65% of the control values. Administration of SQ 29,852 or captopril significantly reduced the lactate levels to 1.6- to 3.1-fold and well preserved the ATP levels to 82% to 93% of the control.

Conclusions: These results suggest that inhibition of ACE activities may be protective for cerebral metabolism against ischemic insult. (Stroke. 1993;24:1561-1567.)

Key Words: angiotensin converting enzyme inhibitors • captopril • cerebral metabolism • rats

During the past decade, angiotensin converting enzyme (ACE) inhibitors have become established antihypertensive drugs that cause few side effects.\(^1\)\(^-\)\(^4\) The inhibitors primarily block the vasoconstricting effects of angiotensin II and induce dilation of small as well as large arteries, thereby reducing peripheral vascular resistance.\(^1\)\(^-\)\(^4\)

Each tissue has respective ACE activities; an example of the ratio is lung to aorta to brain parenchyma = 100:10:3. The activity in the brain is four times greater than that in the heart and kidney.\(^5\)\(^-\)\(^6\) The brain renin-angiotensin system may participate in regulation of blood pressure, cerebral blood flow, sympathetic nerve activity, vasopressin release, thirst, and sodium appetite.\(^7\)\(^-\)\(^8\) The central action of angiotensin II and thus ACE inhibitory potency for neurological symptoms has received attention. Recently, in vivo homogenates of organs, several drugs were compared with their different potencies of inhibitory activity against ACE. Captopril is highly valued as a hypotensive drug, and a small percentage of patients develop certain side effects that are probably related to the sulphydryl moiety in its structure. Karanewsky et al\(^9\) synthesized a new ACE inhibitor, SQ 29,852, with a phosphonic acid group that binds to zinc at the active center of ACE to overcome the problems of captopril. Barnes et al\(^10\) and Costal et al\(^11\) showed that both SQ 29,852 and captopril administered in rats increase the performances in tests of cognitive function and block the neuronal deficits induced by scopolamine. The ability of ACE inhibitors to modulate the neuronal activity and function is disputed and may involve the activation of metabolism of neuropeptides and the cholinergic system.\(^12\)\(^-\)\(^13\)

Recent reports have demonstrated that ACE inhibitors attenuate the consequences of cerebral ischemia in renovascular hypertensive rats\(^14\) and improve neurological outcome from cerebral ischemia in normotensive rats.\(^15\) In the present study, we investigate whether the above-mentioned two ACE inhibitors, SQ 29,852 and captopril, beneficially attenuate the metabolic and circulatory derangement in the ischemic brain in spontaneously hypertensive rats (SHR).

Materials and Methods

Previously, we reported that female SHR are more resistant to cerebral ischemia, and the survival rate is higher than in male SHR.\(^16\) Therefore, we used female...
SHR in this study. Six-month-old SHR, weighing 255 to 280 g, were separated into four groups: (1) control rats (n=7) for the measurement of cerebral blood flow (CBF) and metabolites, (2) vehicle-treated rats (n=7) for the determination of CBF and metabolites after 60 minutes of cerebral ischemia, (3) rats (n=14) subjected to 60 minutes cerebral ischemia after administration of SQ 29,852 0.1 or 10 mg/kg IV, and (4) rats (n=14) with 60 minutes of cerebral ischemia after the treatment of captopril 0.1 or 10 mg/kg IV. The drugs were stored as dry powder at 5°C and protected from light. Just before the study, the drugs were dissolved in 0.9% saline, and a 1 mL/kg solution was made for injection in each rat. Vehicle-treated rats received 1 mL/kg saline.

The rats were anesthetized with amobarbital (100 mg/kg IP), and one femoral artery was cannulated for the continuous measurement of arterial pressure and sampling blood for blood gases. One femoral vein was cannulated for drug administration. A midline incision was made in the neck, and both common carotid arteries were carefully exposed and separated from the surrounding connective tissue and nerve fibers. Supratentorial ischemia for 60 minutes was produced by bilateral carotid artery occlusion with Heifetz clips. The animals breathed room air spontaneously, and the rectal temperature of each rat was maintained close to 37°C throughout the experiment by a heating pad. Arterial blood samples were taken at rest and at 60 minutes of ischemia.

**CBF Measurement**

CBF to the parietal cortex was measured with the H₂ clearance method. The animal's head was fixed in a head holder and the skull bone exposed. A small burr hole was made in the skull 2 mm lateral to the bregma on one side. A Teflon-coated platinum electrode, 200 μm in diameter, with 1 mm at its top uncoated and plated with platinum black, was placed in the parietal cortex 1 mm in depth from the surface of the brain through use of a stereotaxic apparatus. The reference electrode was an Ag-AgCl electrode inserted under the skin in the neck. H₂ clearance curves were obtained after the inhalation of 10% H₂ gas with room air, and blood flow was calculated from the clearance curve using the formula of Aukland et al. After allowing more than 30 minutes for the steady state to be reached, at least two baseline CBFs were measured at intervals of about 10 minutes.

The animals then received 0.1 or 10 mg/kg IV SQ 29,852, captopril, or saline. Arterial blood pressure reached stable levels 15 minutes after administration of the drugs, and new values for CBF were estimated. Cerebral vascular resistance (CVR), calculated by mean arterial pressure/CBF, was determined before and 15 minutes after administration of the drugs in each rat. Then both carotid arteries were occluded, and CBF was measured at 30 and 60 minutes of ischemia.

**Cerebral Metabolism**

At the end of the experiment, a plastic funnel was fitted into the skin by pouring liquid nitrogen over the area. The whole frozen brain was chiseled out carefully and separated grossly into the supratentorial and infratentorial portions. The parts of the brain were weighed rapidly and ground after the addition of cold perchloric acid, 1N. The tissue homogenates, kept at 0° to 4°C, were centrifuged and neutralized with 3N KOH at pH 5.6±0.1. Lactate, pyruvate, and ATP concentrations in the homogenate were determined by a standard enzymatic method as described previously.

**Statistical Analysis**

All data were expressed as mean±SEM. The significance of differences in CBF, arterial pressure, and cerebral metabolites among the groups was examined by ANOVA followed by Scheffé’s test. The changes in CBF and arterial pressure in each group were analyzed by repeated measurement of ANOVA.

**Results**

The resting values in PaO₂ and PaCO₂ were around 95 and 35 mm Hg, respectively, without differences between groups. Bilateral carotid artery occlusion caused hyperventilation in all animals, and PaCO₂ significantly decreased to 19 to 22 mm Hg and pH increased by 0.04 to 0.09 after 60 minutes of ischemia (Table 1). The resting mean arterial pressure (MAP) was 160 to 180

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**TABLE 1. Changes in Arterial Blood Gases and pH After 60 Minutes of Cerebral Ischemia**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=7)</th>
<th>Vehicle (n=7)</th>
<th>0.1 mg/kg (n=7)</th>
<th>10 mg/kg (n=7)</th>
<th>0.1 mg/kg (n=7)</th>
<th>10 mg/kg (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paco₂ (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>35±1</td>
<td>36±1</td>
<td>35±1</td>
<td>35±1</td>
<td>35±1</td>
<td>35±0.4</td>
</tr>
<tr>
<td>60 min</td>
<td>25±1*</td>
<td>22±1*</td>
<td>21±1*</td>
<td>19±1*</td>
<td>20±1*</td>
<td></td>
</tr>
<tr>
<td><strong>PaO₂ (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>94±2</td>
<td>91±2</td>
<td>99±1</td>
<td>94±1</td>
<td>96±2</td>
<td>95±2</td>
</tr>
<tr>
<td>60 min</td>
<td>104±3</td>
<td>117±4</td>
<td>124±6</td>
<td>126±3</td>
<td>114±1</td>
<td></td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>7.38±0.01</td>
<td>7.38±0.01</td>
<td>7.38±0.01</td>
<td>7.39±0.01</td>
<td>7.40±0.01</td>
<td>7.42±0.01</td>
</tr>
<tr>
<td>60 min</td>
<td>7.42±0.02</td>
<td>7.43±0.01</td>
<td>7.45±0.01</td>
<td>7.46±0.01</td>
<td>7.51±0.02</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM. 60 min indicates 60 minutes of ischemia. Number in parentheses is number of rats examined; *P<.01 vs at rest.
mm Hg, and administration of high doses of both SQ 29,852 and captopril, but not low doses, significantly decreased MAP by 15 to 25 mm Hg. In contrast, CBF tended to increase; thus, calculated CVR dose-dependently decreased by 3.3 ± 1.4 and 13.7 ± 4.1% after administration of SQ 29,852 0.1 and 10 mg/kg, respectively, and by 7.4 ± 1.1 and 17.6 ± 1.2% after administration of captopril 0.1 and 10 mg/kg, respectively (P < .05 vs 0.1 mg/kg, respectively; Fig 1). During ischemia, however, CVR increased 11.8- to 13.6-fold the resting value. MAP in all rats increased by 20 to 30 mm Hg soon after bilateral carotid artery occlusion and gradually decreased to around the resting level at 60 minutes of ischemia. CBF also abruptly lowered below 30% of the resting values at 5 minutes, as previously reported, and significantly decreased to around 5 to 10 mL/100 g per minute at 30 and 60 minutes of ischemia. Thus, no significant differences in the levels of CVR, MAP, or CBF during ischemia were observed among the groups (Table 2 and Fig 2).

Supratentorial lactate, ATP, pyruvate, and lactate/pyruvate (L/P) ratio are illustrated in Fig 3. The control values for lactate, ATP, pyruvate, and L/P ratio in nonischemic rats were 1.30 ± .06, 2.80 ± .03, 0.130 ± .01, and 10.3 ± 0.7 mmol/kg, respectively (horizontal dashed lines in Fig 3). After 60 minutes of ischemia, lactate levels in vehicle-treated rats increased 6.6-fold and ATP decreased to 65% of the control values. L/P ratio also increased 5.2 times the control. Administration of ACE inhibitors significantly reduced the rise in such lactate levels to 1.6- to 3.1-fold (P < .05 vs vehicle-treated rats).

The supratentorial ATP was well preserved to 82% to 93% of the control level by administration of high doses of both SQ 29,852 and captopril (P < .05 vs vehicle-treated rats, respectively). Similarly, the levels of pyruvate tended to be well preserved and thus, L/P ratio was significantly lowered to 12 to 17 in SHR treated with SQ 29,852 or captopril than 54 ± 9 in rats treated with vehicle (P < .05, respectively).

**Table 2. Changes in Mean Arterial Pressure and Cerebral Blood Flow After Administration of Angiotensin Converting Enzyme Inhibitors**

<table>
<thead>
<tr>
<th>MAP, mm Hg</th>
<th>Control</th>
<th>Vehicle</th>
<th>SQ 29,852 0.1</th>
<th>10 mg/kg</th>
<th>Captopril 0.1</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>173±4</td>
<td>176±6</td>
<td>175±5</td>
<td>167±4</td>
<td>163±5</td>
<td>174±6</td>
</tr>
<tr>
<td>After 15 min</td>
<td>176±5</td>
<td>174±5</td>
<td>153±4*</td>
<td></td>
<td>158±5</td>
<td>147±4†</td>
</tr>
<tr>
<td>Ischemia 30 min</td>
<td>185±4</td>
<td>189±7</td>
<td>176±6</td>
<td></td>
<td>182±6</td>
<td>176±6</td>
</tr>
<tr>
<td>Ischemia 60 min</td>
<td>180±5</td>
<td>186±8</td>
<td>167±8</td>
<td></td>
<td>177±5</td>
<td>178±9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CBF, mL/100 g per minute</th>
<th>At rest</th>
<th>53±3</th>
<th>52±4</th>
<th>62±3</th>
<th>61±3</th>
<th>51±3</th>
<th>48±5</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 15 min</td>
<td>51±3</td>
<td>64±3</td>
<td>64±4</td>
<td></td>
<td>59±3*</td>
<td>51±4</td>
<td></td>
</tr>
<tr>
<td>Ischemia 30 min</td>
<td>6±2†</td>
<td>7±1†</td>
<td>7±2†</td>
<td>10±2†</td>
<td>7±2†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia 60 min</td>
<td>4±1†</td>
<td>5±1†</td>
<td>6±2†</td>
<td>8±2†</td>
<td>5±2†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; after 15 min, 15 minutes after drug administration; ischemia 30 min and 60 min, 30 and 60 minutes of ischemia; CBF, cerebral blood flow to the parietal cortex. Values are mean±SEM.

*P < .05.
†P < .01 vs at rest.

**Discussion**

Recently, the effects of ACE inhibitors on global and regional CBF in humans have been extensively investigated. Several reports on the potencies of ACE inhibitors indicate that CBF is actually unchanged or rather increased in spite of decrease in systemic arterial blood pressure by administration of ACE inhibitors. A single-photon emission-computed tomographic study and a similar study of the intravenous 153Xe clearance method revealed that both short-term and prolonged (4 to 15 days) administration of captopril preserved the levels of CBF well in patients with heart failure despite reductions of MAP by 5% to 40%. Reduction of peripheral vascular resistance, increase in cardiac output, and dilation of cerebral vessels are the major factors for these favorable hemodynamics. ACE inhibitors first dilate large vessels such as the aorta and carotid arteries, which is accompanied by compensatory constriction.
of the downstream resistant arteries/arterioles, and CBF is restored to the levels compatible with the normal values. During further decreases in systemic blood pressure, smaller arteries downstream would exhibit greater dilatory capacity, explaining the well-maintained CBF. Thus, the lower limits, and the upper limits as well, of CBF autoregulation shift to the lower levels of arterial pressure after short- or long-term treatment with ACE inhibitors.1,4,21,22,26

Acute intravenous administration of high doses, but not low doses, of SQ 29,852 or captopril significantly reduced arterial pressure before cerebral ischemia in SHR. In contrast, calculated CVR dose-dependently decreased, and blood flow to the parietal cortex tended to increase. Previously, we showed that CVR is significantly reduced in the parietal cortex and thalamus after bolus injection of captopril and also during continuous infusion of captopril in SHR.27 Our present results are in accord with reports4,15,23,25 which indicate that inhibition of ACE beneficially redistributes CBF in some pathological conditions.

In addition to the rise in blood pressure, stimulation of angiotensin II receptors in the brain results in modification of multiple biochemical, functional, and behavioral responses.1,2 Altered releases of neurotransmitters and peptide hormones, such as adrenocorticotropic hormone, oxytocin, and prolactin, may contribute to the activation of these responses.12,13,28 Meanwhile, a strong suggestion that inhibition of ACE can significantly influence quality of life came from a double-blind trial that compared different types of antihypertensive therapy.29 In the study,29 captopril was reported to induce a sense of well-being and an improvement of quality of life, such as vitality, cognitive function, and work performance. Furthermore, administration of SQ 29,852 and captopril can improve cognitive performance in a variety of models, such as food-reinforced alteration of T-maze task in rats and objective discrimination task in primates.10,11 Captopril has been shown to significantly inhibit ACE activity in cerebrospinal fluid in humans.30 Cerebral ischemia opens the blood-brain barrier, even transiently, which would allow passage of ACE inhibitors into the brain.

**FIG 2.** Cerebral blood flow tended to increase by bolus injection of SQ 29,852 and captopril and decreased to around 5 to 10 mL/100 g per minute during bilateral carotid artery occlusion. The reduction of the blood flow was not different among the groups. BCO indicates bilateral carotid artery occlusion. Values are mean±SEM. *P<.05, **P<.01 vs at rest.

**FIG 3.** Changes in brain tissue metabolites at 60 minutes of cerebral ischemia. With treatment of SQ 29,852 or captopril, the increases in lactate and lactate/pyruvate (L/P) ratio and depletion of ATP were attenuated. Dashed bars show mean values of lactate, ATP, pyruvate, and L/P ratio in control nonischemic rats. L/P indicates lactate/pyruvate ratio. Values are mean±SEM. *P<.05 vs vehicle.
parenchyma and may alter the release or redistribution of peptides in the brain.\textsuperscript{31} We expected, therefore, that ischemic derangement of the microcirculation and metabolism in the brain could be modulated or attenuated by administration of ACE inhibitors.

Our model of ischemia using SHR has been shown to produce consistent forebrain ischemia in a simple way\textsuperscript{18,19} due to mainly hemodynamic factors. During 60 minutes of bilateral carotid artery occlusion, supratentorial lactate increased 6.6-fold and ATP decreased to 65\% of the control values. Administration of both SQ 29,852 and captopril significantly inhibited the increase in the concentrations of lactate and maintained the levels of ATP well, resulting in the better preserved L/P ratio. During ischemia, CBF decreased around 5 to 10 mL/100 g per minute, and no significant differences in the levels of CBF or blood pressure were observed among the groups. Also, low doses of SQ 29,852 and captopril, which did not change blood pressure before ischemia, had favorable influences, and thus the factors other than vasoactive effects of ACE inhibitors could be primarily involved in the amelioration of metabolism in the ischamic brain.

Capdeville et al\textsuperscript{14} reported that intraperitoneal administration of captopril or Wy-44,655 lowered mortality and attenuated the ischamic brain injury in renovascular hypertensive rats. As far as we know, the effects of ACE inhibitors on the metabolic derangement in incomplete cerebral ischemia have never been studied. Our results indicate that treatments with ACE inhibitors protect neuronal metabolism or function against ischemic insult, although the mechanisms have not been clarified. Recently, Werner et al\textsuperscript{15} found that intravenous administration of captopril improved neurological outcome from cerebral ischemia in normotensive rats and suggested that reduction of angiotensin II levels or an increase in tissue kinin concentrations importantly contributes to attenuate the ischemic brain injury. Since angiotensin II inhibits the release of acetylcholine from human and rodent cortex,\textsuperscript{32} ACE inhibitors may inversely increase the release of acetylcholine or activate the function of cholinergic system in the brain. In contrast, there is also evidence that angiotensin II stimulates the central release of catecholamines and other excitatory neurotransmitters.\textsuperscript{1,4,12,13} Reduction in the concentrations of these neurotransmitters by ACE inhibitors may have improved outcome from transient cerebral ischemia in gerbils and stroke-prone SHR.\textsuperscript{12,15} In this study, however, the rats were anesthetized with barbiturate, which would attenuate any excitatory functions produced by ischemia or angiotensin II. Therefore, it is likely that ACE inhibition was active by some other mechanism. Elevation of substance P, bradykinin, and enkephalines, which are degraded by ACE, may also contribute to ameliorate the ischemic cerebral metabolism.\textsuperscript{13,15}

In conclusion, the modification in the concentrations or redistribution of these peptides in the ischemic brain by ACE inhibitors may play an important role in neurological improvement after ischemic insult. Further studies are needed to clarify the potencies of the protective effects of ACE inhibitors against cerebral ischemia.
The central nervous system is known to possess all the components of the renin-angiotensin system, including renin, angiotensinogen, and angiotensin converting enzyme (ACE). The active autacoid angiotensin II, an octapeptide, is a potent vasoactive substance that is also a potent modulator of sympathetic and parasympathetic functions. However, angiotensin II, acting intraluminally, has little if any significant effects on cerebral blood flow, whereas its degradation product, angiotensin III, may produce vasoconstriction rather than vasodilation. Thus, although locally generated or blood bovine angiotensin II potentially could affect cerebral vessels, their actual physiological role in this respect is not clear. The role of angiotensin II in stroke is also controversial. On the one hand, it was proposed that angiotensin II, by acting to increase collateral flow to ischemic brain tissue, may serve to protect the brain. Furthermore, Brown and Brown proposed a beneficial role for angiotensin II by preserving systemic blood pressure and securing the upper limit of the cerebral autoregulatory curve and or dilatation of small cerebral vessels by local release of prostacyclin.

On the other hand, vasoconstriction, if indeed exercised directly at any level of the cerebral circulation, may act to further compromise blood flow in addition to the systemic hypertensive effect. Interestingly, no clear evidence has been generated in support for a direct neurotoxic effect of angiotensin II on neurons. In view of the paucity of information about the role of angiotensin II in regulation of the cerebral circulation and in stroke, the case for ACE inhibitors in prevention and treatment of stroke is quite perplexing. First, there is no study on the effect of ACE inhibitors in reduction of stroke in hypertensive patients. However, it is commonly accepted that ACE inhibitors, by virtue of reducing the hypertensive state, may provide protection from strokes as do other antihypertensive modalities. However, some beneficial effects of ACE inhibitors may be related to their effect on cerebral autoregulation, resetting it at lower blood pressure thereby protecting the brain from sudden hypotensive events. The downside of lowering the upper limit of autoregulation by ACE inhibitors could be harmful because it would reduce the protection against sudden hypertensive surges.

Recent preclinical work provided evidence in support of the capacity of ACE inhibitors to attenuate consequences of cerebral ischemia in renovascular hypertensive rats and improve neurological outcome from cerebral ischemia in normotensive rats. In the present study by Sadoshima et al (this volume) the authors report that two different ACE inhibitors, SQ 29,852 and captopril, administered 15 minutes before bilateral carotid artery occlusion in spontaneously hypertensive rats reduce lactate accumulation and preserved brain ATP levels 60 minutes after brain ischemia. The mechanism of the ACE inhibitors’ effects on brain energy and anerobic metabolism are not clear. Monitoring cerebral blood flow (H2-clearance, microcirculation) revealed no consistent differences between treated and nontreated animals, suggesting that microhemodynamic factors did not play an important role in the anti-ischemic effect of the ACE inhibitors. Furthermore, the beneficial effects of the low doses of SQ 29,852 and captopril on the energy and metabolic states of the ischemic brain while having no hemodynamic effects further support a nonvascular/circulatory mechanism.

If ACE inhibitors act to protect the brain from ischemic injury via a nonvascular/hemodynamic mechanism, several possibilities must be considered: (1) Angiotensin II may be toxic to the ischemic brain and therefore inhibition if its synthesis results in neuroprotection. (2) A substrate for ACE accumulates in the brain after ACE inhibition. Such a metabolite may include bradykinin, but other kinins or peptides (not yet identified) cannot be ruled out. (3) Finally, other pharmacological properties of the drugs, eg, antioxidants, or a peripheral site of action should not be ignored. In summary, this study, along with a few previous reports, should encourage investigators to explore further the mechanism of the prophylactic and therapeutic potential of ACE inhibitors, a class of more than 15 members approved for clinical use in various therapeutic indication (eg, hypertension, congestive heart failure). In fact, a full-scale study for primary and second-
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