ORIGINAL RESEARCH ARTICLE

Am J Cardiovasc Drugs 2009; 9 (3): 135-142
1175-3277/09/0003-0135/$49.95/0

Management of Hypertension with the Fixed Combination of Perindopril and Amlodipine in Daily Clinical Practice

Results from the STRONG Prospective, Observational, Multicenter Study

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Abstract

Background: Current clinical guidelines recognize that the use of more than one agent is necessary to achieve target BP in the majority of patients. The ASCOT-BPLA trial demonstrated that the free combination of amlodipine and perindopril effectively controlled BP and was better than a β-adrenoceptor antagonist (β-blocker)/diuretic combination in reducing total mortality and cardiovascular outcomes.

Objective: To evaluate the efficacy and tolerability of a fixed combination of perindopril and amlodipine in the clinical setting.

Study design: The STRONG (SafeTy & efficacy analysis of coveRsyl amlodipine in uncOntrolled and Newly diaGnosed hypertension) study was a prospective, observational, multicenter trial.
Setting: This was a naturalistic, real-world, clinic-based, outpatient study involving 336 general practitioners/primary care physicians in 65 cities in India.

Patients: Adults aged 40–70 years with newly diagnosed/untreated stage 2 hypertension (BP ≥160/100 mmHg), hypertension uncontrolled with monotherapy (BP >140/90 mmHg), or hypertension inadequately managed with another combination therapy.

Intervention: Fixed combination perindopril 4 mg/amlodipine 5 mg once daily for 60 days.

Main outcomes measure: The primary outcomes were the mean change in BP from baseline and the proportion of patients achieving adequate BP control (≤140/90 mmHg, or ≤130/80 mmHg in patients with diabetes mellitus) in the intent-to-treat (ITT) population. Secondary analyses included incidence of adverse events (ITT) and treatment adherence rate (completers).

Results: In total, 1250 patients comprised the ITT population: 32.6% with newly diagnosed hypertension; 40.5% with hypertension uncontrolled with monotherapy; and 26.9% with hypertension inadequately managed with another combination therapy. Mean SBP/DBP decreased significantly from baseline (167.4 ± 15.2/101.4 ± 9.1 mmHg) over 60 days (–41.9 ± 34.8/–23.2 ± 21.8 mmHg; $p < 0.0001$). Target BP was achieved in 66.1% of patients in the total population, 68.3% of untreated patients, 68.4% of patients uncontrolled with monotherapy, and 59.9% of patients inadequately managed with combination therapy. In 161 patients with SBP >180 mmHg at baseline (newly diagnosed: n = 50; uncontrolled on monotherapy: n = 53; inadequately managed on combination therapy: n = 58), BP was reduced by 63.2 ± 32.5/29.0 ± 21.9 mmHg ($p < 0.0001$) at day 60. The fixed combination was safe and well tolerated. All 1175 patients completing the 60-day study (94%) adhered to their treatment regimen.

Conclusion: Fixed combination perindopril/amlodipine was found to be an effective and well tolerated antihypertensive treatment, with an excellent rate of treatment adherence in the clinical setting. Fixed combina-

tion perindopril/amlodipine is expected to be useful in the management of hypertension in primary healthcare, with a positive impact on treatment adherence.

Background and Objective

Elevated BP is one of the most important risk factors for cardiovascular morbidity and mortality,[1] and BP lowering is associated with a reduction in coronary events.[2,3] Despite this, less than one-third of hypertensive patients in the community have adequate BP control.[2] Improving rates of adequate BP control, and thereby reducing cardiovascular morbidity and mortality, currently represents a major challenge in daily clinical practice.

Many patients require two or more antihypertensive drugs to achieve guideline-recommended BP targets.[3] In the long-term (5.5 years) ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm), a combination of the calcium channel antagonist (CCA) amlodipine and the ACE inhibitor perindopril was shown to effectively lower BP in most patients and, additionally, to provide significant reductions in total mortality (–11%), cardiovascular mortality (–24%), and cardiovascular outcomes in comparison with a traditional approach based on a β-adrenoceptor antagonist (β-blocker; atenolol) and a thiazide diuretic (bendroflumethiazide).[4] In light of the ASCOT-BPLA findings, a fixed combination of perindopril and amlodipine has recently been made available for once-daily administration.

This paper describes the results of the STRONG (SafeTy & efficacy analysis of coveRsyl amlodipine in uncOntrolled and Newly diaGnosed hypertension) study, a prospective, observational study in the primary healthcare setting for the antihypertensive efficacy of the fixed combination of perindopril and amlodipine in outpatients with uncomplicated hypertension. The aim of the study was to confirm the BP-lowering efficacy of the combination in patients with newly diagnosed hypertension, in patients whose hypertension was uncontrolled with monotherapy, and in patients inadequately managed with another combination therapy.

Methods

Study Design

The STRONG study was a 60-day, prospective, open-label, observational, phase IV study carried out by 336 general practitioners/primary care physicians in 65 cities in India (see Acknowledgments). All investigators were members of the Association of Physicians of India.

Patients

We identified male and female patients aged 40–70 years with any of the following categories of hypertension: (i) newly diagnosed and untreated stage 2 hypertension (i.e. BP ≥160/100 mmHg); (ii) hypertension uncontrolled (i.e. >140/90 mmHg) on monotherapy with an ACE inhibitor, angiotensin II type 1 receptor antagonist, or CCA; or (iii) inadequately managed hypertension (failure to reach target BP, poor adherence to treatment regimens, or intolerant to treatment-associated adverse effects) with any other two-drug combination therapy.

The main exclusion criteria for the study were a previous myocardial infarction (MI),[1] current treatment for angina[1], a cerebrovascular event[1] within the preceding 3 months, fasting triglycerides >4.5 mmol/L, heart failure, uncontrolled arrhythmias, pregnancy or breastfeeding, or any contraindication to the use of ACE inhibitor or CCA therapy. Patients with severe renal impairment or serious hepatic disorders were also excluded.

All patients gave written informed consent prior to initiating the treatment.

Interventions

Since the STRONG study was an outpatient-based, phase IV study conducted in the real-world clinical practice setting, the study medication was prescribed to the patients by the participating clinician based on the clinical examination. Following baseline assessments, patients were instructed to discontinue their current antihypertensive therapy and to take a single tablet of the fixed combination of perindopril *tert*-butylamine 4 mg/amlodipine besylate 5 mg (Coversyl®-AM; Serdia Pharmaceuticals [India] Pvt. Ltd, Mumbai, Maharashtra, India) daily in the morning for the next 60 days. Since this was a study of prospective, observational design, previously treated patients did not undergo a wash-out phase, as this would not usually be part of usual real-world clinical practice. Addition of other antihypertensive drugs was not allowed throughout the study, while treatment of associated disease was allowed at the discretion of the physician. Patients were followed up and reassessed after 15, 30, and 60 days of treatment.

Assessments

The primary endpoints were the proportion of patients achieving BP control and the mean change in BP from baseline. BP

1 According to the protocol, patients should be switched from prior therapy, including β-blockers.

control was defined as BP ≤140/90 mmHg, except in diabetic patients whose target was BP ≤130/80 mmHg.[2] At baseline and at each follow-up visit (day 15, 30, and 60 [end of study]), BP was measured with patients in the seated position, at least twice, at 5-minute intervals using the Korotkoff cuff method with a properly calibrated and validated instrument according to the Seventh Report of the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC 7) guidelines. Secondary endpoints included frequency of adverse events and adherence to study treatment protocol. In the adverse event assessment, performed at each follow-up visit by the treating physician as part of the routine examination, patients were asked open-ended questions about any adverse events experienced since the previous visit, including cough and edema. A serious adverse event was defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospitalization or prolonged existing hospitalization, or resulted in persistent or significant disability, incapacity, or a congenital anomaly/birth defect. The treating physician also assessed whether there was any possible, probable, or definite relationship between study medication and the adverse event. Patient data was documented by the participating clinician on a pre-designed case report form. These were reviewed by the monitors from Serdia Pharmaceuticals (India) Pvt. Ltd. In case of any discrepancy, the data were verified with the participating clinicians.

The medication was purchased by the patients from the retail pharmacy. Adherence to treatment was assessed at each follow-up visit: the investigator interviewed each patient regarding the continuation of their treatment, inquired about missed doses, if any, since the last visit, and ensured that the patients took their medication as prescribed on a daily basis. On the follow-up visit day, the investigator documented the time the study medication was taken a day prior to the visit date.

Statistical Analysis

The efficacy and adverse event analyses were performed on the intent-to-treat (ITT) population. Treatment adherence rates were calculated for those completing the study per protocol (the per-protocol set). Data are expressed as mean ± SD or as the number and proportion of patients [n (%)]. The significance of changes in quantitative variables was tested using the standard error of difference of the means. Significant differences were defined as those with a p-value of <0.05.

Results

Baseline Characteristics

In total, 1250 patients were enrolled into the study and comprised the ITT population. The baseline characteristics of the ITT population are presented in table I, and the mean baseline BP values are shown in figure 1. The average age of the study population was 55.6 years, and the mean baseline BP was 167.4/101.4 mmHg. The study population had moderate cardiovascular risk and one-quarter had diabetes mellitus. Stage 2 hypertension (BP ≥160/100 mmHg) was newly diagnosed and untreated in one-third of patients; remaining patients were either uncontrolled with monotherapy or inadequately managed with combination treatment.

Of the 161 patients with severe hypertension at baseline (SBP >180 mmHg; grade 3 hypertension according to the European Society of Hypertension/European Society of Cardiology 2007 guidelines[3]), 50 were newly diagnosed and untreated, 53 were uncontrolled on monotherapy, and 58 were inadequately managed on combination therapy. Of the 1250 patients in the ITT population, 1175 (94%) completed the study and comprised the per-protocol population for analysis of treatment adherence.

Efficacy Outcomes

Mean SBP and DBP values in the overall population and in each subgroup decreased progressively from baseline during the 60-day treatment period (figures 1 and 2). Overall, there was a mean reduction in SBP of 41.9 ± 34.8 mmHg at day 60 (to 125.4 ± 33.1 mmHg; $p < 0.0001$ vs baseline), representing a decrease of 25.0% (figure 2). Similarly, mean DBP decreased by 23.2 ± 21.8 mmHg, to 78.2 ± 20.3 mmHg ($p < 0.0001$ vs baseline) representing a decrease of 22.9%.

The proportion of the overall population achieving target BP control at 60 days was 66.1% (figure 3). This antihypertensive efficacy was consistent among the different categories of patients selected for the study (BP target was achieved in 68.3% of patients previously untreated, in 68.4% of those uncontrolled on monotherapy, and in 59.9% of patients inadequately managed on combination therapy; figure 3).

In patients with grade 3 hypertension at baseline (n = 161; mean baseline BP 195.2 ± 10.7/109.7 ± 11.3 mmHg), mean BP was reduced by 63.2 ± 32.5/29.0 ± 21.9 mmHg after 60 days ($p < 0.0001$ vs baseline), while the proportion of patients achieving target BP at 60 days was 62.1%.

In patients with diabetes at baseline (n = 311), target BP (≤130/80 mmHg) was achieved in 48.5% (n = 152) at 60 days, and in the subgroup of patients with diabetes and severe hypertension at

Table I. Baseline characteristics (total population, n = 1250)

Characteristics	Value
Demographics	
Mean age (y ± SD)	55.6 ± 9.6
Male [n (%)]	759 (60.7)
Cardiovascular risk factors	
Mean BMI (kg/m^2 ± SD)	26.6 ± 4.2
Mean SBP (mmHg ± SD)	167.4 ± 15.2
Mean DBP (mmHg ± SD)	101.4 ± 9.1
Smokers [n (%)]	243 (19.4)
Current alcohol drinkers [n (%)]	207 (16.6)
Diabetes mellitus [n (%)]	311 (24.9)
Previous stroke or TIA [n (%)]	21 (1.7)
LVH [n (%)]	110 (8.8)
History of AF [n (%)]	4 (0.3)
Disease characteristics [n (%)]	
Untreated (stage 2 hypertension)	407 (32.6)
Uncontrolled hypertension	
with monotherapy	506 (40.5)
with combination treatment	309 (24.7)
Controlled hypertension with two-drug combination	
poor adherence to treatment	15 (1.2)
adverse effects	13 (1.0)
SBP >180 mmHg (ESH/ESC grade 3 hypertension)	161 (12.9)
Laboratory investigations (mg/dL ± SD)	
Mean total cholesterol	211.9 ± 39.5 (n = 1066)
Mean HDL-cholesterol	48.5 ± 17.7 (n = 956)
Mean fasting plasma glucose	111.7 ± 35.0 (n = 1099)
Concomitant treatment [n (%)]	
Lipid-lowering therapy	345 (27.6)
Antidiabetic therapy	265 (21.2)
Platelet inhibitors	207 (16.6)

AF = atrial fibrillation; **BMI** = body mass index; **ESC** = European Society of Cardiology; **ESH** = European Society of Hypertension; **HDL** = high-density lipoprotein; **LVH** = left ventricular hypertrophy; **TIA** = transient ischemic attack.

baseline (n = 51), ten patients (19.6%) achieved BP ≤130/80 mmHg at day 60.

Tolerability and Treatment Adherence

Fixed combination perindopril/amlodipine was well tolerated over the entire study duration (table II). A total of 75 patients did not complete the study, most of whom (n = 65) dropped out during the second half of the study. Reasons for withdrawal during the 60-day study were loss to follow-up (n = 65), personal reasons (n = 1), and treatment-related adverse events (n = 9). Total treatment-related adverse events and their impact on study withdrawal are presented in table II. With the exception of cerebral hemorrhage in a single patient, which resulted in death, none of the reported adverse events were regarded as serious. Loss to follow-up in this naturalistic study comprised patients who did not attend the next scheduled visit (± 7 days) for reasons that were unknown, but likely included change of residence, change of doctor, and the patient feeling better, etc.

All patients who completed the study (n = 1175 [94%]) adhered to their treatment protocol in accordance with the methods described earlier for assessment of treatment adherence.

Discussion

The important finding of the STRONG study is the demonstration that the antihypertensive efficacy of combination therapy seen in rigidly controlled, randomized trials can be reproduced in the 'real world' setting of daily clinical practice, at least in the short term. Thus, the STRONG study demonstrated that fixed combination perindopril/amlodipine once daily for 60 days effectively managed BP in patients in a primary healthcare setting. Patients with grade 3 hypertension at baseline also responded well, although, as expected, the 60-day BP control rate for those with diabetes with the more stringent BP target was lower (approximately half of patients with diabetes achieved BP control vs two-thirds of patients generally).

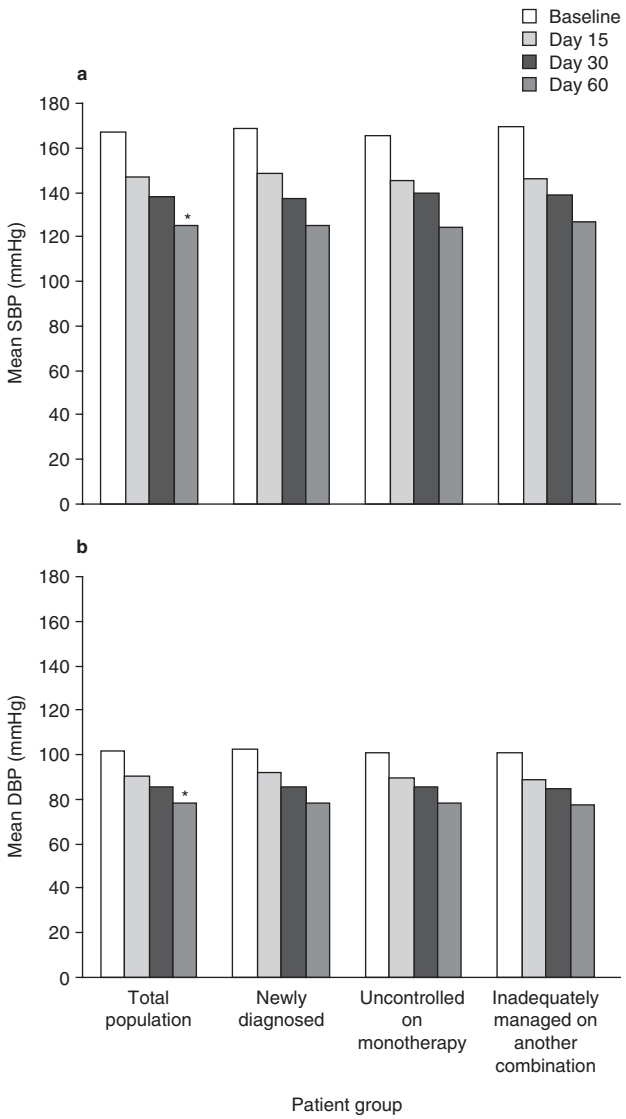

Fig. 1. (**a**) SBP and (**b**) DBP at baseline and after 15, 30, and 60 days of treatment with the fixed combination of perindopril and amlodipine in the total population (n = 1250), patients newly diagnosed and untreated (n = 407), patients uncontrolled on monotherapy (n = 506), and patients inadequately managed on another combination therapy (n = 337). * $p < 0.0001$ vs baseline.

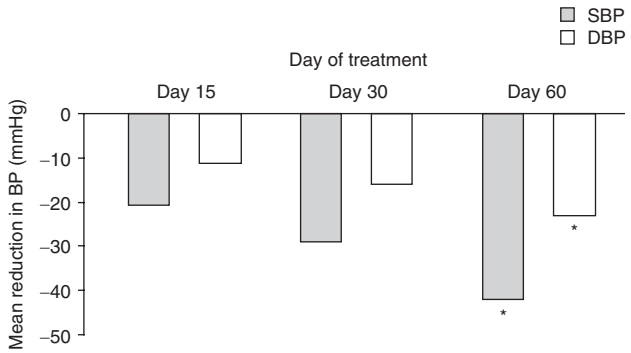

Fig. 2. Mean change in SBP and DBP in 1250 patients with hypertension after 15, 30, and 60 days of treatment with the fixed combination of perindopril and amlodipine. * $p < 0.0001$ vs baseline.

Both components of this fixed combination are established antihypertensive agents, and their BP-lowering efficacy as monotherapy is well documented.[5-7] The rationale for combining these two agents is based on their synergistic action: at the level of vascular smooth muscle, amlodipine causes relaxation/vasodilatation by reducing external calcium entry, while perindopril reduces the vasoconstrictive properties of angiotensin II and provides vasodilatation by reducing internal calcium release and improving nitric oxide release. Both agents also offer a long duration of action, providing 24-hour cover. Indeed, the combination of ACE inhibitor and CCA is recognized as a rational treatment option in patients uncontrolled with monotherapy.[3,8] Data from ASCOT-BPLA[4,9] and from EUROPA (European Trial on Reduction of Cardiac Events with Perindopril with Stable Coronary Artery Disease)[10,11] also indicate that the combination of perindopril and amlodipine can provide synergistic benefits in terms of BP-lowering efficacy and cardiovascular protection. Notwithstanding the differences in patient populations between STRONG and ASCOT-BPLA (patients were younger in the current study and had a lower cardiovascular risk profile overall, including lower rates of smoking, diabetes, and cardiovascular co-morbidities), one might expect that, with continued treatment, the BP-lowering efficacy of the perindopril/amlodipine combination seen in daily clinical practice would be accompanied by similar long-term cardiovascular protective effects.

The good tolerability profile observed in the STRONG study may be explained by the combination of two agents acting in synergy to reduce peripheral edema, which is a well known adverse effect of amlodipine, and cough, the main adverse effect associated with ACE inhibitors. Edema occurs because of vasodilatation that is more pronounced in the pre-capillary than in the

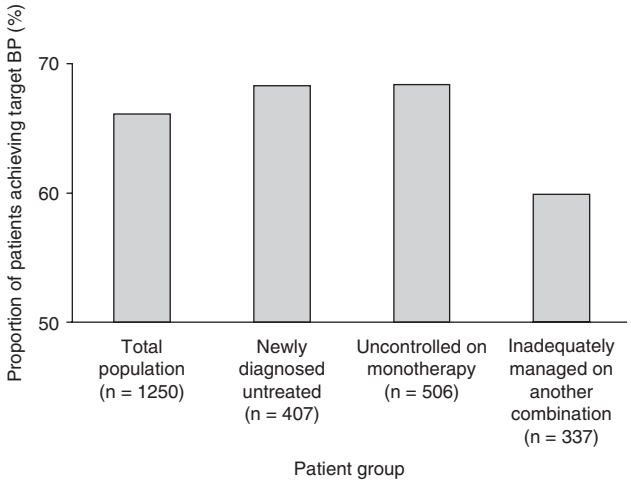

Fig. 3. Proportion of patients achieving target BP (≤140/90 mmHg, or ≤130/80 mmHg in diabetic patients) after 60 days' treatment with fixed combination perindopril and amlodipine (in the total population and patient subgroups).

post-capillary resistance vessels, and ACE inhibitors have been shown to reduce this adverse effect by dilating venous capacitance vessels, thereby normalizing intra-capillary pressure.[12,13] In the current study, the incidence of edema with fixed combination perindopril/amlodipine was 0.7%, lower than that reported in other studies of fixed combination ACE inhibitor/CCA therapy.[13-15] The difference in rates may be due to the difference in reporting and recording adverse events in naturalistic and randomized, controlled trials. Alternatively, or in addition, the relatively low level of adverse events in the current study may be related to the relatively short treatment period (60 days).

Similarly, the incidence of ACE-inhibitor-associated cough in the current study (1.5%) was lower than that seen with quinapril (8.6%) or perindopril (2.7%) monotherapy in the QUALISH (Quinapril in Systemic Hypertension)[16] and EUROPA[11] studies, respectively, and there is evidence that ACE-inhibitor-associated cough is attenuated by CCAs, including amlodipine.[17,18] The incidence of cough with the perindopril/amlodipine combination in the STRONG study, assessed by asking patients open-ended questions about adverse events at each visit, was similar to that observed with placebo in the EUROPA study[11] or with amlodipine monotherapy in other randomized, controlled studies in patients with hypertension[15,19,20] and lower than that reported with a fixed-dose combination of lercanidipine and enalapril.[14]

Our results confirm the advantages of the combination of perindopril and amlodipine, namely excellent BP-lowering efficacy and a benign tolerability profile, both direct consequences of the synergy between the modes of action of the two components. In fixed combination, perindopril and amlodipine can be expected to have a third advantage: improved adherence to treatment, which is often a concern in the primary healthcare setting. The use of fixed-dose combinations simplifies the treatment regimen: a recent meta-analysis has demonstrated that they can improve patient adherence by about 25%.[21] The impact of fixed combinations on the optimization of the management of hypertension has been recognized by international guidelines.[2,3,8]

The main limitations of the STRONG study are that it was an open study, with no comparator, and was conducted over a short duration, which meant that potential long-term benefits could not be assessed. However, taking the findings of the ASCOT-BPLA trial into consideration, it is reasonable to assume that patients in the STRONG study would experience similar long-term benefits with the fixed combination of perindopril and amlodipine as were reported by ASCOT-BPLA. Moreover, only one dosage of the fixed combination of perindopril and amlodipine was used in the STRONG study. The recently available fixed combination of perindopril and amlodipine exists in a full range of dosages, providing more flexibility in terms of up-titration, which was not possible in our trial.

Conclusion

The findings from this observational study confirm those reported from randomized clinical trials and demonstrate that the fixed combination of perindopril and amlodipine is an effective and well tolerated treatment for untreated patients with stage 2 hypertension, patients uncontrolled on monotherapy, and patients inadequately managed on another combination therapy, and the combination provides good rates of BP control in daily clinical practice. The good rates of BP control observed in this study could be explained by the synergistic mode of action of the two components, leading to enhanced BP lowering and reduced side effects, which may have a positive impact on treatment adherence.

Table II. Tolerability to fixed combination perindopril/amlodipine throughout the 60-day study

Treatment-related adverse event	Patients [n (%)]
Resulting in study withdrawal	
Cough	5 (0.4)
Ankle edema	3 (0.2)
Cerebral hemorrhage	1 (0.08)
Not resulting in study withdrawal	
Mild cough	14 (1.1)
Ankle edema	6 (0.5)
Headache with dizziness	4 (0.3)
Nausea	3 (0.2)

Acknowledgments

This study was funded by an administrative grant from Serdia Pharmaceuticals (India) Pvt. Ltd. No other financial consideration was involved and the authors have no conflicts of interest that are directly relevant to the content of this manuscript. Medical writing assistance was provided by Mary Hines, Wolters Kluwer Health.

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