Original Article

Cost-Effectiveness Analysis: Controlled-Release Nifedipine and Valsartan Combination Therapy in Patients with Essential Hypertension: The Adalat CR and Valsartan Cost-Effectiveness Combination (ADVANCE-Combi) Study

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As recommended by the guidelines such as JSH 2004, combination therapy with multiple agents is now being applied to many patients with hypertension. However, a pharmacoeconomic analysis of each therapy has not been fully undertaken in Japan, despite increasing societal interest. In this study, the cost-effectiveness of two calcium channel blockers, each coadministered with an angiotensin receptor blockade, was compared using data from the ADVANCE-Combi study. The ADVANCE-Combi study was a 16-week double-blind, randomized clinical trial to compare the efficacy and safety of two combination therapies (controlled-release nifedipine [nifedipine CR] plus valsartan *vs.* amlodipine plus valsartan) on blood pressure (BP) control in patients with moderate to severe essential hypertension. The incremental cost effectiveness of each cohort was compared from the perspective of insurers. The average total cost per patient was Japanese yen (JPY) 31,615 for the nifedipine CR treatment group and JPY 35,399 for the amlodipine treatment group ($p<0.001$). The achievement rate of the target BP (SBP/DBP<130/85 mmHg for patients aged under 60 years; SBP/DBP<140/90 mmHg for those aged 60 years and over) was significantly higher in the nifedipine CR treatment group (61.2%) than in the amlodipine treatment group (34.6%) ($p<0.001$), with no difference in the incidence of drug-related adverse events. Accordingly, the base case economic analysis demonstrated that the nifedipine CR treatment group was dominant (more efficacious and less costly) to the amlodipine treatment group. This result was supported by univariate and probabilistic sensitivity analyses.These results indicate that nifedipine CR–based combination therapy is superior to amlodipine-based combination therapy for the management of essential hypertension in the Japanese population. (*Hypertens Res* 2008; 31: 1399–1405)

***Key Words*: essential hypertension, controlled-release nifedipine, valsartan, amlodipine, incremental cost-effectiveness**

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*Refer to the Appendix.

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Introduction

In the wake of various large-scale clinical studies and meta-analyses (*1–5*), the importance of strict control of blood pressure (BP) is being increasingly stressed in order to prevent organ damage and to reduce mortality and morbidity associated with hypertension. As monotherapy is often not sufficient to achieve target BP, the guidelines, such as JSH 2004, often recommend combination therapy with multiple agents (*6–9*).

In daily practice, combination therapies using a calcium channel blocker (CCB) plus an angiotensin II receptor blocker (ARB) are widely used in Japan (*10*). In light of the growing burden on the National Health Insurance (NHI) budget to treat cardiovascular disease (Kokumin-Iryohi-no-Gaikyo [National Medical Care Expenditure 2003] [in Japanese]: http://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/03/index.html), it has become quite important to estimate the pharmacoeconomic perspective of combination therapies with CCB and ARB in addition to their treatment efficacy, while clinicians have a variety of choices with a wide range of daily NHI prices. However, as there is a limited availability of clinical data in Japan upon which economic estimates can be based, this kind of economic analysis has been implemented in only a few studies (*11–13*).

We recently reported the results of a clinical study (the ADVANCE-Combi study) of patients with essential hypertension, for whom the combination of controlled-release nifedipine (nifedipine CR) and valsartan was more effective for achieving target BP than the combination of amlodipine and valsartan (*14*). In the present study, we estimated the cost-effectiveness of these two combination therapies in terms of their BP-lowering effects in essential hypertension, based on the results of the ADVANCE-Combi study.

Methods

Data Source

The ADVANCE-Combi study was a double-blind, parallel-arm, randomized clinical trial targeting patients 20–80 years of age with mild to severe hypertension (*14*). In that study, after ≥2 weeks of baseline observation with no antihypertensive medication, 513 eligible subjects (male: 326, female: 187) were randomly allocated to either the nifedipine CR treatment group or the amlodipine treatment group. Mean age was 56.9 years old, and there was no significant difference in gender or age between the treatment groups.

The patients were followed up every 4 weeks during the 16-week double-blind treatment period. At each visit (weeks 4, 8, and 12), if the BP had reached the target level according to JSH 2000 (*15*), the study medication remained unchanged, but if the target BP had not been achieved, the treatment was shifted from regimen I to regimen IV:

Table 1. NHI Price (JPY) of Drug (2004)

	NHI price of drug (JPY per tablet)	
Nifedipine CR	46.7 (20 mg)	87.4 (40 mg)
Amlodipine	46.6 (2.5 mg)	87.5 (5 mg)
Valsartan	87.0 (40 mg)	165.5 (80 mg)

JPY, Japanese yen; NHI, National Health Insurance; nifedipine CR, controlled-release nifedipine.

1) Regimen I (low-dose CCB): Nifedipine CR group: nifedipine CR 20 mg; Amlodipine group: amlodipine 2.5 mg.

2) Regimen II (low-dose CCB + low-dose ARB): Nifedipine CR group: nifedipine CR 20 mg + valsartan 40 mg; Amlodipine group: amlodipine 2.5 mg + valsartan 40 mg.

3) Regimen III (high-dose CCB + low-dose ARB): Nifedipine CR group: nifedipine CR 40 mg + valsartan 40 mg; Amlodipine group: amlodipine 5 mg + valsartan 40 mg.

4) Regimen IV (high-dose CCB + high-dose ARB): Nifedipine CR group: nifedipine CR 40 mg + valsartan 80 mg; Amlodipine group: amlodipine 5 mg + valsartan 80 mg.

Values for the efficacy and safety of each treatment cohort (nifedipine CR treatment group versus amlodipine treatment group) were obtained from the results of the ADVANCE-Combi study (*14*).

Efficacy and Safety Profile

The results demonstrated that achievement rates of target BP (systolic blood pressure [SBP]/diastolic blood pressure [DBP] < 130/85 mmHg for patients aged under 60 years; SBP/DBP < 140/90 mmHg for those aged 60 years and over, according to JSH 2004 (*6*)) were significantly higher in the nifedipine CR treatment group, being 69.8% for SBP and 75.1% for DBP, than in the amlodipine treatment group, being 48.5% for SBP and 50.0% for DBP ($p<0.001$ and $p<0.001$, respectively). The reduction in BP from baseline after 16 weeks of treatment was again significantly greater in the nifedipine CR treatment group (SBP/DBP: $-34.0\pm15.0/-20.1\pm9.5$ mmHg; range, 162/100 to 128/80 mmHg) than in the amlodipine treatment group ($-27.0\pm14.5/-15.9\pm9.7$ mmHg; range, 162/102 to 135/86 mmHg) ($p<0.001$). With regard to safety, adverse events related to the study drug occurred in 31 patients (12.4%) in the nifedipine CR treatment group and in 20 patients (7.6%) in the amlodipine treatment group, indicating no significant difference between the groups. There was 1 case of a serious drug-related adverse event in each group, including hypotension in the nifedipine CR treatment group and cerebral infarction in the amlodipine treatment group.

Cost

The cost of treatment was calculated from the perspective of insurers, based on the NHI Table in April 2004 (Table 1). The

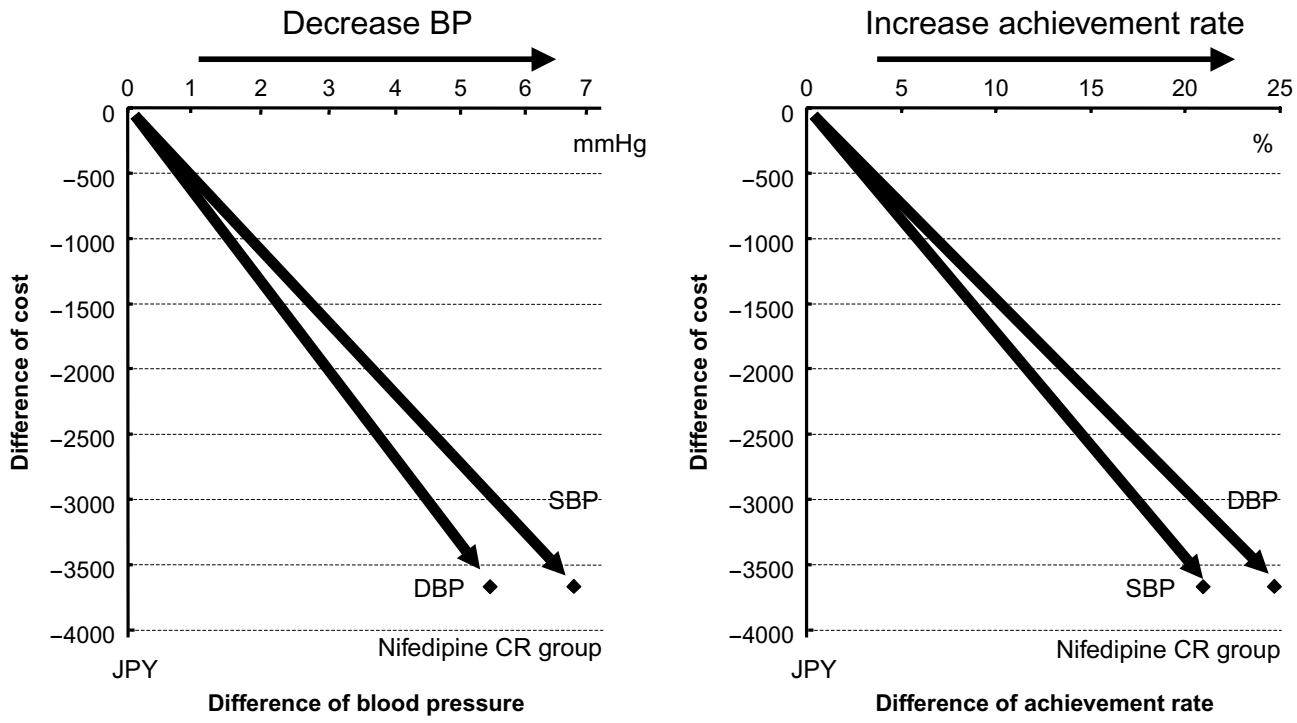

Fig. 1. *Difference in cost and efficacy (left: cost vs. Δ decreased BP; right: cost vs. Δ achievement rate) for the nifedipine CR treatment group compared to the amlodipine treatment group was shown. The former was dominant (higher efficacy and lower incremental treatment cost) to the latter. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

Table 2. Cost of Treatment per Patient (JPY)

	Nifedipine CR treatment group (n=245)	Amlodipine treatment group (n=260)
Average treatment cost per patient during double-blind treatment period	31,615	35,399
Outpatient visit fee (total)	5,660	5,660
Laboratory examination (total)	13,300	13,300
Cost of medication	12,297	13,883
Additional treatment costs for drug-related adverse events	358	2,557
Average treatment cost per patient reaching target blood pressure level		
SBP	45,294	72,988
DBP	42,097	70,798
Both SBP and DBP	51,659	102,309

JPY, Japanese yen; SBP, systolic blood pressure; DBP, diastolic blood pressure; nifedipine CR, controlled-release nifedipine.

cost for each treatment group during the double-blind treatment period was obtained from the data listed in the Case Report Forms of the ADVANCE-Combi study, and the following costs were included (Euro 1 = JPY [Japanese yen] 160):

—Outpatient visit fee = JPY 2,740 (Week 0) + JPY 730×4 times (Week 4, Week 8, Week 12, and Week 16);

—Laboratory examination = JPY 7,400 (Week 0) + JPY 5,900 (Week 16);

—Cost of medication = nifedipine CR 20/40 mg + valsartan 40/80 mg or amlodipine 2.5/5 mg + valsartan 40/80 mg for 16 weeks;

—Additional treatment costs for drug-related adverse events;

—Treatment cost (outpatient visit fee, laboratory examination, cost of medication and any medical procedure) was calculated from the data listed in the Case Report Form and added to the basic treatment cost;

—Cost of over-the-counter drugs was not included because it does not increase insurers' expenditures.

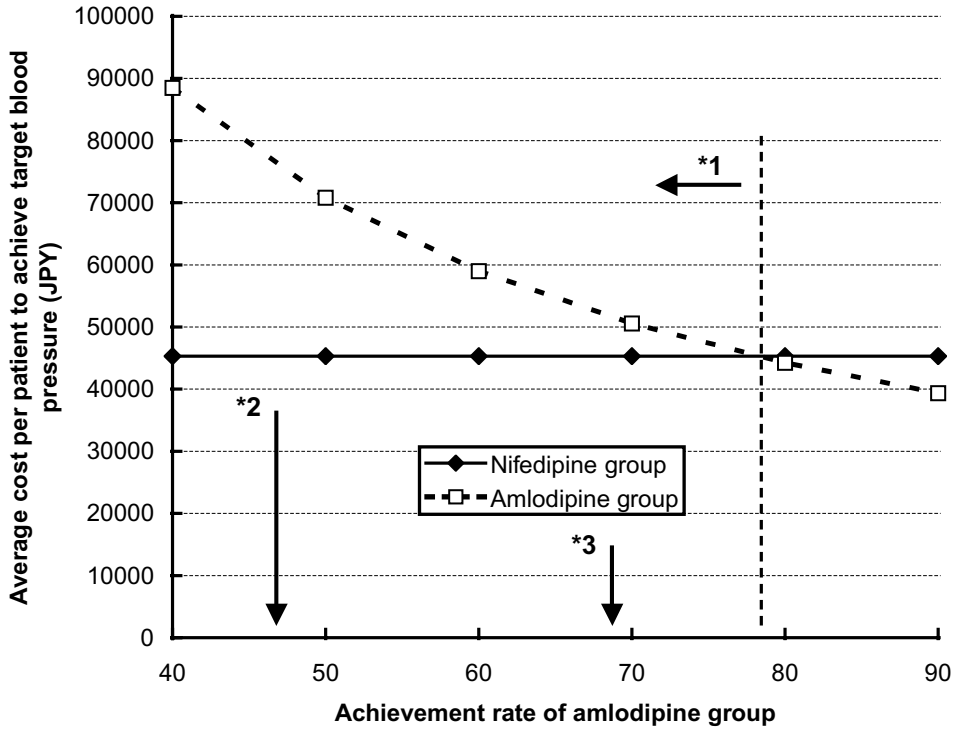

Fig. 2. *The impact of the achievement rate of SBP in the amlodipine treatment group was estimated. The mean cost per patient to achieve target BP is lower in the nifedipine CR treatment group than in the amlodipine treatment group, even when the achievement rate of the latter is raised to that of the former (69.8%). [*1]Average treatment cost per patient reaching target BP is lower in the nifedipine treatment group. [*2]Achievement rate in the amlodipine treatment group observed in the ADVANCE-Combi study. [*3]Achievement rate in the nifedipine CR treatment group observed in the ADVANCE-Combi study.*

The average costs per patient were compared between the treatment groups using the Wilcoxon rank sum test.

Cost Effectiveness

The incremental cost effectiveness of each cohort during the double-blind treatment period was compared.

Sensitivity Analysis

The robustness of the results of the cost-effectiveness analysis was estimated by univariate analysis and probabilistic sensitivity analysis.

Univariate analysis was conducted, raising or reducing the value of some parameters (achievement rate of BP, incidence of adverse events, cost to treat drug-related adverse events) from the base ones observed in the ADVANCE-Combi study.

Probabilistic sensitivity analysis (bootstrap analysis) was also undertaken using SAS software (SAS Institute, Cary, USA) to confirm confidence intervals for cost-effectiveness ratios, by the following four-stage process:

1) Cost/effect pairs were selected randomly from the nifedipine CR treatment group, and mean cost and achievement rate were calculated. 2) Cost/effect pairs were selected randomly from the amlodipine treatment group, and mean cost and achievement rate were calculated. 3) The incremental cost-effectiveness was calculated from these two means. 4) This process was repeated many times to create a sampling distribution of incremental cost-effectiveness.

Results

Cost Effectiveness

The average total cost per patient was JPY 31,615 for the nifedipine CR treatment group and JPY 35,399 for the amlodipine treatment group during the double-blind treatment period. The average cost per patient was significantly lower in the nifedipine CR treatment group than in the amlodipine treatment group ($p<0.001$), while the achievement rate of target BP was significantly higher in the former; the adjusted difference in the achievement rate of SBP (nifedipine CR treatment group − amlodipine treatment group) was 21.3% (95% confidence interval: 12.9–29.6%) and that of DBP was 24.9% (95% confidence interval: 17.2–32.7%).

During the double-blind treatment period, the average treatment cost per patient reaching the target SBP (average total cost during double-blind treatment period/achievement rate

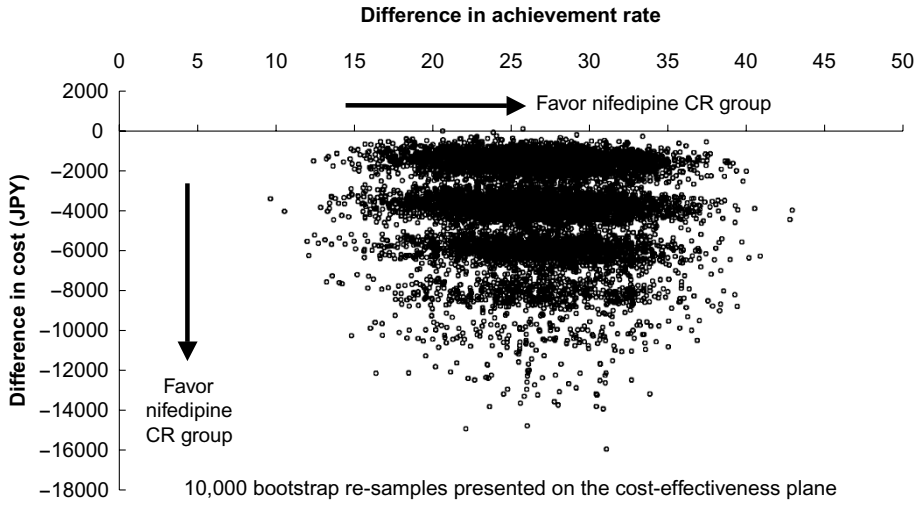

Fig. 3. *Bootstrap analysis: Nearly 100% of the points (X axis: Δ achievement rate; Y axis: Δ cost) are located in the southeast quadrant of the cost-effectiveness plane.*

of target BP) was JPY 45,294 for the nifedipine CR treatment group and JPY 72,988 for the amlodipine treatment group, while it was JPY 42,097 for the nifedipine CR treatment group and JPY 70,798 for the amlodipine treatment group to reach the target DBP.

In this sense, the nifedipine CR treatment group was dominant (higher efficacy and lower average treatment cost per patient) to the amlodipine treatment group (Fig. 1, Table 2).

Sensitivity Analysis

Achievement Rate of Target BP in the Amlodipine Treatment Group

Sensitivity analysis on the achievement rate of target BP in the amlodipine treatment group was conducted, varying the rate between 40 and 80%. Although the adjusted difference in the achievement rate of SBP (nifedipine CR treatment group − amlodipine treatment group) was 21.3% (95% confidence interval: 12.9–29.6%) in the base results, the nifedipine CR treatment group showed a lower average cost per patient to reach target BP than the amlodipine treatment group, even when the achievement rates is raised to that of the nifedipine CR treatment group (69.8%) (Fig. 2).

Other Parameters

The results were robust to univariate sensitivity analyses of the other parameters, such as the incidence of adverse events and the cost to treat drug-related adverse events.

Bootstrap Analysis

The bootstrap incremental cost-effective analysis was applied to calculate the probabilistic distributions of incremental cost-effectiveness by 10,000 times resamplings of the cost/effect data. The results demonstrated that points indicating incremental cost-effectiveness, *e.g.*, a difference in achievement rate (nifedipine CR treatment group − amlodipine treatment group) and difference in cost (nifedipine CR treatment group − amlodipine treatment group), are located in the southeast quadrant of the cost-effectiveness plane with a probability of 9,999 out of 10,000 (Fig. 3).

Impact of Premature Discontinuation Rate

For base case of this analysis, medication cost was estimated, assuming that all patients received 8 weeks treatment, because there was no difference in the premature discontinuation rate between the groups. However, result of ADVACE-Combi study showed that there were 7 subjects (2.8%) in the nifedipine CR group and 6 subjects (2.3%) in the amlodipine group who have discontinued study drug prematurely due to drug-related adverse event. When taking this into account, the average total cost per patient was recalculated to be JPY 30,272 for the nifedipine CR treatment group and JPY 34,119 the amlodipine treatment group during the double-blind treatment period. This did not have any significant impact on the results.

Discussion

The current analysis is quite important because it is the first cost-effectiveness assessment of two widely used CCBs (nifedipine CR and amlodipine) coadministered with ARB to Japanese patients with moderate to severe hypertension. The data were based on the ADVANCE-Combi study, which is the first and only double-blind, randomized clinical comparison of the efficacy of nifedipine CR–based combination therapy with ARB and amlodipine-based combination therapy. The results demonstrated that combination therapy with nife-

dipine CR and valsartan is dominant to that with amlodipine and valsartan. In terms of efficacy, the nifedipine CR treatment group showed a significantly higher achievement rate of target BP than the amlodipine treatment group. Likewise, the nifedipine CR treatment group showed significantly lower treatment cost (*14*).

Among the increasing financial burdens on the Japanese NHI system, one of the largest is the cost of treatment relating to cardiovascular disease, estimated at about JPY 5 trillion per year (including about JPY 690 billion for ischemic heart disease and about JPY 1.7 trillion for cerebrovascular disease), according to statistics of the Ministry of Health, Labour and Welfare in 2003 (Kokumin-Iryohi-no-Gaikyo). Hypertension is a major risk factor for cardiovascular disease, which plays a major etiologic role in the development of cerebrovascular disease, ischemic heart disease, and cardiac and renal failure. Many clinical data prove that treatment of hypertension can reduce these risks (*1–5*), regardless of the type of antihypertensive medication administered (*16*). Amid the increased demands for economic analyses of medical treatment, the current result is worthwhile because its pharmacoeconomic analysis based on the ADVANCE-Combi study (*14*) demonstrated that, among combination therapies for hypertension, nifedipine CR could ease the budgetary burden, accompanied with better control of BP in patients with hypertension. However, some considerations are necessary before we can generalize the results.

First, this analysis was calculated using a surrogate endpoint (*i.e.*, the achievement of target BP). However, it is clear that a higher achievement rate of target BP in the short term demonstrated in the nifedipine CR treatment group will, in general, reduce the risk of major vascular events in the long term (*6*, *17*). Hence, the difference in total treatment cost between the groups observed in this study could be translated into a much bigger one if long-term data were applied. In addition, the difference of non-achievement rate of the target BP during the 16-week study period between the groups should also be considered. When amlodipine therapy is given, coadministration with other antihypertensives in addition to ARB will be required in many patients, further increasing the total treatment cost associated with amlodipine treatment.

Secondly, the ADVANCE-Combi study enrolled patients with moderate to severe hypertension. According to the database of the Ministry of Health, Labour and Welfare in 2002, nearly 7 million Japanese were diagnosed with and treated for hypertension under the NHI system (Overview of Patients Survey in 2002: Section 5. Number of patients with major disease [Table 11]. Database of Ministry of Health, Labour and Wealfare [in Japanese]: http://www.mhlw.go.jp/toukei/saikin/hw/kanja/02/index.html). Many of them were considered to require combination therapy to control their BP (*10*, *18*). Therefore, the present economic analysis is potentially applicable to many of these patients with essential hypertension.

Thirdly, cost-effectiveness was assessed for only one type of combination therapy (*i.e.*, CCB and ARB) in this study, while there are several other types of combination therapy recommended in the guidelines (*6*). Certainly there is a lack of sufficient data to answer how each type of combination therapy differs from a pharmacoeconomic point of view, but it has recently been reported that combination therapy of CCB and ARB is not dominated by other types of combination therapies using diuretics, based on a Markov model, even though diuretics are inexpensive (*11*).

Fourthly, as some recent papers have noted, CCB has the additional effect of decreasing sympathetic nerve system activity and serum catecholamine levels (*19*). This point should also be explored in future clinical investigation.

In light of these considerations, the present cost-effectiveness analysis suggests that a combination of nifedipine CR and valsartan is an effective therapy for achieving target BP without major safety issues, and that it may significantly alleviate the long-term financial burden on both patients and the NHI system in Japan.

In conclusion, the nifedipine CR treatment group was dominant to the amlodipine treatment group in essential hypertensives, indicating that this combination treatment strategy could lighten the financial burden on the NHI system in Japan.

Appendix

ADVANCE-Combi Study Group

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