Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study investigated low-dose combination therapy with controlled-release nifedipine (20 mg/day) plus candesartan (8 mg/day), and up-titrated monotherapy with candesartan (12 mg/day), for the treatment of mild to severe essential hypertension.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised Japanese patients aged 20 to 70 years old, with mild to severe hypertension, who were not sufficiently controlled by the conventional dose of candesartan monotherapy.

Setting
The setting was primary and secondary care. The economic study was carried out in Japan.

Dates to which data relate
The effectiveness evidence and resources used were derived from the Nifedipine and Candesartan Combination (NICE-Combi) study reported in 2005 (Hasebe et al., see 'Other Publications of Related Interest' below for bibliographic details). The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
The study sample consisted of 331 patients who had completely discontinued previous antihypertensive treatment and were given candesartan 8 mg for 8 weeks during the baseline treatment period. Of these, 258 patients (147 males and 111 females) who were not sufficiently controlled by candesartan 8 mg were randomised into two groups. One group received candesartan 8 mg plus controlled-release nifedipine 20 mg for 8 weeks (130 patients), while the other received
candesartan 12 mg for 8 weeks (128 patients) during the randomisation period. The mean age was 55.3 years (range: 27 to 78).

**Study design**
This was a multi-centred, double-blinded, parallel arm, randomised clinical trial. The authors reported only limited information on study design and made reference to the clinical paper (Hasebe et al. 2005). The patients were followed up for 8 weeks.

**Analysis of effectiveness**
The primary outcomes used were the efficacy and safety of each treatment. Efficacy related to the achievement rates of target blood pressure (i.e. <130/85 mmHg for patients aged under 60 years, <140/90 mmHg for those aged 60 to 69 years, and <150/90 mmHg for those aged 70 years and over). Safety was assessed in terms of adverse events. The authors only reported limited information for this field and made reference to the clinical paper (Hasebe et al. 2005). The authors reported that there were no significant differences in gender or age between the treatment groups.

**Effectiveness results**
The achievement rates of target blood pressure were significantly higher in the combination therapy group (28.5% for systolic blood pressure and 40.8% for diastolic blood pressure) than in the up-titrated monotherapy group (17.2% for systolic and 27.3% for diastolic), (p=0.0225 and p=0.0164, respectively.)

Adverse events related to the study drug occurred in 10 patients (7.7%) in the combination therapy group and 12 patients (9.4%) in the up-titrated monotherapy group. There was no significant difference between the groups.

**Clinical conclusions**
Combination therapy was more effective than up-titrated monotherapy for hypertension, and as safe.

**Measure of benefits used in the economic analysis**
The outcome measure used in the economic analysis was the achievement rate of target blood pressure (i.e. the number of patients reaching the target blood pressure). This was directly obtained from the clinical analysis.

**Direct costs**
The direct costs included treatment costs (outpatient visit fee, laboratory examination, cost of medication and additional treatment costs for drug-related adverse events). The cost of treatment was calculated from the perspective of insurers, based on National Health Insurance costs in April 2004. It was assumed that all patients younger than 65 years old were treated by office-based physicians and were dispensed medications at a third-party pharmacy. The cost of each treatment was obtained from the data listed in case report forms of the NICE-Combi study. The cost of over-the-counter drugs was not included because they did not increase the expenditure of insurers. Most of the resource quantities and the unit costs were reported separately. The price year was 2004.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.

**Indirect Costs**
The indirect costs were not included.

**Currency**
Sensitivity analysis
One-way sensitivity analyses were carried out to estimate the robustness of the results. The parameters varied were drug prices (calcium-channel blocker and candesartan 12 mg), premature discontinuation rate, achievement rate of target blood pressure in the up-titrated monotherapy group, assumption on types of health care facility, and the incidence and cost of adverse events. The selection of the ranges appears to have been subjective.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The average cost per patient was JPY 29,943 for the candesartan 8 mg/controlled-release nifedipine 20 mg combination therapy group and JPY 33,182 for the candesartan 12 mg monotherapy group during the randomisation period.

It should be noted that the sample size for the up-titrated monotherapy group was 128 patients. However, the cost calculation for this group seems to have been based on 130 patients (Table 2). This may affect the results of the study.

Synthesis of costs and benefits
Cost-effectiveness ratios were estimated as the average treatment cost per patient reaching the target blood pressure (average total cost for randomisation period/achievement rate of target blood pressure). The results were as follows:

JPY 105,063 for the combination therapy group and JPY 192,916 for the up-titrated monotherapy group to reach the target systolic blood pressure; and

JPY 73,390 for the combination therapy group and 121,544 Japanese yen for the up-titrated monotherapy group to reach the target diastolic blood pressure.

Incremental cost-effectiveness ratios were not estimated since the combination therapy was "dominant" (higher efficacy and lower average treatment cost per patient treated to target blood pressure) over the up-titrated monotherapy.

The sensitivity analysis showed that the results were robust to the cost of drugs, achievement rate of target blood pressure and incidence of adverse drug reactions.

Authors’ conclusions
Combination therapy with controlled-release nifedipine and low-dose candesartan (8 mg) is "dominant" to up-titrated candesartan monotherapy for the treatment of essential hypertension.

CRD COMMENTARY - Selection of comparators
A justification was given for the choice of the alternative technologies. Combination therapy with multiple agents, each at a low dose, rather than up-titrated monotherapy is becoming a commonly used treatment for hypertension in Japan. In addition, guidelines for the treatment of hypertension recommend its use. You should decide if they represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a double-blind, parallel arm, randomised clinical trial, which was appropriate given the study question. It was unclear whether the study sample was representative of the study population because no details of the patients were provided. It is not possible to comment on the internal validity of the effectiveness results since the
authors referred to a separate clinical paper for details of the clinical study. No power calculations were reported. Thus, it was not possible to ascertain whether the results obtained were due to the intervention or to chance.

**Validity of estimate of measure of benefit**
The measure of benefit was the achievement rate of target blood pressure, which was taken directly from the effectiveness study.

**Validity of estimate of costs**
The analysis of the costs was performed from the perspective of the third-party payer. Given that perspective, it appears that all the relevant categories of costs have been included in the analysis. The costs were reported separately from the quantities. It should be noted that, when reporting cost results for the up-titrated monotherapy group, 130 patients rather than 128 patients (sample size for this group) were used, but it is unclear to what extent this might have affected the cost results of the study. Sensitivity analyses were conducted on the prices but not quantities. The authors stated that the cost of treating adverse drug reactions might have been underestimated since some information could have been missed by the case report forms for the study, but this issue was not considered to have affected the results. The price year was reported. The costs do not appear to have been discounted, which is justified given the short time horizon considered at analysis.

**Other issues**
The study findings, in terms of the effectiveness of the treatments, were compared with those from other studies. The authors directly addressed the issue of the generalisability of the results to other settings. The authors stated that the economic analysis based on outcome data after 8 weeks of treatment, instead of long-term outcome data, would not be sufficient to predict the long-term economic impact on antihypertension treatment. They discussed the fact that the total treatment cost for up-titrated monotherapy would always be much higher than that for combination therapy, and that the possible difference in treatment costs between the two treatment regimens in the mid/long term would be greater than the difference observed in the NICE-Combi study. They also discussed why their economic analysis is potentially applicable to many patients with essential hypertension which is not well controlled. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. They did not report further limitations to their study.

**Implications of the study**
The combination treatment strategy could contribute to a decrease in the long-term financial burden on both hypertension patients and the National Health Insurance system in Japan. The authors suggested that a large-sized outcome study would be needed to confirm the current estimates.

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