Study Design

The MAPEC Study was a prospective, randomized, open-label, blinded endpoint (PROBE) trial. A major goal of the study was to assess the effect of treatment-time regimen of prescribed BP-lowering medications on CVD, NOD, and CKD outcomes. Thus, patients were randomized either to ingest all BP-lowering medications upon awakening or the complete daily dose of $\geq 1$ of them at bedtime and the remaining ones (if any) upon awakening. Assignment of participants to the two treatment-time regimens was done according to the order of recruitment, following an allocation table constructed by a computerized random-number generator.

The study did not specify or require one unique investigational hypertension medication; rather, participating physicians were given the choice of prescribing, as first-line therapy in previously untreated patients, one medication of any of the recommended therapeutic classes. Randomization of patients to treatment-time (awakening or bedtime) was done separately for each allowed initial individual hypertension monotherapy (valsartan, telmisartan, olmesartan, ramipril, spirapril, amlodipine, nifedipine GITS, nebivolol, torasemide, doxazosin GITS) to ensure the proportion of patients treated with each medication was similar across the morning and bedtime-treatment arms. If based on ABPM threshold criteria the ABP of a given patient remained uncontrolled at any time during follow-up, additional medications could be added in keeping with current clinical practice.

Participants with resistant hypertension were randomized either to: (i) modification of the nature of their treatment by exchanging one hypertension medication with a new one, and thus without alteration of the total number of medications, but retaining the upon-waking ingestion time for all of them (awakening-treatment regimen); or (ii) the same exchange of one medication with a new one, but
prescribing its ingestion at bedtime instead of morning (bedtime-treatment regimen). If during follow-up ABP remained uncontrolled, investigators were permitted to: (i) exchange additional hypertension medications for others of different classes (keeping always the upon-waking ingestion time schedule of all medications) in patients of the awakening-treatment regimen group; (ii) progressively shift additional hypertension medications (that were being ingested upon awakening) to bedtime in patients of the bedtime-treatment regimen group; or (iii) prescribe additional BP-lowering medications in patients of either group.

Changes in therapeutic scheme during follow-up in uncontrolled patients (those with ABP above the thresholds provided above) were always based on the results from periodic evaluation by ABPM. Adherence to the time-of-day (awakening or bedtime) schedule of treatment and prescribed medication(s) was enforced at each follow-up visit. Adverse events, including type, duration, seriousness, intensity, and possible relation to hypertension treatment, were registered as spontaneously reported by the patient and/or detected by the investigators through non-directive questioning and physical examination.