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A Sub-study of the ASCOT Trial

Ambulatory blood pressure monitoring and 24-h blood pressure control as predictors of outcome in treated hypertensive patients

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Introduction

Ambulatory blood pressure measurement (ABPM) is rapidly gaining acceptance as a valuable technique in clinical practice. However, there are many unresolved issues concerning the advantages of ABPM over conventional clinic blood pressure measurement. During the course of the ASCOT study, each participant will have numerous clinic blood pressure measurements under carefully standardised conditions. In this sub-study, ABPM will be performed in addition to automated clinic blood pressure measurements. Having both methods of measurement available will allow for a number of comparisons between the two techniques. The issue of which measurement technique best predicts outcome will be examined, both in relation to target organ involvement and cardiovascular morbidity and mortality. The relationship of components of the 24-h blood pressure profile, such as the white coat response, variability, day and night-time blood pressures, dipping and non-dipping, will be examined in relation to outcome. The effect of different treatment strategies on clinic measurements will be compared with the influence of treatment on different components of the 24-h profile. It will be possible also to examine the efficacy of treatment in patients with a white coat response according to clinic and ambulatory daytime blood pressures. The ambulatory sub-study also provides the opportunity to assess the efficacy of treatment over the 24-h period for the different treatment strategies, and to study the effect of different drugs on the 24-h profile.

The incorporation of a sub-study on ABPM in the main ASCOT study provides a means, therefore, of addressing many of the controversial issues surrounding ABPM.

Objectives of the sub-study

The objectives of the Ambulatory Sub-study are: (a) To determine whether on-treatment ambulatory blood pressure monitoring data provide additional information to that from repeated clinic measurements in prediction of outcome. (b) To determine whether blood pressure control over 24 h influences clinical outcome. (c) To investigate whether differences between treatment regimens contribute to differences in blood pressure control over 24 h and hence to clinical outcome.

Sub-study methods and design

A sample of 1600 patients from the ASCOT population will be recruited from four centres—Beaumont Hospital, Dublin, the Western Infirmary, Glasgow, St Mary's Hospital, London and St Bartholomew's, London. All participants in ASCOT will be eligible for inclusion in the sub-study, the only

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requirement being the willingness of the subject to undergo ABPM annually.

To allow analysis of at least 100 events, approximately 1600 participants will need to be recruited, which should be representative of the entire ASCOT population, and which should also allow a balance between randomised treatment strategies, and between the lipid and non-lipid lowering arms.

Patients will be followed for the duration of ASCOT. Therefore, this sub-study will be conducted in parallel with the main study, with analysis on completion of ASCOT and a report available around the time of the main study report.

Clinic (office) blood pressure recordings will be carried out according to the methods described in the ASCOT protocol. Clinic blood pressure will be measured in triplicate in the sitting position after 5 min rest using the OMRON HRM 705-CP device. Measurement in two occasions prior to randomisation and up to 12 occasions thereafter (60 months) will yield up to 42 (14×3) readings in total.

Twenty-four hour ABPM will be conducted prior to randomisation and annually thereafter for the duration of the study, ie, up to six recordings in each patient. This will allow maximal utilisation and interpretation of data collected. ABPM monitoring will be conducted using the validated SpaceLabs device (Redmond, WA, USA).[1] The protocol for recordings will be standardised to a recording every 30 min throughout the 24-h period.

All ABPM data will be entered into the DABL98© program. DABL98© is a database program designed to store, retrieve and display an array of clinical and cardiovascular data, including ABPM, in patients with hypertension and other cardiovascular illnesses. It is the seventh version of a series that, at each step, has provided new features to assist physicians in the diagnosis and management of hypertension and cardiovascular disease. New features in DABL98© include automatic natural language summaries, cardiovascular event risk indicators and a facility for determining if management goals are being achieved.

Clinic blood pressures may be entered and analysed with mean standing, sitting, supine, left arm, right arm and overall office blood pressures being displayed. Ambulatory blood pressures are loaded directly from the monitor or from files generated by manufacturer software. They are stored and displayed in a format unique to DABL98© whereby measurements are plotted in a standard format, regardless of their source, against a background showing normal ranges to facilitate diagnosis and comparison. Statistics are presented for systolic and diastolic blood pressure, heart rate and mean arterial pressure for the initial hour, daytime, night-time, and full 24-h periods. The mean, standard deviation and load values are plotted for visual reference. Statistics are provided for median, leese, percentage load, area under curve, coefficient of variation, root mean square of successive deviations, number of load and leese events, duration of maximum load and leese events and empirical and percentage dip values. Durations of initial, daytime and night-time periods can be individually set. A natural language analysis of daytime and night-time pressure is provided in a memo with details of white-coat hypertension where appropriate.[2]

Statistical methodology

The following statistical methods will be employed:

(a) A regression model will be developed to determine whether ambulatory blood pressure data provides additional information to clinic blood pressure data in predicting events (cardiac, cerebrovascular and total) using measurements such as mean 24-h blood pressure, mean daytime blood pressure, mean night-time blood pressure and blood pressure variability at each assessment to summarise ambulatory blood pressure.

(b) To determine whether blood pressure control influences clinical outcome a further regression model will be developed where the explanatory variables define whether target blood pressure was achieved.

Achievement of target blood pressure will be defined as: office blood pressure—systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg; ambulatory blood pressure—average systolic <135 mm Hg (day), <120 mm Hg (night), <130 mm Hg (24 h); average diastolic <85 mm Hg (day), <75 mm Hg (night), <80 mm Hg (24 h); systolic and diastolic load both <15%.

(c) In the comparison of 24-h blood pressure control in the different treatment groups the end points will include 24-h profiles, readings over the final few hours of the dosage interval and 'trough to peak' ratios. In the absence of a true placebo phase or no treatment run-in phase, conventional trough/peak ratios cannot be calculated. However, changes in peak and trough blood pressure from baseline will give an estimate of the efficacy and duration of treatment regimens, allowing estimation of quasi trough to peak ratios. Such modified trough to peak ratios will be used as an index of 24-h control for a given average 24-h blood pressure and related to event rates. Other indices of 24-h control (including day/night variability) will also be analysed.

Discussion

Conventional blood pressure measurement is a strong index of future cardiovascular disease,[3] and it might be expected that the aggregate of these measurements will be a good predictor of clinical outcome. Since clinic blood pressure exhibits considerable variability, the aggregate of repeated measurements should provide an even more precise

estimate of risk. However, in many observational studies, such readings do not appear to correlate well with surrogate markers of outcome of left ventricular mass. There is growing evidence that 24-h ambulatory blood pressure is more reproducible than clinic measurements, particularly if 30 or more ambulatory measurements are obtained.[4,5] However, it is still unclear whether the apparent advantage of ABPM is merely a function of numbers, ie, more measurements, and/or the quality of clinic readings due to non-standardised conditions.

ABPM appears superior to clinic blood pressure in providing an indication of the clinical consequences of hypertension in cross-sectional studies.[6–17] However, the evidence of the clinical superiority of ABPM over clinic blood pressure in terms of outcome in the general population rests on the results of a small series of follow-up studies that suggest a closer association of cardiovascular morbidity or target organ deterioration with ambulatory than with clinic blood pressures.[18–23] The only such longitudinal study reporting on actual cardiovascular events[21,22] lacked a controlled design, did not assess all conventional risk factors and had a loose definition of end points. Other studies have been small and follow-up brief.[18,20,22] Recently, however, systolic ABPM has been shown to be a significant predictor of cardiovascular risk in the elderly over and above conventional blood pressure.[24]

The gain in predictive power for target organ damage of ambulatory blood pressure has been variable, appearing to be most pronounced in studies in which the relationship with clinic blood pressure was weak, possibly because of poor standardisation of clinic blood pressure measurements.[25] Increasing the numbers of standardised measurements strengthens the relationship of clinic pressure with end-organ damage and diminishes the additional predictive power of 24-h blood pressure.[26]

It is unclear which aspect of the 24-h blood pressure profile is most critical in predicting cardiovascular complications. Attenuation of the normal nocturnal drop in blood pressure may be associated with greater risk of end organ disease[15,23,27–36] although results are inconsistent.[37] There is little prospective data to demonstrate the prognostic significance of nocturnal blood pressure,[38] though it would appear that at least in the elderly night-time systolic blood pressure is a more accurate predictor of outcome.[24] Variability in blood pressure over 24 h may have prognostic significance and has been suggested as an additional independent risk for a given average blood pressure level.[13,18,39]

ABPM allows identification of patients with white coat hypertension who may have a relatively low level of risk[22,40] and who may respond little to drugs.[41,42] The risks and benefit from treatment of white coat hypertension remains controversial.[43–45]

Much is made of the importance of 24-h blood pressure control in the management of hypertension but this concept has never been tested in a prospective outcome study. The treatment regimens employed in ASCOT may well provide different profiles of blood pressure over 24-h and differences in profiles might contribute to differences in outcome. Thus, ASCOT proved an opportunity to examine the influence of 24-h control of blood pressure on morbidity and mortality in treated hypertensive patients.

Since ABPM is largely devoid of a placebo effect,[46,47] 24-h monitoring provides a better indication of the antihypertensive effect of therapy in a longitudinal study.[48] ABPM appears to be particularly useful in identifying those patients in whom blood pressure is controlled inadequately or not at all.[49]

In an effort to improve compliance and convenience, once daily drugs are preferred. Most modern drugs, such as amlodipine and perindopril have been developed for once-a-day use.[50–52] Since once daily therapy is usually taken in the morning, the least pharmacological effect will occur at the time of the early morning surge in blood pressure when the incidence of myocardial infarction and sudden death is particularly high.[53–55]

Most drugs appear to have little effect on the shape of the 24-h blood pressure profile[56–58] and the significance of any effect on blood pressure variability is unknown.[59] Beta-blockers tend to attenuate the night-time fall in blood pressure while calcium antagonists and ACE inhibitors tend to accentuate night-time dipping.[60,61] Over-treatment during the sleeping hours may be hazardous, particularly in patients with coronary or cerebral atherosclerosis.[62–64] Since clinic blood pressure, even at the end of the dosage interval, can be misleading,[41,65,66] the prognostic significance of 24-h blood pressure control, including night-time control, and attenuation of the early morning surge in blood pressure can only be tested in prospective controlled trials incorporating ABPM.

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