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CLINICAL STUDY

**A Longitudinal Study of the Yield and Clinical Utility of
a Specifically Designed Secondary Hypertension
Investigation Protocol**

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ABSTRACT

Objective. It has become common practice to use a day-case based approach to identify from the population of hypertensive patients those with an identifiable cause. We aimed to prospectively identify 96 consecutive hypertensive patients undergoing an algorithmic investigation protocol based around two day case hospital attendances. **Methods.** The overall diagnostic yield and associated costs were recorded and the patients were observed for a mean of 2.5 years with ambulatory blood pressure (BP) monitoring every three months. **Results.** A secondary cause of hypertension was identified in 18.1% of patients, three quarters of whom had renovascular disease. There was a fall in blood pressure with time (157/97 vs. 140/85) but this was associated with an increase in the amount of medication required (mean medication score 5.99 vs. 7.65). Improvement in BP occurred irrespective of whether or not a secondary cause was identified. Only 3.2% of patients were cured of their hypertension as a result of enrollment in the protocol. The cost of identifying each case

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of secondary hypertension was Euro 10, 196. **Conclusions.** A comprehensive protocol aimed at identifying secondary hypertension had a low yield, the majority of whom had renovascular disease. In light of recent data illustrating the lack of improvement in BP following dilatation or bypass of atherosclerotic renovascular disease, it is debatable whether searching for it is justifiable.

Key Words: Secondary hypertension; Diagnostic yield; Cost; Renovascular disease; Longitudinal.

INTRODUCTION

Despite the low prevalence, the large number of patients with hypertension in the community means that the number presenting with occult secondary hypertension becomes significant.^[1] The goal in these circumstances is to identify such patients in the most cost-effective manner. Traditionally, the batteries of tests necessary to exclude the various causes of secondary hypertension have been performed as an in-patient. In recent years, efforts have been made to streamline the investigations into various algorithms and to perform the majority of tests in an outpatient setting.

We designed a comprehensive protocol based around two day case visits to the hospital. In this report we aimed to investigate the results of the first 2.5 years of operation of this protocol. We resolved to define the diagnostic and therapeutic yield, to quantify the associated costs, and to identify inefficiencies.

PATIENTS AND METHODS

Patients

All consecutive patients enrolled into a newly developed secondary hypertension investigation protocol over a 2.5 year period were considered eligible for inclusion. Enrollment criteria were two out of the following: (1) Worsening hypertension such that three or more medications were required, (2) Age <35 years, and (3) Adverse clinical characteristics (Nondipping pattern on ambulatory blood pressure monitor-ABPM, left ventricular hypertrophy, retinopathy, or abnormal urinalysis). Of 527 patients assessed at the hypertension referral clinic, 97 were enrolled. Of these, one was subsequently found to be normotensive and consequently not investigated; the remaining 96 patients form the basis of this report. All patients had been assessed at the blood pressure clinic, where history, examination, urinalysis, fasting lipids, electrocardiogram, echocardiogram, and 24h ambulatory blood pressure monitoring (ABPM) had been performed. Data concerning each patient was entered prospectively into a database. An arbitrary medication score was devised (Table 1) and mean day/night 24h ABPM readings were recorded on a 3-monthly basis.

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Table 1. Medication score based upon relative potencies; a score is given if one of the listed medications is used.

Score	Medication
1	Atenolol 25mg, Nicardipine 15mg, Labetalol 100mg
2	Atenolol 50mg, Hydrochlorothiazide 2.5 mg, Amlodipine 5 mg, Lisinopril 5mg, Doxazosin 1mg, Indapamide 2.5 mg
3	Atenolol 75mg, Nicardipine 45 mg, Labetalol 300mg
4	Atenolol 100mg, Amlodipine 10mg, Lisinopril 15mg, Losartan 100mg, Doxazosin 4mg
5	Doxazosin 8mg, Lisinopril 20mg, Amlodipine 20mg
6	Atenolol 200 mg, Losartan 200mg, Doxazosin 16mg

Protocol

Once enrolled, the investigation protocol was algorithmic and comprehensive. It was performed during the course of two day-case visits to the hospital. On day one, the patient had blood pressure and pulse recorded, urinalysis was performed, and blood was drawn for full blood count and urea and electrolyte studies. The patient then underwent mag-3 isotope renography (without the administration of captopril) and abdominal CT scan. On day two, blood was drawn for cortisol and aldosterone studies, urine was collected for catecholamine assay, and a renal arteriogram was performed.

costs

Marginal cost values were obtained for each test and expressed in *Euro* (1 *Euro* = \$1.10). This data was gathered by consultation with the relevant hospital department and with other hospitals (mainly private) in the Dublin area. The overall costs included those for the time of the medical house officer, the consultant, and the nursing staff, in addition to a fixed cost for the day-case bed.

Definitions

Secondary hypertension was diagnosed if a pathology discovered during the course of investigation was deemed to be directly contributing to the patient's hypertension. Those cases where this diagnosis was followed by cure of the hypertension (with cessation of all anti-hypertension medications ≥ 12 months post-procedure) were termed "curable hypertension". Improvement in hypertension after a therapeutic intervention was defined as a 50% reduction in medication requirement without deterioration in blood pressure control, or greater than 20% improvement in mean arterial pressure without the need to increase medication.

Renovascular disease was diagnosed if there was angiographic evidence of $>50\%$ narrowing of the luminal diameter of either or both renal arteries or of a significant



accessory renal artery (supplying >50% of the mass of the kidney). Renal angiography was the primary method of diagnosing renovascular disease; the isotope renogram was felt to be suggestive of renovascular disease if there was evidence of flow asymmetry or globally reduced perfusion. Selective renal vein renin estimation was not used to determine the significance of renal artery stenosis.

Cushing's syndrome, primary hyperaldosteronism and pheochromocytoma were diagnosed on the basis of the appearance of the adrenal glands on CT scan in conjunction with appropriate hormonal assays.

Renal insufficiency was diagnosed if the serum creatinine was $>120 \mu\text{mol/L}$.

Hypokalemia was diagnosed if the serum potassium was $<3.5 \text{ mmol/L}$ on two separate occasions, in the absence of diuretic therapy or obvious gastrointestinal loss.

Statistical Analysis

Values are expressed as mean (95% confidence interval). Changes in medication requirement and blood pressure with time were analyzed using ANOVA.

RESULTS

Patient Characteristics

The mean age of the 96 patients was 54 years (range: 20–77) and 66% were male. Mean duration of follow up was 2.5 years (95% C.I. 2.3 to 2.8). All patients were Caucasian.

Results of Investigations

The results are summarized in Table 2. The diagnostic yield of the work-up was 18.1%; the majority (76.5%) of these patients had renovascular disease, with only two cases of endocrine hypertension. A further six patients had some evidence of renovascular disease but failed to reach the predefined 50% stenosis required for the diagnosis. There were no instances of renal insufficiency following angiography. As a direct result of entering the protocol, 27 patients (28.7%) were referred to the Nephrology service and three patients (3.2%) underwent renal biopsy. One of these biopsies demonstrated the presence of IgA nephropathy and the other two showed evidence of hypertensive nephrosclerosis.

The contributions of individual tests are summarized in Table 3. Of note, the sensitivities of clinical assessment, urinalysis, and electrolyte measurement in detecting secondary hypertension were 17.7, 58.8, and 29.4% respectively. Four cases (24%) of secondary hypertension would have been missed if these measures had been used as the criteria for entry into the protocol (Fig. 1). Of the 13 patients with significant renovascular disease on arteriography, 10 had undergone prior renography, four of which were interpreted as normal. The sensitivity and specificity of CT scan for adrenal disease was 100% and 96% respectively. However, the prevalence of



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Table 2. Breakdown of patients according to the results of investigations.

Result of investigation	Number	Therapeutic interventions
No cause found	77 (81.2%)	
Secondary hypertension	18 (18.8%)	
Renovascular disease	13 (13.8%)	11 angioplasties in eight patients two surgical repair or RAS one nephrectomy
Parenchymal renal disease ^a	1 (1.1%)	
Phaeochromocytoma	1 (1.1%)	Adrenalectomy
Miscellaneous ^b	3 (2.1%)	
Hypertension cured	3 (3.2%)	Two cases of renovascular disease (one with angioplasty and one with surgical repair); one adrenalectomy

^aIgA nephropathy.^bHypothyroidism, Cushing's syndrome, and renal artery aneurysm.

Table 3. Diagnostic accuracy of some of the tests employed.

Test	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Clinical assessment	18	50	50	83
Urinalysis	59	69	24	85
U and E ^a	29	33	28	84
CT scan ^b	100	96	17	86
Renogram	60	82	38	88

^aElectrolyte and renal function measurement.^bFigures are calculated for cases of adrenal disease diagnosed.

adrenal disease was very low and there were many cases of "borderline" CT scans that required further investigation. Thus, the positive predictive value of this test was only 16.7%.

Follow-Up

The mean medication scores at presentation, six months, 12 months, and 24 months and at the time of last follow-up are summarized in Fig. 1. There was a significant decrease in mean daytime systolic and diastolic blood pressure with time (157/97 at presentation vs. 140/85 at last follow up, $P < 0.001$), the largest decrement occurring immediately after referral to the hypertension clinic. Concurrent with this, there was a nonsignificant increase in mean medication score with time (5.99 at presentation vs. 7.65 at last follow-up, $P = 0.13$). Hypertension was successfully cured in three patients (3.2%). During the course of follow-up BP improved (as defined above) in 24 patients (25.0%). However, those patients with an improvement in BP were evenly divided between those with

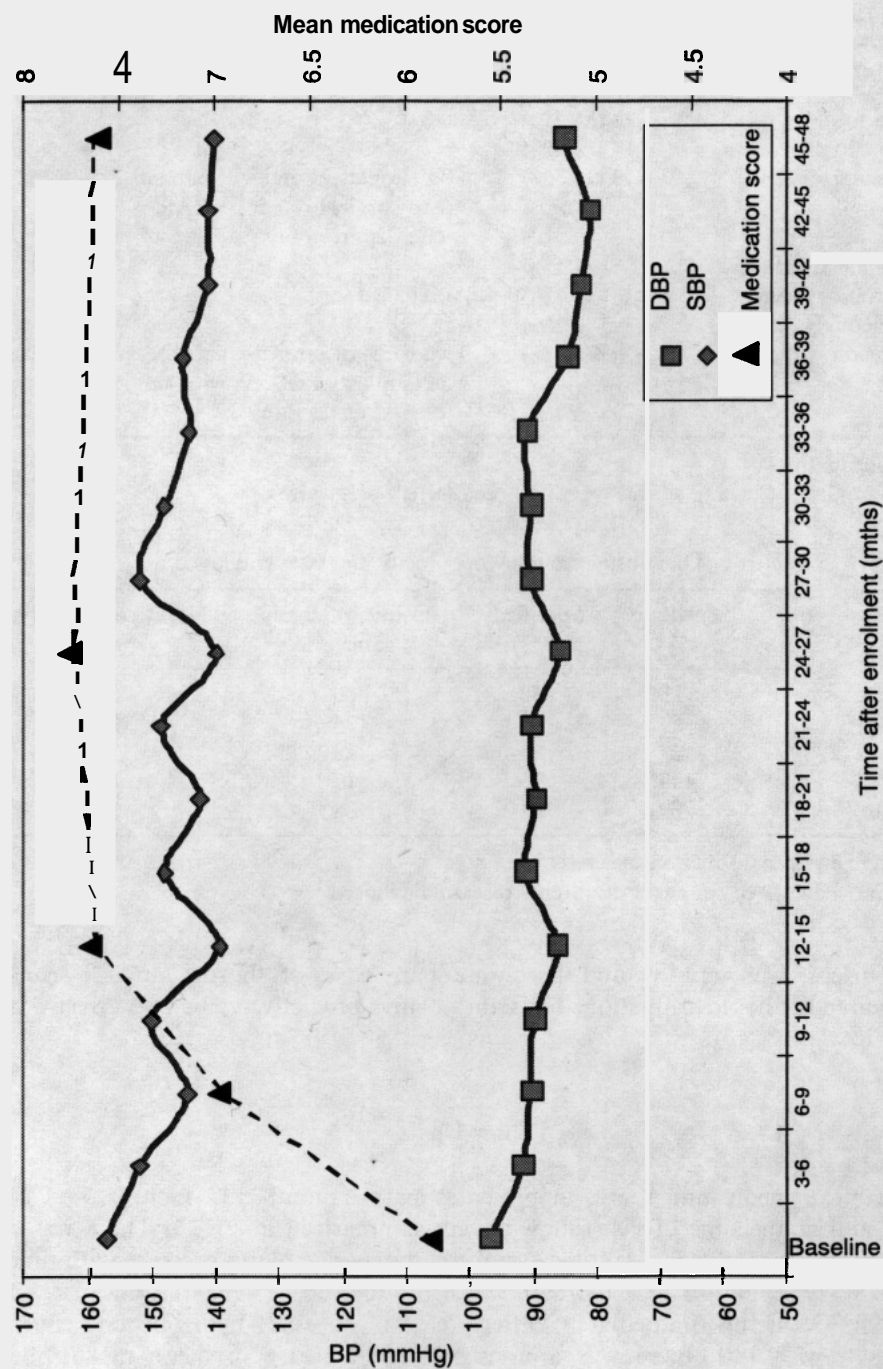


Figure 1. Change in mean daytime systolic and diastolic blood pressure with time, plotted with the change in mean medication score with time. There was a significant decline in systolic and diastolic blood pressure ($P < 0.001$).



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Table 4. Costings for various elements of secondary hypertension protocol.

Variable	Cost (Euro)	Number (%) of patients undergoing test	Contribution to overall cost ^c (%)
Blood tests ^a	72.0	95 (99%)	4.0
Urine tests ^b	101.8	95 (99%)	5.3
CT scan	324	90 (94%)	16.8
Renogram	294.8	72 (75%)	12.2
Renal angiogram	508.2	89 (93%)	26.1
Nurse time	190.6	—	10.6
Doctor time (H.O.)	20.3	—	1.1
Doctor time (consultant)	22.1	—	1.2
Day bed charge	419.3	—	23.2

^aBiochemistry, aldosterone, cortisol.^bCatecholamines, urinalysis.^cMay not total 100% due to rounding.

secondary hypertension ($n=5$, 29%) and those without ($n=19$, 24%). Of the 10 patients who had RAS and underwent angioplasty or surgical bypass, two were cured (as defined above) and in one BP control improved.

costs

Based on the costs listed in Table 4, a mean of Euro1,805 (95% C.I. 1760 to 1851) was spent investigating each patient. This Fig. does not include subsequent costs incurred as a result of follow-up investigations or interventions. The cost of identifying each case of secondary hypertension was Euro10,196 and the cost of identifying each case of secondary hypertension that was eventually cured was Euro57,774.

DISCUSSION

We report on the first 96 patients to be evaluated by a comprehensive, outpatient-based protocol aimed at identifying cases of secondary hypertension. The overall yield in this Caucasian population was 18%, the majority of whom had renovascular disease. Three of the 96 patients (3.2%) were cured of their hypertension after a mean follow-up of 2.5 years. The cost of work-up was Euro10,196 per case of secondary hypertension identified and Euro57,774 per case of secondary hypertension cured.

The prevalence of secondary hypertension has been found to vary between 4.5 and 25% depending on the population under study.^[2-6] The largest community-based study of an unselected hypertensive population found a prevalence of 5.8%.^[4] In a study of 4442 patients referred to a specialty hypertension clinic, Anderson et al. found 10.2% to have secondary hypertension.^[7] Renal disease (parenchymal and vascular) makes up the bulk of cases. The principal motivation for attempting to diagnose secondary hypertension is that some cases are potentially curable. In addition, these patients represent the more severe end of the hypertensive



spectrum and would potentially benefit to a greater extent from definitive management of their blood pressure.

Our study is the first to provide data on the rate of curable hypertension consequent upon a search for secondary causes. However, with a cure rate of only 3.2% this goal would appear to be, on the whole, unattainable. Indeed, our patients received, on average more medication by the end of follow-up, the greatest increment occurring after the first visit. This probably reflects entry into a specialist hypertension clinic. There was no overall reduction in antihypertensive medication as a result of entering the protocol, although there was a minor improvement in blood pressure control.

In addition, it needs to be stated that recent studies into the efficacy of correcting renovascular in the treatment of hypertension raise doubts about whether or not we should look for it in patients at risk of **atherosclerosis**.^[7] Firstly, the belief that, in patients with atherosclerotic **RAS**, the hypertension is caused solely by the reduction in renal flow has been **challenged**.^[7] In many of these patients, it has been established that long-standing essential hypertension is associated with atherogenesis (with consequent renovascular disease) and hypertensive parenchymal renal injury.^[8] In support of this, several recent prospective studies have failed to demonstrate a convincing benefit of revascularizing these kidneys.^[9-11] One careful study by Webster et al.^[9] illustrated the limitations associated with early retrospective series. In this study, there was a statistically significant fall in blood pressure of 26/10 mmHg in the angioplasty group, but the majority of this fall took place in the run-in period, *before the intervention*. This demonstrated that merely attending a dedicated clinic could affect outcome, a finding supported by our results.

The results of **our** study, however, should also be interpreted in the light of its limitations. The patients were drawn from a dedicated hypertension clinic caring for Caucasian patients and are therefore not representative of many patients with hypertension. Nonetheless, the criteria for entry into the protocol are easily applicable to community-based patients. In addition, the study numbers were too small to comment definitively on endocrine causes of hypertension. Of note, after the study had begun, it became apparent that the incidence of adrenocortical hyperplasia might be greatly under-estimated if testing is restricted to adrenal imaging. Gallay et al. found that 17% of patients with poorly controlled hypertension had primary aldosteronism as assessed by measurement of renin-aldosterone **ratios**.^[12] Therefore, our findings should be interpreted in this light.

In summary, the diagnostic yield from a specifically designed, algorithmic secondary hypertension protocol was consistent with reported values in the literature for patients drawn from a tertiary referral clinic. After a mean follow-up of 2.5 years, only 3.2% of patients were cured of their hypertension as a result of entering the protocol. Most cases of secondary hypertension were due to **RAS**. Therefore, rationalizing the protocol with "up-front" renal arteriography followed by endocrine evaluation in those with negative studies may reduce costs without reducing the pick-up rate. In light of **data**^[13,14] concerning the utility of magnetic resonance angiography as a noninvasive screening test for renovascular disease, it may be possible to avoid formal renal arteriography in many cases. This would obviate the need for day case admission. However, as there is now a growing body of evidence indicating the lack of benefit in intervening in many cases of atherosclerotic **RAS**, it is unclear whether such an approach would ultimately benefit the patient.



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