

# This Week's Citation Classic

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Zacharias F J, Cowen K J, Prestt J, Vickers J & Wall B G. Propranolol in hypertension: a study of long-term therapy, 1964-1970. *Amer. Heart J.* 83:755-61, 1972.  
[Clatterbridge General Hospital, Bebington, Wirral, Cheshire, England]

This paper reviews the use of propranolol in 300 hypertensive patients of all grades of severity over a six-year period. Data are provided about the effectiveness of propranolol as a first line antihypertensive drug, both alone and in combination with other remedies, and about its dose range and its profile of adverse effects. [The SCI® indicates that this paper has been cited in over 245 publications since 1972.]

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"In 1950, when I first became interested in the management of hypertension, the available drugs were few in number, unpleasant to take, and unpredictable in their effects.

"Then, following Ahlquist's original paper,<sup>1</sup> and before the first beta blockers were produced, Black correctly predicted that they would be of great value in the treatment of cardiovascular disease, especially angina.<sup>2</sup> What nobody predicted was their outstanding value as antihypertensives.

"My confidence in beta blockers in those days was no more than a hunch, but it was founded on two vital clinical observations by Brian Prichard on patients whom he was treating with propranolol and sotalol and who also happened to have raised blood pressures. Prichard said two things: that beta blockers did lower blood pressure, and that the response of the blood pressure was dose-dependent.<sup>3,4</sup> Both observations met with indifference and the second was widely disbelieved.

"I have always believed that unless hypertension could be managed in ordinary district general hospitals without special human or financial resources, we should never do more than scratch the surface of the problem. Such departments as the Hypertension Unit at Clatterbridge, involving three clinics five days a week, could, I

hoped, deal with long-term studies involving large numbers, and, staffed largely by selected general practitioners, could also help by example to spread the gospel of good management.

"In a sense, therefore, this work was the logical outcome of my philosophy of management, which recognised that the family practitioner had to do most of the work and that the ultimate aim of the hospital physician should be to improve the standard of treatment in general practice.

"The propranolol paper was the preliminary report of a long-term study intended to answer questions of efficacy and safety and also the place of beta blockers in the therapeutic spectrum. It was the first of several such studies involving practolol, atenolol, sotalol, and others. These studies are tedious but if anyone doubts their necessity they have only to recall the practolol saga, in which I was intimately involved. We had 167 patients on practolol under observation for a period of six years, with ultimately more than 40 cases of the oculomuco-cutaneous syndrome.

"Just after the publication of this paper we started to look at atenolol, a drug specifically designed for hypertension, and which after ten years of observation and more than 1,400 patients, I regard as the most satisfactory antihypertensive beta blocker yet produced.

"Several factors may have contributed to the frequent citation of this paper: we had great latitude in the design and development of our study; we had a great range of tablets provided by the pharmaceutical industry; we had a unit of unusual functional design which enabled us to study very large numbers of patients over a very long period of time. These factors helped us to exploit the full potential of this treatment in a way that other investigators could not readily do.

"For a recent review publication in this field, see the proceedings of the symposium at Monte Carlo in 1982 and in particular the opening paper by J.I.S. Robertson."<sup>5,6</sup>

1. Ahlquist R P. A study of the adrenotropic receptors. *Amer. J. Physiol.* 153:586-600, 1948.
2. Black J W. The predictive value of animal tests in relation to drugs affecting the cardiovascular system of man. (Wolstenholme G E & Porter R, eds.) *Drug responses in man*. London: Churchill, 1967. p. 111-18.
3. Prichard B N C & Gillam P M S. Use of propranolol (Inderal) in treatment of hypertension. *Brit. Med. J.* 2:725-7, 1964.
4. ----- Treatment of hypertension with propranolol. *Brit. Med. J.* 1:7-16, 1969.
5. Robertson J I S, Kaplan N M, Caldwell A D S & Speight T M, eds. Symposium on  $\beta$ -blockers in the 1980s: focus on atenolol. (Whole issue.) *Drugs* 25(Suppl. 2), 1983. 346 p.
6. Robertson J I S. State-of-the-art review:  $\beta$ -blockade and the treatment of hypertension. *Drugs* 25(Suppl. 2):5-11, 1983.