Blood Pressure and the U.K. Prospective Diabetes Study

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Abstract

Control of blood pressure is important to people with diabetes. This article provides background information on the design and results of the U.K. Prospective Diabetes Study blood pressure study and the potential difficulties of translating this landmark study into practice. The article addresses the practical and quality assurance issues surrounding blood pressure and offers information about potential pitfalls that can lead to errors of measurement. The article also explores methods of patient participation in the measurement of blood pressure and in decision making about control of high blood pressure and explains why a participatory approach is needed.

Since the publication of the U.K. Prospective Diabetes Study (UKPDS) results, blood pressure targets for people with diabetes have been established as <140/80 mmHg in those without complications, with even lower targets for patients who are at particular risk of microvascular complications. However, some health care professionals report that these targets are impossible for most patients in normal clinical practice settings to achieve. This article explores some of the methodologies used in the UKPDS to investigate some of the difficulties in achieving these targets and to suggest ways of translating the beneficial results of these research studies into everyday practice.

Background

Before 1970, the diabetes community held high hopes that the University Group Diabetes Program would identify the most useful therapies for type 2 diabetes. Unfortunately, this study provided no clear-cut answers except that phenformin was found to cause excess mortality.

Because there were no large-scale studies ongoing, Dr. Robert Turner launched the UKPDS in the mid-1970s, with Oxford University serving as the coordinating center and 23 other centers around England, Wales, Scotland, and Northern Ireland participating. The aim of the UKPDS was to recruit people between the ages of 25 and 65 years with newly diagnosed type 2 diabetes to investigate the effects of each separate antiglycemic drug and to explore the natural history of type 2 diabetes.

In the course of the study, researchers observed that there were excess adverse events in people who had both diabetes and hypertension. Hence, an add-on study was devised to explore this phenomenon. At the same time, research was mounting in support of angiotensin-converting enzyme (ACE) inhibition in diabetes. Therefore, the UKPDS blood pressure add-on was designed to show whether ACE inhibition was preferable to β-blockade in this type 2 population.

People with diabetes have often been excluded from antihypertensive studies. This is because the Veterans I study, of secondary prevention, which included people with diabetes and those who already had a myocardial infarction or stroke, demonstrated a large treatment benefit (reduction in events) for people with diabetes. It was then perceived as unethical to include people with diabetes in such studies because they could not safely be randomized to receive placebo.

The UKPDS took this into account and set the levels for intervention lower than those of the Veterans I study. In effect, it examined mild hypertension, and its “less-tight control” group was defined as up to 200/105 mmHg. If a subject’s blood pressure rose above that level, intervention was started.
Design of the UKPDS
The design was factorial: after a 3- to 4-month run-in period, people who were newly diagnosed were either identified as “diet satisfactory” or randomized to receive diet therapy alone, oral hypoglycemic agents (O H As), or insulin. The UKPDS glycemia study therefore provided an incidence cohort: because subjects were newly diagnosed, potential complications such as neuropathy, retinopathy, nephropathy, and cardiovascular disease would take time to develop and be observed. Thus, the design allows for observation of the natural history of type 2 diabetes, from diagnosis to the development and progression of complications.

The UKPDS blood pressure study was substantially different in design because participants had had diabetes in some cases for several years and could enter the study even if they were already on antihypertensive therapy. Thus, the blood pressure study was a prevalence study. This meant that there were more adverse events in the blood pressure study than in the glycemia study. The blood pressure study provided information on the impact of different antihypertensive therapies as compared to less-tight control and data comparing the use of ACE inhibition versus β-blockade.

Results of the UKPDS
The results of the UKPDS contained the same good news for people with type 2 diabetes, just as results of the Diabetes Control and Complications Trial did for those with type 1 diabetes. It showed that glycemic control to at or near the normal range dramatically prevents the complications of diabetes (Fig. 1). In addition, the UKPDS showed that blood pressure control was also important in preventing adverse events (Fig. 2).

Both the UKPDS glycemic and blood pressure studies demonstrated that there was no threshold to the benefits of reducing HbA1c concentrations or blood pressure. The lower HbA1c and blood pressure could be controlled, the better in terms of avoidance of complications. There were, of course, some limitations, such as the need to balance glycemic control with the potential risk of hypoglycemia and blood pressure control with the potential risk of adverse events (Fig. 2).

The UKPDS Blood Pressure Study
The UKPDS initially focused only on glycemic control. But it eventually became clear that collecting data on blood pressure would also be important. In 1986, the 43% of UKPDS patients who had hypertension had 70% of the study’s cardiovascular endpoints. Power calculations for the blood pressure study were supported by this rate of cardiovascular events, which was similar to that found in the Medical Research Council (MRC) mild hypertension study.

In 1987, the UKPDS blood pressure study was started. People already recruited into the UKPDS were invited to participate, and new subjects were recruited. Eligible patients were those who were hypertensive (defined as ≥160 mmHg systolic or ≥90 mg H g diastolic) and not on any antihypertensive therapy or patients already on therapy with a blood pressure of ≥150 mmHg systolic or ≥85 mmHg diastolic. Exclusion criteria included previous stroke, intermittent claudication, foot ulcer or amputation, angina, heart failure, current malignant hypertension, asthma, chronic obstructive airways disease, Raynaud’s disease, or renal failure with creatinine >1.98 mg/dl. Two-thirds of participants were randomized into “tight control,” with an aim of <150 mmHg systolic and <85 mmHg diastolic. The remaining one-third received “less-tight control,” which aimed for <200 mmHg systolic and <105 mmHg diastolic.

Of those in the tight-control group, half were primarily treated with an ACE inhibitor, and half were treated with a β-blocker. Those in the less-tight group were treated by giving a diuretic, calcium antagonist, or vasodilator if blood pressure rose above therapy decision level. Only if this treatment failed was an ACE inhibitor or β-blocker added.

Results indicated that tight control of blood pressure does bring beneficial outcomes when compared to less-tight control. No differences were
found between ACE inhibition and β-blockade therapies. In other words, control of blood pressure is important, but the method by which control is achieved is not.

**Practical Issues of the Study Design**

**Methods**

Blood pressure was measured using electronic sphygmomanometers (Copal or Takeda). The protocol for measurement was as follows:

1. Have patient sit for 5 min rest.
2. Take one seated measurement and discard.
3. Have patient rest for 2 min to allow arm to “recover.”
4. Take second measurement and record.
5. Have patient rest for 2 min.
6. Take third measurement and record.
7. Have patient rest for 2 min.
8. Take fourth measurement and record.

The results were fed into a preset computer program that calculated the mean of the three readings. The program would not accept too much variance between results. If the variance was outside of acceptable limits, an additional measurement was required.

It was not possible to use the electronic sphygmomanometers in all patients, (for example, in those with atrial fibrillation or those with an arm circumference >33 cm). In such cases, the Hawkesley Random Zero sphygmomanometer was used, discarding the first reading and taking a mean of the next three, following the same protocol as that for the electronic sphygmomanometer.

**Quality Assurance**

The glycemia study was conducted using fasting plasma glucose (FPG) measured at each study center so that therapy decisions could be made at the clinic visit. This meant that standardization of measurement among the sites was crucial. Thus, laboratories were subject to monthly external quality control (QC) reviews.

An external QC program was also devised for the blood pressure study. The electronic sphygmomanometers were connected to a Hawkesley Random Zero sphygmomanometer, which served as the “gold standard.” Simultaneous readings could be achieved in this manner, with the operator listening for the Hawkesley result and the electric device printing off its result. This test was repeated three times.

Each nurse who performed blood pressure checks at each center carried out this QC test at monthly intervals on each device used. The data were sent to the coordinating center, which then calculated the coefficient of variation for each operator and each machine and sent reports back to each center. If the coefficient of variation was outside of acceptable limits, the offending machine would be returned for servicing and calibration. Similarly, if an individual nurse was having problems, the nurse’s center would be required to investigate the problem and report back to the coordinating center.

These processes ensured that each UKPDS center measured blood pressure in the same way so that results of the study could be accepted as real differences between tight and less-tight control.

**The Need for Quality Control**

QC techniques need to become part of routine clinical practice if we are to have confidence in clinical investigations involving blood pressure and blood glucose monitoring. Because people with type 2 diabetes are encouraged to make lifestyle changes based on these results, both healthcare professionals and people with diabetes need to be confident that our measuring techniques are accurate.

The MRC study of hypertension in the elderly, which was undertaken in the 1980s, was performed by nurses who were trained to use a Random Zero sphygmomanometer, and study coordinators undertook regular assessments of technique. Trainers used audiocassettes of Korotkoff sounds and asked trainees to write down the point at which they heard the second and fifth sounds. Then, a double-headed stethoscope was used, with the trainer and trainee independently writing down results so that comparisons could be made. If the compatibility of these results was not within the acceptable range, then retraining and reassessment were required.

Unfortunately, this level of training is unusual, and blood pressure measurement is often poorly performed with little QC effort. In the United Kingdom, practical skills for nurse training are undertaken in clinical settings, with students taught by nurses on the ward, who may have received no special training themselves and may be unaware of the potential pitfalls. The oft-quoted “See one, do one, teach one” method still often applies with no QC to ensure accuracy.

In addition, the equipment available for blood pressure measurement is not always in top condition. An unpublished internal audit conducted in the 1990s by U.K. medical students at Leicester General Hospital, for example, found that many of the hospital’s sphygmomanometers were not functioning adequately. Common equipment problems included:

- the meniscus could not be seen clearly because the mercury column was dirty;
- the mercury column did not return to zero, which could result in overestimates of blood pressure;
- the hinge on the sphygmomanometer would not stay upright, which made accurate observation almost impossible; and
- the valve on the pump was faulty, which made adequate inflation of the cuff difficult.

In addition, most of the devices had only one cuff size available, and there was no documentation of routine servicing and calibration.

Now, more hospitals and health care providers are using electronic equipment, and hospitals often have medical physics departments who undertake routine servicing of equipment. However, there are still many settings in which poorly maintained equipment is used, and the results obtained with this faulty equipment still trigger treatment action or adjustments in therapy.

Recognizing the poor quality of blood pressure measurement, the British Hypertension Society produced a video and booklet containing guidelines for measuring blood pressure and explaining some of the common pitfalls, such as using the wrong size cuff or not supporting the patient’s arm. The video included a
self-assessment program giving Korotkoff sounds and showing columns of mercury. An expert panel had determined correct responses, which in some cases were expressed as an acceptable range rather than a definitive result.

Using this assessment package, a study of clinical practice nurses revealed poor results.11 Errors outside of the accepted range were marked in some cases, with 51% showing some error on diastolic reading and 29% showing error on systolic. Of the nurses, 11% showed errors of >6 mmHg diastolic, and 10% showed errors of >10 mmHg systolic. In some individuals, the errors were >20 mmHg for systolic and diastolic.

The nurses had had no retraining or assessment since their basic nurse training was completed. When the same assessment was given to medical students who would have received more recent training, only 1% had errors >10 mmHg systolic, and 15% had errors >6 mmHg diastolic.

The study also revealed that nurses knew little about the servicing and calibration requirements of the blood pressure equipment. They seemed to think it was someone else’s responsibility but were unclear about just whose responsibility it was.

Decisions about therapy are often made based on blood pressure readings, and people’s lives can be affected by these types of errors. For example, patients who are wrongly diagnosed as having hypertension may face higher insurance premiums and may be prescribed unnecessary medications. Conversely, patients whose hypertension is missed because of measurement error can suffer devastating long-term effects. This is especially true for people already at risk for cardiovascular disease, including those with diabetes.

Studies often identify the importance of blood pressure control, but few provide guidelines on how, when, or how frequently to measure blood pressure. Unless proven otherwise, it should be considered wise to use the same measurement protocols if the same effect is sought.

The Need for Patient Education
When patients were recruited into the UKPDS with newly diagnosed diabetes, they received advice and education about the importance of diet, especially in terms of carbohydrate intake and the benefits of a hypocaloric diet. However, when the UKPDS blood pressure study started, there was little emphasis on the benefits of nonpharmacological interventions, such as reducing salt intake and eating more fruits and vegetables.

Similarly, although health care professionals knew that reducing excess weight could improve blood pressure, this information was not routinely shared with patients.

This lack of emphasis on patient education may have been because it was thought that such information had been given at the start of the glycemia study. However, looking back, it may have been useful to share these additional reasons for behaviour change with patients in the blood pressure study specifically.

Nonpharmacological interventions need to start early. They are an important public health issue because they can shift blood pressure downward for the whole population with minimal cost. And, as was found in the UKPDS, there is no threshold for blood pressure control. The lowest tolerated blood pressure reduces risk the most.

The Natural History of Type 2 Diabetes
Before the UKPDS, the progressive nature of type 2 diabetes was not recognized. As the study progressed, it became obvious that people who were randomized to the dietary intervention needed additional therapies to remain asymptomatic and to keep their FPG <270 mg/dl. Similarly, people randomized to O HAs or insulin required increasing dosages or combination therapies to maintain the target FPG of <108 mg/dl. It is now well accepted that both insulin resistance and progressive β-cell failure contribute to the progressive nature of type 2 diabetes.

The UKPDS also confirmed that most people with type 2 diabetes need more than two different antihypertensive agents to keep their blood pressure at or below target.

Traditionally, polypharmacy has been viewed in a negative light both because of potentially harmful inter-actions and because of patients’ unwillingness to take many different medications. The challenge for diabetes health care professionals is to change this way of thinking both among their colleagues and among their patients. This can be done by sharing the information from landmark studies such as the UKPDS.

New Directions for Optimal Care
There needs to be an awareness that shared responsibility can work: people with diabetes can make informed choices about lifestyle changes, and their health care professionals can support them with medications. Together, patients and providers can explore new ways to ensure that beneficial glycemia and blood pressure targets are met. Following are some evidence-based suggestions for furthering this cause.

1. People with diabetes must actively participate in decisions about their care.

In the 1980s, Greenfield et al.12 showed in a randomized, controlled trial that encouraging patients to take an active role in their consultations with doctors could bring about a reduction in H bA1c of more than 1%. This reduction, which is as much as one could expect from many oral hypoglycemic agents, came at a cost of an average 3 additional minutes of consultation time. Yet most diabetes clinics have not acted on this information and have not devised strategies to incorporate their patients’ active involvement as a routine part of care.

In our unit at Leicester, we have only just secured funding to make this type of interaction a regular part of our service, years after publication of this research. We are collecting data at present to evaluate our efforts.

As diabetes care providers, we now have a wealth of research-based information on the targets that bring about good diabetes outcomes. These include:

• H bA1c <7%,
• blood pressure <140/80 mmHg, and
• total cholesterol <192 mg/dl.

Yet how many of us know whether the people with diabetes in our care know these targets and the potential benefits to their health?

At our clinic, we are now using an
education support worker to encourage our patients to ask for the results of their blood pressure and other assessments and to not settle for the usual response of “Your blood pressure is O.K.,” but rather to obtain the specific results. If patients learn that their measurements are not on target, they are encouraged to ask their doctor why, to discuss what they can do to help themselves (e.g., lose weight, increase activity), and to ask if new medication or adjustments in existing medications are warranted. Although we have been informally working toward this process for some time, it has taken us more than 15 years to formally build this interaction into our clinical care.

2. We must adapt to changes in the health care environment.

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Participants in their own care.

Our findings may offer some insight into why primary care providers find it difficult to achieve blood pressures <140/80 mmHg in people with type 2 diabetes. Because of time constraints during clinic visits, many patients have only one, or at best two, blood pressure measurements at any given visit. A similar study in primary care may be helpful and may lead to fewer return visits for patients.

Different health care systems can influence what advice people choose to take and what they choose to reject. In the U.K., people with diabetes receive all of their medication at hospital diabetes clinic to enable power statistics to be calculated for a definitive study in primary care. Only provisional results have been reported. These initial results suggest that patients who self-monitor their blood pressure and are given the ability to alter their own therapy can achieve blood pressure targets quicker than those receiving conventional care of their blood pressure.

While conducting this study, we wondered whether the full UKPDS protocol was necessary for measurements of blood pressure at home and in the clinic, or whether the results would correlate if we discarded the first reading and took the second reading as the actual blood pressure result. It takes at least 12 min per patient to comply with the UKPDS protocol. Also, some patients identified that having their blood pressure measured in the clinic led to some discomfort. We therefore compared second blood pressure results with those obtained using the UKPDS protocol.

The results showed that, although there was no difference in mean blood pressure, measurements in individuals differed by more than the clinical criteria we had set (i.e., systolic >10 mmHg and diastolic >5 mmHg), with the UKPDS measurements lower than second measurements. Therefore, until we have a method that can identify individuals in whom there is no difference, we will continue to follow the UKPDS protocol.

Audit nonresearch clinic notes showed that therapy decisions can be delayed by months and even years (M.B., A.C.B., unpublished observations).

Resistance to polypharmacy

The UKPDS also demonstrated that polypharmacy is necessary for people to meet their targets for blood pressure, glycemia, and lipids. However, there are known barriers to polypharmacy. The DART study showed that only a small percentage of people actually take their medication regularly. However, it is important to recognize that patients’ noncompliance with one aspect of their care does not necessarily indicate their noncompliance with other parts of their regimen. Health care providers must talk to
patients to try to find out what they are and are not prepared to do. We must not write our patients off because they are unwilling to take another tablet.

**Misinterpretation of targets**
Targets are often misinterpreted because they are not always related to the stage of the disease. In the early stages of type 2 diabetes, most people can easily achieve a target of blood pressure of <140/80 mmHg, but the longer the duration of diabetes, the more medication they are likely to need to achieve this target. Patients may only need positive reinforcement of nonpharmacological blood pressure-lowering in the early stages, as well as pharmacological methods in the later stages. It should not be forgotten that the recommendation is for a blood pressure lower than 140/80 mmHg and that the lowest tolerated blood pressure gives the smallest risk.

**Conclusions**
Many people have interpreted the results of the UKPDS as meaning that blood pressure is more important than glycaemia. But in so doing, they have not taken into account the different designs of the glycaemia and blood pressure studies. Statistically, it is easier to see an effect if there are more events. The design of the blood pressure study meant that there would inevitably be more events than in the glycaemia study because people were recruited later in their disease for the former study than for the latter.

Observational analysis of the UKPDS has shown that addressing both glycaemia and blood pressure is important in preventing the complications of diabetes.

To ensure that the barriers to achieving blood pressure targets are overcome, we need a partnership between people with diabetes and health care providers, working together with the same information toward an agreed target of “the lower the better.”

The Euroaspiré studies in people with coronary heart disease (CHD), have shown “a collective failure of medical practice in Europe to achieve the substantial potential among patients with CHD to reduce the risk of recurrent disease and death.” When the second study, conducted in 1999 and 2000, was compared to the first study, conducted in 1995 and 1996, the prevalence of smoking was unchanged, obesity had increased, and the proportion with hypertension was unchanged, although aspirin continued to be widely used and cholesterol was substantially reduced. This shows that there is substantial room for patients, nurses, and educators to be influential in reducing blood pressure and cardiovascular risks. Patient educational, empowerment, and self-management roles will be needed, with health care professionals encouraging patients to be active participants in their care. Sharing information, skills, and tools between patients and providers will be key.

**References**
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