The Need for Evidence in Hypertension Management: Historical Perspective

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The Task Force of the National Heart, Lung and Blood institute issued the first standardized, algorithmic approach to treating hypertension in 1973.¹ The concept of a stepped-care approach was born at that time. Their initial recommendation for antihypertensive drug therapy was diuretics. Subsequent Joint National Committee (JNC) Reports on Detection, Evaluation, and Treatment of High Blood Pressure recommended that initial drug therapy be either a diuretic or beta-adrenergic blocker, and then either of these two drugs, and then a calcium channel blocker (CCB) or an angiotensin-converting enzyme inhibitor (ACE-inhibitors). The JNC-V then recommended any of the four classes or an α - β -blocker as initial therapy, but diuretics and β -blockers were preferable. That diuretics or β -blockers should be the initial drug for non-complicated hypertensive patient was also the recommendation of the Sixth Joint National committee report.²⁻⁷ Safety issues that arose after introduction ACE inhibitors and CCBs have since been mostly resolved. Drug treatment thresholds varied among the US, Canadian, British and WHO/ISH recommendations despite the fact that all were based on the same set of data. The concept of "the lower the blood pressure the better without causing symptoms" was the rule until the J-curve hypothesis emerged and generated a long debate. Now the current evidence supports the old concept, at least for some conditions such as hypertension in diabetic patients or in those with nephrotic-range proteinuria. Despite the repeated recommendations that thiazide-diuretics are preferred as the initial agent in hypertension treatment, many clinicians ignore these guidelines. This practice has added a significant cost to hypertension treatment worldwide.

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What looks like a complete circle in our understanding of the optimum blood pressure target and the preferred initial agent for pharmacologic treatment are actually two examples of how evidence has helped us to modify our practice. Other examples of issues that have evolved and changed based on newer and more powerful evidence are reflected in the answers to questions such as whether systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse pressure (PP) is more significant prognostically; what is the target BP; which agent to use in treating hypertension; in which patient with which co-morbidity should we treat isolated systolic hypertension in the elderly, and what is the best non-pharmacologic management. This dramatic evolution in the past three decades was the result of an accumulating body of evidence, in addition to the development of newer, more powerful medications that were the basis for conducting several landmark clinical trials.

This review is the first of two on the management of hypertension. The second part, "Update on the Management of Hypertension: The Seventh Joint National Committee and Beyond" will be published in the November issue of the *Annals*. The aim of this review is to look back at some of the major issues in hypertension management within the past three decades and shed light on the evidence that has affected our understanding and eventually, on our practice for this major cardiovascular disease.

What Are the Drug Treatment Thresholds?

The 1999 Canadian Recommendations for the Management of Hypertension suggested BP $\geq 160/100$ mm Hg (or $160/105$ mm Hg if ≥ 60 years old) for those without target organ damage,⁸ as compared with $\geq 140/90$ mm Hg by the Americans in JNC-VI.⁷ The World Health Organization/International Society of Hypertension (WHO/ISH) recommended a BP of $\geq 150/95$ mm Hg.⁹ The British Hypertension Society recommends treating those with target organ damage (TOD), renal disease or diabetes mellitus (DM) at BP $\geq 140/90$ mm Hg¹⁰ as opposed to $\geq 130/85$ mm Hg by JNC VI.⁷

This discrepancy is interesting since all these recommendations and guidelines were largely abstracted from the same set of data. It is well known that the higher the blood pressure, the higher the incidence of complications. Thus, treating severe hypertension is cost-effective since the number needed to treat to prevent one outcome, such as myocardial infarction (MI), cerebrovascular accident (CVA), or sudden death, would be smaller, and as such there is no disagreement. On the other hand, treating mild to moderate hypertension means treating a larger number of patients to prevent one event. The ability to afford the cost of a such policy varies from one country to another. For example, suppose that we will need to treat 50 patients with mild hypertension for 10 years to prevent one death. Assuming that the cost of therapy was USD \$1000 per patient per year that would mean saving one life would cost USD \$50 000.

This cost can be reasonable and affordable to rich countries, and their recommendations would take this into consideration. Other countries may have different spending priorities and cannot afford such a cost; therefore, they would recommend a threshold for initiating drug treatment at higher levels. On doing so, a smaller number would be needed to treat to prevent one death or event. Thus, it is up to each

society to look at their health care expenditures and priorities before they draw the line.

Degree of BP Reduction (J-curve)

The Multiple Risk Factor Intervention Trial (MRFIT) found that among patients randomized to special intervention (SI) to optimally treat their hypertension, hyperlipidemia, and smoking, there was a 23% reduction in coronary heart disease (CHD) mortality for patients with a normal baseline electrocardiogram (ECG) but a 68% increase in mortality for those with baseline ECG abnormalities.¹¹ The difference was still present after 10.5 years follow-up of this cohort. Patients with a normal resting ECG had a 21.1% decrease, while those with baseline abnormal ECG had 17.8% increase in CHD mortality.¹² Several hypothesized explanations for this troubling outcome included the metabolic or arrhythmogenic effect of diuretics, or inadequate control of blood pressure. Another physiologic explanation was that such patients might need a certain pressure to maintain their coronary perfusion. Decreasing the blood pressure below such a threshold can explain the increased mortality. The phenomenon of the J-shaped curve relationship was then born. The concept simply meant that reducing blood pressure up to certain level will reduce the risk of cardiovascular events, but any further reduction of BP will increase the risk again. Data from large epidemiologic cohort as well as clinical trials suggested a J-curve relationship between diastolic as well as systolic blood pressure reduction, and cardiovascular events and death.¹³⁻¹⁷ Up to that time, the philosophy of hypertension treatment was "the lower the better, without causing symptoms".

The controversy about the J-curve relationship persisted through the 1980s without a definitive answer since the evidence came from a mixture of cohort and clinical trials, none of which was intended to answer this question. All were secondary analyses.¹⁸ For over a decade, most clinicians were reluctant to aim for a DBP of less than 85-90 mm Hg, especially in patients with possible or confirmed CHD.

The Hypertension Optimal Treatment (HOT) trial was the only study conducted to specifically assess the optimum DBP in a randomized, placebo-controlled, multicenter, multinational trial. More than 18 000 patients were randomized to one of three groups with a target DBP of ≤ 90 mm Hg, ≤ 85 mm Hg, or ≤ 80 mm Hg. The DBP target achieved for the three groups at the end of the study was 85.2, 83.2, and 81.1 mm Hg, respectively. Treatment was

long-acting and CCB-based (felodipine) with the stepped-care addition of other classes to achieve the target DBP. The study concluded that there was no evidence of a J-shaped curve for the relationship of major cardiovascular events, all myocardial infarctions, all stroke, and cardiovascular mortality with an achieved BP down to 120 mm Hg systolic and 70 mm Hg diastolic. This finding was also true in the subgroup of more than 3000 patients with signs of or a history of CHD at randomization. Diabetic patients in the ≤ 80 mm Hg group had almost a 50% reduction in major cardiovascular events as compared with the ≤ 90 mm Hg group.¹⁹

The study conclusions were not universally accepted,²⁰ but despite the few shortcomings of this mega-trial, it represented a prime example of how high-quality evidence can be generated and used to answer difficult and relevant clinical questions.

Which Initial Pharmacological Agent Do You Use? And What Are the Economic Implications?

The choice of the initial drug recommended by the Canadian group⁸ is either a thiazide diuretic, β -blocker or ACE-inhibitor. The JNV-VI⁷ recommends diuretics or β -blockers, while the WHO/ISH⁹ recommended any of the available classes. For subjects >60 years, all three bodies recommended a diuretic or long-acting CCB's.⁷⁻¹⁰

Following the guidelines for the choice of initial drug treatment could have a substantial cost-benefit. In an Australian study by Ewald et al, they found that the prescription pattern did not reflect the current recommendation for treating uncomplicated hypertensive patients taking monotherapy, and if it did, it would have saved \$45-108 million in 1998 alone.²¹ Following the JNC VI guidelines, the cost of drug therapy, monitoring for and treating side effects, compliance, and switching between medications after therapeutic failures were estimated. Treating with acebutolol, amlodipine, and enalapril was almost 1.5 times the cost of generic chlorthalidone, and only a slightly higher percentage of patients would achieve hypertension control with amlodipine.²²

Stepped-care Approach

The Task Force of the National Heart Lung and Blood Institute first issued its recommendation to use diuretics as the first step in a stepped-care approach for treating hypertension in 1973. Methyldopa and reserpine constituted the second step. If blood pressure was not adequately controlled, hydralazine was

used as the third step and guanethidine was considered the fourth and final step to add or substitute for refractory hypertension. Patients with DBP of 105 mm Hg or more only were treated, those with DBP 90-104 mm Hg were assessed for other risk factors and treatment was individualized.¹ Four years later in 1977, the JNC I report² was released with the same recommendations, except for adding the beta-blocker propranolol as one of the choices for the second step along with reserpine and methyldopa. Criteria for treatment continued to be the same as those outlined in 1973 (Table 1).

In 1980, JNC II continued to recommend thiazide diuretics as the first step.³ The second step then included metoprolol, nadolol, clonidine and prazosin in addition to propranolol and methyldopa. Reserpine was no longer a choice in this algorithm. The results of the Hypertension Detection and Follow-up Program²³ were available at this time and consequently, treatment of mild hypertension (DBP 90-104 mm Hg) was recommended. The JNC-II report also introduced the concept of the "step down" approach to reduce drug dosage and/or number in patients in whom blood pressure was well controlled for an adequate period.

The JNC III of 1984 formalized the concept of non-pharmacologic therapy for the first time.⁴ Unless contraindications exist, the report recommended thiazide diuretics or β -blockers as the initial step with explicit instructions to proceed to a full-dose of

Table 1. Recommendations for initial antihypertensive drug therapy over three decades.

	First step	Second step
1973	Thiazide diuretic	Methyldopa, dopamine, reserpine
1977	Thiazide diuretic	Thiazide diuretic and propranolol
1980	Thiazide diuretic	Adrenergic inhibiting agent
1984	Thiazide diuretic or β -blocker	Other drug (not selected in 1st step)
1988	Thiazide diuretic, β -blocker, CCB, or ACE-I	Another drug from among the four (other than one selected in first step)
1993	Thiazide diuretic or β -blocker	CCB, ACE-I, α - β -blocker
1997	Thiazide diuretic or β -blocker	CCB, ACE-I, α - β -blocker, angiotensin receptor blocker
2003	Thiazide diuretic	β -blocker, CCB, ACE-I, α - β -blocker, angiotensin receptor blocker

either, if needed. The second step depended on your initial choice. If you chose a β -blocker, you added thiazide diuretic, and if you chose a thiazide diuretic, the next step should have been an adrenergic inhibitor. The third and fourth steps remained the same. Two new classes of antihypertensive medications became available in the market: the ACE-inhibitors and CCBs. Both were recommended only for the management of hypertensive emergencies and urgent situations. Management of special populations such as patients with a history of CVA, coronary artery disease (CAD), DM, renal impairment, pregnancy, surgery, and the young and old were outlined in this report.

The fourth JNC report in 1988 represented a revolution in hypertension management.⁶ We had at that time two new potent antihypertensive classes that gained remarkable acceptability by practicing clinicians. So, for the first, and probably the last time, there were four equal classes to choose from as the first step: thiazide diuretics, β -blockers, CCBs or ACE-inhibitors. The second step was to increase the dose of the first drug, add a second drug, or substitute the first drug. The third step was to add a third drug, or substitute the second drug. The fourth step was to do further evaluation for possible secondary causes or add a third or fourth drug. This report again emphasized the importance of a non-pharmacologic approach and a step-down approach for well-controlled patients. Individualized treatment for special populations expanded to include patients with congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD) and asthma, peripheral vascular disease (PVD), and patients with left ventricular hypertrophy (LVH).

The concept of a stepped care approach meant pushing the dose of the first drug up to the maximum recommended dose before you added a second drug according to recommendations up to and including the JNC-III in 1984. This practice, aimed at improving or increasing BP control was, of course, associated with a higher incidence side effects. Side effects of high-dose diuretics or beta-blockers were bothersome and were the major reason for non-compliance with these medications. Starting from the JNC-IV in 1988, the stepped-care approach included the option to add a second class of drugs while the patient was still at the starting dose or a medium dose of the initial drug. Adopting this philosophy gave more flexibility to clinicians and decreased the incidence of side effects without compromising efficacy by using more than one mechanism in controlling blood pressure.

Safety of Newer Agents

Some observational studies have suggested that short-acting CCBs in treating hypertension were inferior to diuretics and β -blockers in decreasing the risks of major cardiovascular complications. In the summer of 1995, Psaty reported, in a case-control study, that the use of short-acting CCBs in treating hypertension was associated with an increased risk of MI. Compared with the use of diuretics alone or β -blockers, the adjusted risk ratio for MI was increased by about 60% among users of CCBs with or without diuretics. While high doses of beta-blockers were associated with a decreased risk of MI ($P=0.04$), high doses of CCBs were associated with an increased risk (trend $P<.01$), i.e., there was a dose-effect relationship which is considered a higher degree of association.²⁴ In a prospective cohort study published a few months later, Pahor reported decreased survival among elderly patients who used short-acting nifedipine as compared with β -blockers.²⁵ These studies raised major public concerns among the millions of patients using this popular class of medications worldwide. However, the argument was that those conclusions were drawn from observational studies, which are good only for generating hypothesis, not proving them. Moreover, possible harm was associated with the short-acting preparations only, and in Pahor's study among patients older than 70 years of age, harm was associated with short-acting nifedipine alone, while short-acting verapamil and diltiazem were comparable to β -blockers and ACE-inhibitors.²⁵

The question raised then was why these new classes of antihypertensive medications were introduced and widely-prescribed based only on potency, without looking at safety? CCBs and ACE-inhibitors were introduced in the 1980s as the "promise" drugs. The advantages were potency, a favorable metabolic profile (no hyperglycemic, hyperlipidemic, hyperuricemic, hypokalemic, hypomagnesemic effect), a different mode of action with antiarrhythmic properties, variable pharmacodynamics/kinetics, and also a better quality of life (no depression, impotence, fatigue, etc). These promises were suddenly questioned. Surrogate end-points, including blood pressure control, and a favorable outcome did not seem to go hand in hand.

Three randomized trials were conducted with newer classes to address these concerns (Table 2). The results of the Captopril Prevention Project (CAPPP) randomized trial were published in February 1999.²⁶ The Intervention as a Goal in Hypertension

Table 2. Trials of newer antihypertensive agents versus older antihypertensive agents.

Trial, year	Design	Number of patients	Patient characteristics	Length of follow-up	Intervention	Endpoints	Results
CAPPP, 1999	P, R, O, BE	10 985	Ages 25-66 yrs DBP>100 mm Hg	5 yrs	Captopril	Fatal and non-fatal MI, CVA, CV death	RR=1.05 (95% CI, 0.90-1.22)
INSIGHT, 2000	P, R, DB	6321	Ages 50-80 yrs SBP/DBP >150/95 or SBP>160, 1 CV risk factor	4 yrs	Nifedipine GITS, co-amliozide	CV death, MI, CHF, CVA	RR=1.10 (95% CI, 0.91-1.34)
NORDIL, 2000	P, R, O, BE	10 881	Ages 50-74 yrs, DBP>100 mm Hg	5 yrs	Diltiazem 180-360 mg D or BB	Fatal and non-fatal MI, CVA, CV death	RR=1.0 (95% CI, 0.87-1.15)

HANE=hydrochlorothiazide, atenolol, nitrendipine, and enalapril, CAPPP=Captopril Prevention Project, INSIGHT=Intervention as a Goal in Hypertension Treatment, NORDIL=Nordic diltiazem
P=prospective, R=randomized, DB=double-blinded, O=open label, BE=blinded endpoint, RR=relative risk

Treatment (INSIGHT)²⁷ and the Nordic Diltiazem (NORDIL) study²⁸ were both published in July 2000. Those three major randomized trials, which included more than 26 000 patients combined, concluded that captopril and long-acting preparations of nifedipine and diltiazem were as equally effective as diuretics and beta-blockers and have comparable protective effects in cardiovascular morbidity and mortality.

Prognosis: Diastolic, Systolic or Pulse Pressure?

For a long time, DBP was considered the predictor of cardiovascular morbidity and mortality. That was largely because malignant or accelerated hypertension was associated mainly with DBP elevations. This concept was the basis for the recommendations of the Task Force and JNC-I and II reports that were based only on diastolic blood pressure.¹⁻³ JNC-III in 1984 and JNC-IV in 1988 acknowledged isolated systolic hypertension (ISH), but its recommendations were based only on DBP since evidence was available for treating these patients^{4,5} With time, it became obvious that SBP was even a more powerful predictor of cardiovascular diseases.²⁹ Systolic hypertension in the elderly though, was considered to be part of the normal aging process and had no prognostic significance. In 1991, the Systolic Hypertension in the Elderly Program (SHEP) trial results were released and showed a decreased incidence of stroke by 36% and major cardiovascular events by 32% from treating ISH.³⁰ These findings were confirmed in another two major clinical trials, Syst-Eur^{31,32} and Syst-China.^{33,34} The initial drug therapy in SHEP was thiazide diuretic-based, while Syst-Eur and Syst-China was CCB-based. Many years after the availability of such convincing

evidence, many practitioners, even today, are hesitant to treat ISH because they believe that elderly patients with atherosclerotic arteries need higher cerebral and coronary perfusion pressures. Lately, pulse pressure (PP) was also identified as a significant predictor of coronary heart disease.³⁵ In a recent analysis from the Framingham Heart Study of over 6000 men and women, aged 20 to 79 years who were free from CHD, the relative importance of DBP, SBP and PP was examined. In the age group <50 years of age, DBP was the strongest predictor of CHD risk (hazard ratio [HR] per 10 mm Hg increment, 1.34; 95%CI 1.18 to 1.51) rather than the SBP (HR, 1.14; 95%CI 1.06 to 1.24) or PP (HR 1.02; 95%CI 0.89 to 1.17) (Figure 1). In the age group 50 to 59 years of age, risks were all comparable for all three BP indexes. In the 60 years and above age group, the strongest predictor of CHD was PP (HR, 1.24; 95%CI 1.16 to 1.33).³⁶

Numbers vs. Agents

One of the most difficult questions yet to be fully answered is whether the achieved BP or the antihypertensive drug used is more important in reducing cardiovascular morbidity and mortality. With suspicion about the possibility of harmful effects with CCBs, especially the short-acting preparations, that was raised by Psaty²⁴ and Pahor et al²⁵ in 1995, and five years later, the results of the INSIGHT,²⁶ and NORDIL²⁷ trials that proved the efficacy and safety of long-acting CCBs, most clinicians felt reassured. Especially since the level of evidence of INSIGHT and NORDIL is I-B as compared to Psaty's and Pahor's studies which are II-B (Table 3).³⁷ This prompted Pahor et al to conduct a meta-analysis of randomized controlled trials (RCTs) that compared

Figure 1. The change in prognostic implications of diastolic and systolic blood pressure and pulse pressure with aging.³⁶

Table 3. Hierarchy of strength of evidence for treatment decisions.³⁷

N of 1 randomized trial (Level I)
Systematic review of randomized trials (Level I-A)
Single randomized trial (Level I-B)
Systematic review of observational studies (Level II-A)
Single observational study (Level II-B)
Physiologic studies (Level III)
Unsystematic clinical observations (case report) (Level IV)

long-acting calcium antagonists to other first-line agents (level of evidence I-A). In nine eligible trials that included 27 743 patients, calcium antagonists had a significantly higher risk of acute myocardial infarction, congestive heart failure, and major cardiovascular events as compared with diuretics, β -blockers, ACE-inhibitors, or clonidine. This increased risk occurred despite comparable control of both SBP and DBP among all groups. Based on their data, the authors concluded that longer-acting calcium antagonists cannot be recommended as first-line therapy for hypertension.³⁸

In the same issue of the *Lancet*, The Blood Pressure Lowering Trialists Collaboration group released their report.³⁹ They separately analyzed published RCTs comparing ACE-inhibitors and CCBs with placebo and other active treatments. As compared to placebo, ACE-inhibitors had a significant risk reduction for stroke (30%, 95%CI 15-43%), CAD (20%, 95%CI 11-28%) major CV events (21%, 95%CI 14-27% and overall mortality (16%, 95%CI 6-24%). CCBs showed a significant risk reduction of

39% (95%CI 15-56%) for stroke and 28% (95%CI 13-41%) for major CV events; however, there was no difference in risk of CAD or overall mortality as compared with placebo. When ACE-inhibitors were compared with diuretics or beta-blockers, there was no significant difference among the three classes. Comparing CCBs to the older agents showed a 13% (95%CI, 2-23) risk reduction for stroke, but a borderline increased risk of major CAD events of 12% (95%CI, 0-26). The conclusion of this metaanalysis was that both groups are superior to placebo, ACE-inhibitors provide similar protection to diuretics and beta-blockers, and CCBs may reduce the risk of stroke compared with other agents, but the risk of major CAD may be higher.

Several major trials results supported the argument that it is the agent or drug used and not the degree of BP control that counts. In the ALLHAT study, they had to stop the β -blocker (doxazocin) arm prematurely because it resulted in almost twice the risk of CHF, and significantly more combined cardiovascular events in general as compared with a thiazide diuretic (chlorothalidone) (Figure 2). This occurred despite adequate control in both groups, i.e. less than 140/90 mm Hg. After four years of treatment, there was an identical reduction in DBP and a 2-mm Hg difference in achieved SBP with chlorothalidone as compared with doxazocine (137/76 mm Hg doxazocine vs 135/76 mm Hg chlorothalidone).⁴⁰

Patients with diabetes who had a previous cardiovascular event or at least one other cardiovascular risk factor were randomized to an ACE-inhibitor, ramipril 10 mg daily or placebo in the HOPE and micro-HOPE study. There was a significant reduction in combined primary outcome—MI, stroke, cardiovascular death, total mortality, revascularization and overt nephropathy with ramipril (Figure 3). The SBP and DBP reduction with ramipril were 2.4 and 1 mm Hg only, and after adjusting for these small changes in BP, ramipril still lowered the combined primary outcome by 25% (95%CI, 12-26%, $P=0.0004$).⁴¹

In patients with hypertension and left ventricular hypertrophy (LVH), losartan resulted in about a 14% reduction in the composite end-point of cardiovascular death, stroke, and myocardial infarction, and a 25% reduction of fatal and non-fatal stroke as compared with atenolol. These benefits were encountered despite an almost identical reduction in BP.⁴²

On the other hand, the UKPDS study found that, in patients with type 2 DM and hypertension, tight BP control reduced the risk of DM-related death, diabetes complications, retinopathy and

deterioration in visual acuity. The tight control arm aimed at <150/85 mm Hg (achieved 144/82 mm Hg) and the less tight arm aimed at <180/105 mm Hg (achieved 154/87 mm Hg). The main drugs used were atenolol or captopril, and the same benefits were observed with both drugs, i.e. it was the degree of BP reduction and not the agent that conferred the benefit in this study.⁴³

Conclusion

Evidence-based medicine is defined by David Sackett as the integration of the best research evidence with clinical expertise and patient values.⁴⁴ Applying this exact principle in the past 30 years has changed our understanding, and consequently management, of hypertension. The prognostic value of systolic, diastolic, and pulse pressure, thresholds for drug therapy, the J-shaped curve relationship, the initial choice of drug to use, the stepped-care approach, the safety of newer agents, the degree of BP control vs. the drug used for preventing complications, and the safety of newer agents, were merely examples. Many more areas such as nonpharmacologic approaches, diabetes and hypertension, hypertension in patients with cerebrovascular disease, hypertension in the elderly, and the need for more than one agent to control BP. Others could have been added, but this historical review was not intended to be exhaustive. This review addressed some of the issues that I felt were important in our journey of accumulating knowledge in this field.

The above-cited reports and evolving recommendations are examples of evidence-based medicine in action. They started even before the term was described. The need for evidence in hypertension management, like any other field of medicine, is great and will continue to be of paramount importance. Our target is to manage patients with hypertension in such a way that their cardiovascular risk will be equal to (or as close as possible to) those without hypertension. It is a great undertaking that needs hard work and a lot of quality research. This quality research would be useless without proper appraisal, grading, and comparing of results with other research in the area in a systematic and methodologically sound way before publishing any recommendations, i.e. "doing it the EBM way".

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Figure 2. 4-year incidence (%) of major cardiovascular events in the ALLHAT study.⁴⁰

Figure 3. Incidence of major cardiovascular events and death after 4.5 years of follow-up in the HOPE and micro-HOPE studies.⁴¹

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