Hypertension: Past, present and future

Hypertension Arterial: Pasado, presente y futuro

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Birth of hypertension: when did blood pressure become clinically measurable?
It is amazing that the history of hypertension starts – so to say – before blood pressure could actually be measured! It is true that, although the concept of hypertension is commonly attributed to Richard Bright, what he really described in 1827 was heart hypertrophy without valvular disease in a number of clinical cases with albuminous urine, a finding he interpreted as due to the possibility that “the altered quality of the blood so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distal subdivisions of the vascular system”. The term “high blood pressure” was first used only about 50 years later by Mahomed, who could simply estimate blood pressure by employing a sphygmomanometer, that is estimating the characteristics of the pulse wave rather than actually measuring blood pressure, and when the term “hypertension arterielle” was first coined by Huchard in his 1889 treatise clinical measurement of blood pressure had not much improved.

It is well known that the development of a mercury sphygmomanometer for practical usage by Riva-Rocci in 1896-1897 ended a century of inferences, and opened a new century in which blood pressure became a quantity measurable at the bedside and an object of more precise clinical and scientific investigation. Hence, the French term “hypertension arterielle” rapidly opened to other languages becoming “ipertensione primitiva” in the articles of C Forlanini, the University chief of Riva-Rocci and “essentielle Hypertonie” in the German medical literature.

What to measure: systolic or diastolic blood pressure or both? The Riva-Rocci method, based on palpation of the arterial pulse during deflation of the arm cuff, only allowed one to actually measure systolic blood pressure, but even after diastolic blood pressure measurement became feasible by the introduction of Korotkoff’s auscultatory method in 1905, the definition of hypertension remained predominantly based on systolic blood pressure. However, physicians should have increasingly become accustomed to measure both systolic and diastolic blood pressure through the 1920s and 1930s if the Actuarial Society of America and the Association of Life Insurance Medical Directors could provide in 1941 mortality tables based both on systolic and diastolic values at the time of insurance, i.e., several years before the time the tables were published.

Unperceivably, around the 1950s, perhaps because of the interest in so-called “malignant” hypertension characterized by severely increased diastolic values, diastolic blood pressure came to call predominant and, often, unique attention both in research and in medical practice, to the point that an authority like George Pickering in the 1968 edition of his famous volume *High Blood Pressure*, after having briefly mentioned “systolic” hypertension, in which only systolic blood pressure was raised, concluded: “This form of hypertension will not be further considered in this book”. Along the same line of thought, as soon as during the 1950s the first effective antihypertensive drugs became available, all therapeutic studies exclusively used diastolic blood pressure values as target for the intervention. As I previously reported, I remember when, sitting on the World Health Organization – International Society of Hypertension Committee that prepared the 1989 Guidelines, I suggested having systolic blood pressure values added to diastolic ones as a guidance for treatment, but I was rebuked by some of my evidence-conscious colleagues, who objected that no evidence of benefit had yet been obtained through deliberate lowering of systolic blood pressure.
tion in 2002 of the largest meta-analysis of 61 observational data in almost 1 million individuals showing that both systolic and diastolic blood pressures are independently predictive of stroke and coronary mortality.

Nowadays, all major hypertension guidelines classify hypertension on the basis of both systolic and diastolic blood pressure values, recognizing that, although in most cases of hypertension both systolic and diastolic values are elevated, there are also cases in which either systolic or diastolic values are elevated in isolation. Table 1 reproduces the classification of hypertension provided by the 2013 European Society of Hypertension and the European Society of Cardiology guidelines.

**TABLE 1.**
Classification of hypertension provided by the 2013 European Society of Hypertension and the European Society of Cardiology.

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>120-129</td>
<td>and/or 80-84</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139</td>
<td>and/or 85-89</td>
</tr>
<tr>
<td>Grade 1 hypertension</td>
<td>140-159</td>
<td>and/or 90-99</td>
</tr>
<tr>
<td>Grade 2 hypertension</td>
<td>160-179</td>
<td>and/or 100-109</td>
</tr>
<tr>
<td>Grade 3 hypertension</td>
<td>≥180</td>
<td>and/or ≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertensive</td>
<td>≥140</td>
<td>and &lt;90</td>
</tr>
</tbody>
</table>

Hypertension: from a disease to a cardiovascular risk factor
The 1950s and 1960s saw a celebrated controversy, known as the Platt-Pickering debate from the names of the famous contenders, Sir Robert Platt and Sir George Pickering, on the nature of hypertension. In more exact terms, the controversy was on hereditability of hypertension, with Platt claiming hypertension hereditability was monogenic, whereas Pickering maintained blood pressure heredity was polygenic. Recalling this past debate might seem unworthy nowadays when molecular genetics has clearly shown blood pressure is inherited polygenically, but there are also rare forms of hypertension the inheritance of which is mono- or paucigenic. The controversy deserves being mentioned not so much for the debate on the number of genes involved, as for the condition either contender was referring to: Robert Platt, whose training was rooted in the long and illustrious British tradition of observational clinical medicine, was referring to hypertension as a definite clinical entity, a specific disease, whereas George Pickering, who had been a disciple of Thomas Lewis, the founder of clinical research in Britain, was referring to blood pressure as a quantitative biological variable, of which hypertension (or, better to say, high blood pressure) was simply one extreme. The debate probably lasted longer than necessary because of the personalities involved, the brilliant language used, and, last but not least, the gladiatorial aspects of the agonists: as a young man just entering the arena of hypertension research I assisted to some of the combats and must confess I enjoyed them tremendously. However, it must be recognized that by the end of the 1950s Pickering’s point of looking at blood pressure had been clearly proven right. Indeed, in 1959 the first publication of the Framingham Study appeared showing that high blood pressure was a major risk factor for developing atherosclerotic cardiovascular events including coronary disease, brain infarction, peripheral artery disease and heart failure. Without detracting from the merits of a fundamental and extremely productive research as that done in the Framingham Study, science is often preceded by life, if it is considered that already in 1914 insurance companies in the USA had calculated that persons with a systolic blood pressure of 161 mmHg at the initial insurance visit had a mortality rate that was twice as high as those with an initial systolic blood pressure of 142 mmHg (and were calculating insurance premiums accordingly).

**Should hypertension be treated? The successful story of blood pressure lowering**
The ability to measure blood pressure in a clinical setting and the gradual development of the concept of high blood pressure as a cardiovascular risk factor could not be immediately translated into coherent attempts to lower blood pressure by drugs not only because of the lack of suitable blood pressure lowering drugs during the first half of the twentieth century, but particularly because medical thought was dominated by a heritage of the old ontological concept of medicine, by which changes in body functions were considered simple compensatory mechanisms to preserve some other function of the body. As at the beginning of the eighteenth century essential fever was considered an affection of life that endeavours to postpone death, so until the mid-twentieth century a large number of medical authorities preached that “hypertension may be an important compensatory mechanism, which should not be tampered with, even were it certain we could control it.”

Hence the ontological attribute of “essential” given to hypertension as it was given to fever in older times. Seen retrospectively, the prejudice was a happy one because, soon after the first effective blood pressure lowering drugs became available around 1950, a series of brilliant controlled therapeutic trials were initiated to test whether blood pressure lowering by drugs was accompanied by greater benefits than harms. The first study was not randomized, and active or no treatments were assigned alternatively, but, starting with 1966, the results of randomized placebo controlled trials started to be published, making of antihypertensive treatment the first among cardiovascular therapies that has been tested by this rigorous approach.
using so-called hard outcomes, such as stroke, myocardial infarction and mortality\textsuperscript{19-20}.

In a systematic survey we have completed recently we have identified 68 randomized controlled trials in which blood pressure lowering drugs have been compared to placebo (or no treatment) or more intense has been compared to less intense blood pressure lowering in cohorts of hypertensive patients (or of predominantly hypertensive patients)\textsuperscript{21}. Forty-seven of these trials were intentionally done to test benefits or harms of antihypertensive treatment and represented the primary objective of our meta-analysis. As summarized in Figure 1, all considered outcomes were significantly reduced by blood pressure lowering, with the risk of stroke and heart failure being reduced to the greatest extent (36% and 43%, respectively, for a standardized systolic / diastolic blood pressure difference between active and control groups of 10/5 mmHg), but also risks of coronary heart disease events and cardiovascular and all-cause death were significantly reduced, though to a lesser extent (16%, 18%, and 11%, respectively). Inclusion of all 68 trials (intentional as well as non-intentional lowering of blood pressure) did not substantially change the relative risk reductions of all outcomes. Figure 1 illustrates that also absolute reduction of the risk of all outcomes was substantially reduced. Meta-regression analyses showed that the risks of stroke, heart failure and cardiovascular death were related in a semi-logarithmic way to the extent of the systolic, diastolic and pulse pressure reductions, without a preference for any of these blood pressures\textsuperscript{21}.

Are all blood pressure lowering drugs equally beneficial? The randomized controlled trials that demonstrated the indisputable benefits of blood pressure lowering used different classes of antihypertensive drugs as active agents. A set of meta-analyses we have recently completed after grouping trials according to the drug class that was compared with placebo is illustrated in Figure 2: diuretics, centrally acting drugs, beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, all were found capable of significantly reducing the risk of stroke and major cardiovascular events, but evidence of risk reduction of other cardiovascular events and mortality was found with some drug classes only\textsuperscript{22}. However, there were marked differences in trial design, total cardiovascular risk, blood pressure differences and sample size, and comparisons of meta-analyses of different class-specific placebo-controlled trials seem unwarranted.

The relative effectiveness of different drug classes can only be estimated by their head-to-head comparison in the same trial. This has been done in as many as 50 trials including 247,000 patients. A recent set of meta-analyses of these head-to-head comparative trials has seen that, for similar blood pressure reductions, the effects of all classes of blood pressure lowering drugs on most cardiovascular outcomes are not significantly different. A few differences can be found, however, particularly in the prevention of cause-specific events, with some drug classes being more effective than others for one type of events and less for another. On the whole, the formulation of a fixed paradigm of drug choice valuable for all hypertensive patients is not possible, and the benefits of blood pressure lowering drugs can be attributed predominantly to blood pressure lowering \textit{per se}, as pointed out by ESH-ESC guidelines\textsuperscript{13,23}.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
Outcome & Trials (n) & Difference SBP/DBP (mmHg) & Standardized RR (95\% CI) & Standardized RR (95\% CI) & Absolute Risk Reduction 1000 pts/5 years (95\% CI) \\
\hline
Stroke & 38 & -8.4/-4.4 & 0.64 (0.58-0.71) & & -17 \\
CHD & 42 & -8.6/-4.4 & 0.64 (0.79-0.90) & & -6 \\
HF & 24 & -9.2/-4.3 & 0.57 (0.46-0.72) & & -14 \\
Stroke + CHD & 39 & -8.6/-4.4 & 0.76 (0.71-0.81) & & -20 \\
Stroke + CHD + HF & 26 & -10.0/-4.8 & 0.75 (0.69-0.83) & & -28 \\
CV Death & 42 & -8.6/-4.4 & 0.62 (0.76-0.89) & & -7 \\
All-cause Death & 46 & -8.6/-4.4 & 0.89 (0.84-0.95) & & -8 \\
\hline
\end{tabular}
\caption{Relative and absolute risk reduction of various outcomes in intentional blood pressure (BP) lowering trials. Standardized risk ratio (RR) is to a systolic/diastolic blood pressure reduction of 10/5 mmHg. CHD: coronary heart disease; CI: confidence interval; CV: cardiovascular; HF: heart failure; n: number; pts: patients. Redrawn from data in Thomopoulos et al\textsuperscript{21}.}
\end{table}
Unanswered issues of antihypertensive treatment: initiation and goals

Unfortunately, a large (and, perhaps, excessive) number of trials have indulged to increment the evidence on the beneficial effects of blood pressure lowering, and on the comparative efficacy of various blood pressure lowering classes. As mentioned above, 67 trials on 245,885 patients have investigated outcome reduction by blood pressure lowering, and we have reported that relative risk reductions for all outcomes so calculated are not substantially different from figures calculated in 1994 when only 17 trials on 47653 patients were available\(^\text{21,24}\). Likewise, 50 trials on 247,006 patients have investigated the comparative efficacy of different antihypertensive drug classes\(^\text{23}\). Consequently, some issues of antihypertensive therapy have remained unanswered despite their crucial importance in daily medical practice, and are given conflicting solutions in current guidelines. The two major unanswered questions concern initiation of antihypertensive treatment and the target blood pressure to be achieved by drug treatment\(^\text{25}\).

The question as to whether individuals with blood pressure values within the range of grade 1 hypertension (systolic...
blood pressure 140 to 159 mmHg or diastolic blood pressure 90 to 99 mmHg) and low-moderate cardiovascular risk has never been approached directly, although it has an obvious reflection on the number of people to be prescribed antihypertensive drugs. The question was indeed explored in the 1970s and 1980s by a series of trials on “mild” hypertension, but unfortunately what was then defined “mild” hypertension has little relation to the current definition of grade 1 hypertension (the definition was then exclusively based on diastolic blood pressure values, with a variable range in most cases with upper limits well above 100 mmHg), and in some trials cardiovascular risk was high.

A 2012 Cochrane meta-analysis focused on individual patients in the old “mild” hypertension trials who could be correctly defined grade 1 hypertensive, but the number of patients so defined was very small and the statistical power of the meta-analysis quite low (for example, only 30 strokes available for analysis), so the results were unconclusive. The Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) has recently tried to increase the statistical power of this meta-analysis by adding “grade 1” hypertension individuals from other nine trials, but unfortunately about half of the newly added individuals were receiving background antihypertensive treatment at baseline and, therefore, could not properly be defined grade 1 hypertensives. When individuals under baseline antihypertensive treatment were excluded from the meta-analysis, only stroke risk was significantly reduced by further blood pressure lowering treatment.

In our recent set of meta-analysis we have followed a different approach, that of using trial data in their entirety or in predefined subgroups, and stratifying them as grade 1, grade 2 and grade 3 hypertension trials according to the average systolic and diastolic blood pressure values at baseline. An advantage of this approach is the high statistical power as all trials in which no antihypertensive treatment was given at baseline can be included in the meta-analysis. A limitation is that of probably including into a given grade a number of patients with blood pressure values out of the range defined for that particular hypertension grade. Figure 3 shows that, when a meta-analysis was done of trials with baseline (untreated) mean blood pressure values within the grade 1 hypertension range and with an average cardiovascular risk in the placebo group within the low-moderate range, risk of stroke, coronary events, major cardiovascular events and all-cause death were significantly reduced by blood pressure lowering treatment.

The question of the target systolic and diastolic blood pressures to be achieved by treatment in order to optimize treatment benefits is of obvious clinical importance, but it has rarely been approached (and mostly in terms of diastolic blood pressure only). In lack of direct randomized trial evidence, the issue has often been explored in post-hoc analyses of trials data by correlating the incidences of cardiovascular outcomes with individual levels of treatment-achieved systolic or diastolic blood pressures, an approach that has generated the concept of the so-called J-shaped curve, suggesting that at low blood pressure values cardiovascular risk may be less effectively prevented than at intermediate levels. Though interesting, this approach is inadequate to provide definite answers to the question, because in this type of analysis randomization is lost and there is no way of understanding whether the increased outcome risk of the individuals achieving the lowest blood pressures is indeed caused by an excessive blood pressure reduction or whether the lowest blood pressures are only a sign of an increased baseline risk and poor clinical conditions of these patients. It is no surprise, therefore, that different guidelines at different times have provided different recommendations.

Meta-analysis of available blood pressure lowering trials, however, may provide some more precise indications.
Among the 68 trials of blood pressure lowering trials we have identified, 32 were found with average systolic blood pressures in the active versus the control group across three predeterminate cut offs (140-149 versus ≥150; 130-139 versus ≥140; <130 versus ≥130), and 29 with average diastolic blood pressures across two predeterminate cut offs (<90 versus ≥90; <80 versus ≥80).  As illustrated in Figure 4, outcome reductions were all statistically significant for comparisons across the two higher systolic cut offs (except for heart failure, less frequently reported as outcome in trials). Systolic blood pressure values below 130 mmHg were associated with significant reductions of strokes, but not coronary events, heart failure and cardiovascular mortality. Absolute risk reductions of most outcomes gradually decreased for systolic blood pressure reductions across progressively lower cut offs. Likewise, reductions of diastolic blood pressure below the 90 and 80 mmHg cut offs reduced the risk of all major outcomes, but when trials with baseline diastolic blood pressures lower than 90 mmHg were excluded, lowering diastolic pressure below the 80 mmHg cut off significantly reduced the risk of stroke only. The conclusion of these meta-analyses is that, while reducing systolic and diastolic blood pressures to below 140 and 90 mmHg, respectively.

Despite this overwhelming evidence, studies performed in all parts of the world concordantly show that awareness of being hypertensive, treatment prescription once hypertension is discovered, and effective reduction of blood pressure below the 140/90 mmHg target when treatment is instituted are discouragingly low. Physician inertia, patient low adherence to chronic therapy, and deficiencies of healthcare systems are correctly considered the main causes of the current practical failure of what should otherwise be consider-

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**FIGURE 4.**

Blood pressure (BP) lowering to systolic blood pressure (SBP) levels below versus above three different cutoffs. Abbreviations as in Figure 1. Redrawn from data in Thomopoulos et al.²⁸

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BP cut-off</th>
<th>Trials (n)</th>
<th>Standardized RR (95% CI)</th>
<th>Standardized RR (95% CI)</th>
<th>P-value for trend</th>
<th>Absolute Risk Reduction 1000 pts/5 years (95% CI)</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>140-149 vs ≥150</td>
<td>8</td>
<td>0.98 (0.60-0.79)</td>
<td>-</td>
<td>0.05</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>130-139 vs ≥140</td>
<td>14</td>
<td>0.83 (0.52-0.77)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&lt; 130 vs ≥130</td>
<td>5</td>
<td>0.68 (0.57-0.83)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CHD</td>
<td>140-149 vs ≥150</td>
<td>8</td>
<td>0.81 (0.68-0.95)</td>
<td>-</td>
<td>0.16</td>
<td>0.35</td>
<td>0.35</td>
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<tr>
<td></td>
<td>130-139 vs ≥140</td>
<td>15</td>
<td>0.77 (0.70-0.86)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&lt; 130 vs ≥130</td>
<td>6</td>
<td>0.87 (0.76-1.00)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HF</td>
<td>140-149 vs ≥150</td>
<td>7</td>
<td>0.52 (0.41-0.65)</td>
<td>-</td>
<td>0.19</td>
<td>-</td>
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<tr>
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<td>130-139 vs ≥140</td>
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<td>0.78 (0.47-1.25)</td>
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<td>-</td>
</tr>
<tr>
<td></td>
<td>&lt; 130 vs ≥130</td>
<td>3</td>
<td>0.92 (0.47-1.77)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Stroke + CHD</td>
<td>140-149 vs ≥150</td>
<td>8</td>
<td>0.73 (0.67-0.82)</td>
<td>-</td>
<td>0.075</td>
<td>-</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>130-139 vs ≥140</td>
<td>15</td>
<td>0.72 (0.63-0.84)</td>
<td>-</td>
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<td>-</td>
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<tr>
<td></td>
<td>&lt; 130 vs ≥130</td>
<td>5</td>
<td>0.84 (0.75-0.93)</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Stroke + HF</td>
<td>140-149 vs ≥150</td>
<td>7</td>
<td>0.69 (0.63-0.76)</td>
<td>-</td>
<td>0.20</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
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<td>130-139 vs ≥140</td>
<td>8</td>
<td>0.74 (0.62-0.88)</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&lt; 130 vs ≥130</td>
<td>3</td>
<td>0.81 (0.67-1.00)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CV Death</td>
<td>140-149 vs ≥150</td>
<td>8</td>
<td>0.73 (0.71-0.89)</td>
<td>-</td>
<td>0.45</td>
<td>0.013</td>
<td>-</td>
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<tr>
<td></td>
<td>130-139 vs ≥140</td>
<td>15</td>
<td>0.81 (0.67-0.97)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&lt; 130 vs ≥130</td>
<td>7</td>
<td>0.88 (0.77-1.01)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>All-cause Death</td>
<td>140-149 vs ≥150</td>
<td>8</td>
<td>0.80 (0.82-0.96)</td>
<td>-</td>
<td>0.64</td>
<td>0.13</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>130-139 vs ≥140</td>
<td>15</td>
<td>0.87 (0.75-1.00)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>&lt; 130 vs ≥130</td>
<td>7</td>
<td>0.88 (0.77-0.96)</td>
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</table>

**Goals for the future**

Through the last 50 years hypertension research has shown by the best evidence based investigation that found on randomized controlled trials, that blood pressure lowering drug treatment dramatically reduces cardiovascular morbidity and mortality of hypertensive patients. Less direct evidence, but nonetheless post-hoc evidence from meta-analyses, supports also treating individuals with grade 1 hypertension and low-moderate risk. Drug treatment of low-moderate risk hypertensives is further supported by another recent set of meta-analysis showing that, by reserving treatment to high risk patients cost-effectiveness of treatment is obviously increased, but the residual risk of the treated patients (that is the incidence rate of cardiovascular events occurring despite treatment) is also dramatically increased. There is also solid evidence of the benefits of reducing systolic and diastolic blood pressures to below 140 and 90 mmHg, respectively.
red one of the greatest successes of medical research in the second half of the past century.
The major goal of hypertension research in the next decades, beyond searching for new drugs (welcomed in any case) is finding realistic solutions to the problem of hypertension control, a task the more and more urgent the higher is the epidemics of cardiovascular diseases spreading from affluent countries to low income parts of the world. Continuing to pay lip service and follow preaching approaches to physician inertia and patient lack of adherence is going nowhere. Fortunately, information technology is providing us with means of bypassing physician inertia, continuously stimulating patient adherence, and overcoming health care system deficiencies. If utilization of these new mobile technologies is actively pursued, there are hopes that the problem of hypertension control, and more in general, of chronic disease control, will be favourably solved.

BIBLIOGRAFÍA


