Is legacy a myth or a reality? We should know, and we do not

François Gueyffier and Michel Cucherat

See original paper on page 2331

The concept of cardiovascular risk factor is spontaneously, intuitively, associated with the notion of legacy, because individuals presenting high levels of risk factors will not suffer immediately from this situation. For example, in the pooled analyses of several trials of antihypertensive drugs against placebo or no treatment in mild-to-moderate hypertension [1], stroke incidence was less than 4% at 5 years in the control groups (Fig. 1).

Three periods do exist in the disease process: complete latency, symptomatic phase, and cardiovascular complications phase. The symptomatic phase does not exist with cholesterol levels, whereas type 2 diabetes and hypertension are possibly associated with symptoms such as polyuria and polydipsia for the former and headaches for the latter. The duration of the first two phases is highly variable from an individual to another, but the evolution of arterial disease can spread over several years or tens of years, before the occurrence of symptoms of complications. A logical hypothesis comes naturally to mind that the duration of the exposure to high levels of risk factors has *per se* a prognostic value, the severity of the disease and of the complications being attributed to the legacy from this exposure. We can also view legacy in negative terms regarding treatment exposure when treatment successfully decreases the risk associated with the risk factor: the legacy of treatment consists in a decreased probability of complications extending beyond the period of the exposure to treatment.

If the concept of legacy, regarding risk factor or its treatment, correctly captures the reality, physicians should consider it, screening the risk factors and treating them as early as possible. Prolonging treatment exposure as much as possible is usually associated with this reasoning, because the concept of lifelong treatment of risk factors prevails. This conclusion contradicts the current guidelines toward cardiovascular prevention, which base therapeutic decision on risk level through scores that integrates several risk factors rather than on the level of the risk factor targeted by the drug treatment. As age is by far the strongest risk factor, guidelines promote a late treatment initiation, leaving people exposed to a high level of risk factors. The risk is low during this abstention period, but under the legacy theory, the unopposed exposure to high risk factor levels would represent an accumulation of risk for subsequent periods. Of note, legacy effect is a very good concept for increasing the drug market.

In this issue of the *Journal of Hypertension*, Nelson *et al.* [2] explore to what extent the past exposure to antihypertensive treatment of individuals without cardiovascular history and recruited in the second Australian National Blood Pressure Study was associated with a difference of prognosis. Although they expected that legacy (of unopposed hypertension or of treatment exposure) would lead to a better prognosis in those previously treated, they did not observe any difference in cardiovascular mortality at 10 years. On the contrary, previous treatment was associated during the trial with higher cardiovascular disease, all-cause mortality rate, and incidence of new-onset diabetes. This clearly contradicts the expectations from a legacy effect and supports the strategy of delaying the start of drug treatment in young hypertensive individuals whose risk within 5 or 10 years is low.

Considering as a risk factor *per se*, the duration of the exposure to a risk factor raises the issue of the precise date at which the risk factor was elevated through life. Prescription habits bias the answer to this question: once the high level of risk factor is diagnosed and a drug treatment is started, the latter is exceptionally interrupted by prescribers, who usually consider that treatment is responsible for the good control of the risk factor. Given the large within-individual variability of risk factors levels, the individuals with false-negative diagnoses of hypertension are submitted to lifelong treatment, without leaving a chance to patients to check whether the treatment is appropriate. This statement concerns blood pressure, glycemia, or cholesterol. A simple simulation illustrates that after 10 medical visits with blood pressure measurements, the individuals presenting the definition criteria of hypertension will include 30% of false positive, or an individual with systolic blood pressure of 130 mmHg will have 64% probability to be misdiagnosed as hypertensive [3].

Journal of Hypertension 2015, 33:2207–2209

UMR5558, Lyon 1 University, Lyon, France

Correspondence to François Gueyffier, BronCedex, France.
E-mail: francois.gueyffier@univ-lyon.fr

DOI:10.1097/HJH.0000000000000728

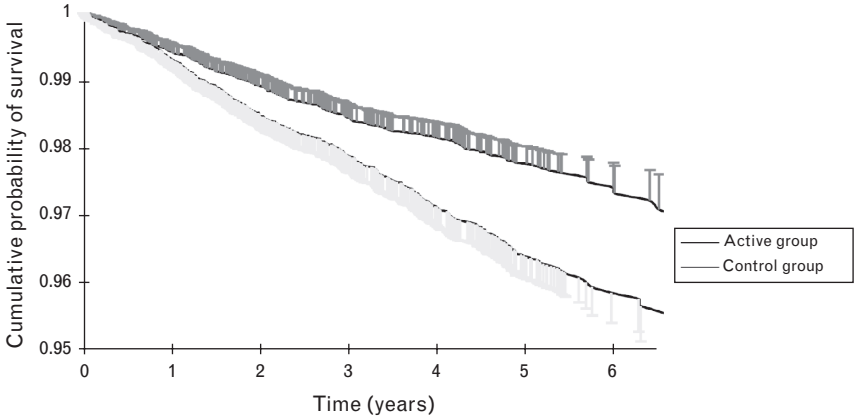

FIGURE 1 Probability of stroke-free survival over time in the pooled control groups of seven trials of the INDANA database.

A first approach to test the legacy theory is to compare the respective impact of past and recent measurements. If the concept of legacy is true then old measure should add their prognostic value to that of the recent ones. From the long-term follow-up of nine cohorts of the Seven Counties study, both past and recent high blood pressure increase the risk of stroke mortality, and both past and recent high serum cholesterol level increase the risk of coronary heart disease mortality. Increased past and recent blood pressure were both associated with increased risk of coronary heart disease mortality. More surprising, the risk was not significantly associated with recent blood pressure once past blood pressure had been accounted for [4]. These results support the legacy effect.

Like Nelson *et al.* [2], we explored the impact of previous exposure to antihypertensive treatments on the mortality in individuals with hypertension recruited in the trials collected in the INdividual Data ANalysis of Antihypertensive (INDANA) trials database [5]. This analysis was conducted in untreated or placebo-treated groups. In line with the results by Nelson *et al.* [2], we found that previous exposure to treatment was associated with a higher rate of coronary and cardiovascular death during the trials follow-up. These results seem to contradict the legacy theory.

In these approaches, multivariate analyses were performed, taking into account several potential confounders, such as age, sex, blood pressure level, and others. However, we never know whether other patients' characteristics, not available in the data set, confounded the results. This is why controlled exposure to treatment during the randomized controlled trials is a better setting to analyze legacy.

In their meta-analyses of 1990, Collins *et al.* [6] and McMahon *et al.* [7] attempted to connect epidemiological data to clinical trials results, to determine whether the risk reduction observed in treated groups did correspond to the observed blood pressure difference attributable to treatment. They concluded that it was the case for stroke, but not for myocardial infarction. They suggested that some chronic processes may be at play. Without naming it, they attributed this limited effect to a treatment legacy playing on a longer period than the usual 5 years follow-up of the trials. However, the close analysis of the treatment effect over time by Boutitie *et al.* [8] did not confirm this explanation: treatment was fully effective on coronary events during the first year of treatment, displaying thereafter a less-pronounced risk reduction, leading to a disappointing effect size at 5 years. On the reverse, there was no effect on stroke during the first year of treatment, which appeared later and was reinforced over time. This latter result did not support the legacy hypothesis as an explanation for the 5-year reduced impact of antihypertensive drugs on coronary events.

Cucherat *et al.* [9] observed that 5 years after the end of the Acébutolol et Prévention Secondaire de l'Infarctus (APSI) trial, the benefit observed with acebutolol compared with placebo in high-risk patients after a myocardial infarction was maintained. But the preservation of a between-groups difference after the study does not demonstrate that the treatment effect persists beyond the treatment withdrawal. It could be a simple carry over effect of the final difference without the subsequent events, occurring at the same rate in both groups after the end of the trial, being in sufficient number to dilute the initial difference.

Similar observations were made for the long-term post-trial results of the Systolic Hypertension in the Elderly Program (SHEP) trial [10] of chlortalidone-based regimen in isolated systolic hypertension after 60 years of age, which displayed positive results at its programmed end. Conversely, the benefit from tight blood pressure control observed initially was not present during the long-term follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) trial [11]. More striking and difficult to interpret are the results from glucose control in UKPDS, which were largely reinforced 10 years after the end of the trial [12]. Of note, an impressive attrition rate was present at this late follow-up. The prolonged follow-up of two more recent trials in type 2 diabetes patients did not show such enthusiastic results, shedding some doubt about the reality of the legacy effect of the antidiabetic drugs [13,14].

As Nelson *et al.* [2] mention, the best way to know whether legacy of treatment is at play or not would be to conduct withdrawal trials [15], ideally stratified on the previous duration of treatment. Obviously, such trials are very rare, the main reasons being that most trials are conducted by the pharmaceutical industry and that

pharmaceutical industry has no interest at all in exploring the best duration of treatment when key opinion leaders affirm that treatment has to be prescribed lifelong.

The reality of a legacy effect would support an early and prolonged treatment of individuals presenting high cardiovascular risk factors levels, even in low-risk situations such as young hypertensive people. Evidence is available in favor and against the reality of legacy. The only unbiased approach is to test the impact of withdrawing preventive treatment, which should be a priority for institutional research efforts. Meanwhile, we should remember that treating low-risk people could be a high-risk strategy [16], in particular, when the level of evidence for benefit is scarce as in mild hypertension [17].

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Gueyffier F, Boutitie F, Boissel JP, Coope J, Cutler J, Ekbom T, *et al*. INDANA: a meta-analysis on individual patient data in hypertension. Protocol and preliminary results. *Thérapie* 1995; 50:353–362.
2. Nelson MR, Chowdhury EK, Doust J, Reid CM, Wing LMH. Ten-year legacy effects of baseline blood pressure 'treatment naivety' in the Second Australian National Blood Pressure study. *J Hypertens* 2015; 33:2331–2337.
3. Marshall TP. Blood pressure variability: the challenge of variation. *Am J Hypertens* 2008; 21:3–4.
4. Boshuizen HC, Lanti M, Menotti A, *et al*. Effects of past and recent blood pressure and cholesterol level on coronary heart disease and stroke mortality, accounting for measurement error. *Am J Epidemiol* 2007; 165:398–409.
5. Gueyffier F, Boissel JP, Pocock S, Boutitie F, Coope J, Cutler J, *et al*. Identification of risk factors in hypertensives: the contribution of randomised controlled trials through an individual patient data base. *Circulation* 1999; 100:e88–e94.
6. Collins R, Peto R, MacMahon S, Hebert P, Fiebach N, Eberlein KA, *et al*. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet* 1990; 335:827–838.
7. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al*. Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335:765–774.
8. Boutitie F, Gueyffier F, Pocock SJ, Boissel JP. Analysis of change of the treatment effect over time in the framework of a meta-analysis. *Stat Med* 1998; 17:2883–2903.
9. Cucherat M, Boissel JP, Leizorovicz A. Persistent reduction of mortality for five years after one year of acebutolol treatment initiated during acute myocardial infarction. The APSI Investigators. Acebutolol et Prévention Secondaire de l'Infarctus. *Am J Cardiol* 1997; 79:587–589.
10. Kostis JB, Cabrera J, Cheng JQ, Cosgrove NM, Deng Y, Pressel SL, Davis BR. Association between chlorthalidone treatment of systolic hypertension and long-term survival. *JAMA* 2011; 306:2588–2593.
11. Holman RR, Paul SK, Bethel MA, Neil AW, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med* 2008; 359:1565–1576.
12. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil AW. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2009; 359:1577–1589.
13. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, *et al*. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014; 371:1392–1406.
14. Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, *et al*. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; 372:2197–2206.
15. Gueyffier F, Bejan-Angoulvant T. Do we need to assess the effect of treatment withdrawal ? The paradigm of life-long prevention. *Stroke* 2007; 38:2629–2630.
16. Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. *BMJ* 2012; 344:e3502.
17. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. *Cochrane Database Syst Rev* (8)2012; CD006742.