Do We Need to Assess the Effect of Treatment Withdrawal?  
The Paradigm of Life-Long Prevention

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See related article, pages 2652–2657.

In this issue of Stroke, Colivicchi et al observe the impact of statin discontinuation after an ischemic stroke: they suggest this phenomenon is not only frequent, but also associated with a significant increase of total mortality. Usually considered as secondary, the question of treatment withdrawal becomes more and more important because of: (1) the regular increase of the number of treatments with a convincing demonstration of preventive effects; (2) the general extension of life expectancy in high income countries, which explains both a dramatic increase in the numbers of elderly, and of the length of exposure to treatment far beyond that over which their effect has been estimated; (3) the high prevalence of treatment discontinuation, as illustrated by Colivicchi.¹

Is Treatment Effect Constant Over Time?

If treatment effect were constant over time, we would expect similar effects across various ages, which is not the case for blood pressure–lowering drugs. A significant 10% to 15% decrease in total mortality has been associated with these treatments in hypertension around 60 years of age, with either diuretics² or ACE-inhibitors³ as first-line drugs. Preliminary results (both from a subgroup meta-analysis⁴ and from a specific pilot trial⁵) suggest that these same drugs are associated with a lack of benefit on mortality, if not an increase, in hypertensive patients above 80 years of age.

Assessing accurately whether treatment effect is constant over time requires performing the analyses at an individual patient level. In primary prevention with hypertension, such a meta-analysis showed unexpected results⁶: the impact on stroke was undetectable during the first year, and increased thereafter, whereas the impact on myocardial infarction reached a maximum within the first year, to decrease thereafter. All these changes were statistically significant. So the paradigm of constant treatment effect does not hold in all situations, even those considered as the most common ones.

Optimal Treatment Duration or Effect of Treatment Withdrawal?

Once admitted there is an interest to examine the question, we have to choose its best formulation and then propose an appropriate experimental design to answer it. The issue of treatment duration covers in fact several aspects: (1) does treatment risk-to-benefit ratio change with age?; (2) does treatment present a favorable risk-to-benefit ratio whatever its duration?; (3) if not, what is its best duration in terms of efficacy, efficiency and effectiveness?; (4) what will the consequences be for a given patient to interrupt the treatment he has taken for several years? This last question corresponds to a very frequent situation, as illustrated by Colivicchi, and accordingly gets practical meaning and implication for a lot of patients.

The Need for a Rigorous Methodology

The results obtained by Colivicchi et al are not in complete agreement with data from clinical trials: (1) they observed a highly significant increase in mortality associated with the discontinuation of statin therapy. However, the results from SPARCL, the first trial having assessed specifically the impact of statin treatment on stroke recurrence, did not suggest any change in mortality⁷; (2) the supposed preventive effect of statins was largely significant within the year after stroke, whereas in the Heart Protection Study (HPS), the most powerful statin trial in general, the effect was not apparent within the first year⁸; (3) the size of the association between statin discontinuation and mortality is impressive, with a hazard ratio of 2.78 (95% CI: 1.96 to 3.72). The relative risk of mortality in HPS was 0.87 (95% CI: 0.81 to 0.94), which corresponds to a relative increase of mortality in the group placebo compared with the simvastatin group of 1.15 (95% CI: 1.06 to 1.23).

The study by Colivicchi is observational and therefore cannot control all biases. Multivariate regression analysis allows for the checking of whether the relationship between mortality and exposure to statin is confounded by other accounted associations. However, a lot of other factors not even measured could play the role of confounder. The experimental design, which would afford the best level of evidence, would be a randomized clinical trial, comparing continuation versus withdrawal, ideally in a double blind fashion.

Some methodological notions can be evoked for such discontinuation trials:

- Randomization should take place at the time of treatment discontinuation. In the prevention of recurrence of deep vein thrombosis with oral anticoagulants, several trials have been conducted to compare various treatment durations⁹.¹⁰ During the initial trial period after randomization, patients were treated similarly in both groups; therefore,
this period did not provide any information regarding the treatment efficacy.

- Patients should be included after a variety of treatment exposures. This will result in more heterogeneous study population, and this has to be taken into account when computing the number of patients to recruit. But this will also result in answering pragmatic questions.
- Double-blind placebo-controlled design should be preferred. Its feasibility has been illustrated for diuretic treatment in the elderly, treated either for hypertension or for heart failure. These methodological constraints have been applied even in the assessment of withdrawal for treatments requiring laboratory monitoring such as anticoagulants.

**A Duty for Public Research Institutes?**

As long as the paradigm of life-long preventive treatment will be the rule in clinical practice, drug manufacturers will not be prone to promote withdrawal trials. So, public research institutes and public health authorities should take up the challenge, and set up or encourage systematic research programs, including: (1) the constitution of databases pooling the results of all relevant trials, at an individual patient level; (2) the detailed exploration of the changes of treatment effect over time and regarding the age of patients; (3) the setting up of specific clinical trials designed to estimate the impact of treatment withdrawal.

Such research programs are essential if we want to inform patients honestly on the impact of any decision regarding the continuation of preventive treatment, and to make the most of the limited resources available to the health system. In addition, understanding the dynamics of drug treatment effects may be an invaluable source of knowledge on the disease process.

**Disclosures**

None.

**References**


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