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Editorial

Legacy effect in medicine—the expanding horizon!

'Legacy' in simple English means what one generation passes on to the next generation or past events affecting the present. In the context of medicine, the 'legacy effect' is defined as a phenomenon of continuous beneficial effect of the intensive control on disease outcomes or complications even after a long duration of cessation of the intervention. The concept underlies the fact that body can essentially 'remember' long control periods, which is termed as the 'memory effect'. The term 'legacy effect' in medicine was used for the first time in the context of diabetes care when long-term follow-up results of two well-known diabetes management trials—the Diabetes Control and Complications Trial (DCCT)[1,2] and the United Kingdom Prospective Diabetes Study (UKPDS)[3]—were published. Subsequently, such legacy effect has been observed in some lipid-lowering trial also.[4–6] However, the long-term beneficial effects of antihypertensive therapy are not well documented because majority of the landmark trials of blood pressure (BP) medications have had follow-up durations of ≤5 years only.[7–11] Considering this, the recently published findings of the Anglo-Scandinavian Cardiovascular Outcomes Trial (ASCOT) Legacy study[12] are quite remarkable. This study has shown that just as with diabetes and lipid management, a legacy effect likely exists with antihypertensive treatment also. These findings may have far-reaching implications; not only they reinforce the need for effective BP control but also suggest that early intervention is critical. Indeed, the suggestion of a potential legacy effect has been shown to be a motivating factor for the patients to adopt early treatment.[13]

1. Legacy effect in diabetes

The DCCT[14] was a trial evaluating the effects of intensive glycemic control in type 1 diabetes patients. A total of 1441 patients with type 1 diabetes were randomly assigned to intensive or conventional therapy for a mean duration of 6.5 years. It was found that the intensive treatment effectively delayed the onset and slowed the progression of diabetic microvascular complications in these patients. These patients were then followed up without active intervention for another 11 years in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions study.[1] The risk of diabetes-related complications remained significantly lower in patients who were intensively treated initially, even though the gap in glycosylated hemoglobin (HbA1c) narrowed over time (8.0 ± 1.2 versus 8.2 ± 1.2). More importantly, the risk of macrovascular complications also decreased significantly during the follow-up. The cumulative incidence of first cardiovascular (CV) event decreased by 42% ($p = 0.02$) in the previously intensively treated group at a mean follow-up of 17 years (including the initial in-trial phase). The between-group difference remained significant even after adjusting for other risk factors. The risk of impaired glomerular filtration rate was significantly reduced (54%, $p < 0.006$) even at 22 years of follow-up.[2]

Similar results were seen in type 2 diabetes in UKPDS.[3] During the initial active phase, any diabetes-related end point decreased by 12% ($p = 0.029$) and microvascular end points decreased by 25% ($p = 0.0099$) in the intensively treated patients after a median follow-up of around 10 years[15]. Subsequently, another 10 years of follow-up of these patients showed persistent benefits even when HbA1c difference was lost at just 1 year.[3] Not only the incidence of microvascular complications remained persistently lower in the previously intensively treated group, significant beneficial effects emerged on macrovascular end points also. The risks of myocardial infarction and death from any cause decreased by 15% ($p = 0.01$) and 13% ($p = 0.007$), respectively, in the sulfonylurea + insulin group and 33% ($p = 0.005$) and 27% ($p = 0.002$), respectively, in the metformin group as compared with the conventionally treated group.

The UKPDS and DCCT have changed diabetes care practice worldwide, by providing enough evidence in favor of intensive glycemic control. The findings from long-term follow-up of these trials have been equally remarkable by showing that good glycemic control has its legacy effect also. The benefits of good glycemic control persisted even when the intervention was stopped, and glycemic control worsened.

2. Legacy effect with lipid-lowering therapy

Subsequent to the publication of DCCT long-term data, similar legacy effect has been reported with lipid-lowering therapy also.

The West of Scotland Coronary Prevention Study was a primary prevention trial in 45–64-year-old men without a history of myocardial infarction but with elevated levels of low-density lipoprotein cholesterol (LDL-C; mean 192 ± 17 mg/dL). Between 1989 and 1991, 6595 men were randomized to 40 mg pravastatin or a placebo for in-trial period of 4.9 years. Subsequent to trial closure, there was a relatively low and comparable use of statins in both the arms. Major incidents were analyzed over a period of 20 years. Despite a low use of statins in the posttrial period, the men who were originally in the pravastatin arm had significantly lower major events at 20 years.[4] There was 13% lower mortality ($p = 0.0007$), 21% lower CV death ($p = 0.0004$), and lesser cumulative hospitalizations for myocardial infarction (24% less) and heart failure (35% less). The event rates were found to be lower even when the data for the posttrial phase were analyzed separately from the initial in-trial phase. More recently, the ASCOT Legacy study has reported

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similar findings at a mean follow-up of 15.7 years.[12] In the lipid-lowering arm (LLA) of the ASCOT, significantly fewer CV deaths [hazard ratio (HR) 0·85, 0·72–0·99, $p = 0·0395$] occurred among patients assigned to atorvastatin than among those assigned to the placebo.

Apart from the individual trials, two meta-analyses have also looked in to the legacy effect of LDL-C reduction.[5,6] In a meta-analysis of eight trials of lipid-lowering therapy including 44,255 patients (five trials of primary prevention and 3 trials of secondary prevention), reduction in mortality persisted after discontinuation of randomized therapy, despite an equal proportion (5%) of the patients using lipid-lowering therapy in both the arms.[5] During the posttrial second phase, there was lower all-cause mortality [odds ratio (OR) 0.90; $p = 0.0035$] and coronary heart disease (CHD) mortality (OR 0.82, $p = 0.0014$) in patients who were initially on lipid-lowering treatment.

3. Legacy effect in the management of hypertension

Although the legacy effect of effective BP control has been brought to attention with the recent publication of the ASCOT Legacy study, a few previous trials had actually provided similar indications in the past.

The Systolic Hypertension in the Elderly Program provided strong evidence that treating isolated systolic hypertension in the elderly was beneficial.[16] During the trial period of 4.5 years, chlorthalidone-based therapy prevented one of two admissions for heart failure, one of three strokes, and one of four CHD events. A 22-year follow-up subsequently reported persistent life expectancy gain in those assigned to active treatment initially.[17] More recently, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial studied the effects of routine BP lowering and intensive glucose control in patients with type 2 diabetes.[18] At the end of 4.5 years of treatment, single-pill combination of perindopril and indapamide was associated with reductions in the risks of death from any cause, death from CV causes, and nephropathy. In the ADVANCE-ON study, at a follow-up of 10 years, there was still a reduction in all-cause mortality (HR 0.91, $p = 0.03$) and CV death (HR 0.88, $p = 0.04$), despite similar care in both the arms.[19] In a meta-analysis of 18 randomized controlled trials of BP management involving 132,854 patients, it was seen that mortality continued to be lower in the posttrial open-label second phase (OR 0.85, $p = 0.0001$), despite similar rates of BP medication usage in both the arms.[20] These evidences suggest that a legacy effect prevails in BP management also. The ASCOT Legacy study has provided further evidence to reinforce these findings.

The ASCOT was a prospective, randomized, open-label trial with a double-blind 2 × 2 factorial design.[21,22] A total of 19,342 patients of hypertension aged 40–79 years and with additional three risk factors for CV disease were randomized to one of the two antihypertensive regimens. The primary hypothesis was that the regimen based on a calcium channel blocker amlodipine with add-on perindopril (as required) would prevent CHD better than the regimen based on a β-blocker (atenolol) with or without a diuretic. Within this BP-lowering arm (BPLA), the patients who had a total cholesterol of 6.5 mmol/L or lower and no previous lipid-lowering treatment were further randomized to either atorvastatin or the placebo, which formed the LLA. The LLA and BPLA were stopped prematurely after median follow-up durations of 3.3 years and 5.5 years, respectively, owing to significant beneficial effects in favor of atorvastatin- and amlodipine-based regimens, respectively.[21,22] In the ASCOT Legacy study, 8580 United Kingdom–based patients were further followed up for a total period of 15.7 years.[12] It was observed that the overall magnitude of the effect of amlodipine-based versus atenolol-based treatment on stroke mortality remained unchanged from the in-trial period [HR 0·69, 95% confidence interval (CI) 0·40–1·21, $p = 0·2013$] to the end of the extended follow-up (HR 0·71, 95% CI 0·53–0·97, $p = 0·0305$), becoming statistically significant with time due to accrual of more events. However, the effect of amlodipine-based versus atenolol-based treatment on CV death decreased between the in-trial period (0·74, 95% CI 0·58–0·95, $p = 0·0177$) and the total follow-up (0·90, 95% CI 0·81–1·01, $p = 0·0776$). Nonetheless, in the 3975 patients in the non-LLA group, there was significant reduction in CV deaths (adjusted HR 0·79, 95% CI 0·67–0·93, $p = 0·0046$) and CHD deaths (adjusted HR 0·76, 95% CI 0·59–0·99, $p = 0·044$) even at the extended follow-up among those assigned to amlodipine-based treatment compared with atenolol-based treatment. It needs to be remembered that unlike other trials exploring legacy effect, in the ASCOT Legacy study, the benefits of amlodipine-based regimen were assessed against an active treatment arm and not against a placebo.

4. Mechanism of legacy effect and its implications

In most of the trials providing long-term follow-up data of the patients randomized during the initial active, in-trial phase, the difference in the target parameter (e.g. HbA1c, LDL-C, or BP) decreased gradually during the posttrial phase, because of either cessation of the drug by the patients in the active-treatment group or the uptake of the study medication by those in the placebo group. In the ASCOT, the difference in BP between the two arms was minimal (the average difference throughout the trial was 2·7/1·9 mmHg) even during the in-trial phase because the comparison was between two active treatment regimens.[12] These findings suggest that the vascular protection (e.g., reduced vascular injury, plaque stabilization, etc.) afforded during the active trial phase has lasting benefits that are responsible for the legacy effect observed subsequently. In addition, the lesser number of nonfatal cardiac events occurring during the in-trial phase may lead to lesser all-cause and CV mortality on the extended follow up.

The role of vasculoprotective effects is even more apparent in the ASCOT, in which there was only a small difference in BP between the two treatment arms, which is unable to explain the continued significant difference seen in stroke mortality during the long-term follow-up. This beneficial effect on CV end points could be attributed to the reduction in central aortic pulse pressure[23] and low visit-to-visit variability of BP[24] associated with amlodipine- and perindopril-based treatment. In the Conduit Artery Function End-point substudy of the ASCOT,[23] amlodipine–perindopril combination resulted in substantial reduction in central aortic systolic BP (4.3 mm Hg; 95% CI 3.3 to 5.4, $p = 0.0001$) and central aortic pulse pressure (3.0 mm Hg; 95% CI 2.1 to 3.9, $p = 0.0001$), despite similar brachial systolic BPs between the treatment groups. Central aortic pulse pressure was found to be the only independent predictor of a post hoc–defined composite outcome of total CV events/procedures (unadjusted, $p = 0.0001$; adjusted for other variables, $p = 0.05$). In yet another analysis, it was demonstrated that the visit-to visit variability, in terms of systolic BP standard deviation, was lower in the amlodipine- and perindopril-based regimen than in the atenolol group throughout the follow-up period ($p < 0.0001$)[24]. The lower risk of stroke and coronary events in the amlodipine arm was partly attenuated by adjusting for mean systolic BP during the follow-up but was abolished by adjusting for within-individual standard deviation of clinic systolic BP, implying a role of lower visit-to-visit BP variability in better CV outcomes observed with this regimen.

The legacy effect is likely to be proportional to duration and intensity of initial therapy. Moreover, timing of initial therapy is

crucial because just as there is 'good legacy', there is 'bad legacy' as well. For example, in the DCCT, retinopathy continued to worsen during the first year of treatment in the secondary prevention arm, and the benefit emerged only later, suggesting that the body remembers periods of bad glycemic control and it takes longer time to erase the effects of bad metabolic milieu.[25,26] Therefore, for the legacy effect to manifest, it is important that the treatment is initiated early, before sufficient vascular damage has already occurred. In a meta-analysis of eight statin trials,[6] the posttrial legacy effects were seen on both CV mortality (HR = 0.87; 95% CI 0.79–0.95) and on all-cause mortality (HR = 0.90; 95% CI 0.85 to 0.96) in the three primary prevention studies, but when all the eight studies (which included 5 secondary prevention studies) were analyzed together, legacy effect was seen only on all-cause mortality ($p = 0.01$) and not on CV mortality. Similarly, although a legacy effect was observed in UKPDS, which recruited relatively younger patients with new-onset diabetes, no such effect was seen in ADVANCE trial,[27] which had a much longer (>10 years) duration of diabetes.

5. Conclusion

The evidences from the fields of diabetes management, lipid-lowering therapy, and hypertension management suggest that timely intervention with intensive treatment not only provides protection during active treatment period but also leaves a legacy of favorable effects which are sustained for many years after completion of the original study period. This 'legacy effect' should be yet another reason for greater and early adoption of interventions aimed at effective control of these CV risk factors.

Conflict of interest

No conflict of interest to declare for any of the authors.

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