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The long-term benefits of early intensive therapy in chronic diseases—the legacy effect

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ABSTRACT

The 'legacy effect' refers to the long-term benefits of intensive therapy that are observed long after the end of clinical trials and trial interventions in chronic diseases such as diabetes, hyperlipidaemia and hypertension. It emphasizes the importance of intensive treatment to prevent long-term complications and mortality. In chronic kidney disease (CKD), the legacy effect is evident in various studies. Long-term nephroprotection in diabetes is well documented in major studies in the early stages of diabetes, such as Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC), UK Prospective Diabetes Study (UKPDS) and Intensified Multifactorial Intervention in Patients with Type 2 Diabetes and Microalbuminuria (STENO-2). These studies highlight the importance of intensive glycaemic control in reducing microvascular complications, including nephropathy, in patients with recently diagnosed type 1 and type 2 diabetes. However, the legacy effect is less evident in patients with long-term, established diabetes. In chronic glomerulonephritis, studies on immunoglobulin A nephropathy showed that early immunosuppressive treatment could have long-term beneficial effects on kidney function in children and adults with CKD. The Frequent Hemodialysis (FH) and the EXerCise Introduction To Enhance Performance in Dialysis (EXCITE) trials indicated that frequent haemodialysis and a personalized walking exercise program could improve clinical outcomes and reduce the long-term risk of death and hospitalization. The legacy effect concept underscores the importance of intensive intervention in chronic diseases, including CKD. This concept has significant implications for public health and warrants in-depth basic and clinical research to be better understood and exploited in clinical practice. However, its limitations should be considered when interpreting long-term observational data collected after a clinical trial. Appropriate study designs are necessary to investigate an unbiased legacy effect.

Keywords: CKD, diabetes, dialysis, glomerulonephritis, hyperlipidemia, hypertension, legacy

The term 'legacy effect' originates in the early nineties in ecology studies [1]. In medicine, a legacy effect was described for the first time in studies reporting the 10-year post-trial observations in patients participating in the United Kingdom Prospective Diabetes Study (UKPDS) [2]. During the active phase of this trial, which lasted 10 years, patients in the conventional treatment group had a higher risk of microvascular complications than those on intensive glucose-lowering treatment. After the trial, patients in both arms were recommended to start (conventional arm) or maintain intensive therapy. As a result, serum glycated haemoglobin (Hb1Ac) concentrations in the two groups converged after 1 year. Notwithstanding almost identical Hb1Ac, the reduction in the risk of microvascular disease that emerged in the intensive therapy arm during the trial persisted over the 10-year post-trial follow-up. Notably, the risk reduction for microvascular disease was accompanied by a parallel risk reduction for myocardial infarction and death. This long-term protective effect of early intensive therapy was attributed to a 'legacy effect' of the earlier tighter control of glucose levels in the active group during the trial that also generated health benefits years later.

The legacy effect concept had obvious primary cardiovascular disease prevention implications. A new paradigm centred on early cardiovascular risk factors modification was proposed [3]. Various subsequent randomized trials testing the effect of glucose-lowering interventions [4] and antihypertensive drugs [5] in diabetic patients or cholesterol-lowering drugs in people with dyslipidaemia [6] registered favourable long-term health outcomes also several years after completing these trials (Fig. 1).
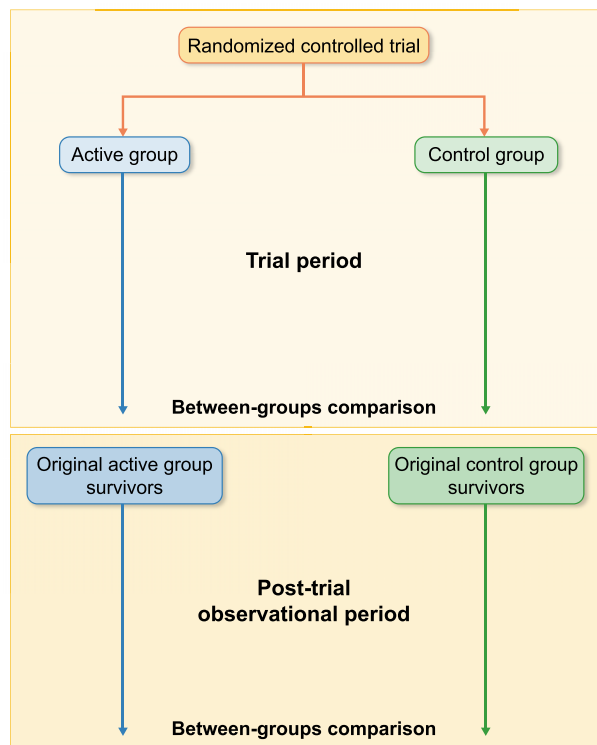
Figure 1: Typical structure of a randomized clinical trial (upper panel) and the subsequent observational follow-up of trial participants. In the post-trial observational period (depicted in grey), the original active group survivors and the original control group survivors may (or may not) receive the treatment of interest. In other words, in the post-trial observation, patients re-enter normal clinical follow-up at their centres.

Well beyond the long-term, post-trial effects of interventions impacting human health, the concept of legacy is inherent to that of risk factor. Indeed, healthy individuals harbouring a given risk factor (e.g. high cholesterol levels) only in the future will suffer the adverse health effects of the risk factor in question. Three stages characterize chronic diseases. The first is a sub-clinical or latent phase where no symptoms or complications of the disease are noted; the second clinical phase is when symptoms emerge; and the third is the complications phase when disease-related major events ensue, e.g. myocardial infarction or heart failure in cardiovascular diseases, end-stage kidney disease in chronic kidney disease (CKD), or retinopathy and nephropathy in diabetes. The duration of the first two stages is variable, and the evolution of the disease can spread over decades before the occurrence of complications. Coronary heart disease goes directly from an asymptomatic phase to cardiovascular events. Hypercholesterolemia does not pose any immediate health risk, but the duration of the exposure to this risk factor sets a legacy for remote, future coronary heart disease. In the Framingham Offspring Cohort in adults without clinical evidence of coronary heart disease at the age of 55 years, at median 15-year follow-up, this complication occurred in 4.4% of those without a history of hypercholesterolemia, in 8.1% of those with a 1- to 10-year exposure to this risk factor and in 16.5% of those with an 11- to 20-year exposure [7]. The intensity and duration of exposure to risk factors are unquestionably important [7] and early intervention reduces both. The incident risk for cardiovascular disease of hypercholesterolemia depends on cumulative prior exposure to this risk factor and, independently, the time course of risk accumulation. Compared with older age, the same risk accumulation at a younger age results in a greater Increase in the incident risk for cardiovascular disease events [7]. Thus, complications in older age can be seen as the legacy of exposure to this risk factor at a younger age. We can also view legacy regarding exposure to effective treatment as the opposite phenomenon, the legacy of treatment being a decreased probability of complications through reducing or removing the exposure to the risk factor extending beyond the period of exposure to treatment. Thus, the concept of legacy extends after the immediate benefits of treatment. The longer the treatment, the higher the expected benefit. A corollary to this way of conceptualizing treatment of risk factors is that the health benefits of treatment will go well beyond the period of exposure to treatment. Figure 2 shows the potential effects of the timing and duration of therapy for cardiovascular risk factors on the occurrence of myocardial infarction. It will take time for a new surge of the risk factor in question to rebuild the organ damage that eventually engenders clinical events.

The legacy effect is well demonstrated in hypertension. In one of the first studies that investigated this problem—a meta-analysis of three clinical trials in about 5000 cardiovascular disease-free, mildly hypertensive people at low cardiovascular risk—no differences were seen between early vs late treatment strategies during the in-trial period (5 years) or post-trial follow-up (10 years), which apparently negates a legacy effect of early treatment of hypertension [8]. In contrast, in the Systolic Blood Pressure Intervention Trial (SPRINT) study, a trial that focused on patients at high cardiovascular risk, targeting a systolic blood pressure of <120 mmHg resulted in lower rates of death and major cardiovascular events than targeting a systolic blood pressure of <140 mmHg, both during and 1 year after the trial [9]. A large meta-analysis of 18 trials including 132 854 patients published in 2010—before the SPRINT trial—showed that the favourable impact of antihypertensive drugs on mortality
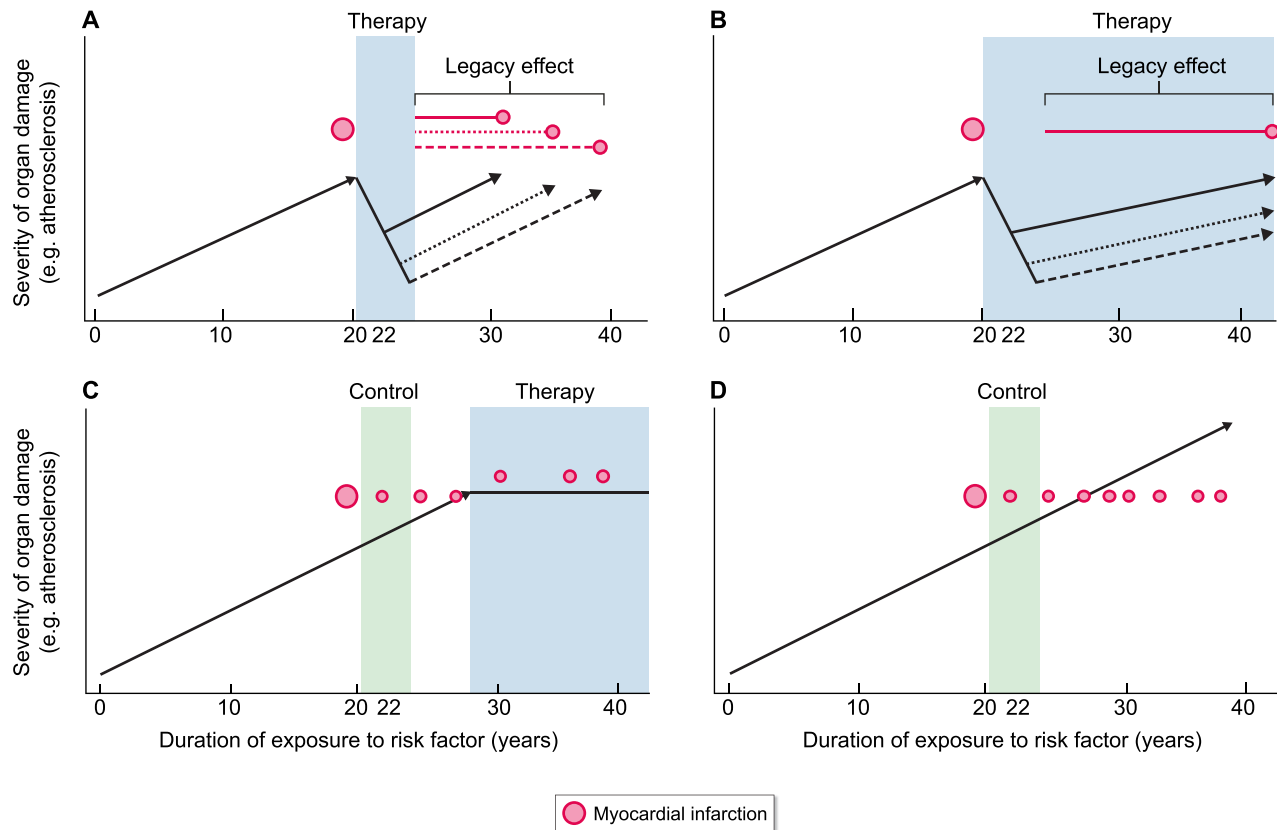
Figure 2: Following an atherosclerotic event (e.g. myocardial infarction, denoted by grey filled circles), an early short-term therapeutic intervention during a trial may partially or fully repair organ damage. Depending on the success of the repair, the next atherosclerotic event will be postponed for a shorter or longer period. This is called the legacy effect of early intervention (**A**). If therapy is continued after the trial, the incidence rate of cardiovascular events will be reduced, and the legacy effect will be extended (**B**). If therapy is given only late, the organ damage may not be repaired, and some atherosclerotic events may continue to occur even while on therapy (**C**). If no therapy is given, many more atherosclerotic events may follow (**D**).

during the trial (risk reduction 16%) persisted after the end of the same trials (risk reduction 15%). No heterogeneity among studies pointed to a real legacy effect [10].

BASIC MECHANISMS OF THE LEGACY EFFECT

Chronic diseases like diabetes, hyperlipidaemia and hypertension can lead to long-term pathophysiological changes in affected tissues and organs. Enhanced glycation of proteins and oxidative stress are notorious consequences of persistent hyperglycaemia [11]. Hyperlipidaemia leads to inflammation, plaque formation and plaque complications [12]. Hypertension causes vascular hypertrophy and, eventually, vascular rigidity and fibrosis [13]. Early and intensive intervention can prevent or mitigate these changes, resulting in better long-term outcomes.

Evidence is accruing that epigenetic modifications are crucial in the legacy effect (Fig. 3). DNA methylation and histone modifications can be influenced by environmental factors, like the aforementioned risk factors and other factors, including environmental pollution [14]. These epigenetic changes can persist after the initial stressor is removed or mitigated, preventing the reversal of the pathologic process. Such a phenomenon explains why early but not late interventions often reverse tissue damage, thereby contributing to favourable health outcomes persist-

ing beyond the application of actual interventions, i.e. the legacy effect. Similarly, exposure to hyperglycaemia [15], hypertension [13] or dyslipidaemia [16] at the cell level can lead to changes in biological functions and signalling pathways that may persist even after normalizing these risk factors. Conversely, early restoration of cell function can contribute to the lasting effects of early and intensive interventions. As a matter of fact, early and intensive intervention can improve vascular function and structure, reducing the risk of long-term complications such as cardiovascular events and nephropathy [17]. In this regard, the critical window hypothesis posits a crucial period during a chronic disease when early intervention can impact long-term outcomes. Among patients with newly diagnosed diabetes and 10 years of survival, HbA1c level ≥6.5% for the first year after diagnosis, regardless of the HbA1c after the first year, was associated with worse outcomes indicating that immediate, intensive treatment for newly diagnosed patients may be necessary to avoid irremediable long-term risk for diabetic complications and mortality [18].

In summary, the concept of the legacy effect in medicine revolves around the idea that early and intensive intervention in chronic diseases can induce long-lasting changes in pathophysiology, epigenetics, cellular memory, vascular function and structure, leading to improved long-term outcomes even after the intervention has ceased or relaxed.
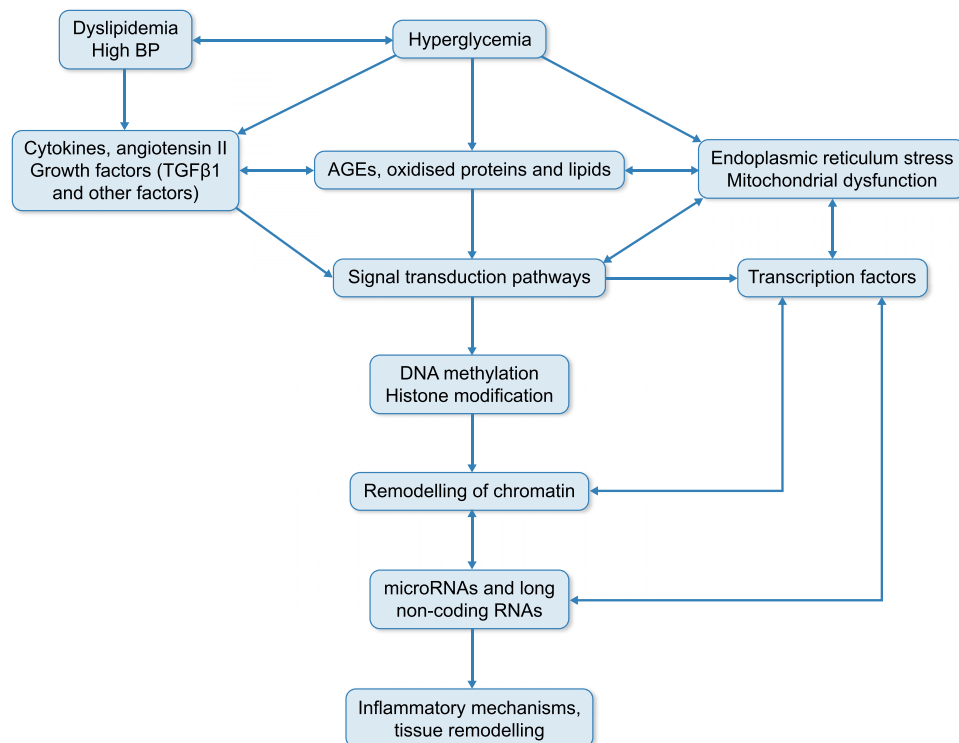
Figure 3: In type 2 diabetes, hyperglycaemia, hypertension and hyperlipidaemia stimulate the expression of angiotensin II (AngII), growth factors, cytokines and advanced glycation end products (AGEs) and oxidized proteins and lipids, and, in parallel mitochondrial dysfunction and endoplasmic reticulum (ER) stress. Growth factors, such as transforming growth factor-β1 (TGFβ1), activate signal transduction pathways. As a result DNA methylation, histone modifications and the expression of non-coding RNAs (microRNAs and long non-coding RNAs (lncRNAs) are set into motion. The process eventually alters the expression of target genes. This persistent process generates a 'metabolic memory', maintaining cell and organ damage.

LEGACY EFFECTS IN CHRONIC KIDNEY DISEASE

The legacy effect has been extensively studied in patients with diabetes and those with hypertension and dyslipidaemia, and in the foregoing, we briefly commented on studies in these conditions. Thorough reviews on these conditions have been published [19–21]. Herein we discuss the legacy effect in patients with CKD, an area still scarcely covered in the current literature.

Long term nephroprotection in diabetes

The legacy effect related to treating early and established diabetes encompasses long-term nephroprotection. Three studies in early diabetes investigated this problem. First, the Diabetes Control and Complications Trial (DCCT, a trial lasting an average of 6.5 years) comparing patients with recent type 1 diabetes treated intensively with an external insulin pump or three insulin injections daily with patients on conventional treatment (i.e. two insulin injections daily). In the intensively treated group, there was a reduction in microvascular complications, including albuminuria, compared with standard glycaemic control [22]. In the post-trial observation of this study, known as the Epidemiology of Diabetes Interventions and Complications (EDIC) study [23], after 17–30 years, notwithstanding that the HbA1c levels equalized in the two study arms 1 year after the trial termination, the intensive arm continued to have a significantly lower rate of microvascular complications, albuminuria included. The risk reduction for this alteration was 45% in the intensive therapy arm compared with the conventional therapy arm. Importantly, this risk reduction was accompanied by a 44% risk reduction of incident CKD, defined as a sustained estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [23].

In the second study, the UK Prospective Diabetes Study (UKPDS, a trial with a median duration of 10 years), newly diagnosed type 2 diabetics randomized to intensive treatment had a 25% relative risk reduction compared with the conventional therapy arm during the trial [24]. As in the DCCT-EDIC, serum glucose levels equalized 1 year after the study ended. Ten years after the study ended, a 24% risk reduction for microvascular events—including the risk for incident renal failure, retinal photocoagulation and vitreous haemorrhage—persisted in the intensive control arm [2]. Furthermore, at 9 and 12 years, in the intensively treated group, there was a significant risk reduction in microalbuminuria and proteinuria, –24% and –37% respectively, compared with the conventionally treated group [25].

The third study, the Intensified Multifactorial Intervention in Patients with Type 2 Diabetes and Microalbuminuria (STENO-2) study which had an 8-year follow-up, involved 160 patients with type 2 diabetes and microalbuminuria randomly assigned to either conventional or intensified, multifactorial treatment, including behavioural, lifestyle and pharmacological approaches. After 8 years, the study continued as an observational follow-up with all patients receiving intensive therapy, including those in the control arm. In line with the previously discussed studies in early diabetes, in STENO-2, progression to diabetic nephropathy (macroalbuminuria) was reduced by 48% in the intensive-therapy group during a follow-up extended to 21 years [26].

The legacy effect was less obvious in studies in patients with established diabetes. In the largest trial looking at this problem performed so far, the 'Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release-Controlled Evaluation' (ADVANCE, a trial with a median duration of 5 years), 11 140 participants with pre-existing diabetes were randomized to receive intensive glycaemic control vs standard glycaemic control for 5 years [27]. This study found a significant 21% reduction in the risk of nephropathy with a trend toward reducing the risk (–36%, $P = .09$) for kidney failure or death from renal causes. Notably, in the post-trial follow-up, the reduced risk for kidney failure was maintained and attained statistical significance at 10 years (risk reduction –66%; $P = .007$), again despite the convergence of HbA1c levels after the trial ended [4]. However, the number of kidney failure events was small (29 vs 53 events), and survivor bias cannot be excluded in this trial.

Like the STENO-2 study, another small, randomized trial evaluated the effect on the progression of CKD of intensive multifactorial–multidisciplinary intervention, including behavioural/dietary and pharmacological strategies in a team setting aimed at several modifiable risk factors in 120 patients with established type 2 diabetes of long duration (15 years) and stage G3–4 CKD compared with conventional care [28]. During the trial, lasting 2 years, 28% of patients in the control arm progressed to kidney failure. In contrast, the corresponding figure in the multifactorial intervention arm was much lower (13%). The difference between the two groups was significant at 1 year ($P = .024$) but not at 2 years ($P = .08$) and was annihilated during a 2-year post-trial observation (active arm 24%, control arm 21%).

Overall, the duration of diabetes before the intervention aimed at controlling hyperglycaemia and microvascular disease is critical for the legacy effect to manifest. In long-standing diabetes, existing micro- and macrovascular damage limits the benefit of interventions both in the short and long term. The critical relevance of the cumulative vasculotoxic effects of metabolic alterations in type 2 diabetes is exemplified by a large retrospective observational cohort study including over 4500 obese patients with type 2 diabetes who underwent bariatric surgery [29]. In this cohort, the risk for incident microvascular disease was higher in patients with type 2 diabetes for 5 years or more before surgery compared with people with type 2 diabetes for <1 year before surgery (excess risk 46%), in those on insulin at the time of surgery (excess risk 41%), and in those with an HbA1c >6.5% before surgery compared with HbA1c <6% (excess risk 37%) which rose to 56% for those with HbA1c >8.0%. Notably, patients who experienced diabetes remission after bariatric surgery also experienced a 29% reduction in risk of incident microvascular complications up to 7 years after surgery. In addition, even those who relapsed still showed a 19% risk reduction per year in remission before relapsing. Thus, not only pharmacologic interventions but also bariatric surgery has a legacy effect post-surgery because it induces long-lasting protection from nephropathy, retinopathy and neuropathy.

Long-term nephroprotection in chronic glomerulonephritis

Beyond diabetes, treating glomerular diseases may also have long-term kidney benefits. In a 2-year trial by Kamei et al., children with early immunoglobulin A (IgA) nephropathy exhibiting a normal GFR and minimal/moderate proteinuria but severe mesangial proliferation a combination therapy (prednisolone, azathioprine, heparin–warfarin and dipyridamole) reduced proteinuria and mesangial proliferation more than anticoagulation

alone. In the post-trial, long-term (10 years) follow-up, the children who had had the immunosuppressive combination therapy had better renal survival (defined as GFR >60 mL/min/1.73 m^2) in the originally active arm than those in the original control arm (97% versus 85%, $P = .03$) [30]. Similarly, in another study by Shima et al. [31] in a 2-year trial of children with IgA nephropathy and severe mesangial proliferation, the same therapy leads to a resolution of IgA mesangial deposits. Ten years post-trial, children in whom IgA deposits had disappeared during the trial had a significantly higher frequency of proteinuria-free survival [31]. The possibility of a legacy effect of early aggressive treatment in IgA nephropathy is not limited to the paediatric population. Indeed, in the Italian trial testing a 6-month intensive therapy with a high dose of steroids in adults with IgA nephropathy, favourable renal outcomes were registered in the active arm of the trial [32] and were maintained 10 years after the trial [33]. The legacy effect of immunosuppression in IgA nephropathy might extend to mycophenolate mofetil. In a short trial comparing the effects of this drug with angiotensin-converting enzyme inhibitors in patients with mild histology lesions and persistent proteinuria (>1 g/day), mycophenolate at the end of 6 months of treatment reduced proteinuria by 30% [34]. Remarkably, 6 years after the end of the trial, the incidence rate of kidney failure was substantially lower in the group originally treated with mofetil than in the control group—10% and 27%, respectively [35]. Thus, even though trials performed so far in patients with IgA are all with modest statistical power, early immunosuppressive treatment likely has long-term beneficial effects on the kidney in children and adults with this disease.

Long-term nephroprotection in CKD in general—the Modification of Diet in Renal Diseases (MDRD)

A quite robust legacy effect emerged in the most research-intensive trial ever done in nephrology, the Modification of Diet in Renal Diseases (MDRD) [36]. MDRD investigated the effects of dietary protein restriction and blood pressure control on kidney outcomes in patients with moderate to severe CKD. Compared with the usual-protein and the usual-blood-pressure groups, the low-protein and low-blood-pressure groups had a more rapid decline in the GFR during the first 4 months after randomization, and a slower decline thereafter. However, the projected mean decline in the GFR at 3 years did not differ significantly between the diet or blood pressure groups. There was no delay in the time to end-stage kidney disease (ESKD) or death [36]. However, after a median follow-up of 11 years, in patients originally randomized to a low blood pressure target, a significant legacy effect was observed, with a 28% reduction in the risk of death [hazard ratio 0.72, 95% confidence interval (CI) 0.60–0.86] and a 34% reduction in the risk of ESKD (hazard ratio 0.66, 95% CI 0.52–0.84) compared with patients who had received standard blood pressure control [37].

Long-term, post-trial effects in intervention trials in dialysis patients

Dialysis patients have an almost uniquely high cardiovascular and non-cardiovascular burden and a short life expectancy. The Frequent Hemodialysis Network (FHN) trial was a randomized controlled trial designed to investigate the effects of frequent haemodialysis (six times per week) compared with conventional haemodialysis (three times per week) on clinical outcomes in patients with ESKD [38]. The trial enrolled 245 patients and was

conducted between 2006 and 2010. The primary results of the trial, published in the *New England Journal of Medicine* in 2010, showed that frequent haemodialysis significantly improved the composite coprimary endpoint of death or change in left ventricular mass compared with conventional haemodialysis. However, the number of deaths in this study was very small (5 deaths in the FH arm and 9 in the conventional haemodialysis arm), and there was no significant difference in mortality among the two arms of the trial. Yet, a subsequent analysis of 5-year, post-trial follow-up data [39] showed that patients who had received frequent haemodialysis during the trial had a significantly lower risk of death than those who had received conventional haemodialysis (hazard ratio 0.63, 95% CI 0.44–0.92). Additionally, patients who had received frequent haemodialysis had a lower risk of hospitalization for cardiovascular events (hazard ratio 0.66, 95% CI 0.49–0.89).

The EXerCise Introduction To Enhance Performance in Dialysis (EXCITE) was a 6-month randomized, multicentre trial that tested whether a simple, personalized walking exercise program at home improves functional status in adult patients on dialysis [40]. The exercise intervention—an intervention impacting lifestyle—improved physical performance (as measured by the six-minute walking test and the five times sit-to-stand test) and the quality of life (as measured by the Kidney Disease Quality of Life Short Form questionnaire). Furthermore, in an analysis restricted to patients who completed the trial, the hospitalization-free survival was higher ($P = .04$) in patients in the active group than in the control group. This effect was confirmed on long-term follow-up after a median post-trial observation period of 36 months. Indeed, the subgroup of patients with high adherence (>60% of prescribed sessions) during the trial, on long-term follow-up, had a 45% lower risk for hospitalization as compared with the control group (hazard ratio 0.55, 95% CI 0.35–0.87) [41]. In crude and adjusted analyses, the reduced risk of hospitalization was accompanied by a postponement of the loss of walking performance naturally occurring in the dialysis population. When interpreting per protocol analyses comparing adherers to non-adherers requires extensive adjustment for time-varying confounding, which is rarely done in analyses of randomized trials [42].

Methodology issues

Knowledge of the legacy effect is primarily based on findings from randomized controlled trials. Since clinical trials have strict inclusion and exclusion criteria, the generalizability of the legacy effect to broader populations cannot be taken for granted. A second issue is that adherence to therapies is variable, and the response to treatment is heterogeneous [43], which may amplify the variability of the legacy effect. However, this heterogeneity may be attributed to social and psychological factors and individual genetic, epigenetic and environmental differences; therefore, the problem is open to investigation. A third problem is the difficulty in establishing causality. The legacy effect is often based on observational data from long-term follow-up of randomized trials, which may be subject to confounding and bias. Post-trial observational studies allow for assessing the long-term health benefits of the original randomized intervention. However, post-trial observations often lack an adequate control group; thus, it remains unknown whether patients who had benefited from the intervention did so because of the intervention or because they would have done so anyway. Bias by indication—i.e. the fact that patients at the highest risk are more likely to receive treatment—is another obvious limi-

tation in studies of this kind. Due to advanced organ damage, these patients often show small or no benefit from therapy, a phenomenon that can lead to the flawed conclusion that the intervention was ineffective. Selection bias may also be present. In other words, apparently beneficial effects of interventions may depend on the fact that patients that provide information post-trial are a selected subgroup of patients with a more favourable risk profile or other (unmeasured) confounding factors. On the other hand, it should be underlined that the concept of 'metabolic memory' was developed for diabetes, and experimental studies in this disease reasonably support the validity of this concept. However, similar constructs for hyperlipidaemia and hypertension have a weaker experimental basis [44]. Another difficult problem is that the optimal duration of early and intensive intervention to achieve a legacy effect remains unclear. Indeed, existing studies vary in the duration of the intervention, making it difficult to establish a standardized timeline. Furthermore, the legacy effect concept is rooted in studies conducted several years ago. With advancements in medical therapies and technologies, the relevance of the legacy effect in the context of newer treatments needs to be further investigated (e.g. for newer treatments such as sodium-glucose cotransporter 2 inhibitors and non-steroidal mineralocorticoid receptor antagonists). The legacy effects are commonly estimated by considering trial and post-trial data altogether. A methodological approach restricted to the post-trial period would produce better estimates than the 'all-data approach' [45]. However, only focusing on post-trial data can miss a relatively low magnitude legacy effect because the post-trial sample size is smaller than that including trial and post-trial follow-up data combinedly [45]. Thus, post-trial studies should have an adequate sample size and sufficient power to address potential legacy effects and to distinguish such effects from those simply due to the persistence of a direct effect of a given intervention. Finally, one should bear in mind that starting an effective treatment after the end of a trial in the control group inevitably tends to dilute the possibility of capturing statistically significant purported legacy effects.

CONCLUSION

The legacy effect concept has provided valuable insights into the importance of early and intensive intervention for chronic diseases. This concept is important for public health, and needs in-depth basic and clinical research to be better understood and eventually exploited in clinical practice. The limitations of this concept should be considered when interpreting the findings of long-term observational data collected posteriorly to a clinical trial. Interpreting the phenomenon in the existing literature is not bias-free, and appropriate designs should be adopted to study the legacy effect unbiasedly [45].

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

C.Z. is member of the *CKJ* editorial board.

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