REVIEW

Clinical significance of 'cardiometabolic memory': a systematic review of randomized controlled trials

Hiroshi Itoh, Isao Kurihara, Kazutoshi Miyashita and Masami Tanaka

'Cardiometabolic memory' has been proposed based on clinical evidence to explain how, even after the cessation of a clinical trial, the superiority of one treatment over the outcome persists. To understand the cardiometabolic memory phenomenon, we performed a systematic review of randomized controlled trials (RCTs) using PubMed in August 2016. The search terms 'randomized controlled trial', 'post-trial follow-up' and 'diabetes, hypertension or dyslipidemia' were used, and articles published after the year 2000 were searched. We judged the memory phenomenon to be positive when the cardiovascular outcome at the end of the post-trial follow-up period in the intervention group was significantly superior even though the favorable control of a risk factor (blood glucose, blood pressure or lipid level) during the trial period was lost after the cessation of the intervention. Among 907 articles retrieved in the initial screening, 21 articles were judged as describing a positive memory phenomenon. Eight, six and seven of the articles concerned diabetes, hypertension and dyslipidemia, respectively. Transient intensive glucose lowering rather easily induced memory for the suppression of diabetic microangiopathies, while memory for the suppression of macroangiopathies tended to be first evident in the post-trial follow-up period. Transient intensive blood pressure lowering was generally effective in the formation of memory for the suppression of cardiovascular events and had an especially strong impact on risk reduction of chronic heart failure. Transient intensive LDL cholesterol lowering clearly had a long-term beneficial effect on risk reduction of cardiovascular events. Our systematic review revealed the clinical relevance of cardiometabolic memory.

INTRODUCTION

In several randomized controlled clinical trials, the 'cardiometabolic memory phenomenon' or 'legacy effect' has been proposed based on clinical evidence to show that even after the cessation of the clinical trial, the superiority of one treatment over the outcome persists. This effect has now been highlighted for its medical significance.

The 10-year post-trial follow-up of the UKPDS (United Kingdom Prospective Diabetes Study) revealed that intensive glucose control in type 2 diabetic patients resulted in relative reduction of cardiovascular risks even though the difference in glycemic control was lost between the intensive and standard glucose control groups soon after the trial ended.[1] For blood pressure control, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation)-ON showed a beneficial post-trial 'memory phenomenon' in type 2 diabetes.[2] The significant difference in blood pressure between the groups receiving active antihypertensive medication and placebo (ΔBPs 5.6/ΔBPd 2.2 mm Hg, $P < 0.001$) that was observed during the randomized ADVANCE trial[3] disappeared 6 months after the end of the randomized period (137/74 mm Hg in the active treatment group *vs.* 136/74 mm Hg in the placebo group). However, the reductions in the risk of death from cardiovascular

causes (hazard ratio, 0.82; $P = 0.03$), which were observed in the active treatment group during the randomized period, were still significant at the end of the post-trial follow-up (hazard ratio, 0.88; $P = 0.04$). For lipid management, the result of the 20-year follow-up of the WOSCOPS (West of Scotland Coronary Prevention Study), which showed a legacy benefit of statin treatment, has been published.[4] Recently, several articles reporting the results of post-trial follow-up of randomized controlled trials (RCTs) have been published. However, the frequency or clinical relevance of the 'memory phenomenon' is not clear.

To more systematically understand the entity of the cardiometabolic memory phenomenon in clinical settings, we performed a systematic review of RCTs that investigated the post-trial effects of the transient intervention for the control of cardiovascular risk factors.

SEARCH STRATEGY FOR OUR SYSTEMATIC REVIEW

We performed a comprehensive literature search using PubMed in August 2016. For the initial screening, the search terms 'randomized controlled trial', 'post-trial follow-up', and 'diabetes, hypertension or dyslipidemia' were used, and articles published after the year 2000 were searched. For the second screening, titles and abstracts of the

Division of Endocrinology, Metabolism, and Nephrology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan
Correspondence: Dr H Itoh, Division of Endocrinology, Metabolism, and Nephrology, Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail: hiito@keio.jp

Table 1 Memory phenomenon-positive trials

Study name	Intervention	Subjects	N	Intervention period (year)	Follow-up period (year)	Control status at the end of intervention period	Control status at the end of follow-up period	Outcome at the end of intervention period	Outcome at the end of follow-up period	Reference
Diabetes										
ACCORD Follow-On (ACCORDION)-Eye	Intensive vs. conventional	Type 2 DM	1310	3.7	4	HbA1c: intensive 6.4% vs. conventional 7.5%*	HbA1c: intensive 7.8% vs. conventional 7.9%	Progression of retinopathy -33%*	Progression of retinopathy -58%*	5
ADVANCE-ON	Intensive vs. conventional	Type 2 DM	8494	5	5.4	HbA1c: difference between the groups 0.67%*	HbA1c: intensive 7.5% vs. conventional 7.5%	ESKD -65%* Renal death -15%	ESKD -46%* Renal death -11%	6
DCCT/EDIC	Intensive vs. conventional	Type 1 DM	1441	6.5	23.5	HbA1c: intensive 7.2% vs. conventional 9.1%*	HbA1c: intensive 8.0% vs. conventional 8.0%	Macrovascular disease -41%	CVD -30%* Non-fatal MI, stroke, or CV death -32%	7
VADT	Intensive vs. conventional	Type 2 DM	1655	5.6	4.2	HbA1c: intensive 6.9% vs. standard 8.4%*	No difference	Major CV event -12%	Major CV event -17%*	8
DCCT/EDIC	Intensive vs. conventional	Type 1 DM	1441	6.5	18	HbA1c: intensive 7.2% vs. conventional 9.1%*	HbA1c: intensive 8.0% vs. conventional 8.0%	Progression of retinopathy -76 %*	Progression of retinopathy -46%* New proliferative retinopathy -47%* New macular edema -35%* New photocoagulation -39%*	9
DCCT/EDIC	Intensive vs. conventional	Type 1 DM	1441	6.5	16	HbA1c: intensive 7.2% vs. conventional 9.1%*	HbA1c: intensive 7.9% vs. conventional 8.0%	Number of the events (eGFR <60) intensive 1 vs. standard 3	eGFR <60-50%*	10
UKPDS 80	Intensive (SU, insulin) vs. conventional	Type 2 DM	3277	10	10	HbA1c: intensive 7.0% vs. conventional 7.9%*	Baseline differences in HbA1c between groups were lost by 1 year	DM-related endpoint -12%* Microvascular endpoint -25%* MI -16% Death from any cause -6%	DM-related endpoint -9%* Microvascular disease -24%* MI -15%* Death from any cause -13%*	1
DCCT/EDIC	Intensive vs. conventional	Type 1 DM	1441	6.5	11	HbA1c: intensive 7.4% vs. conventional 9.1%*	HbA1c: intensive 7.9% vs. conventional 7.8%	Onset of retinopathy -76%* Progression of retinopathy -54%* Onset of microalbuminuria -39%* Onset of neuropathy -60%*	CVD -42%* Non-fatal MI, stroke, or death from CVD -57%*	11
Hypertension										
MDRD	Intensive vs. conventional	CKD (GFR 13–55 ml min^{-1} per 1.73m^2)	840	4	17	Difference in MAP between groups 4.7 mm Hg*	Hypertension: intensive 81.3% vs. conventional 85.6%	Decline in GFR: no difference between groups Time to ESRD or death: no difference between groups	Death after ESRD onset -28%* Death regardless of ESRD -18%* CHF -45%* CAD -52%*	12
ADVANCE-ON	Perindopril and indapamide vs. placebo	Type 2 DM	8494	4.5	5.9	BP: perindopril and indapamide 134.7/74.8 mm Hg vs. placebo 140.3/77.0 mm Hg*	BP: perindopril and indapamide 137.5/74.3 mm Hg vs. placebo 137.6/74.5 mm Hg	Death from any cause -14%* Death from CV cause -18%*	Death from any cause -9%* Death from CV cause -12%*	2

Table 1 (Continued)

Study name	Intervention	Subjects	N	Intervention period (year)	Follow-up period (year)	Control status at the end of intervention period	Control status at the end of follow-up period	Outcome at the end of intervention period	Outcome at the end of follow-up period	Reference
TROPHY	Candesartan vs. placebo	Prehypertension	772	2	2	BP: lower in candesartan group*	SBP: 2 mm Hg lower* in candesartan group DBP: 1.1 mm Hg lower* in candesartan group	Onset of stage 1 hypertension −66.3%*	Onset of stage 1 hypertension −15.6%*	13
HOPE-TOO	Ramipril vs. placebo	Patients at high risk of vascular event	4528	4.5	2.6	Mean BP: ramipril 136/76 mm Hg vs. placebo 139/77 mm Hg*	Mean BP: similar between the 2 groups (136/74 Hg)	MI, stroke, or CV death −22%* MI −20%* Stroke −32%* CV death −26%* All-cause mortality −16%* Revascularization −15%* New diagnosis of DM −34%*	MI, stroke, or CV death −17%* MI −19%* Stroke −21%* CV death −14%* Revascularization −16%* New diagnosis of DM −31%*	14
TRACE	Trandolapril vs. placebo	Post MI and LV dysfunction	1749	2–4	10–12	BP: not available	BP: not available	All-cause mortality −22%* CHF −24%* All-cause hospitalization −8%* CV hospitalization −8%*	All-cause mortality −11%* CHF −15%* All-cause hospitalization −8%* CV hospitalization −5%*	15
SOLVD	Enarapril vs. placebo	CHF (EF <35%, NYHA II-III,)	6797	2.6	8.6	BP: lower in enalapril group by 4.7/4.0 mm Hg*	BP: not available	All-cause mortality −16%* Death or hospitalization for CHF −26%* CV death −18%*	All-cause mortality −10%* Life span +9.4 months*	16
Dyslipidemia										
WOSCOPS	Pravastatin vs. placebo	Hypercholesterolemia	6595	4.9	15	Pravastatin: TC −20%*, LDL-C −26%*, TG −12%*, HDL-C +5%* Placebo: no changes in lipids	Lipid data: not available	All-cause mortality −24%* CV mortality −34%* CHD mortality −34%* Stroke mortality −1% Cancer mortality −16%	All-cause mortality −13%* CV mortality −21%* CHD mortality −27%* Stroke mortality +15% Cancer mortality −4% Hospitalization for any coronary event −18%* Hospitalization for MI −24%* Hospitalization for CHF −35%*	4
ALLHAT-LLT	Pravastatin (open label) vs. usual care	Hypertension with mild hypercholesterolemia, Black	3908	4–8	4–5	TC reduced by 17% with pravastatin, 8% with usual care* LDL-C: reduced by 28% with pravastatin, 11% with usual care*	Lipid data: not available	All-cause mortality +1% CHD mortality and non-fatal MI −27%*	CHD mortality −26%* Hospitalization for CHD −21%*	17
ASCOT-LLA	Atorvastatin vs. placebo	High risk hypertension	4605	3.02	8	LDL-C: lower in the atorvastatin group*	LDL-C: almost identical in the two groups	All-cause mortality −8% CV mortality −17% Non-CV mortality −1% Cancer mortality +5%	All-cause mortality −14%* CV mortality −11% Non-CV mortality −15%* Cancer mortality −8%	18

Table 1 (Continued)

Study name	Intervention	Subjects	N	Intervention period (year)	Follow-up period (year)	Control status at the end of intervention period	Control status at the end of follow-up period	Outcome at the end of intervention period	Outcome at the end of follow-up period	Reference
ASCOT-LLA	Atorvastatin vs. placebo	High risk hypertension	10 305	3.3	2.2	LDL-C: atorvastatin 2.32 mmol l⁻¹ vs. placebo 3.27 mmol l⁻¹*	LDL-C: atorvastatin 2.33 mmol l⁻¹ vs. placebo 2.36 mmol l⁻¹	Non-fatal MI and fatal CHD −35%* Total CV events and procedures −23%* Total coronary endpoint −29%* Non-fatal MI and fatal CHD −38%* All-cause mortality −13% Fatal and non-fatal stroke −25%	Non-fatal MI and fatal CHD −36%* Total CV events and procedures −19%* Total coronary endpoint −27 % Non-fatal MI and fatal CHD −37%* All-cause mortality −15%* Fatal and non-fatal stroke −23%*	19
ALERT	Fluvastatin vs. placebo	Renal transplant recipients	2102	5.1	2	LDL-C: lower in fluvastatin group*	LDL-C: similar between both groups	All-cause mortality +2% Cardiac death, non-fatal MI, CABG, or PCI −17% Cardiac death or non-fatal MI −28%* Cardiac death −38%* CABG +3% PCI −20%	All-cause mortality +2% Cardiac death, non-fatal MI, CABG, or PCI −21%* Cardiac death or non-fatal MI −29%* CABG or PCI −33%*	20
Scandinavian Simvastatin Survival Study (4S)	Simvastatin vs. placebo	Previous MI or angina	4444	5.4	5	TC: 25% decreased, LDL-C: 35% decreased, HDL-C: 8% increased in pravastatin group*	Lipid data: not available	All-cause mortality −30%* All CV mortality −36%* Coronary mortality −43%* Cancer mortality −9%	All-cause mortality −15%* All CV mortality −17%* Coronary mortality −24%* Cancer mortality −20%	21
LIPID	Pravastatin vs. placebo	Previous MI or unstable angina	9014	6	2	TC: 18% decreased, LDL-C: 25% decreased*, TG: 11% decreased*, HDL-C: 5% increased* in pravastatin group	LDL-C: pravastatin 2.66 mmol l⁻¹ vs. placebo 2.63 mmol l⁻¹	All-cause mortality −22%* CV mortality −25%* MI −29%* Total stroke −19%*	All-cause mortality −21%* CV mortality −25%* MI −26%* Total stroke −20% %	22

Abbreviations: BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LV, left ventricular; MAP, mean arterial pressure; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SU, sulfonylurea; TC, total cholesterol; TG, triglyceride.
* Statistically significant (*P*<0.05).

Table 2 Memory phenomenon-negative trials

Study name	Intervention	Subjects	N	Intervention period (year)	Follow-up period (year)	Control status at the end of intervention period	Control status at the end of follow-up period	Outcome at the end of intervention period	Outcome at the end of follow-up period	Reference
Diabetes										
ACCORD Follow-On (ACCORDION)-Eye	Fenofibrate *vs.* placebo	Type 2 DM	762	3.7	4	TG:fenofibrate 120 mg dl^{-1} *vs.* placebo 147 mg dl^{-1}*, HDL-C: fenofibrate 40 mg dl^{-1} *vs.* placebo 39 mg dl^{-1}*	TG:fenofibrate 186.5 mg dl^{-1} *vs.* placebo 182.8 mg dl^{-1}, HDL-C: fenofibrate 38.2 mg dl^{-1} *vs.* placebo 38.9 mg dl^{-1}	Progression of retinopathy -40%*	Progression of retinopathy $+13\%$	5
Hypertension										
UKPDS 81	Intensive *vs.* conventional	Type 2 DM with hypertension	884	8.4	10	BP: intensive 144/82 mm Hg *vs.* conventional 154/87 mm Hg*	BP: difference between the groups disappeared within 2 years	DM-related endpoint -24%* DM-related death -32%* Stroke -44%* Microvascular disease -37%*	DM-related endpoint: -7% DM-related death -16% Stroke -23% Microvascular disease -16%	23
Dyslipidemia										
HPS	Simvastatin *vs.* placebo	Patients at high risk of vascular and non-vascular event	20 536	5.3	6	TC: simvastatin 4.2 mmol l^{-1} *vs.* placebo 5.4 mmol l^{-1}* LDL-C: simvastatin 2.3 mmol l^{-1} *vs.* placebo 3.2 mmol l^{-1}*	TC: simvastatin 4.3 mmol l^{-1} *vs.* placebo 4.4 mmol l^{-1} LDL-C: simvastatin 2.6 mmol l^{-1} *vs.* placebo 2.6 mmol l^{-1}	Major vascular event -23%* Major coronary event -27%* Stroke -24%* Revascularization -24%* Vascular mortality -18%* Non-vascular mortality -6%	Major vascular event -5% Major coronary event -4% Stroke -2% Revascularization -7% Vascular mortality -2% Non-vascular mortality -3%	24

Abbreviations: BP, blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglyceride.
* Statistically significant ($P < 0.05$).

Table 3 Trials with carry-over effects of the intervention

Study name	Intervention	Subjects	N	Intervention period (year)	Follow-up period (year)	Control status at the end of intervention period	Control status at the end of follow-up period	Outcome at the end of intervention period	Outcome at the end of follow-up period	Reference
Diabetes										
Finnish DPS	Lifestyle modification	IGT	522	4	9	Weight reduction: intervention −3.5 kg vs. control − 0.8 kg*; FPG: intervention −2 mg dl⁻¹ vs. control +3 mg dl⁻¹; Decreased consumption of fat: intervention 87% vs. control 70%* Increased exercise: intervention 36% vs. control 16%*	Body weight: lower in intensive*, Physical activity: higher in intensive* Calorie intake: lower in intensive*	Onset of DM −58%*	Onset of DM −39%*	25
DCCT/EDIC	Intensive vs. conventional	Type 1 DM	1441	6.5	4	HbA1c: intensive 7.2% vs. conventional 9.1%*	HbA1c: intensive 7.9% vs. conventional 8.2%*	Progression of retinopathy −76%*	Progression of retinopathy −72%*	26
China Da Qing Diabetes Prevention Study	Lifestyle modification	IGT	577	6	14	FPG: intervention 7.0 mmol l⁻¹ vs. control 7.58 mmol l⁻¹* 2-h plasma glucose: intervention 10.63 mmol l⁻¹ vs. control 12.5 mmol l⁻¹* BMI: intensive 25.2 kg m⁻² vs. control 25.8 kg m⁻²	FPG: intervention 7.9 mmol l⁻¹ vs. control 8.7 mmol l⁻¹* 2-h plasma glucose: intervention 11.5 mmol l⁻¹ vs. control 13.8. mmol l⁻¹* BMI: intensive 24.5 kg m⁻² vs. control 24.4 kg m⁻²	Onset of DM: −51%* First CVD event −4% All-cause mortality +33%	Onset of DM: −43%* First CVD event −2% CVD mortality −17% All-cause mortality −4%	27
Hypertension										
COBRA	Lifestyle modification	Hypertension	1341	2	5	Education	Observation	Decrease in SBP*	Decrease in SBP* Decrease in LDL-C* All-cause mortality −19%	28
TOHP	Dietary sodium reduction	Prehypertension	3126 (744 from TOHP I and 2382 from TOHP II)	1.5	10–15	Sodium reduction to 44 mmol per day (TOHP 1) or 33 mmol per day (TOHP 2) mmol per day vs. usual salt intake	Reported that they disliked salty foods: 48% vs. 32%*, Reported that they liked low sodium foods: 71% vs. 64%*	BP: −1.7/0.8 mm Hg* in TOHP 1, −1.2/0.2 mm Hg* in TOHP 2	CV event (MI, stroke, CABG, PTCA or CV death) −25%*	29

Abbreviations: BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CVD, cardiovascular disease; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; LDL–C, high-density lipoprotein-cholesterol; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure.
* Statistically significant (*P*<0.05).

retrieved articles were examined by the authors to select RCTs satisfying the following inclusion criteria: (1) written in English, (2) more than 100 participants, (3) longer than 1-year post-trial follow-up period and (4) appropriately focused on the post-trial memory phenomenon of the intervention. Finally, full-text screening of the relevant articles was performed to extract information on patient backgrounds, number of participants, intervention details, control status of the risk factors and cardiovascular outcomes at the end of both the trial period and follow-up period. When plural articles were retrieved for one clinical trial, the articles that were thought to be redundant were omitted.

We judged the memory phenomenon of the transient intervention as positive when the cardiovascular outcome at the end of the post-trial follow- up period in the intervention group was significantly superior even though the favorable control of a risk factor during the trial period was lost after the cessation of the intervention. These risk factors included blood glucose, blood pressure or serum lipid (low-density lipoprotein (LDL)-cholesterol or triglyceride) levels. In contrast, we defined the memory phenomenon as negative when the cardiovascular outcome at the end of the post-trial follow-up period in the intervention group was equivalent to that of the control group. In these cases, the beneficial effects of the transient intervention were not maintained in the follow-up period after the favorable control of a risk factor during the trial period was lost.

In some studies, when a significant suppression of cardiovascular outcomes was observed in the intensive treatment group, a significant reduction in risk factors at the end of the post-trial follow-up period was also detected. In these cases, we described the prolonged effects of the transient intervention as 'carry-over effects.' In these situations, the favorable cardiovascular outcomes observed at the end of the follow-up period were considered to be derived from carry-over effects rather than from the memory phenomenon.

OVERALL FINDINGS OF OUR SYSTEMATIC REVIEW

In the initial screening, 907 articles were retrieved. A total of 479, 274 and 154 articles were on clinical trials for diabetes, hypertension and dyslipidemia, respectively. In the second screening, 35 articles fulfilled the above-mentioned inclusion criteria, and 15, 10 and 10 articles were on diabetes, hypertension and dyslipidemia, respectively.

After the full-text screening, 21 articles were judged as describing a positive memory phenomenon, as shown in Table 1. Of these, eight,[1,5–11] six[2,12–16] and seven[4,17–22] articles were about diabetes, hypertension and dyslipidemia, respectively. As shown in Table 2, only three articles[5,23,24] were judged as describing a negative memory phenomenon. In the ACCORDION (Action to Control Cardiovascular Risk in Diabetes Follow-On)-Eye study,[5] the memory effect for both glucose and lipid (triglyceride) control was examined. The former was judged as positive and the latter as negative. As shown in Table 3, five articles[25–29] were judged as demonstrating carry-over effects of the transient intervention.

REPRESENTATIVES OF CARDIOMETABOLIC MEMORY-POSITIVE TRIALS

The results of our systematic review showed that 21 articles reported a cardiometabolic memory phenomenon in the RCTs on diabetes, hypertension, or dyslipidemia. This systematic review included many RCTs whose observation period was more than 10 years. Therefore, it is suggested that cardiometabolic memory lasts for a long time. Because the clustering of hyperglycemia, hypertension, and dyslipidemia is strongly associated with atherosclerosis,[30] cardio-metabolic memory produced in the metabolic syndrome had a

substantial effect on the clinical course and prognosis of non-communicable diseases.

One of the most representative reports that revealed the memory phenomenon was the long-term follow-up of the DCCT (Diabetes Control and Complications Trial).[11] This study showed that intensive therapy for type 1 diabetes for a mean of 6.5 years reduced the risk of any cardiovascular disease by 42 percent ($P = 0.02$) during the 17 years of the post-trial follow-up period.[11] In this article, this prolonged effect of early intervention was referred to as 'metabolic memory.' Since then, this term has been used widely. Similarly, the term 'legacy effect' has been used frequently, as the publication of an article reporting the results from a 10-year post-trial follow-up of the UKPDS.[1]

Regarding cardiometabolic memory, controversies between blood pressure and blood glucose control have been reported. In the 10-year post-trial follow-up of UKPDS, a legacy effect was shown for blood glucose (UKPDS 80),[1] but not blood pressure control (UKPDS 81).[23] In contrast, in the ADVANCE-ON study, a beneficial post-trial memory was shown for blood pressure control, but not for blood glucose control.[2]

Treatment with statins for hypercholesterolemia also demonstrated the existence of a cardiometabolic 'memory phenomenon.' The 20-year follow-up of the WOSCOPS revealed that 5-year treatment with pravastatin reduced cardiovascular events over a 20-year period.[4] Another statin, simvastatin, was also shown to have a 'memory phenomenon' in the 4S (Scandinavian Simvastatin Survival Study),[21] namely, a post-trial benefit for lowered coronary mortality.

OCCURRENCE OF HYPERTENSION AND THE MEMORY PHENOMENON

Both cardiovascular risk and the occurrence of hypertension were suggested as targets for the 'memory phenomenon.' Prehypertension, which is reported to be associated with abdominal obesity and elevated serum levels of high-sensitivity C-reactive protein,[31] is a high risk status for the development of hypertension. The TROPHY (Trial of Preventing Hypertension) study demonstrated that 2-year transient renin-angiotensin system (RAS) inhibition by candesartan in the stage of prehypertension reduced the risk of transition from prehypertension to hypertension, and this beneficial effect was sustained even after the medication was stopped.[13] The STAR CAST (Short Treatment with Angiotensin Receptor Candesartan Surveyed by Telemedicine) study we conducted previously demonstrated that 1-year treatment of stage 1 essential hypertension with candesartan postponed the reoccurrence of hypertension compared with treatment with a calcium channel blocker.[32] These phenomena were originally shown in hypertension-prone animal models;[33–36] therein, we called it 'angiotensin block memory,' and we are currently investigating the molecular basis of this 'memory phenomenon'.[37–41] In contrast, RAS activation in youth was shown to induce hypertension even after a certain interval after discontinuation of RAS activation.[42]

CLINICAL FEATURES OF THE MEMORY PHENOMENON

Our systematic review revealed the following clinical features of the memory phenomenon:

1. Each intervention type, that is, glucose lowering, blood pressure lowering, or LDL cholesterol lowering, possessed unique characters of the memory phenomenon to some extent.
2. Transient intensive glucose lowering rather easily induced memory for the suppression of diabetic microangiopathies (ACCORDION-Eye,[5] ADVANCE-ON,[6] DCCT/EDIC (Epidemiology

of Diabetes Interventions and Complications),[9] and UKPDS 80[1]), while memory for the suppression of macroangiopathies tended to be first evident in the post-trial follow-up period (DCCT/EDIC,[7] VADT (Veterans Affairs Diabetes Trial),[8] and UKPDS 80[1]).

3. Transient intensive blood pressure lowering was generally effective in the formation of memory for the suppression of cardiovascular events (ADVANCE-ON,[2] HOPE-TOO (Heart Outcomes Prevention Evaluation-The Ongoing Outcomes)[14]) and had an especially strong impact on risk reduction of chronic heart failure (CHF) and CHF-related mortality (MDRD (Modification of Diet in Renal Disease),[12] TRACE (Trandolapril Cardiac Evaluation)[15]).

4. Transient intensive LDL-lowering clearly had a long-term beneficial effect on risk reduction of cardiovascular events (WOSCOPS,[4] ALLHAT-LLT (Lipid-Lowering Trial component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),[17] ASCOT-LLA (Lipid-lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial),[18] ALERT (Assessment of Lescol in Renal Transplantation),[20] 4S,[21] LIPID (Long-term Intervention with Pravastatin in Ischemic Disease)[22]). In some cases, memory for the suppression of macroangiopathies emerged only in the post-trial follow-up period (ASCOT-LLA[19] and ALERT[20]), which was similar to the memory induced by transient intensive glucose control.

5. Lifestyle modification aimed at glucose lowering was very effective in the suppression of new onset diabetes even after the termination of the trial (Finish DPS (Diabetes Prevention Study)[25] and the China Da Qing Diabetes Prevention Study[27]), although the 'carry-over effects' described above could explain this phenomenon.

CHARACTERISTICS OF CARDIOMETABOLIC MEMORY-NEGATIVE TRIALS

There were only a few studies that denied the existence of the memory phenomenon (Table 2). This trend, however, could be explained by the possibility that negative results in clinical trials are likely to be unpublished. We identified three trials that failed to show the memory phenomenon. All three studies were conducted with two-by-two factorial comparisons. This type of study design sometimes yields incidental uneven grouping or potential interactions between two factors. In UKPDS 81,[23] transient intensive blood pressure control failed to show beneficial effects on cardiovascular outcomes in the post-trial period, but there was a difference in HbA1c levels; that is, there was a significantly higher blood glucose level in the intensive blood pressure control group. In the ACCORDION-Eye study,[5] fenofibrate treatment failed to reduce the progression of retinopathy in the post-trial period despite obvious improvement in the trial period, however, the proportion of females was significantly lower in the intensive treatment group. The Heart Protection Study (HPS) was also designed as a two-by-two factorial including cholesterol-lowering therapy and antioxidant vitamin supplementation.[24] There might be a certain difference between the statin treatment and placebo groups, although the detailed profiles were not fully presented in the post-trial study.

SIGNIFICANCE OF THE 'CARRY-OVER EFFECT'

Clinical trials of lifestyle modification often cause carry-over effects and bring favorable cardiovascular outcomes because the changes in lifestyle are usually prolonged even after termination of the trial. We found five articles that demonstrated carry-over effects of the transient intervention, as shown in Table 3. In the TOHP (Trials of Hypertension Prevention),[29] it was shown that salt restriction could reduce long-term risks of cardiovascular events. Ohta *et al.*[43] reported that salt intake of school-aged children exceeded the recommended amounts and was positively correlated with that of their parents. Education about salt restriction from childhood in the family is important for the prevention of hypertension and cardiovascular disease.[43] In the post-trial follow-up study of the DCCT published in 2000,[26] a significant reduction in diabetic retinopathy was observed in the transient intensive treatment group at the end of the post-trial follow-up period. However, the blood glucose level was significantly lower even at the end of the post-trial follow-up period, which was four years after the cessation of the intensive treatment. Although the report stated that the results could be regarded as an example of the memory phenomenon, we judged that the favorable cardiovascular outcome was due to carry-over effects of the transient intervention in this study.

POSSIBLE MECHANISMS OF THE CARDIOMETABOLIC MEMORY PHENOMENON

Regarding the mechanism of the memory phenomenon, a few explanations were mentioned in the articles. Some reports suggested that reduced generation of the glycation end products during the trial period might contribute to the memory phenomenon after the trial (UKPDS 80[1] and DCCT/EDIC[7]). Suppression of vascular or cardiac remodeling during the trial period might also cause the memory phenomenon (HOPE-TOO[14] and TRACE[15]).

LIMITATIONS

Several possible limitations must be considered in our systematic review. First, the possibility of selection bias cannot be ruled out because we retrieved only articles written in English using a small number of search terms. Second, the possibility of publication bias cannot be excluded because the articles with positive results might be more easily published. It may be difficult to publish studies reporting the loss of beneficial effects after the termination of the intervention, as mentioned earlier. Third, clinical trials with relatively small sample sizes were included in our analysis. Unknown cofounders can be mingled in such cases. Finally, we used data only from RCTs. Patients enrolled in an RCT might not be representative of patients observed in clinical settings. Therefore, our results might not always be applicable to our routine medical care.

CONCLUSIONS

In conclusion, our systematic review showed the existence and clinical significance of cardiometabolic memory. To understand and prevent cardiovascular events, the impact of cardiometabolic memory should be highly emphasized as a concept supporting the importance of intensive intervention in hypertension, diabetes, and dyslipidemia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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