EVALUATION OF METHODS TO DETECT LEGACY EFFECTS IN CARDIOVASCULAR POST-TRIAL STUDIES

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A Thesis Submitted in Fulfillment
of the Requirements for the Degree of

Doctor of Philosophy

School of Public Health, Faculty of Health
Univeristy of Technology Sydney

2021

Certificate of Original Authorship

I, Lin Zhu declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Public Health, Faculty of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

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Date: 20/12/2020

Abstract

Post-trial follow-up studies after randomized controlled trials (RCT) are increasingly used to investigate the clinical effectiveness of an intervention in the long term. "Legacy effect", which was proposed in the context of such studies, describes the effects of an intervention that are only observed after the end of trial and are not due to the direct effects observed during the trial period itself. Much of the clinical interest in legacy effects has been in the drug treatments for cardiovascular disease prevention, as the finding of such effect could provide support for earlier initiation of the intervention. However, limited attention has been paid to the methodological challenges of analysing post-trial data.

In this thesis, I provide a summary of the methods used, and evaluate the potential for bias, in the cardiovascular post-trial studies. I also investigate how we might best analyze data from a matching RCT and post-trial follow-up study, specifically, the choice of time period and trial participants to include in analysis and the strategy to correct for potential selection bias and confounding. Simulations are conducted to compare the performance of different methods. I use data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and its follow-up data to illustrate the application of different approaches.

Analyses combining both the initial trial period and the post-trial follow-up period have often been incorrectly interpreted as evidence of a legacy effect, which is better assessed on the basis of separate post-trial analysis. To address the issues of selection bias and potential confounding requires appropriate study designs and rigorous methods of analysis. The choice of statistical methods should consider the availability of post-trial data, size of direct treatment effect and causal pathway of legacy effect. It is recommended to conduct a sensitivity analysis to check the robustness

of the findings. Better reporting of legacy effects is needed to realize their full value in informing clinical practice and health policy.

Acknowledgements

First and foremost, I would like to thank my two supervisors, Professor Andrew Hayen and Associate Professor Katy Bell, for their patient guidance, invaluable advice and huge investment of time in me. It has been a privilege to work under their supervision over the past four years. Andrew gave me the freedom to pursue my study interest and provided his best support. His positive outlook in my research inspired me and made me more confident. Katy provided a great deal of insightful feedback on my research ideas and written works, from where I learnt a lot. Her enthusiasm for research has always motivated me to work harder and aim higher.

I gratefully acknowledge the funding received towards my Ph.D. from Australian Government Research Training Program Scholarship. I am also grateful to University of Technology Sydney for providing me the financial support to attend conferences and training courses. I thank the National Heart, Lung, and Blood Institute for providing the data used in this thesis.

I would also like to thank my colleagues and staff members in the Faculty of Health, Sarita, Kirsten, Krishna, Pauline, Penny, Zhuoyang, Priya and Julia for their support and encouragement along the way. I am grateful to my friends, Lei, Peng, Tao, Yu, Zhaoqing, Juanwen and Xiaohang, for their help in my study and life, and the wonderful times we shared in Sydney.

Finally, I wish to express my deepest gratitude to my partner and parents. This would not have been possible without their unselfish support and love at all times.

List of Publications

Journal Publications

1. **Zhu L**, Bell K, Nayak A, Hayen A. A Methods Review of Post-trial Follow-up Studies of Cardiovascular Preven-tion Finds Potential Biases in Estimating Legacy Effects *Journal of Clinical Epidemiology* 131, 51-58 (2021)

2. **Zhu L**, Hayen A, Bell K. Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study. *Cardiovascular Diabetology* 19, 28 (2020)

3. **Zhu L**, Bell K, Hayen A. Estimated legacy effects from simulated post-trial data were less biased than from combined trial/post-trial data. *Journal of Clinical Epidemiology* 114, 30–37 (2019).

4. Nayak A, Hayen A, **Zhu L**, McGeechan K, Glasziou P, Irwig L, Doust J, Gregory G, Bell K. Legacy effects of statins on cardiovascular and all-cause mortality: A meta-analysis. *BMJ Open* 8, 1–11 (2018)*

Conference Publications

1. **Zhu L**, Bell K, Hayen A. Using marginal structural models to account for selection bias in the analysis of legacy effect. *2020 World Congress of Epidemiology*

2. **Zhu L**, Bell K, Hayen A. Statistical methods for estimating legacy effect: a simulation study. *2018 Australasian Epidemiological Association Annual Scientific Meeting*

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*This article was published during my candidature. It is not a part of this thesis.

3. **Zhu L**, Hayen A, Bell K. Research methods for detecting legacy effect: a scoping review. *2017 Australasian Epidemiological Association 30th Anniversary Scientific Meeting*

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Abbreviation

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCORDION	Action to Control Cardiovascular Risk in Diabetes Follow-on
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	Cardiovascular Disease
DAG	Directed Acyclic Graph
HbA1c	Hemoglobin A1c
HDL	High-density Lipoprotein
HF	Heart Failure
HR	Hazard Ratio
IPW	Inverse Probability Weighting
LDL	Low-density Lipoprotein
MI	Myocardial Infarction
MSE	Means Square Error
MSM	Marginal Structural Model
PS	Propensity Score
RCT	Randomized Controlled Trial
SD	Standard Deviation
SE	Standard Error
T2DM	Type 2 Diabetes Mellitus
TRIG	Triglycerides

Chapter 1

Introduction

1.1 Background

The randomised controlled trial (RCT) is the ideal study design for generating clinical evidence on the effectiveness of interventions. However, these trials are generally resource-intensive to run and include relatively short follow-up periods, which may fail to capture the long-term effects of the interventions. Advances in information technology and data computing have created new possibilities for increasing the value of RCTs by post-trial extension studies using linkage to existing administrative or registry data (Fitzpatrick et al., 2018). Prolonged monitoring of RCT participants after the end of the scheduled trial period may provide valuable information and allow a more comprehensive understanding of treatment effects (Heerspink de Zeeuw, 2014; Llewellyn-Bennett et al., 2018). The term "legacy effect" is often used in the context of such studies, which describes the effects of an intervention that are observed after the end of trial and are not due to the direct effects observed within the trial period.

Legacy effect was first proposed in the report of post-trial monitoring after the United Kingdom Prospective Diabetes Study (Chalmers Cooper, 2008; Holman et al., 2008). In that randomized controlled trial of intensive versus conventional blood glucose control, participants who were allocated to conventional treatment had a higher risk of microvascular complications than those on intensive treatment over

the 10-year period of the active trial (UK Prospective Diabetes Study Group, 1998). After the randomized controlled trial ended, the trial investigators recommended that all participants aim for more intensive control and the glycated hemoglobin levels of the two groups converged after 1 year. However, among participants undertaking follow-up after the trial, the statistically significant relative reduction in the microvascular diseases was found to have persisted, and additional statistically significant reductions in myocardial infarction and all-cause mortality also emerged for those originally randomized to the intensive-control group compared with those in the original conventional control group. These findings were hypothesized to be a "legacy effect" of the earlier tighter glycemic control for the intervention group during the trial period that was only being realized years later.

Determining possible legacy effects has been of particular interest for the interventions aimed at primary cardiovascular disease prevention (Ho et al., 2020; Kostis et al., 2020; Nayak et al., 2018). This is because the legacy effect concept could be used to support the case that early preventative treatment at a relatively young age may prevent cardiovascular disease in later life. Many large-scale randomized controlled trials examining the effect of cardiovascular preventative treatment (drugs to control glucose in people with diabetes and to lower blood pressure or cholesterol in people with or without diabetes) have reported the long-term health outcomes beyond the end of the trials. For instance, the 20-year follow-up of the West of Scotland Coronary Prevention Study report found that statin treatment for 5 years was associated with a legacy benefit, with improved survival and a substantial reduction in cardiovascular disease events detected at long term follow up (Kashef Giugliano, 2016; Vallejo-Vaz et al., 2017). The basic design of such studies is shown in Figure 1.1.

Besides the drug treatments for cardiovascular disease prevention, there is also interest in possible beneficial effects of earlier intervention through surgery, disease

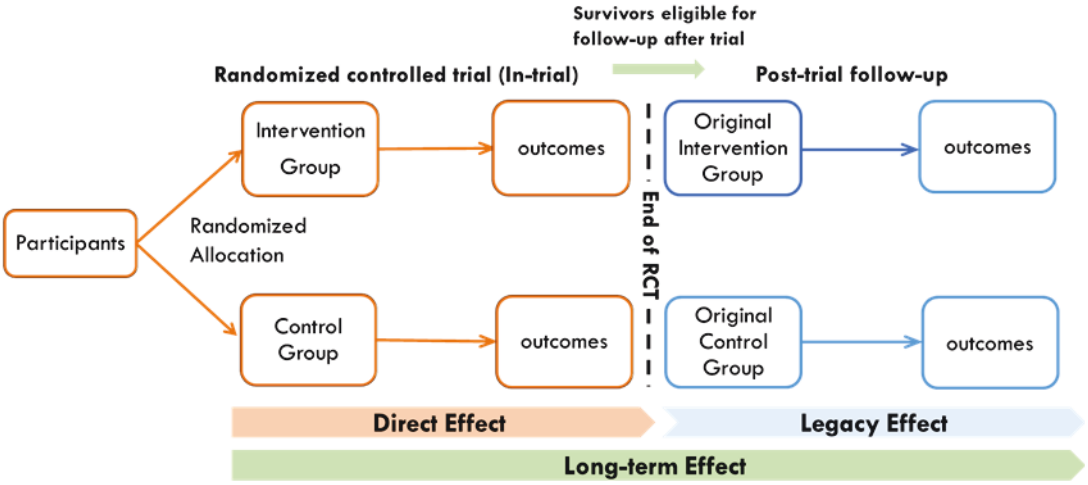

Figure 1.1 Design of post-trial study and legacy effect

screening and health promotion program. While examining the potential legacy effects through post-trial follow-ups of initial randomized controlled trials are becoming popular, limited attention has been paid to research design and analysis methods of such studies. For instance, the level of close monitoring undertaken during the RCT is not typically retained in the post-trial period due to the level of funding needed to support this. Some important information might be missing thereby limiting the studies' reliability. There are also analytic challenges for these studies that arise from comparing groups that, unlike at the start of the trial period, are no longer at equivalent risk. At the end of a trial for an effective intervention (and at the start of the post-trial study), more participants are likely to survive in the intervention group than in the control group. However, the surviving intervention participants will be at higher risk of a cardiovascular event than the surviving control participants, and analysis without adjustment will lead to biased estimates. Other sources of bias include continued differential use of medication between study arms, differential retention of participants (for example, differential non-retention due to death, loss to follow up, unwilling to attend the post-trial study) and differences in time-dependent covariates across the original randomized groups (Hernán

et al., 2013; Manson et al., 2016). The evaluation of the legacy effect requires the use of appropriate statistical methods that account for these issues to ensure the findings' robustness and validity.

In addition, it remains unexplored what is the most appropriate choice of time period and trial participants to include in the analysis of legacy effect, and how different choices could impact the estimates. Analyses combining both the initial trial period and the post-trial follow-up period (long-term effect) have often been mistakenly cited as evidence of a legacy effect. The focus of these reports has been on whether there is a survival benefit to the group randomized to active therapy, which is still detectable at long term follow-up. This raises the concern that the reported legacy effects might in fact be due in part, or entirely, to the direct treatment effects observed during the within-trial period. An incorrect conclusion of a legacy effect may inappropriately influence clinicians to prescribe interventions more aggressively.

1.2 Research Objectives

This program of research aims to illustrate the methodological issues that arise when estimating the legacy effects of treatments and explore potential solutions. The specific objectives of my thesis include:

i. summarize the statistical approaches that have been used for detecting legacy effects so far and identify any additional statistical approaches that may be suitable.

ii. investigate the choice of time period and trial participants to include in the analysis of legacy effect.

iii. compare the performance of different strategies in handling selection bias and potential confounding in the estimation of legacy effect.

iv. apply the statistical approaches identified to assess the legacy effects using ACCORD trial and its follow-up data. Specifically, we aim to evaluate the legacy effects of fibrate add-on therapy among diabetic patients with dyslipidemia.

1.3 Thesis Organization

This thesis uses a publication style with six chapters. There are four papers in this thesis: three have been published (Chapter 2, Chapter 3 and Chapter 5), and the other one (Chapter 4) is currently being prepared for submission.

- Chapter 1 introduces the background, objectives and structure of my thesis.
- Chapter 2 provides a methods review of post-trial studies after randomized controlled trials of interventions to prevent CVD. This chapter presents an evaluation of the methods used and potential for bias in these studies, and illustrates the methodological issues faced in analyzing legacy effect.
- Chapter 3 investigates the choice of time period and trial participants to include in the analysis of legacy effect. Different analysis approaches are conducted and compared in a simulation.
- Chapter 4 explores methods for correcting the selection bias and confounding that may arise in the analysis of legacy effect. Methods identified in the review and other relevant methods identified will be compared in simulated scenarios, to explore how these choices may impact on the results.
- Chapter 5 evaluates possible "legacy effects" of fibrate add-on therapy on mortality and major cardiovascular outcomes in diabetic patients with dyslipidemia using the ACCORD trial and its follow-up data.
- Chapter 6 discusses the key findings of this thesis. I will also discuss the strengths and limitations of my research, the implications of the research find-

ings, recommendations and directions for future research.

1.4 Ethics

Ethical approval for this study was obtained University of Technology Sydney Human Research Ethics Committee (ETH18-2736).

Chapter 2

A Methods Review of Post-trial Follow-up Studies of Cardiovascular Prevention

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Research Paper I

Title: A Methods Review of Post-trial Follow-up Studies of Cardiovascular Prevention Finds Potential Biases in Estimating Legacy Effects

Authors: **Lin Zhu**, Katy J.L. Bell, Agnish Nayak and Andrew Hayen

Journal: Journal of Clinical Epidemiology

Type of publication: Review

Stage of publication: Published online on 21 November 2020

URL: https://doi.org/10.1016/j.jclinepi.2020.11.008

Academic peer-reviewed: Yes.

ELSEVIER

Journal of Clinical Epidemiology 131 (2021) 51−58

Journal of Clinical Epidemiology

A methods review of posttrial follow-up studies of cardiovascular prevention finds potential biases in estimating legacy effects

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Accepted 13 November 2020; Published online 21 November 2020

Abstract

Objectives: The objective of the study was to assess the methods used, and potential for bias, in posttrial studies of cardiovascular disease (CVD) where legacy effects may be estimated.

Study Design and Setting: We undertook a methods review of posttrial studies after randomized controlled trials (RCTs) of interventions to prevent CVD. For each included article, we extracted information on important aspects of the design and analysis of the study, and on the reporting of legacy effects.

Results: Of 2,622 retrieved articles, 46 were included in the review: 13 on blood glucose control, 13 on blood pressure control, and 20 on blood lipid control. The median duration for the RCT and posttrial follow-up studies was 5.0 and 5.7 years, respectively. At least 80% of initial RCT participants were enrolled in the posttrial study in 32 of the reports. Most reports used both linkage to routine administrative data sources and active data collection for the posttrial study. Of the 46 included articles, the authors assessed and reported posttrial covariate balance in 29 and made statistical adjustments in the analysis for potential confounding in 25. Posttrial results were reported separately to overall results (from time of randomization) in 21 articles. Legacy effects were claimed in 19 reports, of which 16 could be justified on the basis of the posttrial results.

Conclusion: Posttrial studies may provide valuable information for investigating legacy effects, but better reporting of results is needed to realize their full potential. Robust methods of data collection and analysis may address the risk of selection and confounding biases in posttrial studies.

Keywords: Legacy effects; Randomized controlled trial; Posttrial follow-up; Method review

1. Introduction

The randomized controlled trial (RCT) is the ideal study design for generating evidence on the effectiveness of clinical interventions. However, because trials are resource intensive to run, they commonly include relatively short follow-up periods and may fail to capture long-term effects of the intervention. A relatively low-cost option that trialists may choose to extend follow-up is to undertake a posttrial cohort study of surviving participants after the end of the active trial period [1]. The term "legacy effect" is often used in the context of such studies, which describes the effects of an intervention that are only observed after the end of trial and are not the direct effects observed during the trial period itself.

The finding of a legacy effect may provide support for earlier initiation at a younger age (or potentially cessation at a younger age) of the intervention under study. Much of the clinical interest in legacy effects has been in drug treatments for cardiovascular disease (CVD) prevention. An increasing number of studies have reported legacy effects for cardiovascular prevention drug treatments on the basis of results from posttrial follow-up studies after RCTs [2−4]. Several systematic reviews have also investigated legacy effects [5−8].

Posttrial analyses, which assess the treatment effects beyond the end of the trial, can provide information for the management of patients [9]. However, there are analytic

Declaration of interest: The authors declare no conflict of interest.

Source of funding: L.Z. was supported by an Australian Government Research Training Program Scholarship at the University of Technology Sydney.

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https://doi.org/10.1016/j.jclinepi.2020.11.008

What is new?

Key findings

- Fifty-four percent of posttrial studies reported only analyses that combined initial trial and posttrial follow-up data. This fails to make full use of the data and may lead to incorrect conclusions on legacy effects.
- Sixty-three percent of posttrial studies compared between-group difference of covariates for the participants enrolled in the posttrial period, and fifty-four percent of studies made adjustment in their analysis. Most comparisons and adjustments were made using baseline measurements of covariates at start of the RCT, rather than the more appropriate time point at the start of the posttrial study.

What this adds to what was known?

- This review has added to current evidence that some posttrial studies use inappropriate methods of analysis and that there is a need to improve the reporting of legacy effects.

What is the implication and what should change now?

- Researchers should be aware of the potential for confounding and selection bias when designing posttrial studies. By using appropriate methods of data collection and analysis, they may minimize bias in estimates of long-term and legacy treatment effects.

challenges for these studies that arise from comparing groups that, unlike at the start of the trial period, are no longer at equivalent risk. For instance, at the end of the Diabetes Control and Complications Trial, the conventional and intensive treatment randomized groups differed on several established CVD risk factors (e.g., body mass index and triglycerides) and in levels of the surrogate outcome of asymptomatic microvascular disease (microalbuminuria and albuminuria) [10]. Other sources of bias include continued differential use of medication between study arms, treatment confounder feedback, differential loss to follow-up, and differences in time-dependent covariates across the original randomized groups [11]. Analysis that fails to consider these issues may lead to biased results. In addition, the results of trial and posttrial analyses may be misinterpreted. Analyses combining both the initial trial period and the posttrial follow-up period (long-term effect) have often been incorrectly interpreted as evidence of a legacy effect, which is better assessed on the basis of separate posttrial analysis [12]. An incorrect assumption of a beneficial legacy effect may inappropriately influence clinicians to prescribe interventions more aggressively at a younger age, or similarly influence clinical guideline recommendations to the same effect.

Although posttrial studies have become more common, limited attention has been paid to the design and analysis of such studies. In this article, we conduct a review of the methods used in posttrial studies after RCTs of drug interventions to prevent CVD. Our objectives were to assess the design characteristics, methods of analysis used, and the quality of reporting of legacy effects.

2. Methods

We registered the protocol for this review on the international prospective register of systematic reviews (PROSPERO, CRD42017063969). We included all reports on follow-up after randomized, controlled trials in adults (age >18 years) of drug interventions to lower blood glucose, blood pressure, and cholesterol (including placebo-controlled studies or lower vs. higher targets for treatment).

2.1. Search strategy

We searched the following electronic bibliographic databases (to 31st December 2019): MEDLINE, EMBASE, and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register). Other sources included reference lists of included articles, hand searching key journals, conference proceedings, and forward citation searching of included studies. The search strategy is provided in supplementary materials.

2.2. Study selection and data extraction

Detailed inclusion and exclusion criteria for study selection are listed in Table 1. Two reviewers (L.Z. and A.N.) checked the titles and abstracts of all citations identified through the database searches and forward citation search. We obtained full text if either reviewer judged the article as being potentially relevant. The same two authors then independently checked all the full-text articles for eligibility, resolving disagreements through discussion with two further reviewers (K.B. and A.H.).

2.3. Data extraction and assessment

L.Z. extracted data using standardized forms, and the results were reviewed by A.H. and K.B. In addition to descriptive information of both the RCT and posttrial follow-up, we extracted the following data on the design and analysis of the posttrial study and on the reporting of legacy effect [13]:

(i)
Method of data collection: The methods of data collection were divided into three categories: 1) active follow-up,

Table 1. Inclusion and exclusion criteria for study selection

Inclusion criteria	• Posttrial reports of randomized controlled trials evaluating intensive vs. standard blood pressure control or lipid control or glucose control in diabetics (including placebo-controlled studies or lower vs. higher targets for treatment). • Adults (≥18 years) • The randomized controlled trial was ≥12-month duration • Studies in any setting (primary or secondary CVD prevention)
Exclusion criteria	• Clinical cardiovascular disease outcomes (fatal or nonfatal) during posttrial follow-up period not reported. • Posttrial follow-up period less than 12 months • Data not reported separately for each randomized group

Abbreviations: CVD, cardiovascular disease.

such as clinic visits, laboratory examinations, questionnaires, or telephone interviews; 2) data linkage, where follow-up data were obtained by linkage to administrative data sets such as hospital records, death certificates, or population registries; and 3) a combination of 1) and 2).

(ii)

Information collected in the posttrial period, including medication use, relevant surrogate outcomes (e.g., blood glucose, blood pressure, low-density lipoprotein cholesterol, total cholesterol), and other cardiovascular risk factors.

(iii)

Assessment of between-group difference in relevant covariates. We extracted information on comparisons of covariates between the trial arms of participants and on whether the comparison was made based on the covariates measured at baseline or during the study.

(iv)

The primary statistical method used in the posttrial analysis.

(v)

Statistical adjustment in the posttrial analysis. We extracted information on whether the analysis accounted for relevant covariates and whether the adjustment was made based on baseline data or updated data during the posttrial study.

(vi)

Reporting of results: posttrial result only, trial and posttrial combined (overall result only), both posttrial result and overall result.

(vii)

Types of effects claimed in the abstract: legacy effect, long-term effect, both legacy and long-term effects.

(viii)

Justification of legacy effect: whether the claims on legacy effect were justified by reporting a separate posttrial result.

3. Results

3.1. Results of the search

Figure 1 shows the flow diagram of the posttrial study selection process. Of the 2,622 records we identified, 2,524 were ineligible based on screening of abstracts, and 98 full-text articles were assessed for eligibility. Of these 98 articles, we assessed 44 as eligible, and we identified two further articles through searches of references and forward citations. In total, we included 46 articles from 37 unique follow-up studies. Detailed information on included studies is provided in the supplementary materials Table S1.

3.2. Characteristics of the RCTs and posttrial follow-up

We summarize the characteristics of the RCTs and posttrial follow-up in Table 2. Of the 46 articles, 13 (28%) investigated blood glucose control, 13 (28%) investigated blood pressure control, and 20 (44%) investigated lipid control. About one-third of these interventions were for primary prevention. The median duration for RCT and posttrial follow-up period was 5.0 and 5.7 years, respectively.

Thirty percent of RCTs recruited fewer than 2,000 participants, whereas 40% had more than 5,000 participants. Most articles reported a between-group difference in levels of surrogate outcomes (lipids, blood pressure, blood glucose) in the trial period, and about 60% articles reported a significant primary endpoint for trial. Although in all studies the investigated treatment was recommended to all participants (on the basis of the RCT results), it was actively provided to all participants in five posttrial studies, whereas the other posttrial studies were purely observational. Thirty-four (74%) articles used the same primary outcome for the posttrial follow-up as the initial RCT.

Figure 2 summarizes the design and analysis of posttrial studies. At least 80% of the trial participants were enrolled in the posttrial follow-up study in 32 (70%) of the 46 articles. The percentage of participants enrolled in posttrial follow-up was similar between those who were initially in the intervention and in the placebo groups in 25 articles (difference less than 2%), whereas some reports showed larger differences. For example, in the Steno-2 study, the percentages of enrollment for the active and placebo group were 84% and 79%, respectively. Among the 46 reports, 14 (30%) collected data by active follow-up; 12 (26%) obtained posttrial information by data linkage, and the remaining 20 (44%) reports used both methods. Data on medication use in the posttrial period were collected by

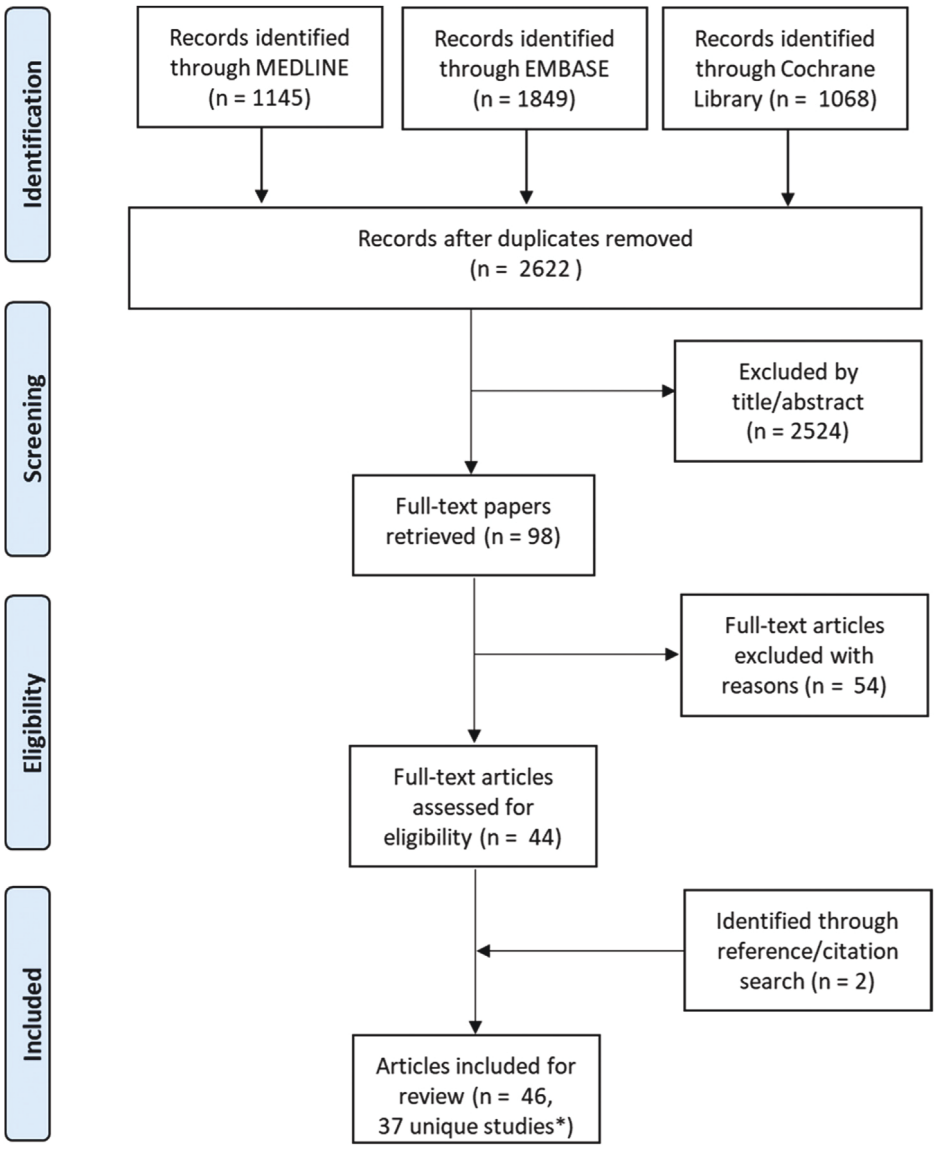

Fig. 1. The flow diagram of the posttrial study selection process. * 31 studies each had one corresponding report; three studies each had two corresponding reports (ADVANCE-ON Blood Glucose study, Veteran Affairs Diabetes Trial, and Systolic Hypertension in the Elderly Program), and three studies each had three corresponding reports (Epidemiology of Diabetes Interventions and Complications study, Anglo-Scandinavian Cardiac Outcomes Trial, and West of Scotland Coronary Prevention Study).

most reports (32, 70%). Surrogate outcomes were reported in 30 articles (65%), whereas information on other risk factors was available in 21 reports (45%).

The between-group differences in covariates were assessed in 29 articles (63%), but in 22 (48%) reports, this was based on baseline measurements at start of the RCT rather than the posttrial study. Information on the between-group difference with regards to covariates, surrogate outcomes, and medication use in the posttrial period is provided in supplementary materials Table S2. Cox proportional hazard was the most frequently used method in the posttrial analysis (37, 80%). Twenty-five reports (54%) made statistical adjustments for covariates in their analysis. In addition to time invariant demographic factors such as age, gender, and race, eight reports also adjusted for time-varying covariates. For example, in the Epidemiology of Diabetes Interventions and Complications study, the updated mean glycosylated hemoglobin value, the development of renal disease, microalbuminuria, and albuminuria were included as time-dependent covariates in analysis [10,14].

Nineteen (41%) articles reported results for both posttrial and the whole study period, whereas two (4%) only reported the results of the posttrial period and 25 (54%) articles only reported an overall result. Long-term effects were claimed in the abstract of 27 (59%) articles. Legacy effects were claimed in the abstracts of 19 reports, of which 16 provided posttrial results that justified the claim.

Table 2. Characteristics of the RCTs and posttrial follow-up

Period	Characteristics	No. of reports (%, $N = 46$)
RCT	Type of intervention	
	Blood glucose	13 (28)
	Blood pressure	13 (28)
	Lipid	20 (44)
	Type of prevention	
	Primary prevention	15 (33)
	Secondary prevention	31 (67)
	Length of trial follow-up	
	Median (mean)	5.0 (4.9)
	<4	11 (24)
	4–8	33 (72)
	≥8	2 (4)
	No. of participant initial RCTs	
	Median (mean)	4,446 (5,236)
	<500	2 (4)
	500–2,000	12 (26)
	2,000–5000	15 (30)
	5000–10,000	8 (20)
	≥10,000	9 (20)
	Mean age of the participant	
	Median (mean)	60 (58)
	<45	5 (11)
	45–65	30 (65)
	≥65	11 (24)
	Between-group different surrogate Levels reported	43 (93)
	Statistically significant primary end point	27 (59)
Posttrial follow-up	Length of posttrial follow-up	
	Median (mean)	5.7 (8.5)
	<5	15 (33)
	5–10	14 (30)
	≥10	17 (37)
	Percentage of participants enrolled in posttrial	
	Median (mean)	89% (84%)
	>90%	17 (37)
	80–90%	15 (33)
	≤80%	14 (30)
	Between-group difference in posttrial study enrollment[a]	
	<2%	25 (54)
	2–5%	16 (35)
	≥5%	1 (2)
	N.A.	4 (9)
	Observational posttrial follow-up study[b]	41 (89)
	Primary outcome same as the RCT	34 (74)

Abbreviations: RCT, randomized controlled trial.

[a] Difference in enrollment of posttrial follow-up between those initially enrolled in active and control groups.

[b] Examining if the posttrial follow-up is observational or the posttrial treatment was provided by the investigators.

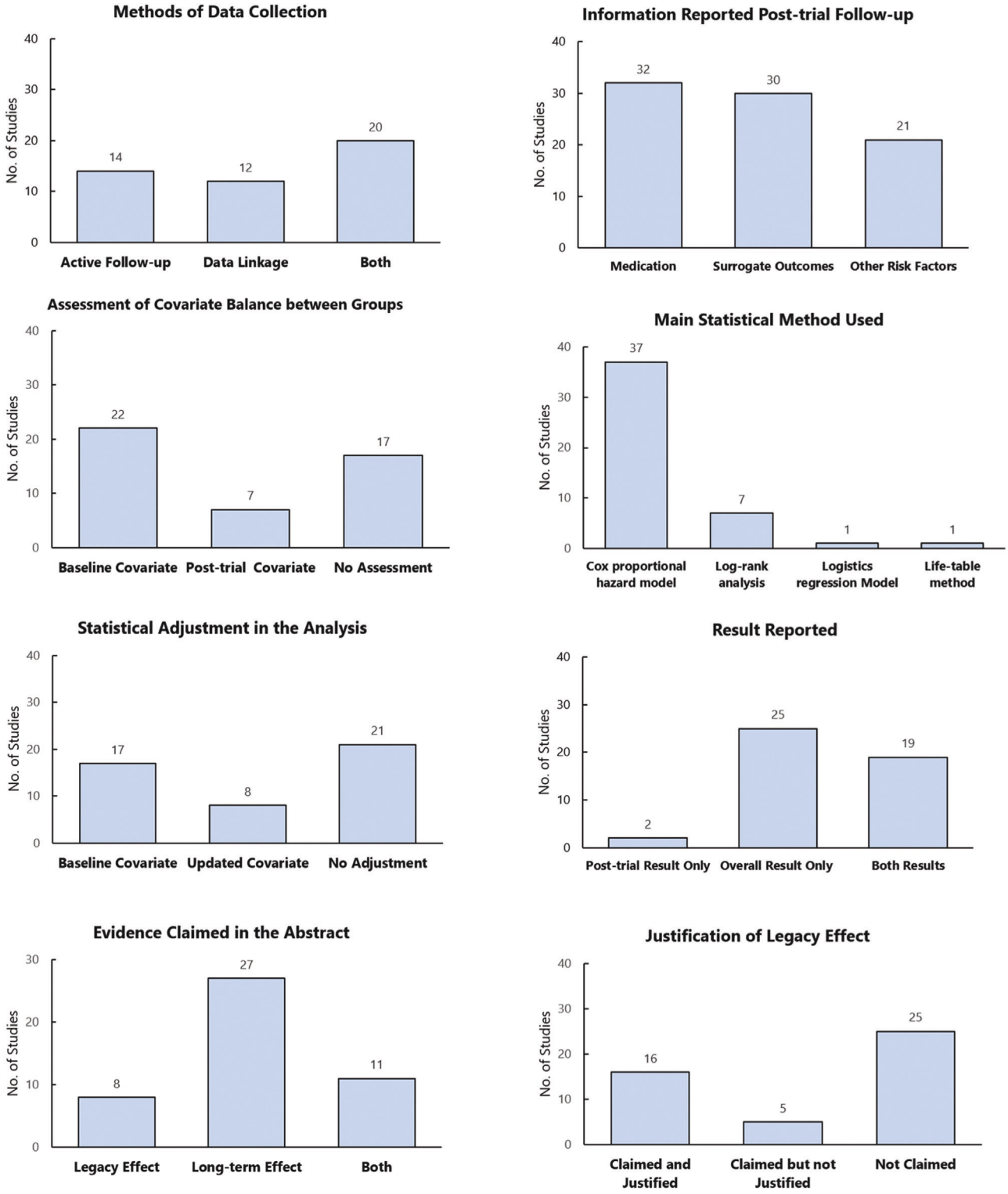

Fig. 2. The design, analysis, and reporting of the posttrial studies.

4. Discussion

In this methods review of posttrial studies for a range of cardiovascular interventions, we found potential for biased estimates of legacy effects from the study designs and methods of analysis most commonly used. We also found important deficiencies in the reporting of these studies, and in particular, that a separate posttrial analysis was infrequently reported.

We found that posttrial studies are often missing information on important covariates that would allow

assessment and adjustment for potential selection bias and confounding [1,15]. About one-third of the articles did not report the posttrial medication use or measurements of surrogate outcomes (such as BP, HbA1c, lipids), and the information on the other potential confounders was not collected in more than half of the reports. Where initial RCTs are very large, it may be prohibitively expensive to collect the data of all the patients [16]. Random sampling may be a solution for such studies. For instance, of 8,494 participants enrolled in the posttrial study of the Action in Diabetes and Vascular Disease trial, a random subset of 2,000 patients, balanced across regions and across the prior randomized treatment arms, were invited to undergo laboratory examinations to determine whether in-trial differences in surrogate outcomes persisted in posttrial [17].

Even where sufficient data were collected that could allow for assessment and adjustment for bias in analysis, we found that most posttrial studies failed to do so. The main challenge of posttrial analyses is that there is no longer a randomized comparison of intervention vs. control, and the study design is that of a cohort study. Although 46% of studies collected information on posttrial covariates, only about 15% studies assessed the balance of posttrial covariates and made corresponding adjustment in their analysis. As it is hard to determine to what extent the risk of CVD remains equivalent, we suggest that both unadjusted and adjusted results should be reported to ensure the robustness of findings. In addition, methods used to deal with time-dependent confounding and selection biases in observational studies, such as causal inference approaches (G-methods), could also be applied to the posttrial analysis [18].

Our review also highlights the need for improved reporting of treatment effects in posttrial studies. We found that most studies only focused on long-term treatment effects [19,20]. Among the articles claiming legacy effect, about one-quarter failed to report a separate posttrial result to justify the evidence. As both direct effects and legacy effects could contribute to the long-term effects of the intervention, long-term effects alone do not provide proof of legacy effects. For example, in the Scandinavian Simvastatin Survival Study, the investigators found simvastatin treatment for 5 years in trial was associated with a survival benefit over 10 years. The hazard ratio and corresponding confidence interval reported for trial and whole follow-up period were 0.70 (0.58−0.84) and 0.85 (0.74−0.97), respectively. However, the risk calculated by the separate posttrial analysis was 1.03 (0.86−1.24) [21]. Although a sustained survival benefit was found after the end of the trial, it was apparently due to the direct effect during the trial, rather than a legacy effect emerging in the posttrial follow-up.

Our review has some limitations. We only focused on the posttrial studies of RCTs evaluating cardiovascular interventions. In previous reviews of long-term follow-up of randomized trial participants, other common types of interventions included surgery, cancer screening, and behavioral change interventions [1,15]. The extent to which the issues we found applies to these other interventions and settings is unknown. We also did not search for non-English language studies, or the gray literature (including unpublished studies). However, it seems unlikely that we missed important methods in our search.

5. Conclusion

As posttrial studies are becoming increasingly common, it is important for readers to be aware of important methodological issues related to the estimation and interpretation of legacy effects. Trialists aiming to investigate legacy effects need to ensure appropriate study design and methods of analysis are used. In particular, trialists should design and conduct posttrial studies using methods of data collection and analysis that allow potential confounding and selection bias to be addressed.

CRediT authorship contribution statement

Lin Zhu: Conceptualization, Investigation, Methodology, Writing - original draft. **Katy J.L. Bell:** Conceptualization, Investigation, Methodology, Supervision, Writing - review & editing. **Agnish Nayak:** Investigation, Writing - review & editing. **Andrew Hayen:** Conceptualization, Investigation, Methodology, Supervision, Writing - review & editing.

Appendix A

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2020.11.008.

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Chapter 3

Simulations to investigate the choice of time period and trial participants to include in the analysis of legacy effect

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Research Paper II

Title: Estimated legacy effects from simulated post-trial data were less biased than from combined trial/post-trial data

Authors: **Lin Zhu**, Katy J.L. Bell and Andrew Hayen

Journal: Journal of Clinical Epidemiology

Type of publication: Research paper

Stage of publication: Published online on 22 May 2019

URL: https://doi.org/10.1016/j.jclinepi.2019.05.010

Academic peer-reviewed: Yes.

Journal of Clinical Epidemiology 114 (2019) 30–37

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Estimated legacy effects from simulated post-trial data were less biased than from combined trial/post-trial data

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Accepted 18 May 2019; Published online 22 May 2019

Abstract

Objectives: "Legacy effects" describe the phenomena where treatment effects are apparent during the post-trial period that are not attributable to the direct effects observed within the trial. We investigate different approaches to analysis of trial and extended follow-up data for the evaluation of legacy effects.

Study Design and Setting: We conducted a simulation to compare three approaches, which differed in terms of the time period and selection of trial participants included in the analysis.

Results: The most common approach used for estimating legacy effects in the literature, which combines initial trial and post-trial follow-up data, gave the most biased estimates. Approaches using post–randomized controlled trial data had better performance in most scenarios. When the size of the legacy effect was set to differ according to whether or not drugs were taken after trial, the stratified approach using post-trial data but only from participants taking the drug after trial was less biased but often had lower power to detect a legacy effect.

Conclusion: When estimating legacy effects, approaches to analysis that are restricted to post-trial follow-up data are preferred. If data are available on participant drug use after trial, then both stratified and unstratified approaches to analysis of the post-trial data should be investigated.

Keywords: Legacy effects; Randomized controlled trial; Post-trial follow-up; Cardiovascular disease

1. Introduction

The term "legacy effect" was first used in the context of cardiovascular disease prevention, in reports of the post-trial follow-up after the United Kingdom Prospective Diabetes Study [1]. In that randomized controlled trial of intensive vs. conventional glycemic control, participants who were allocated to conventional treatment had a higher risk of microvascular complications than those on intensive treatment over the 10-year period of the active trial [2]. After the randomized controlled trial (RCT) ended, the trial investigators recommended that all participants aim for more intensive control and the glycated hemoglobin levels of the two groups converged after 1 year. However, among participants undertaking follow-up after the trial, the statistically significant relative reduction in microvascular disease was found to have persisted and additional statistically significant reductions in myocardial infarction and all-cause mortality also emerged for those originally randomized to the intensive-control group compared with those in the original control group. These findings were hypothesized to be a "legacy effect" of the earlier tighter glycemic control for the intervention group during the trial period that was only being realized years later.

Although the definition of legacy effects is not well specified, the term has generally been used to describe long-term effects of a treatment that are observed after the trial has ended and that are not due to the direct (shorter term) effects of the treatment that were observed during the trial. These effects are thought to occur despite a similar proportion of individuals in the intervention and placebo group taking the active drug after the trial has ended and attaining similar mean levels of the intermediate outcome (such as glycated hemoglobin, blood pressure, or total cholesterol) in the post-trial period [3–5].

Conflict of interest: The author declares no conflict of interest.

Lin Zhu receives funding support from an Australian Government Research Training Program. Katy Bell receives funding support from an Australian National Health and Medical Research Council (NHMRC) Center for Research Excellence Grant (#1104136).

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https://doi.org/10.1016/j.jclinepi.2019.05.010

What is new?

Key findings

- The most common approach used to estimate legacy effects, which combines initial trial and post-trial follow-up data, usually gives biased estimates and is likely to wrongly conclude that there is a legacy effect when in truth none exists.
- The sample size calculated for the initial trial may often be insufficient to detect a statistically significant legacy effect in the post-trial period, particularly if this is small.

What this adds to what was known?

- When estimating the extent of legacy effects, methods that restrict analysis to post-trial follow-up data are recommended.

What is the implication and what should change now?

- More attention should be paid to the design and analysis of post-trial follow-up for evaluating possible legacy effects.

Determining possible legacy effects may be of particular interest for interventions aimed at primary cardiovascular disease prevention. Here, the legacy effect concept has been used to support the case that early preventative treatment at a relatively young age may prevent cardiovascular disease at a much older age [6]. Many large-scale randomized controlled trials examining the effect of cardiovascular preventative treatment (drugs to control glucose in people with diabetes and to lower blood pressure or cholesterol in people with or without diabetes) have reported the long-term health outcomes beyond the end of the trials [4,7,8]. The basic design of these studies is shown in Figure 1.

In most of these studies, the long-term effects of the drugs have been calculated using data from both the trial period and the post-trial follow-up period. These reports focus on whether there is a survival benefit to the group randomized to active treatment, which is still detectable at long-term follow-up [9]. Although such findings have been used to argue that legacy effects exist, it is possible that the observed effects might be due in part, or entirely, to the direct treatment effects observed during the within-trial period [10]. Analysis without disentangling the contribution of within-trial and post-trial effects will result in biased estimates. In this simulation study, we investigated how we might best analyze data from a matching RCT and post-trial follow-up study, to detect a legacy effect. Our objectives were to compare the performance of three different approaches to the choice of time period and trial participants to include in analysis in terms of ability to correctly detect when a legacy effect was, or was not, present.

2. Method

2.1. Simulation design

We formulated a setting that combined a RCT and an extended follow-up study. Independent data sets were generated with a known legacy effect or no legacy effect of the drug, in addition to a direct effect of the drug in all scenarios. We then evaluated three different approaches to analysis by applying each of them to the simulated data. The simulated data were designed to broadly reflect data that might be observed in a clinical trial for cardiovascular disease prevention, and the distributions of the simulation variables were based on the review of legacy effects of statin drugs [10].

2.2. Clinical question of interest: do statins have legacy effects in preventing cardiovascular disease?

A current subject of clinical debate is the age at which drugs to prevent cardiovascular disease (such as statins, blood pressure–lowering drugs, and diabetic drugs for tighter glucose control) should be offered to people at risk [11]. Advocates of earlier intervention argue that some

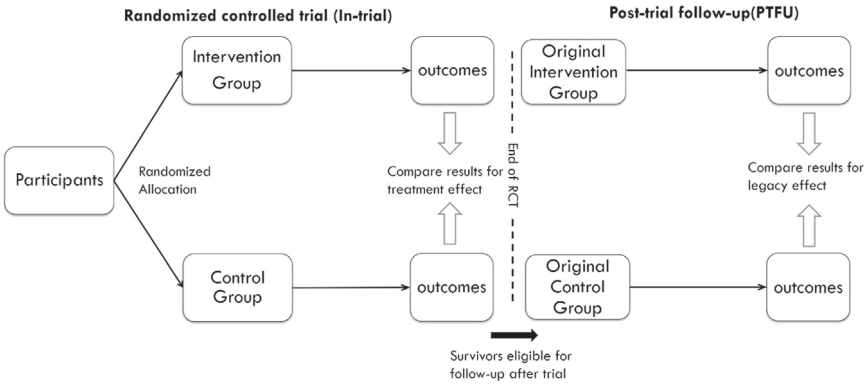

Fig. 1. The basic design of study for evaluating legacy effect (randomized controlled trials and post-trial follow-up).

people who are currently displaying no symptoms or signs of disease, and who are not at high short-term absolute risk of cardiovascular disease, may benefit from starting preventative medication at an early age [12]. The hypothesis that the earlier one starts these drugs, the lower one's risk of a cardiovascular event in the long term, has not been directly tested in an RCT, and because of feasibility issues, it is unlikely to be. However, the hypothesis may be indirectly tested using data from post-trial follow-up after large controlled RCTs. A finding that randomization to the active drug rather than comparator during the trial has a "legacy" effect in protecting the person from cardiovascular disease after the trial would suggest that earlier intervention may be worthwhile. An approach to data analysis that is able to reliably and accurately identify legacy effects is needed to use post-trial follow-up for this purpose.

2.3. Scenarios investigated

Simulation settings were divided into two main scenarios, based on different assumptions on the size of the legacy effect for people who continued or discontinued using the drug post-trial. In the first scenario, "noncompounding legacy effect," we assumed legacy effects were the same among the participants randomized to active treatment in the trial, irrespective of whether they continued to use the drug or not after trial. This scenario simulates the situation where the protective effect from earlier treatment (with statins for example) occurs whether or not the person continues to take the drug after trial. In the second scenario, "compounding legacy effect," we assumed that there were legacy effects only if the person continues to take the drug after the trial, and no legacy effects if they did not. This scenario simulates the situation where there is only a protective effect from earlier treatment if the person continues to take the drug after trial, as otherwise the underlying natural disease progression catches up and the protection is undone.

We varied the size of legacy effects and proportion using the drug in the post-trial follow-up across simulations. The size of the legacy effect was defined as relative to the initial (direct) treatment effect and included 0 (no legacy effect), 50%, and 100% of the direct treatment effect. Proportions using the drug in the post-trial follow-up were assumed to be the same in the two groups and ranged from 20% to 100%. This resulted in a total of 30 subscenarios, and 10,000 simulations were run for each subscenario. Table 1 provides a summary of all variables considered in the simulations.

2.4. Data generation

The starting point for simulation was to generate a cohort of patients with an underlying distribution of survival times. These survival times were generated from a Weibull distribution [13]. The shape parameter ν was set at 0.5, which assumes the event rate is increasing over time, a situation often observed empirically in cardiovascular disease [14]. The scale parameter λ was chosen, so that approximately 90% of participants who receive no treatment will survive after the 5-year RCT. The initial (direct) treatment effect was set as 0.8 (HR = 0.8), and the sample size for each simulation was chosen at 8,000 people (4,000 in each randomized group) [8,15].

For greater generalizability, the risk for each participant h_{risk} was simulated with a log-normal distribution. The mean and standard deviation on the log scale were set as −0.4 and 0.5, respectively, and so about 80% of patients were at low risk ($h_{risk} < 1$) [16,17].

Participants were assumed to have entered the RCT at t_0, and the initial trial ended at t_1. The surviving participants were followed up until the end of the follow-up period at t_2. The timepoints t_1, t_2 were set as 5 years and 15 years, which assumes the duration of the initial trial and post-trial follow-up were 5 and 10 years, respectively.

If $U(0,1)$ denotes a standard uniform distribution, then individual survival times can be generated using the formula:

$$T = \begin{cases} \left(\dfrac{-\log(1-U)}{\lambda h_{\text{risk}} \exp(\beta' X(t))} \right)^{1/\nu} & -log(1-U) < \lambda h_{\text{risk}} \exp(\beta' X(t)) t_1^{\nu} \\ \left(t_1^{\nu} + \dfrac{-\log(1-U) - \lambda h_{\text{risk}} \exp(\beta' X(t)) t_1^{\nu}}{\lambda h_{\text{risk}} \exp(\beta' X(t) + \beta_{LE})} \right)^{1/\nu} & -log(1-U) \geq \lambda h_{\text{risk}} \exp(\beta' X(t)) t_1^{\nu} \end{cases}$$

In the equation above, $X(t)$ is a time-varying variable that takes a value of 0 while a participant is assigned to placebo and 1 when assigned to active treatment [18]. β is the regression coefficient associated with the assigned treatment (representing direct treatment effects), whereas β_{LE} is the regression coefficient associated with legacy effects. If the algorithm generates a participant's survival time beyond the end of post-trial follow-up, then the participant is considered censored and the survival time replaced by t_2.

Table 1. Summary of variables used in the simulation

Variable	Value
Weibull parameter	Scale parameter $\lambda = 0.01$ and shape parameter $\nu = 1.45$
Log-normal parameter	Mean and standard deviation on log scale, mean = −0.4, SD = 0.5
Sample size	8,000
Length of randomized controlled trial and post-trail follow-up	5 yr and 10 yr
Initial treatment effect	0.8
Size of legacy effect (compared with treatment effect)	0, 50%, 100%
Proportion of treatment receiving in post-trail follow-up	20%, 40%, 60%, 80%, 100%

For simplicity, nonadherence with treatment and loss to follow-up were not considered in this study.

2.5. *Comparison of approaches to analysis of data from long-term follow-up after RCT*

Analysis for each scenario was performed according to the intention-to-treat principle, whereby participants are analyzed in the groups to which they were randomly allocated at the start of the trial. Cox proportional hazard models were fitted to estimate the legacy effects, and individual risk was included as a covariate in the model. Three approaches were compared; these differed in terms of the choice of time period and trial participants to include in analysis.

1. All trial participants: Data from the start of the RCT to end of post-trial follow-up were used (all data).
2. Participants surviving after trial. Post-trial follow-up data were used (post-trial data).
3. Participants surviving after trial and who took the drug during post-trial follow-up. Post-trial data were used (post-trial data−drug strata).

2.6. *Performance indicators*

Indicators used to assess the approaches to analysis were the bias, mean square error (MSE), coverage of 95% confidence intervals (CIs), and empirical power/size [19]. Bias was calculated as the difference between the average estimates over all simulations and the true value. Additionally, the mean of lower and upper limits of the corresponding 95% confidence interval was also calculated for comparison. Mean square error was calculated as the average squared difference between the estimated values and true value, according to the formula: $\text{MSE} = (\widehat{\beta} - \beta)^2 + (SE(\widehat{\beta}))^2$, where $SE(\widehat{\beta})$ is the empirical standard error of the estimate of interest over all simulations. MSE is a useful measure of the overall accuracy, which incorporates both measures of bias and variability. The coverage of 95% CI was calculated as the proportion of times that the obtained CI included the true specified parameter value. Empirical size/power was used to indicate the probability of making a correct statistical inference. Empirical size was calculated as the percentage of rejections of the null hypothesis for each data scenario created under the null hypothesis, and empirical power was calculated as the percentage of rejections of the null hypothesis for each data scenario created under the alternative hypothesis [20].

3. Results

The mean of hazard ratios (95% CIs) estimated by the different approaches to analysis in simulations for each of the two scenarios are presented in Figure 2. In most simulated scenarios, the estimates using the ‘‘all data’’ approach were considerably biased. The hazard ratios were overestimated (i.e., away from null) when there was no or a small legacy effect and underestimated (i.e., toward null) when there was a large legacy effect. In the ‘‘noncompounding legacy effect’’ scenario, where legacy effects for patients allocated to active treatment in the RCT were the same whether or not they continued to use the drug after trial, both ‘‘post-trial data’’ and ‘‘post-trial data−drug strata’’ approaches gave unbiased estimates for hazard ratios, but the former had better performance in terms of MSE (Figure 3). The ‘‘post-trial data−drug strata’’ approach, which use the least amount of the available data, generally had estimates with a larger MSE than the other approaches. In the ‘‘compounding legacy effect’’ scenario, where there were legacy effects for patients allocated to active treatment in the RCT only if they continued to use the drug after trial, ‘‘post-trial data’’ showed better performance than the ‘‘all data’’ approach, but ‘‘post-trial data−drug strata’’ approach had the least biased estimates. In addition, it showed more robust performance in terms of MSE compared with other methods.

The 95% coverage of the three approaches across the different scenarios are displayed in Figure 4. The ‘‘post-trial data−drug strata’’ approach had consistently good coverage among all scenarios investigated. In the ‘‘noncompounding legacy effect’’ scenario, the ‘‘post-trial data’’ approach also had good coverage. The ‘‘all data’’ approach to analysis had the worst coverage, with especially poor performance where there was no or small legacy effects. In the ‘‘compounding legacy effect’’ scenario, lower coverages were observed at different levels for ‘‘all data’’ and ‘‘post-trial data’’ approaches.

Figure 5 shows the results of empirical power/size. The ‘‘all data’’ approach to analysis always tended to accept the hypothesis of legacy effect. In addition, the power of the ‘‘post-trial data−drug strata’’ approach increased with the amount of the available data used in analysis in most scenarios. In the ‘‘noncompounding legacy effect’’ scenario, power was mainly lower using the ‘‘post-trial data−drug strata’’ approach than the ‘‘post-trial data’’ approach, whereas in the ‘‘compounding legacy effect’’ scenario, the reverse was true.

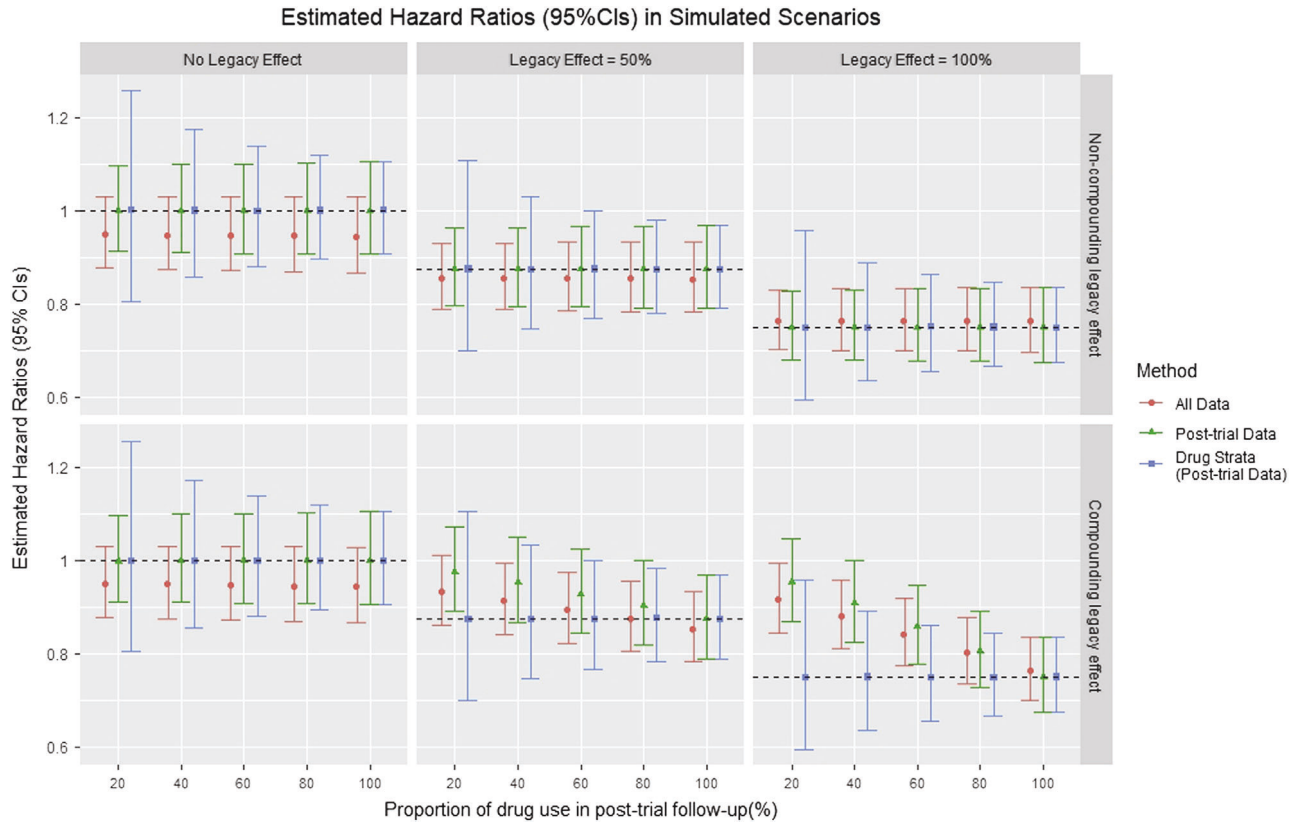

Fig. 2. Hazard ratios estimated by different methods in simulated scenarios*. *The points with confidence intervals (CIs) show the mean of estimated hazard ratios and the corresponding 95% CIs for each method in different scenarios, and the dash lines indicate the true values in each setting. Bias can be obtained by comparing the estimate and true values. The initial (direct) treatment effect was set as 0.8 (HR = 0.8), and the size of the legacy effect was defined as relative to the initial treatment effect.

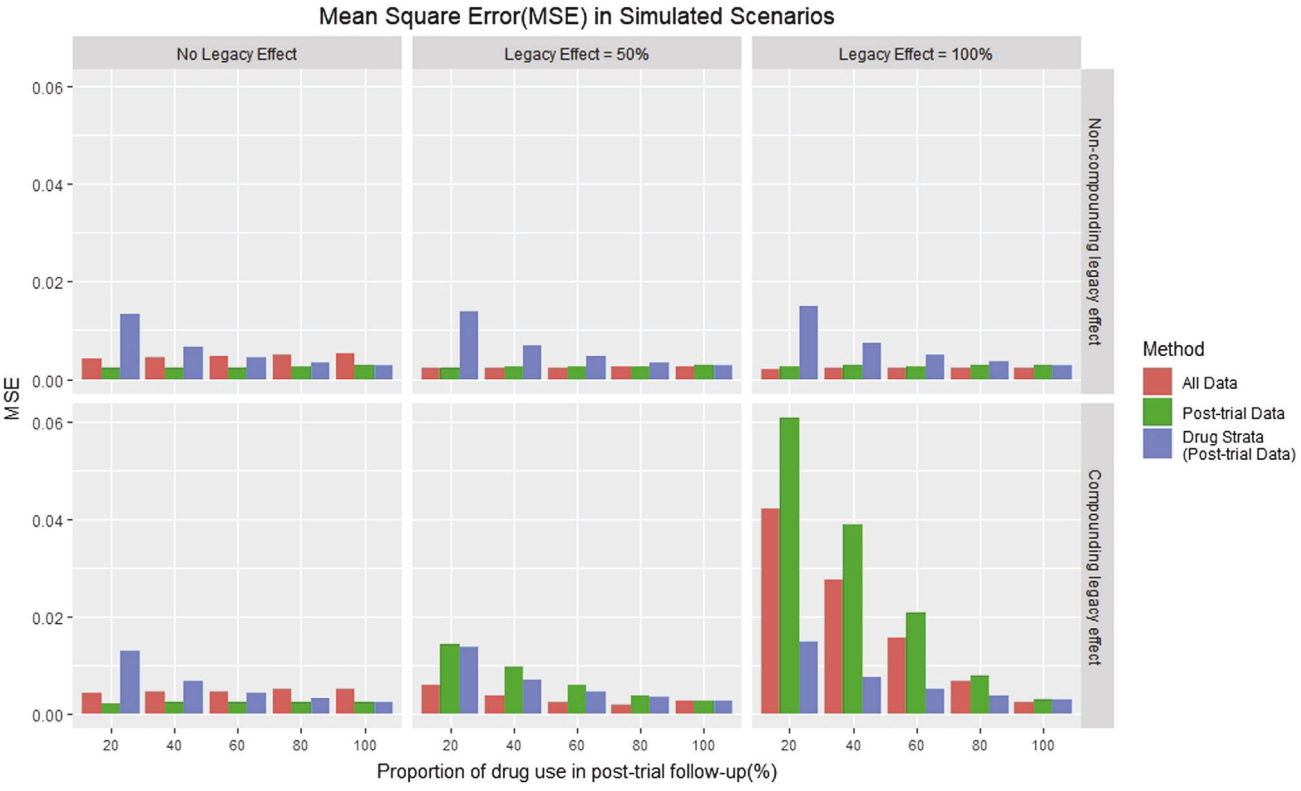

Fig. 3. Mean square error of different methods in simulated scenarios.

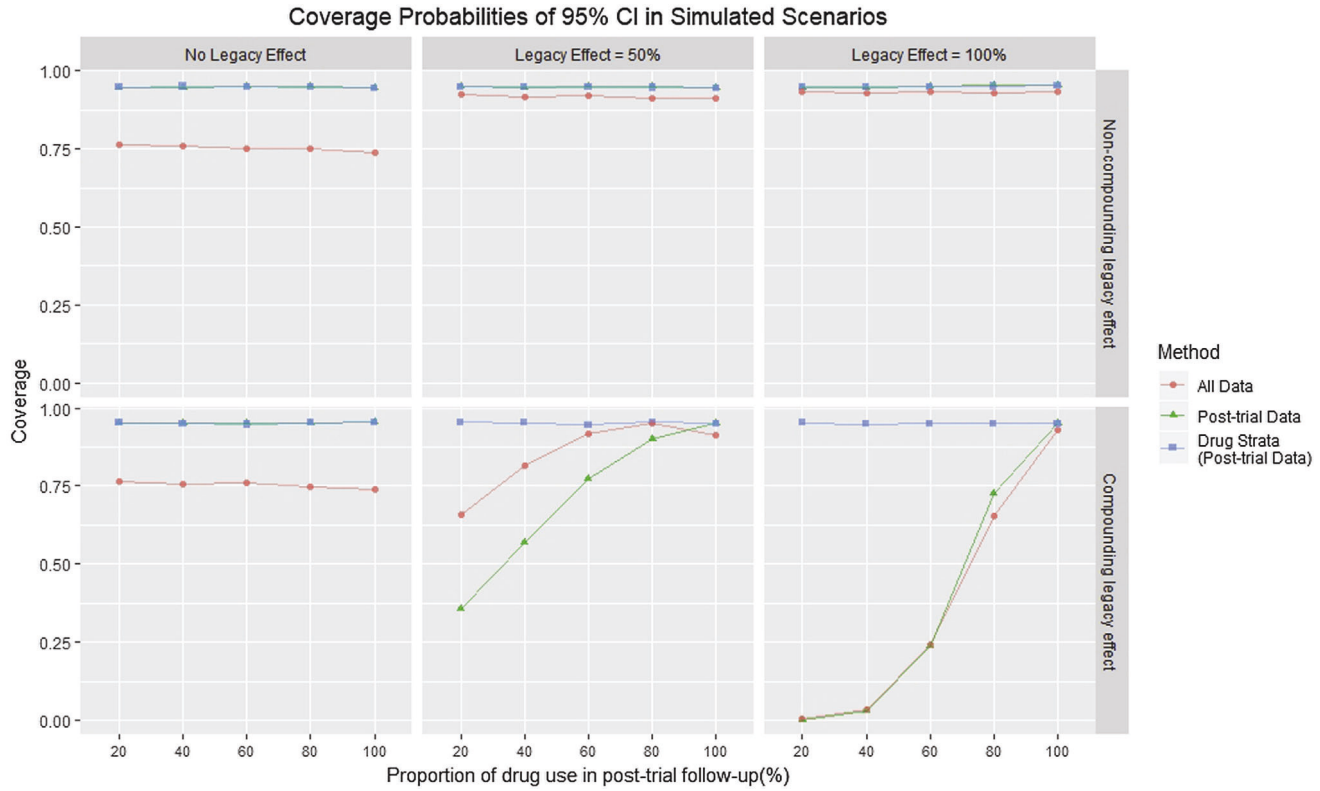

Fig. 4. Coverage probabilities of 95% confidence interval (CI) of different methods in simulated scenarios*. *The lines for ''post-trial data'' and ''post-trial data—drug strata'' are basically overlapped in the ''no legacy effect'' scenario and ''noncompounding legacy effect'' scenario.

4. Discussion

An ''all data'' approach to analysis is usually taken for studies that contain an RCT and post-trial follow-up and is an indication of long-term treatment efficacy [21,22]. However, this approach appears to be inappropriate for the evaluation of legacy effects, as it results in biased estimates of the true legacy effect in most situations. In addition, this approach often falsely concludes that there is a legacy effect when in truth none exists (i.e., type I error). The results of our simulation confirm our earlier hypothesis that to disentangle the direct effects of treatment during the RCT from legacy effects occurring after trial, we need to restrict our analysis to the post-trial period [10].

Our study also shows that approaches to analysis that use only post-trial data may miss detecting a small size legacy effect, especially where sample sizes are small, which is to be expected [23]. The sample size calculated for the initial trial, while sufficient to detect the (usually larger) direct treatment effect within the trial, may be insufficient for detecting a legacy effect in the post-trial period. Pooling data from several post-trial follow-up studies in an individual participant data meta-analysis may be needed to overcome issues of insufficient power in the primary studies. In addition, for many pragmatic post-trial studies which use linkage to administrative data to track the participants' health outcomes, some important individual information, such as medication status, is not available [8,10]. Therefore, only ''post-trial data'' (not stratified) analysis can be conducted. Although the ''post-trial data—drug strata'' analysis performed better in the ''compounding legacy effect'' scenarios, we need information on the use of drugs in the post-trial period for this analysis. This requires the post-trial study to be prespecified and funded.

Where data on post-trial drug use are available, the analysis limited to people who took the drug after trial may provide evidence about the benefits of starting treatment at a younger age, whereas the analysis limited to people who did not take the drug after trial may provide evidence about the safety of stopping drugs at an older age. We also found the ''post-trial data—drug strata'' approach to analysis to be more robust to variation in the assumptions made about the size of the legacy effect for people who continue or discontinue using the drug in the post-trial period. But as the stratified approach uses relatively less amount of the available data, estimates tended to have a larger MSE.

Our study has some limitations. Although the risks for each individual were adjusted in the post-trial analysis in the simulation, we did not consider other confounders for simplicity. Potential sources of confounding include the differential use of medication, imbalanced levels of risk factors, differential loss to follow-up, and other differences

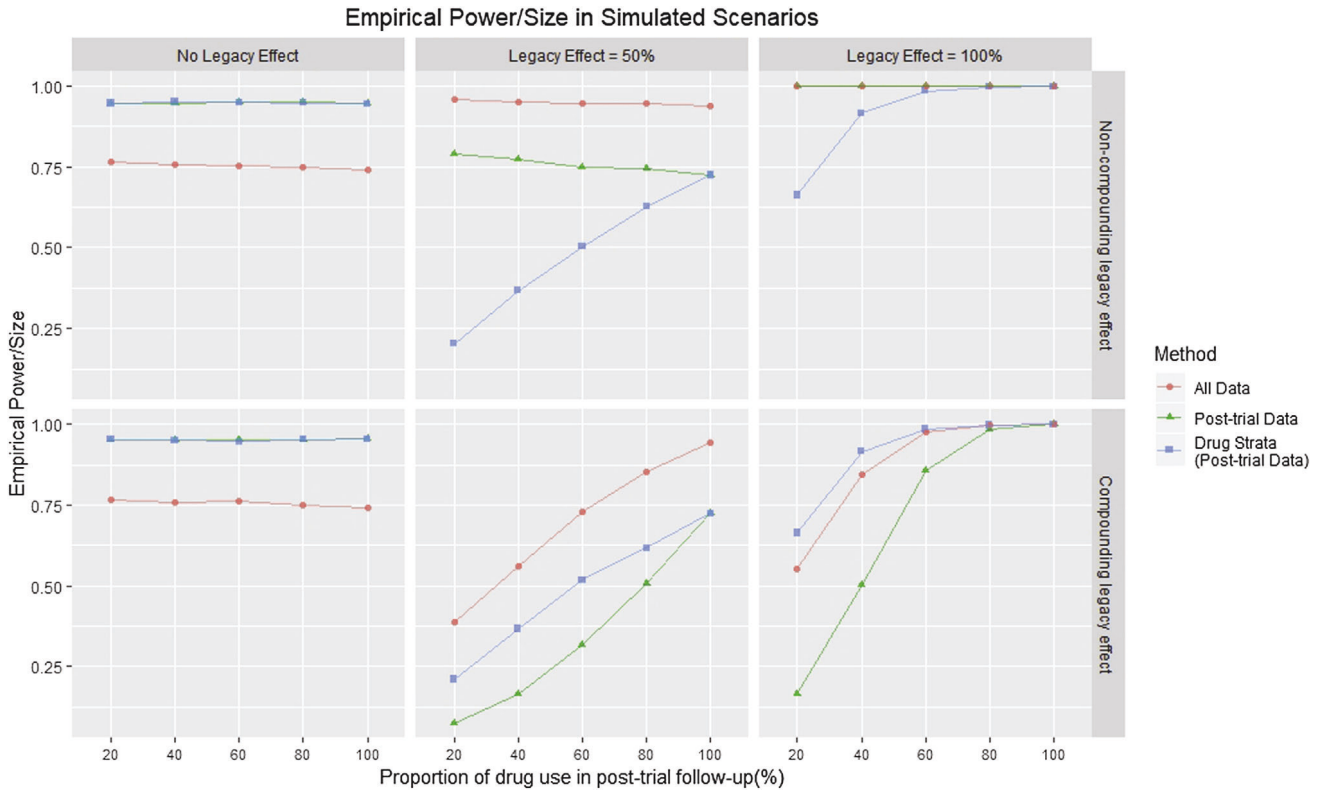

Fig. 5. Empirical power/size of different methods in simulated scenarios *. *The lines for ''post-trial data'' and ''post-trial data–drug strata'' are basically overlapped in the ''no legacy effect'' scenario and ''Legacy = 100%'' of the ''noncompounding legacy effect'' scenario.

between trial arms. These are likely to occur in post-trial follow-up studies in real life, especially when the size of treatment effect is large [24]. We did not allow for competing events, which might become an increasingly important issue in the long duration of the post-trial follow-up, with the potential to bias the estimates of legacy effects [25]. In addition, our simulations were based on plausible scenarios of treatment using statins for primary prevention of cardiovascular disease and these might not be generalizable to other types of interventions, such as surgical and behavioral interventions [26]. We were necessarily constrained in the number of possible scenarios that we were able to investigate in this study.

In conclusion, our study found that the approach most commonly used to estimate legacy effects is usually not appropriate as results may indicate the persistence of the direct effects of treatment rather than a legacy effect. When estimating the extent of legacy effects, approaches to analysis that are restricted to post-trial follow-up data are preferred. The selection of participants to include in the post-trial analysis is less clear cut, and we recommend using both the unstratified and stratified approaches to analysis if data on drug use after trial are available. Importantly, more attention should be paid to the design of post-trial studies for evaluating possible legacy effects to ensure adequate sample sizes and study power to detect possible legacy effects [27].

CRediT authorship contribution statement

Lin Zhu: Conceptualization, Formal analysis, Methodology, Writing - original draft. **Katy J.L. Bell:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Andrew Hayen:** Conceptualization, Methodology, Supervision, Writing - review & editing.

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Chapter 4

Simulations to explore methods for correcting the bias and confounding arising in the analysis of legacy effect

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Research Paper III

Title: Correction for selection bias in the post-trial study aiming to investigate legacy effect: modelling strategies and considerations

Authors: **Lin Zhu**, Andrew Hayen, Katy J.L. Bell

Journal: To be determined

Type of publication: Research paper

Stage of publication: Ready for submission

URL: Not available

4.1 Introduction

Post-trial follow-up after randomized controlled trials (RCTs) allows for the evaluation of longer term effects of an intervention. This type of study design has been used for a range of interventions including pharmaceutical products, surgery, screening for disease and health-promoting behaviors [1]. Unlike the direct effect of the intervention, which is evaluated in the original trial, a "legacy effect" is estimated in a post-trial analysis, and provides evidence on additional effects when there is no longer a treatment contrast across randomized arms.

There has been particular interest in possible legacy effects of drugs to prevent cardiovascular disease (CVD), with a number of large-scale randomized controlled trials reporting the results of post-trial monitoring after the end of the initial trials [2–4]. For instance, the United Kingdom Prospective Diabetes Study (UKPDS), a landmark RCT of glycaemic therapies in patients with newly diagnosed type 2 diabetes, found additional risk reduction in myocardial infarction and all-cause mortality as a result of earlier improved glucose control, despite equalization in anti-hyperglycaemic therapy and HbA1c levels between randomized arms in the post-trial period [5,6]. Evidence of beneficial legacy effects such as this could strengthen the case for the early initiation of preventative treatment.

An analytic challenge of post-trial studies is that there is usually no longer a randomized comparison between the intervention and control group, as analysis is done conditioning on the survivors enrolled in the post-trial study. This type of study design is therefore a cohort study, which like other observational studies is at risk of selection and confounding biases, including imbalances in covariates and medication use across study groups. These limitations have been infrequently mentioned in post-trial reports to date [7]. The objectives of this study are: first, to use directed acyclic graphs (DAGs) to illustrate the concept of legacy effects and the potential

for bias in post-trial follow-up studies after RCTs to prevent cardiovascular disease [8]. Second, to conduct a simulation to quantify how the bias may be impacted by varying the underlying absolute CVD risk in the study population, and the size of the direct treatment effect, and to compare the performances of different modelling strategy. Third, to illustrate our findings using the real-world data from post-trial follow up of Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

4.2 Notation and Definition

Consider an intervention **A** and outcome **Y**, and a measured covariate **L** that represents the severity of disease (summary of risk). We assume participants entered a randomized controlled trial (RCT) at t_0, and the initial trial ended at t_1 (Figure 4.1). The surviving participants were followed until the end of the follow up period at t_2. Therefore, A_0 represents the intervention assigned at the start of the trial, and L_0 represents the baseline risk; due to randomization, they are independent of each other. L_1 represents the risk after the trial (start of post-trial period) and A_1 is the post-trial choice of treatment. Y_1 and Y_2 denote the cardiovascular outcomes at the end of the initial trial and at the end of post-trial follow-up, respectively.

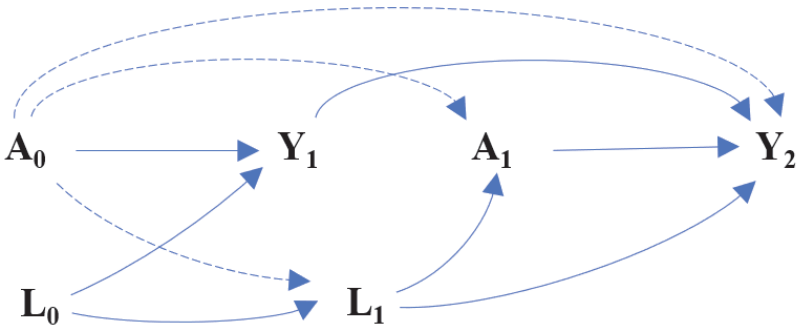

Figure 4.1 An illustration of legacy effect through directed acyclic graph. The dashed lines are the potential pathways legacy effects may occur.

Legacy effects generally refers to the effects of an intervention on the health outcome

observed after the end of the trial (A_0 on Y_2) which are not due to the direct effect observed within the trial period ($A_0 \rightarrow Y_1 \rightarrow Y_2$). As illustrated, there are at least three different causal pathways through which a legacy effect could occur. One possible pathway is where the trial intervention has an impact on the exposure to intervention during post-trial period ($A_0 \rightarrow A_1$). For example, in some health promotion programs (e.g., smoking cessation, low-salt diet), participants randomized to the intervention may be more likely to have healthy behaviors after the end of the trial. A second possible pathway is where the trial intervention has modified the risk ($A_0 \rightarrow L_1$),and a beneficial effect – or a potential risk of treatment side effect – are life-long once it was implemented (e.g., cancer screening, surgery). A third possible pathway is where the intervention has an effect on long term outcomes (direct pathway $A_0 \rightarrow Y_2$). This last causal pathway is the most common type of legacy effect examined in post-trial studies of drugs to prevent cardiovascular disease. Here and through this paper, we refer this third pathway as the legacy effect of interest.

4.3 Different Modeling Strategies

We assume a setting of a post-trial study after a RCT that evaluated the effects of a CVD prevention drug treatment and a comparator. Participants return to the community or hospital-based health care, with no attempt to maintain previously randomized therapies. The medication use is according to their clinical needs, basing on the findings of the trial or existing guidelines (no pathway from $A_0 \rightarrow A_1$). Depending on whether the absolute CVD risk at the end of the original trial is influenced by the trial treatment or not (if the pathway $A_0 \rightarrow L_1$ exists), we consider two scenarios. A potential selection bias results from conditioning on the surviving participants when the trial treatment has a direct effect on the trial outcome (Y_1, , a collider which opens up back door paths through L_0 and L_1) [9]. Here we build upon this common structure for selection bias and demonstrate how it could affect

the post-trial analysis under different modelling strategies.

Figure 4.2 shows different modelling strategies. In Diagram a), no adjustment is made to correct the selection bias. The presence and degree of the selection bias depends on if the treatment has a direct effect on the trial outcome and the size of the effect. In Diagram b), the changes of time dependent covariates are similar in the two groups ($L_0 \rightarrow L_1$) and independent of trial treatment, then the selection bias induced by conditioning on the trial outcome might be controlled by adjusting L_0. However, if A_0 also predicts L_1, then the estimate remains biased due to the pathway $A_0 \rightarrow L_1 \rightarrow Y_2$; that is the adjustment for L_0 will not account for the treatment effect on the outcome that is mediated through the intermediate variable L_1. In Diagram c), the potential selection bias has been adequately accounted for by adjusting on the post-trial covariates L_1. An expansion of the DAGs to include unmeasured confounders, and implications for the modelling strategies, is included in the appendix.

In addition to these conventional modelling strategies, the inverse probability weighting approach has been used to handle selection bias due to censoring in observational studies. It creates a "pseudo-population" in which nobody is censored by assigning IP weights - the censored individuals are replaced by copies of the uncensored individuals with similar characteristics, thus eliminating the bias.

4.4 Simulation to Compare Different Modeling Strategies

We conducted a simulation to compare different model strategies and explore influencing factors of the selection bias. The setting of simulation combined a randomized controlled trial and a post-trial follow-up study, to broadly reflect data that may be observed in a clinical trial for cardiovascular disease prevention. We generated independent data sets with, and without, a legacy effect of the CVD prevention

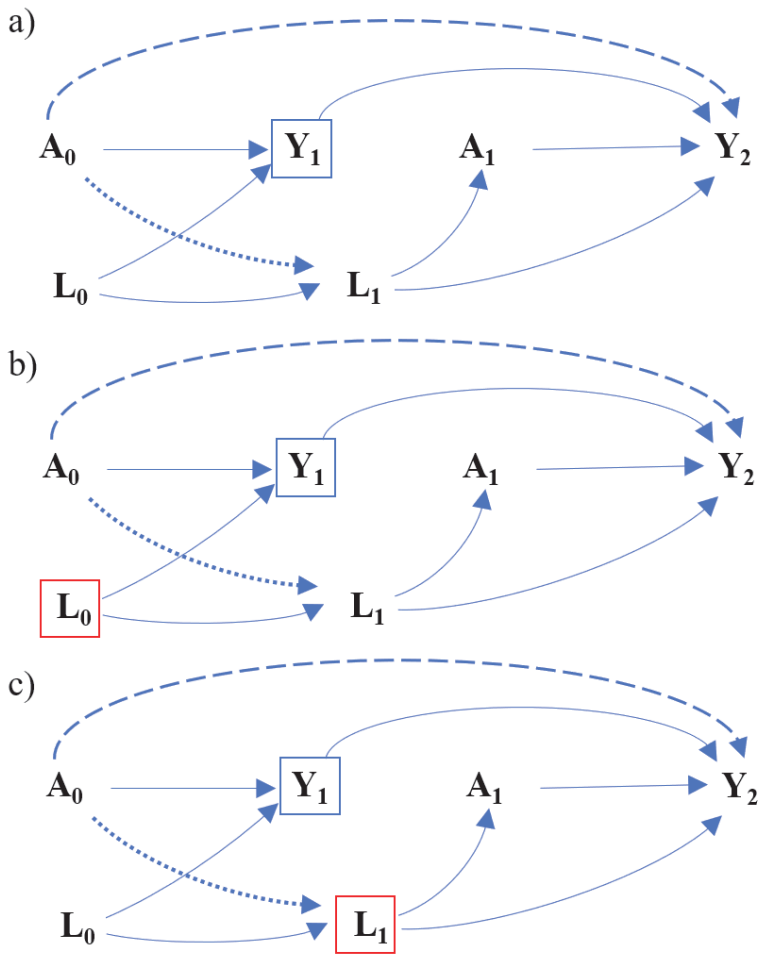

Figure 4.2 Causal diagrams for different modeling strategy. The dashed lines are the legacy effects on interest. The dotted lines show the scenarios that the risk of disease post-trial is influenced by the trial treatment.

drug. We then evaluated the four different modelling strategies outlined above, by applying each of them to the simulated data. The starting point for simulation was to generate the cohort of patients with an underlying distribution of survival times. These survival times were generated from an exponential distribution. The scale parameter was chosen so that approximately 90%, 80% and 70% of participants who receive no treatment will survive after the 5-year RCT. The sample size for each simulation was set at 8,000 people.

For greater generalizability, the distribution of baseline risk L_0 for participant was simulated with a log-normal distribution. The mean and standard deviation on the log scale were set as 0 and 0.5 respectively. We assume the duration of both initial trial and post-trial follow-up were 5 years. Simulation settings were divided into two main scenarios, based on if the pathway $A_0 \rightarrow L_1$ exists or not. In the first scenario, we assumed the pathway $A_0 \rightarrow L_1$ does not exist and the post-trial risk L_1 was only determined by L_0. L_1 was calculated by $1.25L_0$ +0.01, which was derived from the comparison of the individual risk at baseline and post-trial of ACCORD trial. In the second scenario, we assumed the pathway $A_0 \rightarrow L_1$ exists, and the patients who received treatment during the trial would have 10% reduction of the post-trial risk. Letting U(0,1) denotes a standard uniform distribution, then the survival times in scenario A and B can be generated by:

$$T = \begin{cases} \dfrac{-\log(1-U)}{\lambda L_0 \exp(\beta_{treat} A_0)}; & -\log(1-U) < \lambda L_0 \exp(\beta_{treat} A_0) t_1 \\ t_1 + \dfrac{-\log(1-U) - \lambda L_0 \exp(\beta_{treat} A_0) t_1}{\lambda L_1 \exp(\beta_{treat} A_1 + \beta_{legacy} A_0)}; & -\log(1-U) \geq \lambda L_0 \exp(\beta_{treat} A_0) t_1 \end{cases}$$

We varied the sizes of direct treatment effect and legacy effects across simulations. The treatment effects (hazard ratios) were defined as 0.8, 0.7 and 0.6, representing a low, moderate, and high effect, respectively. The size of the legacy effect was defined as relative to the initial (direct) treatment effect and included 0 (no legacy effect), 50%, and 100% of the direct treatment effect. This resulted in a total of 27 sub-scenarios, and 1,000 simulations were run for each sub-scenario. Table 4.1 provides a summary of all variables considered in the simulations. For simplicity, we assumed there are no unmeasured confounding and measurement error, and nonadherence within the trial and loss to follow-up were not considered in the simulation.

Four approaches were compared in this simulation: i) modeling without any adjustment; ii) modelling that adjusted for the baseline covariate L_0; iii) modelling that using inverse probability weighting (IPW). The weights were calculated by the

Table 4.1 Summary of variables used in the simulation

Variable	Value
Exponential parameter	$\lambda = 0.02, 0.04, 0.07$
Log-normal parameter	mean = 0, SD = 0.5
Sample size	8000
Length of RCT and PTFU	5 years, 5 years
Direct Treatment effect	log (0.8), log (0.7), log (0.6)
Size of legacy effect	0, 1/2 and 1 of direct treatment effect

inverse of probability of survival by the end of the trial, and the survival probability was estimated by the baseline covariate L_0 and treatment within the trial A_0. These weights were then applied to the observed population to account for the selection bias by creating a new pseudo-population. Depending on whether the post-trial covariate was available or not, the analysis on the pseudo-population was conducted in adjusted and unadjusted manner. iv) modelling that adjusted for post-trial covariate when L_1 is available. Participants were analyzed in the groups to which they were randomly allocated, and Cox proportional hazard models were fitted by these four approaches.

The estimated legacy effect (mean of hazard ratios) using the different approaches are presented in Figure 4.3 and Figure 4.4. In the scenario that the pathway $A_0 \rightarrow L_1$ does not exist, the estimates without making any adjustment were most biased and the degree of the bias increased with the increasing direct drug effect within the trial, and underlying absolute CVD risk of the study population. The estimates with adjustment for baseline risk were similar to those with adjustment for post-trial risk and IPW (post-trial data available) in most simulation settings, and were the least biased of the modelling strategies. The IPW using only the baseline data also

reduced the selection bias compared to no adjustment, and performed especially well in the scenarios with lower underlying risk of the study population.

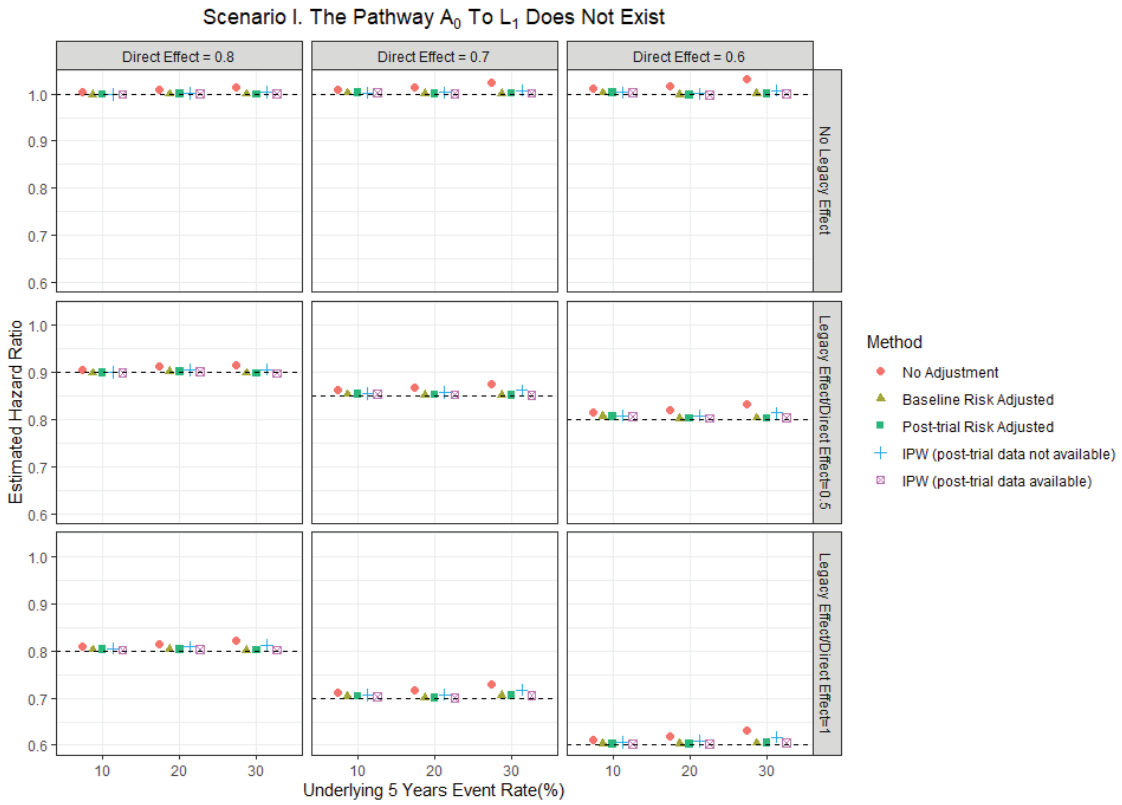

Figure 4.3 Estimated legacy effects (hazard ratios) using the different modelling strategies when the pathway $A_0 \rightarrow L_1$ does not exist. Dashed lines are the true legacy effects in each scenario.

In the scenario that the pathway $A_0 \rightarrow L_1$ exists, both the adjusted method and IPW using the post-trial risk had good performance on the estimation for legacy effects. In contrast, the other methods (no adjustment, baseline risk adjusted, IPW where post-trial data not available) tended to over-estimate the size of the legacy effect.

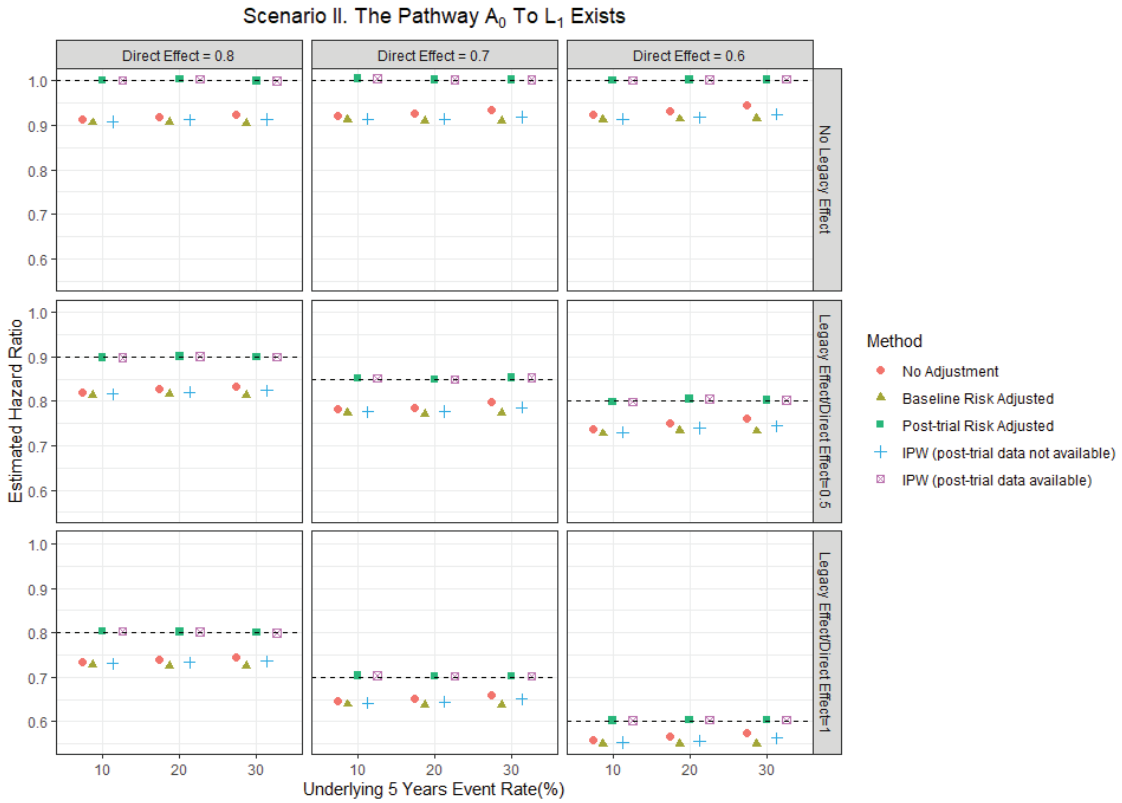

Figure 4.4 Estimated legacy effects (hazard ratios) using the different modelling strategies when the pathway $A_0 \rightarrow L_1$ exists. Dashed lines are the true legacy effects in each scenario.

4.5 Motivating Example : ACCORD and Its Follow-up Study

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a two-by-two factorial randomized controlled trial, which evaluated the effects of intensive glucose control, intensive blood pressure control, and combined fibrate-statin treatment, on the prevention of cardiovascular disease in people with T2DM. It enrolled 10,251 people (mean age 62 years), who had a history of type 2 diabetes for a median duration of 10 years, with mean glycated hemoglobin (HbA1c) level of 8.3%. Participants had either a history of previous cardiovascular disease or had elevated risk factors levels. After a median follow-up of 3.7 years, the trial was stopped early

because intensive glycemic control was associated with increased all-cause mortality [10]. The blood pressure and lipid therapy trials were completed as planned. In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mmHg, as compared with less than 140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events [11]. The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction or nonfatal stroke, as compared with simvastatin alone [12]. However, a possible benefit was found for patients with pre-specified dyslipidemia (both a high baseline triglyceride level and a low baseline level of high-density lipoprotein cholesterol).

The direct treatment effects on total mortality of these three studies and the percentage of enrollment into the post-trial period are shown in Table 4.2. The blood pressure and lipid post-trial studies enrolled similar proportions of participants across the two original groups, while a higher percentage of patients from active group were followed in the dyslipidemia subgroup study than the placebo group.The comparisons of other variables were provided in the appendix.

Table 4.2 Direct treatment effects and percentages of enrollment into the PTFU

Study	Direct effect	Enrollment into the PTFU (%)		
		Overall	Active	Placebo
BP Trial	1.07 (0.85, 1.35)	93.7	93.6	93.9
Lipid Trial	0.91 (0.75, 1.10)	92.3	92.7	92.0
Dyslipidemia Subgroup	0.68 (0.44, 1.04)	90.7	92.3	89.0

We compare the different modeling strategies by applying them to these three studies. Table 4.3 shows the estimated legacy effects of treatments on total mortality in ACCORD. The covariate adjusted included age, gender, race, education, CVD his-

tory, clinical center, smoking status duration of diabetes, HbA1c, systolic blood pressure, total cholesterol and HDL-C. The probability of survival in the IPW method was estimated using the covariate listed and trial treatment assignment.

Table 4.3 The estimates of legacy effects by different modelling strategies

Study	Modeling strategies of post-trial analysis				
	Unadjusted	Baseline Adjustment	Post-trial Adjustment	IPW	
				PT covariate not available	PT covariate available
BP Trial	1.03 (0.86, 1.24)	0.99 (0.82,1.20)	0.97 (0.62, 1.50)	1.00 (0.83,1.22)	0.99(0.62, 1.58)
Lipid Trial	0.95 (0.81, 1.11)	0.94 (0.80, 1.10)	0.87 (0.64, 1.17)	0.96 (0.82, 1.13)	0.92(0.72,1.18)
Dyslipidemia Subgroup	0.64 (0.45, 0.91)	0.61 (0.42,0.89)	0.54 (0.30, 0.99)	0.57 (0.35, 0.94)	0.56 (0.29, 1.12)

In the BP and Lipid trial, where the direct effects were found to be neutral, the unadjusted estimates for legacy effects were similar to those of other methods. In the dyslipidemia subgroup, where the direct effects were found to be possibly beneficial, all the models aiming to correct the selection bias show potential larger legacy effects compared with the unadjusted estimates.

4.6 Discussion

In this paper, we used directed acyclic graphs (DAGs) to illustrate the concept of legacy effects and the causal pathways through which legacy effects may operate. Although the setting of simulation and motivating example was focused on the CVD drug treatment, the methodological considerations may also apply to other interventions (both drug and non-drug).

We have highlighted the potential selection bias due to conditioning on the survivors enrolled in the post-trial period. However, there may be minimal selection bias if the trial treatment does not affect the post-trial risk, or the event of interest

is less common (lower underlying risk in the study population), as the treatment arms could be expected to remain almost balanced for covariates (Scenario I). We previously found that the median proportion of trial participants who were enrolled in post-trial studies of a CVD preventive intervention was about 90%, and that there was balance of covariates across study groups where this was measured [7]. In addition, the impact of bias also depends on the extent of heterogeneity: the more heterogeneity, the higher the risk of bias. In randomized clinical trials where the inclusion criteria are strict, the study population are less prone to selection bias due to heterogeneity. When post-trial data on covariates are not available or not well-collected, adjusting for the baseline covariates may be used to correct the selection bias. We found that it may have the similar performance to adjusting for post-trial covariates when the trial assignment does not affect the post-trial covariates.

In the second scenario, when we assume a pathway $A_0 \rightarrow L_1$ exists, the methods without using post-trial data gave biased results. Given sufficient post-trial data, adjustment of the post-trial covariates could provide more accurate estimates, which removes the potential influence of the intermediate variable. When post-trial data is not available, it is difficult to identify the causal pathway for the legacy effect - whether it is because the post-trial risks have been modified through the intermediate variable, or there exists unknown causal pathways, or a combination of both. The post-trial data could provide information to infer the mechanism of legacy effect, and investigators should be aware of the limitation of the estimation without post-trial data. We also recommend performing a sensitivity analysis to assess how different assumptions influence the effect estimates.

We found the IPW approach could also be used to correct the selection bias. When the post-trial data were not available, it did not show superior performance compared with the traditional adjustment methods in the first scenario. This may be

because the propensity score weighting should be optimized through case-by-case examination: the choice of weighted estimator, appropriate balance diagnostics and trimming levels of extreme weights [13]. We did not optimize the models in our simulation. The result of IPW might be impacted by the less well-specified models [14,15]. Where post-trial data were available, the IPW showed similar performance with the post-trial adjusted method. IPW and other 'G-methods' for casual inference have been used in observational studies to handle analytic challenges such as time-variant covariates and treatment-confounder feedback [16]. However the most common methods currently used in post-trial studies are same as the conventional statistical models used in the primary trials, and more flexible models have rarely been used [7]. We anticipate that the casual inference methods may have better performance in the analysis of real-world data with more complex issues [17,18].

Our study has some limitations. We did not consider unmeasured confounders, such as genetic or environmental risk factors, which may influence the results of post-trial analysis The robustness of the results with respect to unmeasured confounding should be assessed using sensitivity analyses [19]. In addition, we did not consider the non-collapsibility issues of hazard ratios [20]. In our simulation, the legacy effects were generated as conditional hazard ratios, while the estimates of unadjusted and IPW approaches should be marginal hazard ratios. The magnitude of the difference between marginal and conditional estimates is unknown.

4.7 Conclusion

In conclusion, the choice of modeling strategy of post-trial analysis should consider the availability of data, type of intervention, causal pathway of legacy effect, and size of direct effect. We also recommend performing sensitivity analyses to assess how different assumptions and unmeasured confounders may influence the effect estimates. More flexible models may be used to address complex issues that arise

using real world data in post-trial studies.

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Chapter 5

Analysis of data from ACCORDION to investigate the legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia

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Research Paper IV

Title: Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study

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Journal: Cardiovascular Diabetology

Type of publication: Research paper

Stage of publication: Published online on 05 March 2020

URL: https://cardiab.biomedcentral.com/articles/10.1186/s12933-020-01002-x

Academic peer-reviewed: Yes.

Zhu *et al. Cardiovasc Diabetol* (2020) 19:28
https://doi.org/10.1186/s12933-020-01002-x

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study

Lin Zhu[1*], Andrew Hayen[1] and Katy J. L. Bell[2]

Abstract

Background: The Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid study found no evidence of a beneficial effect of statin-fibrate combined treatment, compared to statins alone, on cardiovascular outcomes and mortality in type 2 diabetes mellitus after 5 years of active treatment. However, a beneficial reduction in major CVD events was shown in a pre-specified sub-group of participants with dyslipidemia. The extended follow-up of this trial provides the opportunity to further investigate possible beneficial effects of fibrates in this group of patients. We aimed to evaluate possible "legacy effects" of fibrate add-on therapy on mortality and major cardiovascular outcomes in patients with dyslipidemia.

Methods: The ACCORD-lipid study was a randomized controlled trial of 5518 participants assigned to receive simvastatin plus fenofibrate vs simvastatin plus placebo. After randomized treatment allocation had finished at the end of the trial, all surviving participants were invited to attend an extended follow-up study (ACCORDION) to continue prospective collection of clinical outcomes. We undertook a secondary analysis of trial and post-trial data in patients who had dyslipidemia. The primary outcome was all-cause and cardiovascular mortality, and secondary outcomes were nonfatal myocardial infarction, stroke, congestive heart failure and major coronary heart disease. We used an intention-to-treat approach to analysis to make comparisons between the original randomized treatment groups.

Results: 853 participants with dyslipidemia had survived at the end of the trial. Most participants continued to use statins, but few used fibrates in either group during the post-trial period. The incidence rates in the fenofibrate group were lower with respect to all-cause mortality, CVD mortality, nonfatal myocardial infarction, congestive heart failure and major coronary heart disease than those in the placebo group over a post-trial follow-up. Allocation to the combined fibrate-statin treatment arm during the trial period had a beneficial legacy effect on all-cause mortality (adjusted HR = 0.65, 95% CI 0.45–0.94; $P = 0.02$).

Conclusions: Fibrate treatment during the initial trial period was associated with a legacy benefit of improved survival over a post-trial follow-up. These findings support re-evaluation of fibrates as an add-on strategy to statins in order to reduce cardiovascular risk in diabetic patients with dyslipidemia.

Trial registration clinicaltrials.gov, Identifier: NCT00000620

Keywords: Fibrate, Dyslipidemia, Type 2 diabetes, Cardiovascular diseases, Legacy effect

Background

Dyslipidemia is a major contributor to the increased risk of cardiovascular disease (CVD) among patients with type 2 diabetes mellitus (T2DM). While other types of lipid abnormalities can be found in people with diabetes,

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the typical diabetic dyslipidemia (also called atherogenic dyslipidemia) is characterized by elevated triglycerides, small dense low-density lipoproteins (LDL) particles, and low levels of high-density lipoproteins (HDL) cholesterol [1]. Recommended first line measures for CVD prevention in people with diabetes who have dyslipidemia include non-drug interventions (dietary regulation, exercise, moderation of alcohol intake and weight loss) and LDL-cholesterol lowering with statin drug therapy [2, 3]. The use of statins as the primary drug treatment option is supported by a large body of evidence. For example, a meta-analysis of 14 randomized trials which included more than 18,000 people with diabetes, found that for every mmol/L reduction in LDL cholesterol there was a 21% proportional reduction in the risk of a major vascular event [4]. This proportional risk reduction is similar to that observed in people without diabetes [5], but because the baseline absolute risk is on average higher in people with diabetes, the absolute benefits are greater. However, the trial data also show substantial "residual risk" in people with T2DM who are on statin treatment [6–8], and often the absolute risk is still higher than that in people without diabetes who are not on statin treatment [9–11]. This indicates that preventative treatment with statins alone may not be enough in people with T2DM and additional therapies may need to be considered. There is also evidence from Mendelian randomization studies that high triglycerides are causally related to CVD, and so drug therapy targeting this lipid abnormality could help to further reduce CVD risk in people with T2DM [12–14].

Fibrates are an example of such a drug therapy, as they both decrease triglyceride levels and increase HDL-C [15]. To investigate if these effects on lipid biomarkers translates into a reduction in CVD, the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid study randomized 5518 people with T2DM to combined statin-fibrate therapy vs statin therapy alone. Although the ACCORD-Lipid study found no benefit between randomized groups overall, a beneficial reduction in major CVD events was found in a pre-specified sub-group analysis of study participants with dyslipidemia (triglyceride greater than 204 mg/dl and high-density lipoprotein less 34 mg/dl) [16, 17]. The authors hypothesized that fibrate therapy, offered as an add-on to statin therapy, may be beneficial for people with diabetes who are found have hypertriglyceridemia and/or reduced HDL-C. This hypothesis is supported by the findings of several systematic reviews of RCTs of fibrate therapy [18–21].

At the end of the ACCORD-Lipid trial, participants were unblinded from their randomized groups, and passively followed up for an additional 5 years through follow-up clinics and routine data collection methods. The post-trial follow-up data provide a unique opportunity to evaluate the effect of add-on fibrate therapy in the longer-term, and the possibility of the emergence of "legacy effects". Legacy effects describe intervention effects observed in the post-trial period which are not due to the direct effects observed during the trial period [22]. The finding of a legacy effect would have important clinical implications, including the potential benefits of early initiation of fibrate treatment in the setting of diabetic dyslipidemia. Although potential legacy effects for statin treatment have been investigated in a number of post-trial follow up studies [23], those for combined statin-fibrate treatment remain unexplored [24, 25]. Post-trial data after a statin-fibrate RCT provide the opportunity to investigate potential legacy effects in people with T2DM and dyslipidemia. Therefore, we conducted a secondary analysis of data from the ACCORD-Lipid trial and the ACCORDION post-trial follow-up study, in order to determine whether or not there is evidence for legacy effects for fibrate add-on strategy to statins in diabetic patients with dyslipidemia.

Methods

Study participants and setting

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial was a randomized, double 2×2 factorial design study, which evaluated the effects of intensive glycemic control, intensive blood pressure control, and combined fibrate statin treatment, on the prevention of cardiovascular disease in people with T2DM [26]. It enrolled 10,251 people (mean age 62 years), who had a history of T2DM for a median duration of 10 years, with mean glycated hemoglobin (HbA1c) level of 8.3%. Participants had either a history of previous cardiovascular disease or had elevated risk factors levels. The lipid substudy was conducted in 5518 of the trial participants. In addition to fulfilling the overarching ACCORD entry criteria, the LIPID participants needed to meet all of the following additional criteria: (1) 60 mg/dl < LDL-C < 180 mg/dl (1.55 to 4.65 mmol/l) if not on a lipid lowering agent during screening, or, if on a lipid-lowering agent, the LDL-C needed to be between prespecified drug/dose-specific cut points, and (2) HDL-C less than 55 mg/dl (1.42 mmol/l) for women or African-Americans, or HDL-C less than 50 mg/dl (1.29 mmol/l) for all other gender and ethnic groups, and (3) triglycerides < 750 mg/dl (8.47 mmol/l) on no therapy or < 400 mg/dl (4.52 mmol/l) on treatment with lipid lowering drugs. Participants were randomly assigned to either simvastatin plus fenofibrate or simvastatin plus placebo. The starting dose of open-labeled simvastatin were determined by presence of cardiovascular disease and the dose of masked fenofibrate/placebo were determined by calculated glomerular

filtration rate at randomization. Further changes to the dose of both drugs were made during the trial in accordance to the trial guidelines [16]. At the end of the trial, all surviving ACCORD participants who could be contacted were invited to enter an observational follow-up study (ACCORDION) [27, 28]. No active trial therapy was provided in this period, and medical care was provided by the participant's local primary care provider. Data on health outcomes (e.g. hospital records, death certificates, etc.) and medication usage were collected by phone and clinic visits. Physical examinations were conducted at the first and last clinic visits, include the collection of urine and blood samples for analysis [28].

In the ACCORD-Lipid trial, dyslipidemia was prespecified as the combination of the highest tertile of triglyceride (204 mg/dl) and lowest third of HDL-C (34 mg/dl) at baseline [16]. We used the same definition for dyslipidemia in the current analysis. Our primary outcomes were all-cause mortality and cardiovascular mortality, and our secondary outcomes were nonfatal myocardial infarction, stroke, congestive heart failure and a major coronary heart disease event [16, 28]. Although there was event adjudication during the ACCORD trial, this was done in only a randomly selected 10% of events during the post-trial follow-up period (for the purpose of quality control). For consistency across all follow up data, we used outcomes reported by site investigators during both trial and post-trial period (unadjudicated events).

Statistical methods

Participants' characteristics at baseline of trial and first post-trial visit were summarized for the two randomized groups using means, standard deviations, and percentages. The measured lipid levels at each study visit, including total cholesterol, triglycerides, HDL-C, LDL-C and VLDL-C, were compared between randomized groups. VLDL-C was obtained by subtracting HDL-C and LDL-C from total cholesterol. Primary and secondary outcomes were analyzed according to the intention-to-treat principle. Hazard ratios (HRs) and 95% confidential intervals were estimated using Cox proportional hazards models. Kaplan–Meier estimates were used to obtain the proportion of patients who had an event during follow-up. The direct effects of treatment were estimated by fitting models for the trial period (short term effects), and the entire study period (from baseline of trial through to end of post-trial, long term effects). The legacy effects of treatment were estimated by fitting models for the post-trial period alone. This analysis was based on survivors who consented to additional follow-up, and their follow-up times were calculated by the difference between full follow-up time and censoring time for the trial. These analyses were adjusted for age, sex, ethnicity, network, education status, CVD history, blood glucose trial treatment assignment and years of diabetes. To examine the robustness of these findings, sensitivity analyses were undertaken to (i) account for effects of medications taken in the post-trial follow-up period, and (ii) to account for possible imbalance in confounders between the two groups at the start of post-trial follow-up (using inverse probability weighting). All analyses were performed with R (version 3.5.1).

Results

Characteristics of the participants at baseline and 1st post-trial visit

Of a total of 5518 patients enrolled in the ACCORD Lipid trial, 940 (17.0%) were identified as having dyslipidemia. 484 of them were assigned to fenofibrate and simvastatin therapy, and 456 participants received simvastatin and placebo. Of these participants, 853 had survived at the end of the trial, and 765 (90.0%) consented to enter the post-trial follow-up study. The median follow-up time in the post-trial period was 4.9 years. Table 1 shows characteristics of the participants at the trial baseline and at the first post-trial visit. The mean age at baseline was 61.8 years, and the fenofibrate group was slightly younger than the placebo group. Most of the patients were male and about forty percent of patients had a history of CVD disease. The HbA1c, blood pressure and lipid levels were well matched across treatment groups both at baseline and 1st post-trial visit.

Trial adherence and use of lipid-modifying medication after trial

Participants' adherence during the trial and the use of statin/fibrate post-trial is shown in Table 2. The adherence for both simvastatin and fenofibrate/placebo during the trial period was high. In the post-trial period, most participants continued to use statin therapy, while few used fibrates in either group (likely due to the finding of no benefit overall in the ACCORD-Lipid study).

Efficacy of fenofibrate in lipid-modifying

Figure 1 compares the plasma lipids of the two groups at each study visit during the within trial and post-trial periods. During the trial, allocation to fenofibrate resulted in improvements in almost all lipids compared with placebo, but the largest differences were seen for plasma triglyceride concentrations and VLDL-C levels. Further, although the differences in HDL-C and LDL-C levels between randomized groups decreased over time, they were maintained for levels of triglycerides ($P=0.01$) and VLDL-C ($P=0.006$) through to the end of the trial. At the first post-trial visit there were minimal differences

Table 1 Characteristics of the participants at baseline and 1st post-trial visit

Characteristics	Baseline		P	1st post-trial visit		P
	Fenofibrate (n = 484)	Placebo (n = 456)		Fenofibrate (n = 395)	Placebo (n = 370)	
Age	61.4 ± 6.2	62.2 ± 6.7	0.04	67.2 ± 6.3	67.6 ± 6.6	0.32
Sex			0.96			0.59
Male	388 (80.2%)	364 (79.8%)		319 (80.8%)	292 (78.9%)	
Female	96 (19.8%)	92 (20.2%)		76 (19.2%)	78 (21.1%)	
Years of diabetes	9.2 ± 6.6	9. 6 ± 6.6	0.37	14.6 ± 6.5	15.2 ± 6.6	0.22
Ethnicity			0.17			0.51
White	365 (75.4%)	362 (79.4%)		305 (77.2%)	294 (79.5%)	
Non-White	119 (24.6%)	94 (20.6%)		90 (22. 8%)	76 (20.5%)	
CVD history			0.93			0.98
Yes	195 (40.3%)	186 (40.8%)		153 (38.7%)	142 (38.4%)	
No	289 (59.7%)	270 (59.2%)		242 (61.3%)	228 (61.6%)	
BG trial assignment			0.36			0.36
Intensive group	251 (51.8%)	222 (48.7%)		203 (51.4%)	177 (47.8%)	
Standard group	233 (48.2%)	234 (51.3%)		192 (48.6%)	193 (52.2%)	
HbA1c (%)	8.4 ± 1.1	8.4 ± 1.0	0.94	7.9 ± 1.9	7.6 ± 1.3	0.07
SBP (mm Hg)	134.1 ± 17.6	133.9 ± 18.6	0.87	131.0 ± 17.1	131.8 ± 17.3	0.66
CHOL (mg/dl)	187.0 ± 38.5	189.0 ± 42.1	0.45	154.6 ± 42.5	152.8 ± 32.8	0.64
TG (mg/dl)	327.2 ± 125.3	325.0 ± 154.2	0.81	216.6 ± 124.1	222.7 ± 115.2	0.61
VLDL-C (mg/dl)	61.2 ± 18.6	61.2 ± 25.4	0.97	41.4 ± 20.8	42.63 ± 20.1	0.55
LDL-C (mg/dl)	96.3 ± 32.0	98.4 ± 32.9	0.34	79.2 ± 32.7	76.6 ± 26.1	0.38
HDL-C (mg/dl)	29.5 ± 3.8	29.5 ± 3.7	0.76	33.9 ± 7.3	33.6 ± 7.2	0.60

Plus–minus values are mean ± SD

HbA1c glycated hemoglobin A1c, *SBP* systolic blood pressure, *CHOL* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *VLDL-C* very low-density lipoprotein cholesterol

between randomized groups for any of the lipids, and this remained the case through to the last clinic visit.

Clinical outcomes

The incidence rate of the primary and secondary outcomes and the hazard ratios of allocation to the fenofibrate plus simvastatin versus simvastatin alone during the ACCORD-lipid trial, ACCORDION and the full follow-up period are shown in Table 3. We found that the incidence rates in the fenofibrate group were lower with respect to all-cause mortality, CVD mortality, nonfatal myocardial infarction, congestive heart failure and major coronary heart disease than those in the placebo group over the post-trial follow-up. Allocation to the combined fibrate-statin treatment arm during the trial period resulted in a statistically significant beneficial legacy effect on all-cause mortality observed in the post-trial period (adjusted HR = 0.65, 95% CI 0.45–0.94; P = 0.02, other effects not statistically significant). Long-term beneficial effects were also found when trial and follow up periods were combined (9.7 years follow-up from time of randomization) for all-cause mortality, CVD mortality and major coronary heart disease events (effects on CVD

Table 2 Trial adherence and use of lipid-modifying medication post-trial

Time	Treatment	Proportion on-treatment (%)	
		Fenofibrate group	Placebo group
Year 1	Fenofibrate/placebo	91.4	91.2
	Simvastatin	94.5	95.5
Year 2	Fenofibrate/placebo	88.8	91.5
	Simvastatin	93.6	96.1
Year 3	Fenofibrate/placebo	87.2	90.2
	Simvastatin	91.3	92.9
Year 4	Fenofibrate/placebo	85.3	86.3
	Simvastatin	92.9	92.5
Trial exit visit	Fenofibrate/placebo	82.7	86.3
	Simvastatin	93.1	91.0
1st post-trial visit	Fibrate	7.2	7.4
	Stains	77.1	78.4
Last post-trial visit	Fibrate	5.4	4.8
	Stains	72.0	74.0

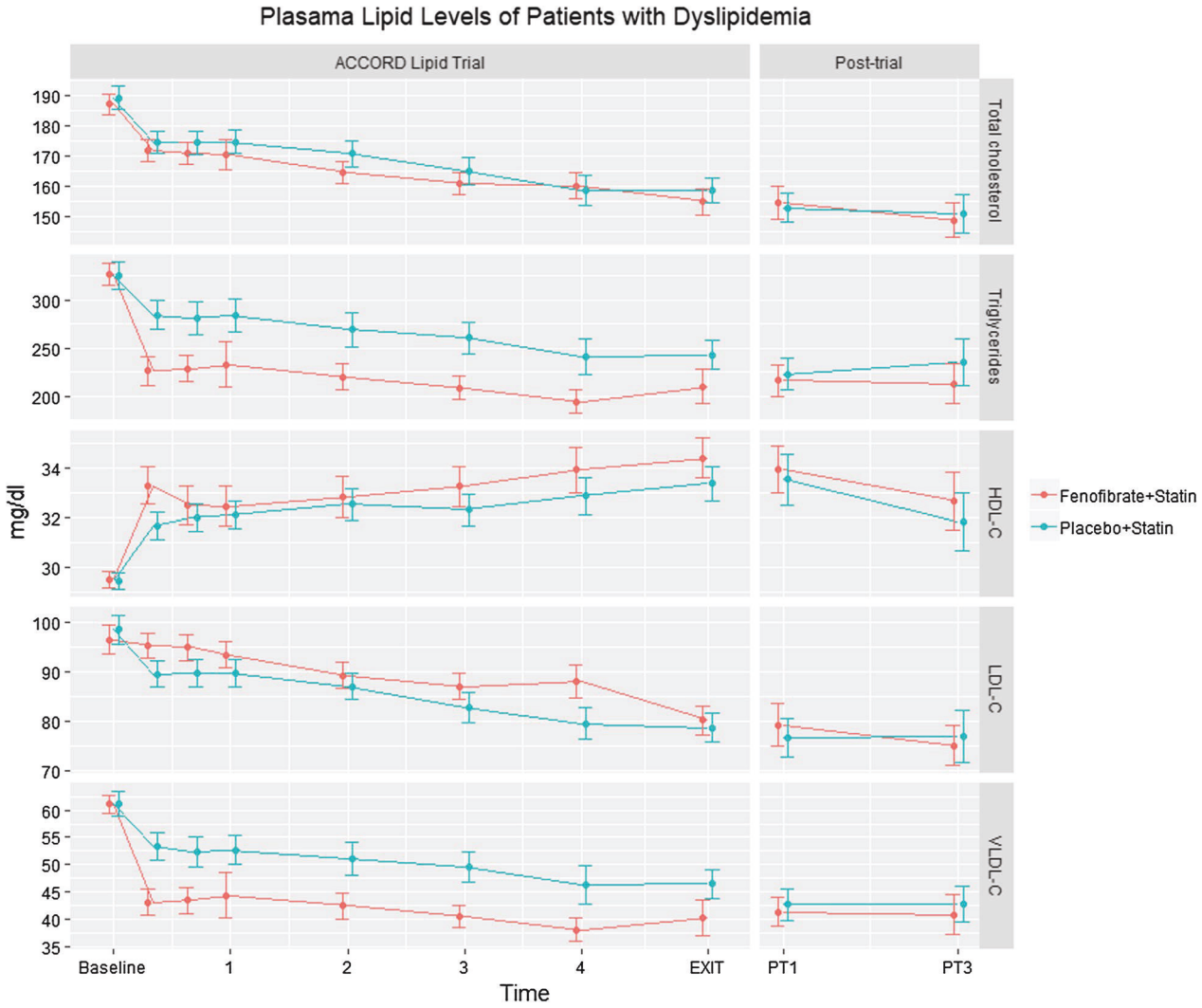

Fig. 1 Plasma lipid levels of patients with dyslipidemia at each study visit. The line charts show the means of lipid levels and corresponding 95% CI at 1/2/3/4 year, exit visit, 1st post-trial visit and last post-trial visit. *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *VLDL-C* very low-density lipoprotein cholesterol, *PT1* first post-trial clinic visit, *PT3* last post-trial clinic visit

mortality and all-cause mortality were statistically significant). Kaplan–Meier cumulative event curves for primary outcome and selected secondary outcomes are consistent with findings from the Cox models and are presented in Fig. 2. Sensitivity analyses adjusting for medication use of post-trial follow-up and for other potential confounders, using inverse probability weighting, resulted in similar findings (Additional file 1: Table S1).

Discussion

We found that patients with dyslipidemia who were randomized to statin-fibrate treatment during the trial had higher survival in the 5 years after the trial than those randomized to statin-placebo. This effect was observed despite similar achieved lipid profile during the extended observational follow-up, which suggests a legacy effect of fibrate add-on therapy on all-cause mortality. Although estimated legacy effects on all other outcomes were not statistically significant, the effect estimates suggest that improved survival is likely to be largely explained through effects on CVD. No information was available on non-CVD causes of death, which meant we were not able to explore other possible explanations for the all-cause mortality reduction. The overall long-term benefits for CVD mortality appeared to be driven by both within-trial treatment effects and legacy effects emerging post-trial. Other studies suggest that fibrates may also have beneficial effects on microvascular outcomes, including

Table 3 Clinical outcomes by randomized treatment during ACCORD-lipid trial, ACCORDION and full follow-up period

Event	During ACCORD-lipid (short-term effect)			*P*	Post-trial only (legacy effect)			*P*	Full follow-up (long-term effect)			*P*
	Rate of events (100 person-years)		Hazard Ratio (95% CI)		Rate of events (100 person-years)		Hazard ratio (95% CI)		Rate of events (100 person-years)		Hazard ratio (95% CI)	
	Fibrate	Placebo			Fibrate	Placebo			Fibrate	Placebo		
All-cause mortality	1.54	2.26	0.68 (0.44, 1.04)	0.07	3.05	4.43	0.65 (0.45, 0.94)	0.02	2.23	3.24	0.68 (0.52, 0.88)	< 0.01
CVD mortality	0.67	1.28	0.53 (0.29, 0.98)	0.04	1.12	1.53	0.77 (0.43, 1.39)	0.38	0.88	1.39	0.63 (0.42, 0.95)	0.03
Nonfatal MI	1.76	2.45	0.72 (0.47, 1.09)	0.12	0.85	1.07	0.74 (0.33, 1.66)	0.47	1.40	1.91	0.74 (0.51, 1.06)	0.10
Stroke	0.56	0.74	0.75 (0.36, 1.56)	0.44	0.56	0.55	0.87 (0.33, 2.29)	0.78	0.58	0.67	0.88 (0.5, 1.56)	0.66
CHF	1.39	1.51	0.90 (0.55, 1.47)	0.68	0.65	0.93	0.69 (0.30, 1.57)	0.38	1.07	1.27	0.82 (0.54, 1.24)	0.35
Major CHD	3.01	4.60	0.65 (0.48, 0.90)	0.01	2.17	3.27	0.64 (0.40, 1.03)	0.07	2.67	4.09	0.66 (0.51, 0.86)	< 0.01

MI myocardial infarction, *CHF* congestive heart failure, *CHD* coronary heart disease

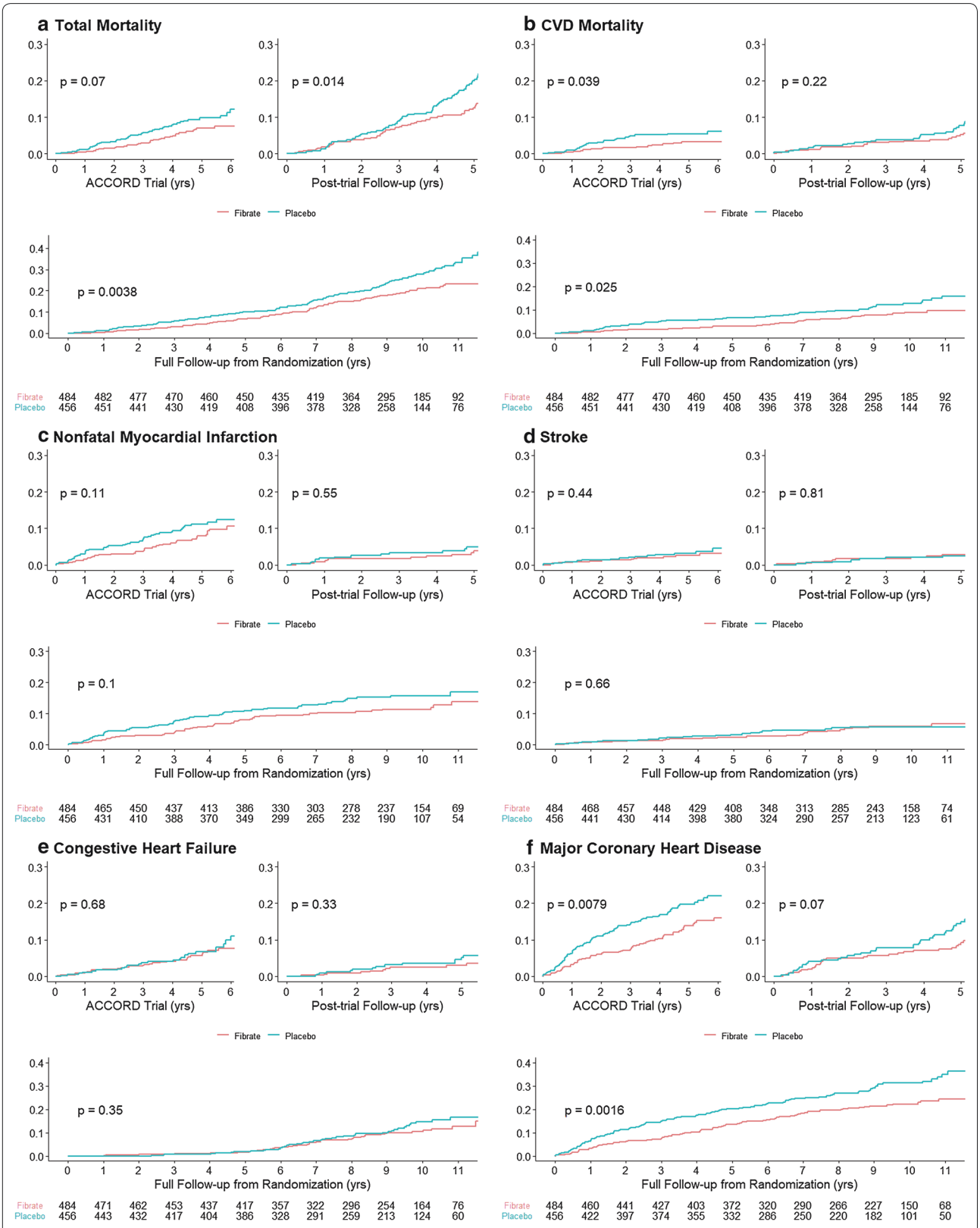

Fig. 2 Kaplan–Meier cumulative event curves for primary and secondary outcomes. The Kaplan–Meier curves display the time to event for the all-cause mortality (**a**) and cardiovascular mortality (**b**), nonfatal myocardial infarction (**c**), stroke (**d**), congestive heart failure (**e**) and a major coronary heart disease event (**f**) during trial period, post-trial and the entire study period. The numbers of individuals at risk are shown for each time point

on renal and liver function [29], but we didn't have data to explore this.

During the trial period, fibrate add-on therapy reduced triglycerides and VLDL-C beyond that achieved with statins only, but HDL-C was increased by only a limited amount. These findings have been observed in other clinical trials of fibrate—for example in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, allocation to fenofibrate resulted in a 20% reduction of baseline TG, but HDL-C remained almost unchanged at study close [30–32]. The improvement of the triglyceride-rich environment may explain the reduced risk of CVD observed during the trial period in these patients [15, 33]. As most of participants in active arm discontinued the use of fibrate in post-trial, between group differences in triglycerides and VLDL-C soon disappeared. This suggests continuous treatment is necessary to maintenance a lower TRIG/VLDL-C.

Our findings on potential beneficial effects on CVD mortality reduction are supported by a recent report of a large propensity matched cohort study that found a (non-statistically significant) reduction in CVD mortality associated with fibrate use [23]. Results from the ongoing Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study will also provide evidence regarding short term effectiveness; further follow up studies are needed for longer term legacy effects [34, 35].

Our study has several limitations. First, our analysis examined a relatively small subset of the full trial and the power to detect smaller effects is limited [36]. The findings for this prespecified subgroup with dyslipidemia must be interpreted with caution, and further larger studies in people with dyslipidemia are needed. Second, as in ACCORD, the diabetic dyslipidemia was defined in a data-driven manner, however the thresholds used are similar to other definitions of dyslipidemia [3, 37]. Third, we used the investigators reported (unadjudicated) cause of death data for both trial and post-trial periods. A previous report from ACCORD study group has shown the CVD mortality was under-reported by the investigators compared to the adjudicated Committee [28], suggesting potential misclassification of cause of death using these data. Fourth, although we adjusted analyses for potential imbalance between randomized groups in confounders during the post-trial period, measurement error in these, and the presence of other unmeasured confounders could bias our estimates [22].

Conclusion

In conclusion, this secondary analysis found evidence of legacy effects of fenofibrate-statin combined therapy on all-cause mortality in diabetic patients with dyslipidemia. This finding suggests fibrate treatment may be an effective means of reducing residual cardiovascular risk in these patients.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12933-020-01002-x.

Additional file 1. Results of the sensitivity analysis.

Abbreviations

CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ACCORDION: Action to Control Cardiovascular Risk in Diabetes Follow-On; TRIG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; MI: Myocardial infarction; CHF: Congestive heart failure; CHD: Major coronary heart disease.

Acknowledgements

We thank the National Heart, Lung, and Blood Institute for providing us data of ACCORD main study and the ACCORDION ancillary study.

Authors' contributions

AH and KB conceived the study and design, interpreted the data, supervised the study, and revised for important intellectual content. LZ conceived the study and design, analyzed and interpreted the data, drafted and revised the manuscript. All authors read and approved the final manuscript.

Funding

Lin Zhu receives funding support from an Australian Government Research Training Program. Katy Bell is the recipient of an Australian National Health and Medical Research Council Investigator Grant (#1174523).

Availability of data and materials

The datasets analyzed during the current study are available from the National Heart, Lung, and Blood Institute on reasonable request.

Ethics approval and consent to participate

We received ethical approval from UTS Human Research Ethics Committee (ETH18-2736). Written informed consent for participation in the study was obtained from all the subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 6 December 2019 Accepted: 18 February 2020
Published online: 05 March 2020

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Publisher's Note

Chapter 6

Discussion

6.1 Summary of Key Findings

A summary of the key results of this thesis is given below and separated by the objectives of this thesis.

Objective I: To summarize the methods that have been used for detecting legacy effects in post-trial studies

Studies that use extended follow-up beyond the end of the RCTs have been conducted for a variety of cardiovascular interventions. The methods review in Chapter 2 summarized the basic characteristics of these studies and evaluated the potential for biased estimates of legacy effect from the method that is most used to date. It also demonstrated the deficiencies in the reporting of these studies, that a separate post-trial analysis was infrequently reported to justify the legacy effects.

This review highlighted post-trial analyses are likely to no longer be a randomized comparison of intervention versus control, and the study design is that of a cohort study. For instance, at the end of Diabetes Control and Complications Trial (DCCT), the conventional and intensive treatment randomized groups differed on several established CVD risk factors (e.g., BMI and triglycerides) and in levels of the surrogate outcome of asymptomatic microvascular disease (microalbuminuria and albuminuria) (Gubitosi-Klug et al., 2016). In the Veterans Affairs Diabetes Trial (VADT) extension study, the proportion of participants taking insulin remained

higher in those originally randomized to intensive control than in those randomized to standard control early on in the post-trial period (78.2 % versus 66.1% at the end of trial; 79.5% and 76.8% at the 4 year of post-trial follow-up), with the direction of this difference reversed by the end of follow up at 10 years post-trial (70.2% vs. 74.5%) (Reaven et al., 2019).

I found that post-trial studies are often missing information on important covariates which would allow assessment and adjustment for potential selection bias and confounding. It is usually not feasible to retain the level of close monitoring undertaken during the RCTs in the post-trial period due to the level of funding needed to support this (Fitzpatrick et al., 2018b; Llewellyn-Bennett et al., 2018). Given the large scale of some post-trial studies (40% enrolled more than 5,000 participants), it may be prohibitively expensive to collect the required data of all the patients. Random sampling may be a solution for such studies. For example, in the post-trial study of the Action in Diabetes and Vascular Disease trial (ADVANCE-ON), a random subset of 2,000 from 8,000 participants enrolled, balanced across regions and across the prior randomized treatment arms, were selected to undergo laboratory examinations to determine whether in-trial differences in surrogate outcomes persisted in post-trial (Zoungas et al., 2014).

Even where sufficient data were collected that could have allowed for assessment and adjustment for potential bias in analysis, I found that most post-trial studies failed to do so. Although nearly half studies collected information on post-trial covariates, only about 15% studies assessed the balance of post-trial covariates and made corresponding adjustments in their analysis. The statistical methods used are generally the same conventional methods as that for the analysis of the trial period. More flexible models such as causal inference methods (G-methods), could also be applied to better address complex issues that may arise in the post-trial follow-up

such as time-dependent confounding.

There is a need for improved reporting of treatment effects in post-trial studies. I found that most studies only focused on long-term treatment effects (F. P. Brouwers et al., 2011; Lloyd et al., 2013). Among the articles claiming legacy effect, about one quarter failed to report a separate post-trial result to justify the evidence. As both direct effects and legacy effects could contribute to the long-term effects of the intervention, long-term effects alone do not provide proof of legacy effects. Better reporting of post-trial studies is needed to realize their full potential in informing clinical practice and health policy.

Objective II: To investigate the choice of time period and trial participants to include in the analysis of legacy effect

The simulation in Chapter 3 explains why the 'All Data' approach which contains an RCT and post-trial follow-up is inappropriate for evaluation of legacy effects. This approach often falsely concludes that there is a legacy effect when in truth there is not (i.e., type I error). The results of the simulation confirm my earlier hypothesis in the methods review, that in order to disentangle the direct effects of treatment during the RCT from legacy effects occurring post-trial, we need to restrict our analysis to post-trial period.

The simulation also shows that approaches to analysis that use only post-trial data are unlikely to detect a small size legacy effect, especially where sample sizes are small, which is to be expected (Dumas-Mallet et al., 2017). Similarly, in real study settings, the sample size calculated for the initial trial - in which the in-trial direct effect is likely to be larger than any post-trial legacy effect - might also lead to a low chance of discovering a true legacy effect in post-trial period. Pooling data from several post-trial follow up studies in an individual participant data meta-analysis

may be needed to overcome issues of insufficient power in the primary studies.

If data on post-trial drug use are available, then a stratified analysis of post-trial data may be informative, especially when the mechanisms of the legacy effects are thought to be the compounding. It can be used to test the heterogeneity of the legacy effect across the strata. If there is heterogeneity, then it is preferable to report separate result for each stratum, as they have different clinical implications: analysis limited to people who took the drug post-trial may provide evidence about the benefits of starting treatment at a younger age, while analysis limited to people who did not take the drug post-trial may provide evidence about the safety of stopping drugs at an older age. I found these stratified approaches to analysis of post-trial data to be more robust to variation in the assumptions made about the size of the legacy effect for people who continue or discontinue using the drug in the post-trial period. But as the stratified approaches use relatively less of the available data, estimates tended to have a larger mean square error.

Objective III: To compare different strategies of handling selection bias and potential confounding in the analysis

In Chapter 4, I used directed acyclic graphs to illustrate the concept of legacy effects and the mechanisms by which legacy effects may occur. I have highlighted the potential selection (collider) bias resulted from the analysis conditioning on the uncensored participants. The magnitude of selection bias depends on size of direct effect, heterogeneity of underlying risk, and whether the treatment has an impact on post-trial risk. The simulation shows it is relatively small when the event of interest is rare, as the treatment arms could be expected to remain almost balanced. In such studies, it might be more efficient to conduct an analysis that adjusts for the baseline covariates which have been collected already. Adjusting for baseline covariates may also be sufficient when the trial assignment does not affect the post-trial covariates.

In contrast, when a pathway between trial treatment and post-trial exists, all the modellings without using post-trial data gave biased results. It is difficult to identify the causal pathway for the legacy effect - whether it is because the post-trial risks have been modified through an intermediate variable, or there exists unknown causal pathways, or a combination of both. Given sufficient post-trial data, adjustment of the post-trial covariates may provide more accurate estimates. It could provide useful information to infer the mechanism of legacy effect, and investigators should be aware of the limitation of the estimation without post-trial covariates. On the other hand, we need to make sure not adjust for the intermediate outcome (mediating variable) which is part of the causal pathway for the legacy effect. Therefore, the choice of modeling strategy should consider the availability of data, type of intervention, mechanism of legacy effect and size of direct effect. Sensitivity analyses are recommended to assess how different assumptions and unmeasured confounders may influence the effect estimates.

I found the inverse probability weighting approach could also be used to correct the selection bias. A set of casual inference methods (G-methods) has been used in observational studies to handle the analytic challenges, but they have so far been rarely used in post-trial analysis. We may expect the casual inference methods to have better performance than conventional methods in the analysis of real-world data with more complex issues, such as differential loss-to follow-up, drop-in/out and treatment confounder feedback. More flexible models are recommended to be used to deal with the methodological issues arising during the post-trial follow-up.

Objective IV: To evaluate the legacy effects of fibrate add-on therapy among diabetic patients with dyslipidemia

The analyses in Chapter 5 assessed the legacy effect of statin-fibrate treatment among diabetic patients with dyslipidemia. During the trial period, fibrate add-

on therapy reduced triglycerides and VLDL-C beyond that achieved with statins only, but HDL-C was increased by only a limited amount. These findings have been observed in other clinical trials of fibrate - for example in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, allocation to fenofibrate resulted in a 20% reduction of baseline TG, but HDL-C remained almost unchanged at study close (The FIELD Study investigators, 2005). The improvement of the triglyceride-rich environment may explain the reduced risk of CVD observed during the trial period in these patients (Keating, 2011; Park et al., 2019). As most of participants in active arm discontinued the use of fibrate in post-trial, between group differences in triglycerides and VLDL-C soon disappeared. This suggests continuous treatment is necessary to maintain a lower TRIG/VLDL-C.

I found patients who were randomized to fibrate group during the trial had higher survival in the post-trial follow-up than those randomized to placebo group. This effect was observed despite lipid profile of the two original groups were similar during the extended observational follow-up, which suggests a legacy effect of fibrate add-on therapy on all-cause mortality. My findings on potential beneficial effects on CVD mortality reduction are supported by a recent report of a large propensity matched cohort study that found a (non-statistically significant) reduction in CVD mortality associated with fibrate use (Kim et al., 2019). However, no legacy effects were shown for most macrovascular outcomes, particularly nonfatal myocardial infarction, stroke and congestive heart failure. One possible explanation is participants in this study had been diagnosed with diabetes for 10 years on average and more than 40% had CVD history. Their underlying atherosclerosis progress and cardiovascular injury might be too advanced to be effectively altered by lipid-modifying.

This was a subgroup analysis that examined a relatively small subset of the full trial and the power to detect smaller effects is limited. In addition, the finding

of a legacy effect in this pre-specified subgroup could be a false positive due to a chance finding from multiple comparisons. It must be interpreted with caution, and further larger studies in people with dyslipidemia are needed. Results from the ongoing Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study will provide evidence to support or refute short term effectiveness; further follow up studies are needed for longer term legacy effects (Pradhan et al., 2018).

6.2 Strengths and Limitations

My thesis provides a structured explanation on the concept of legacy effects, proposes the main methodological issues arising in post-trial analysis and explore potential solutions. I used simulations to show that a separate post-trial analysis is more appropriate to generate evidence on legacy effect and the analysis combining trial and post-trial period will lead to biased results. Different modeling strategies were also compared in different settings in terms of underlying absolute risks, mechanisms of legacy effect, availability of post-trial data and size of direct effect. The results of simulations could provide guidance on the choice of appropriate methods for research that aiming to assess legacy effects. These findings may also help further trialists to improve their study design to maximise their potential value and ensure results are interpreted appropriately.

A potential limitation of thesis is I only focused on the post-trial studies of RCTs evaluating cardiovascular interventions. In previous reviews of long-term follow-up of randomized trial participants, some other common types of interventions included surgery, cancer screening and behavioral change interventions (Fitzpatrick et al., 2018; Llewellyn-Bennett et al., 2018). The assessment of legacy effects for other types of interventions are less explored in this thesis. The choice of analysis method needs to be tailored to the proposed mechanism of legacy effect in each intervention

and setting.

For simplicity, I did not consider some other potential analysis issues in the simulations, which are likely to occur in post-trial follow up studies in real life. For example, drop-in/out within the trial, differential loss to follow-up between groups, different length of treatment due to the run-in period of large scale RCT, and unmeasured confounding were not considered (Manson et al., 2016). I did not allow for competing events in my study, which is a threat to the post-trial studies with a long follow-up period (Austin et al., 2016).

6.3 Recommendations For Further Research

Rigorous post-trial design and statistical methods are required to ensure the robustness and validity of findings. Future post-trial studies aiming to investigate legacy effects should consider if data on some important variables are available for the post-trial period. Insufficient information on potential sources of bias in the post-trial period will substantially limit the studies' reliability and possibilities of different analysis strategies.

It is important to realize the difference between the whole period combined analysis and the separate post-trial analysis. We recommend researchers check the balance of covariates between groups in the post-trial period when the data are available, and the potential for bias should be addressed using the appropriate statistical method. It is also important for authors to justify their choice of method and discuss any limitations. Because different modelling strategies of addressing potential selection bias may lead to differences in the legacy effect estimates, the application of different methods and comparison of these results (a sensitivity analysis) is highly recommended.

Methods used in observational studies to address methodological issues, such as

casual inference approaches (G-methods), could be applied to the post-trial analysis (Hernán et al., 2013). We also need to realize that the design of "RCT + post-trial follow-up" is not the only way to investigate legacy effects. Well-conducted observational studies could also provide useful evidence on this important topic (Laiteerapong et al., 2019). Further research is needed regarding the use of more diversified design and flexible models in the evaluation of legacy effects.

6.4 Conclusion

My thesis provides a structured explanation on the concept of legacy effects and the main analytic challenges arising in post-trial analysis. While I focused predominantly on the interventions of cardiovascular diseases prevention, the methodological considerations are applicable to other types of interventions. Trialists aiming to investigate legacy effects need to ensure appropriate study design and method of analysis are used, allowing potential confounding and selection bias to be addressed. Future post-trial studies should consider the evidence learned from the simulations in this thesis to ensure that all important factors are considered in their evaluations.

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Appendices

A Search Strategy of the Methods Review

Database: Ovid MEDLINE 1946 to Present with Daily Update

Search Date: 31 Dec 2019

Part I: RCT+follow-up

1. (legacy adj effect*).tw.

2. follow up.mp.

3. (post trial or after trial or longterm or long term or extended or extension).tw.

4. (1$ year follow up or 2$ year follow up or 3$ year follow up or 4$ year follow up or 5$ year follow up or 6$ year follow up or 7$ year follow up or 8$ year follow up or 9$ year follow up).tw.

5. (2 and 3) or 4

6. random*.mp. or placebo.tw.

7. 5 and 6

Part II: Interventions on blood pressure

8. exp thiazides/

9. exp sodium potassium chloride symporter inhibitors/

10. ((loop or ceiling) adj diuretic?).tw.

11. (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hy- drochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thi- azide?).tw.

12. (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw.

13. exp angiotensin-converting enzyme inhibitors/

14. ((angiotensin$ or kininase ii or dipeptidyl$) adj3 (convert$ or enzyme or inhibit$ or recept$)).tw.

15. (ace adj3 inhibit$).tw.

16. acei.tw.

17. exp enalapril/

18. (alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or idapril or imidapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril or aliskiren or enalkire or remikiren).tw.

19. exp Angiotensin II Type 1 Receptor Blockers/

20. exp losartan/

21. (KT3-671 or candesartan or eprosartan or irbesartan or losartan or olmesartan or tasosartan or telmisartan or valsartan).tw.

22. (angiotensin$ adj4 receptor$ adj3 (antagon$ or block$)).tw.

23. exp calcium channel blockers/

24. (calciumchannel block$ or amlodipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxins or diltiazemor felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or magnesium sulfate or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or verapamil or omega-agatoxin iva or omega-conotoxin gvia or omega-conotoxins).tw.

25. (calcium adj2 (inhibit$ or antagonist? or block$)).tw.

26. (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dop-

ergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa ormethyldihydroxyphenylalanine ormethyl dopa ormulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp.

27. (reserpine or serpentina or rauwolfia or serpasil).mp.

28. (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st- 155 or st 155 or tesno timelets).mp.

29. exp hydralazine/

30. (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw.

31. exp adrenergic beta-antagonists/

32. adrenergic beta antagonist?.tw.

33. (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or

iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw.

34. (beta adj2 (antagonist? or receptor? or adrenergic? block$)).tw.

35. exp adrenergic alpha antagonists/

36. (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw.

37. (andrenergic adj2 (alpha or antagonist?)).tw.

38. ((andrenergic or alpha or receptor?) adj2 block$).tw.

39. or/8-38

40. hypertension/

41. hypertens$.tw.

42. ((high or elevat$ or rais$) adj2 blood pressure).tw.

43. or/40-42

44. 39 and 43

Part III: Interventions on cholesterol

45. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/

46. (hydroxymethylglutaryl* or HMG-CoA* or statin or statins or atorvastatin or cerivastatin or fluvastatin or lovastatin or pravastatin or simvastatin or lipitor or baycol or lescol or mevacor or altocor or pravachol or lipostat or zocor or mevinolin or compactin or fluindostatin or rosuvastatin or dalvastatin or cranoc or canef or locol or lochol or leucol or lescol or monacolin or medostatin or mevinacor or livalo

or pitava or pitavastatin or pravasin or mevalotin or gerosim or lipex or zenas or crestor or meglutol).tw.

47. or/45-46

48. exp Hyperlipidemias/

49. exp Cholesterol/

50. Coronary disease/

51. hyperlipid*.tw.

52. hypercholesterol*.tw.

53. cholesterol*.tw.

54. hypercholester?emia*.tw.

55. hyperlip?emia*.tw.

56. triglycerid*.tw.

57. hypertriglycerid?emia*.tw.

58. hyperlipoprotein?emia*.tw.

59. LDL.tw.

60. HDL.tw.

61. or/48-60

62. 47 and 61

Part IV: Interventions on diabetes (Both Type I and Type II)

63. exp Diabetes Mellitus, Type 1/

64. exp Diabetic Ketoacidosis/

65. (IDDM or T1DMor T1D).tw,ot.

66. (("insulin* depend*" or "insulin?depend*") not ("non-insulin* depend*" or "non insulindepend*")).tw,ot.

67. ("typ? 1 diabet*" or "typ? I diabet*" or "typ?1 diabet*" or "typ?I diabet*").tw,ot.

68. ((acidos* or juvenil* or child* or keto* or labil* or britt*) adj2 diabet*).tw,ot.

69. ((auto-immun* or autoimmun* or sudden onset) adj2 diabet*).tw,ot.

70. (insulin* defic* adj2 absolut*).tw,ot.

71. or/63-70

72. exp Diabetes Insipidus/

73. diabet* insipidus.tw,ot.

74. 72 or 73

75. 71 not 74

76. ((intensiv* or conventional* or regular or tight* or usual or routin* or standard) adj3 (control* or therap* or treatment* or intervention* or management*)).tw,ot.

77. 75 and 76

78. exp Blood Glucose/

79. exp Hyperglycemia/

80. exp Hemoglobin A, Glycosylated/

81. (blood glucos$ or hyperglyc?emi$ or h?emoglobin$ A).ab,ti.

82. (HbA1C or Hb A or HbA 1c or HbA or A1Cs).ab,ti,ot.

83. (glycosylated adj6 h?emoglobin$).ab,ti.

84. (glucos$ adj3 management$).ab,ti.

85. or/78-84

86. exp Diabetes Mellitus, Type 2/

87. exp Diabetes Complications/

88. (MODY or NIDDM or T2DM).tw,ot.

89.(non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend).tw,ot.

90. ((typ$ 2 or typ$ II) adj3 diabet$).tw,ot.

91. ((keto?resist$ or non?keto$) adj6 diabet$).tw,ot.

92. (((late or adult$ or matur$ or slow or stabl$) adj3 onset) and diabet$).ab,ti.

93. or/86-92

94. exp Diabetes Insipidus/

95. diabet$ insipidus.tw,ot.

96. 94 or 95

97. 93 not 96

98. 85 or 97

99. ((intensi$ or conventional$ or regular or tight or usual or routin$ or standard) adj3 (control$ or therap$ or treatment or intervention$ or management$)).ab,ti.

100. 98 and 99

Part V: Part I and (Part II or Part III or Part IV)

101. 7 and (44 or 62 or 77 or 100)

102. 1 or 101

103. limit 102 to humans

B Information of the Studies Included in the Methods Review (Table 7.1)

Study	Author; Year of Publication	Population	N	Intervention	Length of		Enrollment of Post-trial (%)	Data Collection Method Post-trial?	Medication Use collected Post-trial?	Surrogate Outcomes Collected Post-trial?	Other Risk Factors Collected Post-trial?	Separate Post-trial Result Reported?	Overall Result Reported?	Analysis Method Post-trial
					RCT	Post trial								
Action to Control Cardiovascular Risk in Diabetes Follow-on(ACCORDION)-BG[1]	The ACCORD Study Group; 2016	Type 2 diabetes and other cardiovascular risk factors	10251	Intensive vs. standard glycemic control	3.7	5	84	Combined	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
ADVANCE-ObservatioNal-ESKD[2]	Muh Geot Wong; 2016	Type 2 diabetes and at least one additional risk factor for cardiovascular disease	11140	Intensive glucose control vs. Standard glucose control	5	5.4	76	Active	Yes	Yes	Yes	Yes	Yes	Cox proportional hazard model
ADVANCE-ObservatioNal[3]	S. Zoungas; 2014	Type 2 diabetes and at least one additional risk factor for cardiovascular disease	11140	Intensive glucose control vs. Standard glucose control	5	5.4	76	Active	Yes	Yes	Yes	Yes	Yes	Cox proportional hazard model
Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study[4]	L. G. Mellbin; 2011	Patients with type 2 diabetes and suspected acute myocardial infarction	1253	Insulin-based treatment vs. conventional treatment.	2.1	2	86	Combined	No	No	No	No	Yes	Logistic regression model

Epidemiology of Diabetes Interventions and Complications (EDIC) study[5]	DCCT/EDIC Study Research Group; 2005	Patients with type 1 diabetes mellitus	1441	Intensive vs. conventional therapy	6.5	11	92	Combined	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
Epidemiology of Diabetes Interventions and Complications (EDIC) study[6]	DCCT/EDIC Study Research Group; 2015	Patients with type 1 diabetes mellitus	1441	Intensive vs. conventional therapy	6.5	20	92	Combined	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
Epidemiology of Diabetes Interventions and Complications (EDIC) study[7]	DCCT/EDIC Study Research Group; 2016	Patients with type 1 diabetes mellitus	1441	Intensive vs. conventional therapy	6.5	23	92	Combined	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
Steno-2[8]	Peter Gæde; 2016	Patients with type 2 diabetes and microalbuminuria	160	Conventional therapy vs. intensified, treatment	7.8	13.2	81	Combined	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
Outcome Reduction With an Initial Glargine Intervention (ORIGIN)[9]	ORIGIN Trial Investigators; 2016	Cardiovascular risk factors plus impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes	12537	Insulin glargine vs. standard care	6.2	2.7	38	Combined	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
Stockholm Diabetes Intervention Study (SDIS)[10]	B. Rathsman; 2016	Type 1 diabetes	102	Intensified conventional treatment vs. standard treatment	7.5	21	97	Combined	Yes	Yes	Yes	No	Yes	Log-rank analyses

United Kingdom Prospective Diabetes Study (UKPDS) BG[11]	Rury R. Holman; 2008	Patients with newly diagnosed type 2 diabetes	4209	Conventional therapy vs. intensive therapy	10	10	78	Active	Yes	Yes	Yes	Yes	Yes	log-rank analyses
Veteran Affairs Diabetes Trial (VADT)[12]	Rodney A. Hayward; 2015	Military veterans with type 2 diabetes	1791	Intensive vs. standard glucose control	5.6	3	92	Combined	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
Veteran Affairs Diabetes Trial (VADT)[13]	Peter D. Reaven; 2019	Military veterans with type 2 diabetes	1791	Intensive vs. standard glucose control	5.6	8	92	Combined	Yes	Yes	Yes	Yes	Yes	Cox proportional hazard model
Action to Control Cardiovascular Risk in Diabetes Follow-on(ACCORDION)-BP[14]	Leo Buckley; 2018	Patients aged 50 years or older and SBP 130-180 and one of clinical or subclinical CV disease	1284	Intensive vs. standard BP control	5	4	70	Combined	No	Yes	Yes	No	Yes	Cox proportional hazard model
ADVANCE-ObservatioNal BP[3]	S. Zoungas; 2014	Type 2 diabetes at elevated risk of vascular disease	11140	Perindopril-indapamide vs. placebo	4.3	5.9	76	Active	Yes	Yes	Yes	Yes	Yes	Cox proportional hazard model
Hypertension Detection and Follow-up Program (HDFP)[15]	HDFP Cooperative Group; 1988	Persons with high blood pressure	10940	Stepped care (SC) vs. referred care (RC)	6.7	2	90	Active	Yes	Yes	No	Yes	Yes	Standard lifetable method

Heart Outcomes Prevention Evaluation (HOPE) study[16]	HOPE/HOPE-TOO Study Investigators; 2005	Patients with vascular disease and/or diabetes without heart failure or known left ventricular dysfunction	9297	Ramipril vs. placebo	4.5	2.6	49	Active	Yes	Yes	Yes	Yes	Yes	log-rank analyses
Oslo Hypertension Study[17]	Ingar Holme; 2015	Mild to moderate hypertension without CVD and diabetes	785	Antihypertensive drug treatment vs. control	5	35	98	Combined	No	No	No	No	Yes	Cox proportional hazard model
Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)[18]	Folkert W. Asselbergs; 2011	low-risk patients with Microalbuminuria	864	Fosinopril vs. placebo	4	5.50	93	Combined	No	Yes	No	No	Yes	log-rank analyses
ROADMAP observational follow up (OFU)[19]	Jan Menne; 2014	Patients with type 2 diabetes and normoalbuminuria	4447	Olmesartan medoxomil vs. placebo	3.2	3.3	40	Active	Yes	Yes	Yes	Yes	No	Cox proportional hazard model
Systolic Hypertension in the Elderly Program (SHEP)[20]	SHEP Cooperative Research Group; 2008	Patients aged 60 years and over with isolated systolic hypertension	4736	Chlorthalidone-based stepped-care therapy vs. placebo	4.5	14.3	90	Data Linkage	No	No	No	Yes	Yes	Cox proportional hazard model
Systolic Hypertension in the Elderly Program (SHEP)[21]	John B. Kostis; 2011	Patients aged 60 years and over with isolated systolic hypertension	4736	Chlorthalidone-based stepped-care therapy vs. placebo	4.5	17	90	Data Linkage	No	No	No	No	Yes	Cox proportional hazard model

Studies of left ventricular dysfunction (SOLVD)[22]	Philip Jong; 2003	Patients with ejection fractions of 0·35 or less	6769	Enalapril vs. placebo group	3.2	8.6	76	Combined	No	No	No	No	Yes	Cox proportional hazard model
Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT)[23]	Henrietta Reicher-Reiss; 1998	Myocardial infarction (MI) patients	2276	Nifedipine therapy vs. placebo	1	4	94	Data Linkage	No	No	No	No	Yes	Cox proportional hazard model
Systolic Hypertension in Europe (Syst-Eur) Trial[24]	Jan A. Staessen; 2004	Patients with >60 years and an untreated blood pressure of 160–219 mmHg systolic and below 95 mmHg diastolic.	4695	Nitrendipine vs. placebo	2	4	75	Active	Yes	Yes	Yes	Yes	Yes	Cox proportional hazard model
United Kingdom Prospective Diabetes Study (UKPDS) BP[25]	Rury R. Holman; 2008	Newly diagnosed type 2 diabetes mellitus with hypertension	1148	Tight vs. less-tight blood-pressure control regimens	8.4	8	77	Combined	Yes	Yes	Yes	Yes	Yes	log-rank analyses
ACCORD-Lipid[26]	Marshall B. Elam; 2017	T2MD and other CVD risk factors	5518	Fenofibrate vs. placebo	4.7	5	84	Combined	Yes	Yes	Yes	Yes	Yes	Cox proportional hazard model
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy Study-UK participants[27]	Ajay Gupta; 2018	Hypertensive patients with risk factors for cardiovascular disease	4605	Atorvastatin vs. placebo	3.3	13.2	96	Data Linkage	No	No	No	Yes	Yes	Cox proportional hazard model

Anglo-Scandinavian Cardiac Outcomes Trial - lipid-lowering arm (ASCOT-LLA)[28]	Peter S. Sever; 2009	Hypertensive patients with risk factors for cardiovascular disease	10305	Atorvastatin vs. placebo	3.3	2.2	98	Active	Yes	Yes	No	No	Yes	Cox proportional hazard model
Anglo-Scandinavian Cardiac Outcomes Trial - lipid-lowering arm (ASCOT-LLA)-UK participants[29]	Peter S. Sever; 2011	Hypertensive patients with risk factors for cardiovascular disease	4605	Atorvastatin vs. placebo	3.3	8.25	96	Data Linkage	No	No	No	Yes	Yes	Cox proportional hazard model
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)-2013[30]	L. Julian Haywood; 2013	Hypertensive participants with moderate hypercholesterolemia	10199	Pravastatin vs. usual care	4.8	4	85	Data Linkage	No	No	No	Yes	Yes	Cox proportional hazard model
Assessment of LEscol in Renal Transplantation (ALERT) Extension study[31]	H. Holdaas; 2005	Renal transplant recipients	2102	Fluvastatin vs. placebo	5	2	74	Active	Yes	Yes	No	No	Yes	Cox proportional hazard model
Bezafibrate Infarction Prevention(BIP) Study[32]	Yaron Arbel; 2016	Patients with with a history of MI and/or stable angina pectoris	3090	Bezafibrate vs. placebo	6.2	13	90	Data Linkage	No	No	No	No	Yes	Cox proportional hazard model
Heart Protection Study (HPS)[33]	HPS Collaborative Group; 2011	Patients at high risk of vascular and non-vascular outcomes	20536	Simvastatin vs. placebo	5.3	11	85	Active	Yes	Yes	No	Yes	No	log-rank analyses

Helsinki Heart Study(HHS)[34]	Leena Tenkanen; 2006	Dyslipidemic middle-aged men	4081	Gemfibrozil therapy VS. PLACEBO	5	13	95	Combined	Yes	Yes	No	No	Yes	Cox proportional hazard model
Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[35]	The LIPID Study Group; 2002	Patients with previous myocardial infarction or unstable angina	9014	Pravastatin vs. placebo	6	2	85	Combined	Yes	Yes	Yes	Yes	Yes	Cox proportional hazard model
LIPID study[36]	Wendy E. Hague; 2016	Patients with previous myocardial infarction or unstable angina	9014	Pravastatin vs. placebo	6	10	85	Combined	Yes	Yes	No	Yes	Yes	Cox proportional hazard model
Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)[18]	Folkert W. Asselbergs; 2011	Low-risk patients with Microalbuminuria	864	Pravastatin vs. placebo	4	5.5	93	Combined	No	Yes	No	No	Yes	Log-rank analyses
PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)[37]	Suzanne M. Lloyd; 2013	Aged 70–82 years with a history of, or risk factors for, vascular disease	5804	Pravastatin (40 mg per day) vs. placebo	3.2	5	89	Data Linkage	No	No	No	Yes	Yes	Cox proportional hazard model
Scandinavian Simvastatin Survival Study (4S)-2000[38]	Terje R. Pedersen; 2000	Patients with a history of myocardial infarction or angina pectoris	4444	Simvastatin therapy vs. placebo	5.4	2	90	Active	Yes	Yes	Yes	No	Yes	Cox proportional hazard model
Scandinavian Simvastatin Survival Study (4S)-2004[39]	Timo E Strandberg; 2004	Patients with a history of myocardial infarction or angina pectoris	4444	Simvastatin therapy vs. placebo	5.4	5	90	Data Linkage	Yes	No	No	Yes	Yes	Cox proportional hazard model

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH)[40]	Jeffrey L. Probstfiel; 2018	Patients with established CV disease, low baseline HDL-C, and elevated triglycerides levels	3414	Niacin vs. placebo	3	1.1	77	Active	Yes	No	No	No	Yes	Cox proportional hazard model
4D (Die Deutsche Diabetes Dialyse) Study[41]	Vera Krane; 2016	Hemodialysis patients with type 2 diabetes	1255	Atorvastatin vs. placebo	4	7.5	51	Active	Yes	Yes	No	No	Yes	Cox proportional hazard model
West of scotland coronary prevention Study (WOSCOPS)[42]	Ian Ford; 2007	Men with high cholesterol and no history of myocardial infarction	6595	Pravastatin vs. placebo	4.9	10	96	Data Linkage	Yes	No	No	Yes	Yes	Cox proportional hazard model
West of scotland coronary prevention Study (WOSCOPS)[43]	Ian Ford; 2016	Men with high cholesterol and no history of myocardial infarction	6595	Pravastatin vs. placebo	4.9	15	96	Data Linkage	Yes	No	No	No	Yes	Cox proportional hazard model
West of scotland coronary prevention Study (WOSCOPS)[44]	Antonio J. Vallejo-Vaz; 2017	Men with high cholesterol; no history of myocardial infarction; LDL-C ≥190 mg/dL	2560	Pravastatin vs. placebo	4.9	15	97	Data Linkage	Yes	No	No	No	Yes	Cox proportional hazard model

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C Summary of Findings for the Studies Included in the Methods Review (Table 7.2)

Study	Original Trial	Post-trial Follow-up
Action to Control Cardiovascular Risk in Diabetes Follow-on(ACCORDION)-BG[1]	As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality (hazard ratio = 1.22; 95% CI, 1.01 to 1.46; P = 0.04) and did not significantly reduce major cardiovascular events (hazard ratio=0.90; 95% confidence interval, 0.78 to 1.04; P = 0.16).	Intensive glucose lowering during the original trial had a neutral long-term effect on the primary composite outcome, all-cause death, and an expanded cardiovascular event.
ADVANCE-ObservatioNal[3]	Intensive glucose control reduced the incidence of combined major macrovascular and microvascular events (hazard ratio=0.90; 95% CI, 0.82 to 0.98; P = 0.01). There were no significant effects of the type of glucose control on major macrovascular events, death from cardiovascular causes or death from any cause.	There was no evidence that intensive glucose control during the trial led to long-term benefits with respect to all-cause mortality or macrovascular events; the hazard ratios were 1.00 (95% CI, 0.92 to 1.08) and 1.00 (95% CI, 0.92 to 1.08), respectively.
Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study[4]	Cardiovascular mortality was not influenced by metformin, sulphonylureas, or insulin. The risk for non-fatal myocardial infarction and stroke increased significantly in patients on insulin (HR = 1.73, 95% CI 1.26-2.37; P = 0.0007), whereas this risk was lower among those on metformin (HR = 0.63, CI 0.42-0.95; P = 0.03) and unchanged with sulphonylureas.	There were no significant differences between treatment groups in mortality. Insulin treatment was associated with non-fatal cardiovascular events (OR = 1.89 95% CI 1.35-2.63; P = 0.0002), but not with mortality (OR = 1.30, 95% CI 0.93–1.81; P = 0.13). Metformin was associated with a lower mortality rate (HR=0.65, 95% CI 0.47-0.90; P=0.01) and a lower risk of death from malignancies (HR=0.25, 95% CI 0.08-0.83; P = 0.02).
Epidemiology of Diabetes Interventions and Complications (EDIC) study[5,6,7]	Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with insulin-dependent diabetes mellitus.	After a mean of 27 years' follow-up of patients with type 1 diabetes, 6.5 years of initial intensive diabetes therapy was associated with a modestly lower all-cause mortality rate (hazard ratio = 0.67, 95% CI, 0.46-0.99; P = 0.045) when compared with conventional therapy.
Steno-2[8]	Patients in the intensive group had significantly lower rates of progression to nephropathy (odds ratio=0.27; 95% CI 0.10-0.75), progression of retinopathy (0.45; 0.21-0.95), and progression of autonomic neuropathy (0.32; 0.12-0.78) than those in the standard group.	At 21.2 years of follow-up, 7.8 years of intensified, multifactorial, target-driven treatment of type 2 diabetes with microalbuminuria demonstrated a median of 7.9 years of gain of life (HR=0.55; 95% CI 0.36-0.83, P = 0.005).

Outcome Reduction With an Initial Glargine Intervention (ORIGIN)[9]	Insulin glargine had a neutral effect on cardiovascular outcomes compared with the standard care group.	From randomization to the end of posttrial follow-up, no differences were found between the glargine and standard care groups in myocardial infarction, stroke, or cardiovascular death; myocardial infarction, stroke, cardiovascular death, revascularization, or hospitalization for heart failure.
Stockholm Diabetes Intervention Study (SDIS)[10]	A mean of 7.5 years intensified insulin treatment as compared with standard treatment, retards the development of microvascular complications in patients with type 1 diabetes.	All-cause mortality, cardiovascular morbidity and progression to end-stage renal disease did not differ in people with Type 1 diabetes earlier randomized to intensified insulin treatment.
United Kingdom Prospective Diabetes Study (UKPDS) BG[11]	Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes.	Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up.
Veteran Affairs Diabetes Trial (VADT)[12,13]	Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or micro-vascular complications.	Participants with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had a lower risk of cardiovascular events than those who received standard therapy only during the prolonged period in which the glycated hemoglobin curves were separated. There was no evidence of a legacy effect or a mortality benefit with intensive glucose control.
Action to Control Cardiovascular Risk in Diabetes Follow-on (ACCORDION)-BP[14]	In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.	After an average total follow-up of 9 years, intensive BP control reduced the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke by 25% (hazard ratio = 0.75; 95% confidence interval, 0.60-0.95; P=0.02).
ADVANCE-ObservatioNal BP[3]	Compared with patients assigned placebo, the relative risk of a major macrovascular or microvascular event was reduced by 9% (hazard ratio = 0.91, 95% CI 0.83–1.00, P=0.04) in active therapy group.	The reductions in the risk of death from any cause and of death from cardiovascular causes that had been observed in the group receiving active blood-pressure–lowering treatment during the trial were attenuated but significant at the end of the post-trial follow-up; the hazard ratios were 0.91 (95% CI, 0.84 to 0.99; P = 0.03) and 0.88 (95% CI, 0.77 to 0.99; P = 0.04), respectively.

Hypertension Detection and Follow-up Program (HDFP)[15]	Five-year mortality from all causes was 17% lower for the stepped care group compared to the referred care group.	The absolute mortality advantage found at 6.7 years persisted and increased throughout the posttrial period of follow-up despite discontinuation of the formal SC therapy program.
Heart Outcomes Prevention Evaluation (HOPE) study[16]	Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.	The benefits of ramipril observed during the active period of the HOPE trial were maintained during posttrial follow-up for cardiovascular death, stroke, and hospitalization for heart failure. Additional reductions in myocardial infarction, revascularization, and the development of diabetes were observed during the follow-up phase despite similar rates of ACEI use in the 2 randomized groups.
Oslo Hypertension Study[17]	Total mortality was the same in both groups. However, the coronary heart disease mortality rate at 10 years was significantly greater in the drug-treated group than in the untreated control group.	There was no trend towards reduction in total mortality by treatment. A nominally significant increase in risk of death at first myocardial infarction was observed in the trial treatment group across the follow-up period, HR=1.51 (1.01–2.25); (P=0.042).
Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)[18]	The composite primary endpoint of CV death, CV hospitalizations, or end-stage renal disease occurred less frequently in the fosinopril arm vs placebo, although not significantly (HR = 0.60, 95% CI 0.33-1.10, P=0.098).	The benefits of 4-year treatment with fosinopril were sustained during posttrial follow-up for cardiovascular mortality and morbidity.
ROADMAP observational follow up (OFU)[19]	Slightly fewer patients in the olmesartan group than in the placebo group had nonfatal cardiovascular events - 3.6% as compared with 4.1% - but a greater number had fatal cardiovascular events - 0.7% as compared with 0.1% patients (P = 0.01), a difference that was attributable in part to a higher rate of death from cardiovascular causes in the olmesartan group than in the placebo group among patients with pre- existing coronary heart disease (P = 0.02).	RAS blockade with Olmesartan might cause sustained reduction (legacy effect) of micro- and macrovascular events.
Systolic Hypertension in the Elderly Program (SHEP)[20,21]	Antihypertensive stepped care reduced the incidence of total stroke by 36% (P= .0003).	In SHEP, chlorthalidone-based treatment reduced the risk of cardiovascular death after 14 years of extended follow-up.

Studies of left ventricular dysfunction (SOLVD)[22]	The angiotensin-converting—enzyme inhibitor enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations, as compared with the rates in the group given placebo, among patients with asymptomatic left ventricular dysfunction.	Treatment with enalapril for 3-4 years led to a sustained improvement in survival beyond the original trial period in patients with left ventricular systolic dysfunction, with an important increase in life expectancy.
Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT)[23]	The post-discharge mortality was 5.0% in the placebo group and 5.9% among patients receiving nifedipine (P=0.37).	The 5-year mortality risk ratio associated with randomization to nifedipine over 1 year, adjusted for age, gender, past MI, angina, diabetes, hypertension, MI location, and therapy, was 1.00(95% CI: 0.81–1.22). The results do not support an association between nifedipine therapy and a late harmful effect on long-term mortality.
Systolic Hypertension in Europe (Syst-Eur) Trial[24]	Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications.	Immediate compared with delayed treatment prevented 17 strokes or 25 major cardiovascular events per 1000 patients followed up for 6 years. These findings underscore the necessity of early treatment of isolated systolic hypertension.
United Kingdom Prospective Diabetes Study (UKPDS) BP[25]	There was a non-significant reduction in all-cause mortality. Reductions in risk in the group assigned to tight control compared with that assigned to less tight control were 24% in diabetes related end points (95% confidence interval 8% to 38%) (P=0.0046), 32% in deaths related to diabetes (6% to 51%) (P=0.019), 44% in strokes (11% to 65%) (P=0.013), and 37% in microvascular end points (11% to 56%) (P=0.0092).	The benefits of previously improved blood-pressure control were not sustained when between-group differences in blood pressure were lost. Early improvement in blood-pressure control in patients with both type 2 diabetes and hypertension was associated with a reduced risk of complications, but it appears that good blood pressure control must be continued if the benefits are to be maintained.
ACCORD-Lipid[26]	The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone.	Extended follow-up of ACCORD-lipid trial participants confirms the original neutral effect of fenofibrate in the overall study cohort. The continued observation of heterogeneity of treatment response by baseline lipids suggests that fenofibrate therapy may reduce CVD in patients with diabetes with hypertriglyceridemia and low high-density lipoprotein cholesterol.
Anglo-Scandinavian Cardiac Outcomes Trial -lipid-lowering arm (ASCOT-LLA)[27,28]	In the atenolol-based group, atorvastatin reduced coronary heart disease death and nonfatal MI by 25% (CI 0.57–0.97, P=0.03), stroke by 10% (CI 0.69–1.18, P=0.43) and total cardiovascular events and procedures by 13% (CI 0.76–1.0, P=0.05).	The long-term beneficial effects on mortality of lipid-lowering with a statin: patients on atorvastatin had fewer cardiovascular deaths more than 10 years after trial closure. Overall, the ASCOT Legacy study supports the notion that interventions for blood pressure and cholesterol are associated with long-term benefits on cardiovascular outcomes.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)-2013[30]	Pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL.	During the post-trial period, no significant differences appeared in mortality for pravastatin versus usual care (hazard ratio = 0.96; 95% CI, 0.89-1.03), or other secondary outcomes.
Bezafibrate Infarction Prevention(BIP) Study[32]	An overall trend in a reduction of the incidence of primary end points was observed (fatal or nonfatal myocardial infarction or sudden death).	During long-term follow-up bezafibrate-allocated patients experienced a modest but significant 10 % reduction in the adjusted risk of mortality. This effect of bezafibrate was more prominent among patients with baseline hypertriglyceridemia.
Heart Protection Study (HPS)[33]	Allocation to 40 mg simvastatin daily reduced the rates of myocardial infarction, of stroke, and of revascularisation by about one-quarter.	More prolonged LDL-lowering statin treatment produces larger absolute reductions in vascular events. Moreover, even after study treatment stopped in HPS, benefits persisted for at least 5 years without any evidence of emerging hazards.
Helsinki Heart Study(HHS)[34]	A 34% reduction in cardiac end points was shown in gemfibrozil group, but no difference in all-cause mortality.	Long-term mortality follow-up showed that patients with dyslipidemia benefited from beginning treatment with gemfibrozil early, especially if their dyslipidemia entailed factors related to the metabolic syndrome.
Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[35,36]	Patients originally assigned pravastatin had a lower risk of death from all causes, coronary heart disease (CHD) death and CHD death or non-fatal myocardial infarction.	In LIPID the absolute survival benefit from 6 years pravastatin treatment appeared to be maintained for the next 10 years, with a similar risk of death among survivors in both groups after the initial period. Treatment with statins does not influence cancer or death from noncardiovascular causes during long-term follow-up.
Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT)[18]	There was no difference in the composite primary endpoint of CV death, CV hospitalizations, or end-stage renal disease (HR = 0.87, 95% CI 0.49-1.57, P=0.65).	4 years of fosinopril treatment resulted in a risk reduction of 45% (95% CI 6%-75%, P = 0.04) in this group compared with placebo. Subjects originally assigned to pravastatin had no overall risk reduction in the primary end point (P = 0.99).
PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)[37]	The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a placebo-controlled trial of pravastatin, demonstrated a 19% reduction in coronary outcomes (P = 0.006) after a mean of 3.2 years, with no impact on stroke outcomes or all-cause mortality.	Pravastatin treatment of elderly high-risk subjects for 3.2 years provided long-term protection against CHD events and CHD mortality.

Scandinavian Simvastatin Survival Study (4S)[38,39]	Treatment with simvastatin for up to 8 years in patients with CHD is safe and yields continued survival benefit.	Simvastatin treatment for 5 years in a placebo-controlled trial, followed by open-label statin therapy, was associated with survival benefit over 10 years of follow-up compared with open-label statin therapy for the past 5 years only. No difference was noted in mortality from and incidence of cancer between the original simvastatin group and placebo group.
The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH)[40]	Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow-up period.	At a mean total follow-up of 4.1 years, 3 years of ERN treatment did not lower CV event rates in patients with CV disease and atherogenic dyslipidemia on statin-based therapy.
4D (Die Deutsche Diabetes Dialyse) Study[41]	Comparing 4 years of treatment with atorvastatin to placebo in hemodialysis patients with type 2 diabetes, the primary end point of cardiovascular events (cardiac death, myocardial infarction, and stroke) was non-significantly reduced by 8%.	Statin treatment non-significantly affected the former primary outcome (relative risk = 0.91; 95% confidence interval, 0.78–1.07). The risk of all cardiac events combined and the risk of cardiac death were significantly lower in the original statin group compared to placebo (0.83, 0.70–0.97, and 0.80, 0.66–0.97). No significant effect was detected on cerebrovascular events, fatal stroke, fatal cancer, non-vascular, or all-cause death.
West of scotland coronary prevention Study (WOSCOPS)[42,43,44]	After an average of approximately 5 years, the combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction was reduced from 7.9% in the placebo group to 5.5% in the pravastatin group (P<0.001), and the risk of death from definite or suspected coronary heart disease was reduced from 1.9% to 1.3% (P = 0.04). There was a trend toward a reduction in the risk of stroke, and there was no evidence of an increased risk of death from noncardiovascular causes or of an increased risk of incident cancer. Mortality from any cause was 4.1% in the placebo group and 3.2% in the pravastatin group (P = 0.051)	Statin treatment for 5 years was associated with a legacy benefit, with improved survival and a substantial reduction in cardiovascular disease outcomes over a 20-year period, supporting the wider adoption of primary prevention strategies. (Circulation.

D Between-group-difference in Covariates, Surrogate Outcomes and Medication Taking in Post-trial Follow-up (Table 7.3)

Study*	Intervention	Information collected for participants that enrolled in the post-trial follow-up		
		Difference in surrogate outcomes and other covariates at the end of trial/start of post-trial)	**Non-clinical surrogate outcomes during post-trial follow-up**	**Proportion taking the medication of interest**
Action to Control Cardiovascular Risk in Diabetes Follow-on(ACCORDION)-BG[1]	Intensive vs. standard glycemic control	When the ACCORD trial ended, the mean glycated hemoglobin level was 7.4% (1.2%) in the intensive group and 7.8% (1.3%) in the standard group (P<0.001)	This HbA1c difference persisted during the ACCORDION follow- up period. At the end of the ACCORDION follow-up, these levels were7.8% (1.4%) and 8.0% (1.4%), respectively (P = 0.005)	The proportion taking insulin was 63% in the intensive group and 60% in the standard group.
ADVANCE-ON[3]	Intensive glucose vs. Standard glucose control	The mean level of HbA1c at the end of the randomised trial was 0.67% lower in the intervention arm.	The mean level of HbA1c at the first post-trial visit (mean 2.9 years post-trial) was 0.08% lower in the intervention group. Levels remained similar at the conclusion of the post- trial follow-up.	The proportion taking glucose lowering medication at the first post-trial visit (2.9 years post-trial) was 1.2% higher in the intervention group (73.7% vs. 72.5%); and at the final visit was 0.5% higher (91.6% vs. 91.1%).
Epidemiology of Diabetes Interventions and Complications (EDIC) study[5,6,7]	Intensive vs. conventional therapy	At trial end, the conventional and intensive treatment groups had higher BMI (26.6 vs.25.1) and but lower triglycerides (84 vs. 88 mg/dl) and differed in the levels of microvascular outcomes.	Early in post-trial, the previously established separation in glycemia between the intensive and conventional groups diminished by year 5. At year 11 of EDIC, the HbA1c was 7.9% in the intensive group and 7.8% in the conventional group.	At the end of post-trial follow-up, the proportion of intensive diabetes management were the same. (98% vs. 98%)

Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno-2)[8]	Intensified multifactorial treatment vs. conventional therapy	At the end of intervention period, the two group were significantly different in blood pressure (systolic and diastolic), LDL cholesterol and Triacylglycerol.	At the end of post-trial follow-up, the HbA1c was 7.4% in the intensive group and 7.5% in the standard group.	Self-reported glucose-lowering medication at the end of post-trial follow-up was 98% in the intensive group and 100% in the standard group.
Outcome Reduction With an Initial Glargine Intervention (ORIGIN)[9]	Insulin glargine vs. standard care	Comparison of the participants randomized to insulin glargine or standard care who continued in the posttrial follow-up showed no important differences in baseline characteristics.	At the end of posttrial follow-up, median HbA1c were 6.55% in the insulin group and 6.70% in the standard group.	Any Glucose-lowering medication 79% in the insulin group vs. 76% in the standard group.
United Kingdom Prospective Diabetes Study (UKPDS BG)[11]	Conventional therapy vs. intensive therapy	The sulfonylurea–insulin group had lower levels of mean glycated hemoglobin and fasting plasma glucose but had a higher median weight and mean BMI at baseline.	Differences in mean glycated hemoglobin levels between the intensive therapy group and the conventional-therapy group were lost by 1 year, with similar glycated hemoglobin improvements thereafter in all groups.	Differences in combinations of glucose therapy disappeared by 5 years.
Veteran Affairs Diabetes Trial (VADT)[12,13]	Intensive vs. standard glucose control	No meaningful differences were observed between the baseline characteristics of the two groups.	The difference in the glycated hemoglobin level declined to 0.5% one year after the end of the trial and remained at 0.2 to 0.3% from 3 years after the end of the trial until the end of follow-up.	Insulin use in the original intensive and standard group was 78.2 % vs. 66.1% at the end of trial; 79.5% and 76.8% at 4 year; and 70.2% vs. 74.5% at the end(10 year).
ADVANCE-ObservatioNal BP[3]	Perindopril indapamide vs placebo	The prerandomization characteristics of the two groups were similar.	The mean between-group difference in blood pressure observed during the randomized ADVANCE trial was no longer evident 6 months after the end of that part of the trial.	Blood pressure lowering medication taking at last visit was 77% in the intervention group and 80% in the placebo group.

Heart Outcomes Prevention Evaluation (HOPE) study[16]	Ramipril vs. placebo	At the end of the trial, mean blood pressure in the ramipril group was 136/76 mm Hg compared with 139/ 77 mm Hg in the placebo group.	At the end of the 2.6 years of extended follow-up, the mean blood pressure in the 2 groups were similar, 136/74 mm Hg.	The proportion taking an ACE inhibitor during the study extension was slightly higher in those allocated to ramipril and placebo (68% vs. 67% at the beginning; 73% vs. 68% at 1 year; and 72% vs. 68% at the end).
Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP)observational follow up (OFU)[19]	Olmesartan medoxomil vs. placebo	At the final visit of the trial the two groups were differed in blood pressure (SBP:128 vs.124mm Hg and DBP:75 vs. 73 mm Hg) and eGFR (78 vs 82 mL/min).	Systolic blood pressure increased to mean values of 135 mm Hg in both groups	RAS blocking agent taking was 62.9% in the intervention group and 60.1% in the placebo group.
Systolic Hypertension in Europe (Syst-Eur) Trial[24]	Nitrendipine vs. placebos	No differences of clinical features of treatment groups at randomization among patients enrolled in the open follow-up study beside the blood pressure.	The systolic differences averaged 9.4 mmHg at enrolment in the open follow-up study and 0.7 mmHg at the last visit. The corresponding diastolic differences were 3.8 mmHg and 0.5 mmHg, respectively.	The proportion treated for hypertension at the last visit was: 94.9% in the intervention group and 95.9% in the placebo group.
United Kingdom Prospective Diabetes Study (UKPDS-BP)[25]	Tight vs. less-tight blood-pressure control regimens	The two groups were differed in blood pressure and baseline Hba1c (Median 8.3% vs. 7.5%)	Differences between the groups in mean systolic and diastolic blood pressures were lost by year 1 and year 2, respectively.	The proportion taking two or more blood pressure lowering drugs at year 5 post-trial was 73% for tight-control and 75% for less-tight control.

ACCORD-Lipid (Action to Control Cardiovascular Risk in Diabetes)[26]	Fenofibrate vs. placebo	The two groups were differed in triglyceride, LDL-C and HDL-C level.	During the posttrial period, difference in triglyceride, LDL-C and HDL-C levels were lost.	Following completion of ACCORD, 74.1% ACCORDION participants continued to be prescribed statin therapy post-trial. In contrast, only 4.3% ACCORDION participants were continued or started on fibrate therapy in post-trial.
Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[35,36]	Pravastatin vs. placebo	Baseline characteristics were very well balanced among those patients who were alive and followed up in the extended follow-up period.	During the first 2 years, the average LDL cholesterol levels were almost identical for the two groups: 2.66 mmol/L for placebo patients and 2.63 mmol/L for pravastatin patients.	85% of the original pravastatin group and 84% of the placebo group continued taking statin treatment post-trial. (averaged over a 4-year period)
Scandinavian Simvastatin Survival Study (4S)[38,39]	Simvastatin therapy vs. placebo	Serum lipid concentrations between patients treated with placebo and simvastatin differed. (total cholesterol, LDL-C, HDL-C, triglycerides)	Mean total cholesterol concentrations were 5·16 mmol/L in the original placebo group and 5·11 mmol/L in the original simvastatin group.	During the 5-year extension, 86% of the statin group and 82% of the placebo group reported taking lipid-lowering drugs.

*Only the studies reported on this information were included

E R Syntax for Data Generation

```
##parameter##
RR_treatment<-c(0.8,0.7,0.6)
size_lamda<-c(0.02,0.04,0.07)
size_legacy<-c(1,0.5,0)
parameter<-expand.grid(RR_treatment=RR_treatment,
                       size_legacy=size_legacy,
                       size_lamda=size_lamda)
#samlpe size,length of trial and post-trial#
N<-8000; ti<-5; tp<-5
##data generation function##
data.gen<-function(N,ti,tp,lamda,size_legacy,RR_treatment){
  id<-c(1:N)
  condition<-gl(2,N/2,labels=c("Placebo","Drug"))
  treatment_trial<-c(rep(0,N/2),rep(1,N/2))
  risk<-rep(c(rlnorm(N/2,  meanlog = 0, sdlog = 0.5)),2)
  tc<-ti+tp
  #set how to calculate the post-trial risk#
  RR_legacy<-1-size_legacy+size_legacy*RR_treatment
  risk_pt<-risk*1.25+0.01
  sim.data <- data.frame(id,condition,treatment_trial,risk,risk_pt)
  expit <- function(x) {
    exp(x)/(1+exp(x))
  }
  #treatment allocation at post-trial#
  sim.data$ptr <- expit(log(sim.data$risk_pt))
  sim.data$treatment_pt<-rbinom(N,1,sim.data$ptr)
```

```
  sim.data$risk_trial<-sim.data$risk*RR_treatment
  ^sim.data$treatment_trial
  sim.data$risk_posttrial<-sim.data$risk_pt*
    (RR_treatment^sim.data$treatment_pt)*
    (RR_legacy^sim.data$treatment_trial)
  NLU <- -log(runif(N))
  sim.data$time<-ifelse(NLU<lamda*sim.data$risk_trial*ti,
                        NLU/(lamda*sim.data$risk_trial),
                        ti+(NLU-lamda*sim.data$risk_trial*ti)/
                          (lamda*sim.data$risk_posttrial))
  sim.data$event <- ifelse(sim.data$time>tc, 0, 1)
  sim.data$time <- pmin(sim.data$time,tc)
  return(sim.data)
}
```

F Covariates of the ACCORD Trial Participants at Baseline and the First Post-trial Visit

Table 7.4 Covariates of the ACCORD-BP trial participants at baseline and the first post-trial visit

Covariates	Baseline		1st Post-trial Visit		P
	Intensive (n=2362)	Standard (n=2371)	Intensive (n=1960)	Standard (n=1997)	
Age	62.8 ±6.6	62.8 ±6.8	67.2 ±6.3	67.6 ±6.6	0.76
Sex					0.84
Male	1234 (52%)	1241 (52%)	1034 (53%)	1046 (52%)	
Female	1128 (48%)	1130 (48%)	926 (47%)	951 (48%)	
Ethnicity					0.07
White	1413 (60%)	1368 (58%)	1203 (61%)	1168 (58%)	
Non-White	949 (40%)	1003 (42%)	757 (39%)	829 (42%)	
CVD History					0.98
Yes	804 (34%)	789 (33%)	614 (31%)	627 (31%)	
No	1558 (66%)	1582 (67%)	1346 (69%)	1370 (69%)	
BG Trial Assignment					0.24
Intensive Group	1178 (50%)	1193 (50%)	954 (49%)	1010 (51%)	
Standard Group	1184 (50%)	1178 (50%)	1006 (51%)	987 (49%)	
HbA1c (%)	8.36 ±1.09	8.30 ±1.08	7.79 ±1.50	7.78 ±1.47	0.79
SBP (mm Hg)	139.0 ±16.1	139.4 ±15.6	129.5 ±16.7	134.5 ±17.3	<0.01
CHOL (mg/dl)	194 ±45	191 ±44	167 ±41	168 ±42	0.75
TRIG (mg/dl)	195 ±178	191 ±185	162 ±105	151 ±101	0.02
VLDL (mg/dl)	37 ±29	36 ±29	32 ±19	29 ±18	<0.01
LDL (mg/dl)	111 ±37	109 ±36	89 ±34	90 ±36	0.54
HDL (mg/dl)	46 ±13	46 ±14	47 ±13	49 ±15	<0.01

Plus–minus values are mean ± SD

Table 7.5 Covariates of the ACCORD-Lipid trial participants at baseline and the first post-trial visit

Covariates	Baseline		1st Post-trial Visit		P
	Fenofibrate (n=2765)	Placebo (n=2753)	Fenofibrate (n=2331)	Placebo (n=2313)	
Age	62.8 ±6.6	62.8 ±6.8	67.2±6.3	67.6 ±6.6	0.79
Sex					0.96
Male	1914 (69%)	1910 (69%)	1607 (69%)	1592 (69%)	
Female	851 (31%)	843 (31%)	724 (31%)	721 (31%)	
Ethnicity					0.21
White	1823 (66%)	1789 (65%)	1560 (67%)	1507 (65%)	
Non-White	942 (34%)	964 (35%)	771 (33%)	806 (35%)	
CVD History					0.88
Yes	1008 (36%)	1008 (37%)	816 (35%)	804 (35%)	
No	1757 (64%)	1745 (63%)	1515 (65%)	1509 (65%)	
BG Trial Assignment					0.48
Intensive Group	1374 (50%)	1383 (50%)	1145 (50%)	1161 (50%)	
Standard Group	1391 (50%)	1370 (50%)	1186 (50%)	1152 (50%)	
HbA1c (%)	8.28 ±1.03	8.27 ±1.03	7.79 ±1.57	7.72 ±1.47	0.20
SBP (mm Hg)	133 ±17	134 ±18	132 ±17	132 ±17	0.95
CHOL (mg/dl)	175 ±37	176 ±38	153 ±40	152 ±34	0.65
TRIG (mg/dl)	189 ±110	186 ±115	162 ±121	160 ±100	0.51
VLDL (mg/dl)	37 ±19	36 ±20	32 ±22	31 ±16	0.27
LDL (mg/dl)	100 ±30	101 ±31	80 ±30	80 ±28	0.93
HDL (mg/dl)	38 ±8	38 ±8	40 ±10	41 ±10	0.82

Plus–minus values are mean ± SD

G Directed Acyclic Graph of Legacy Effects with the Unmeasured Variable

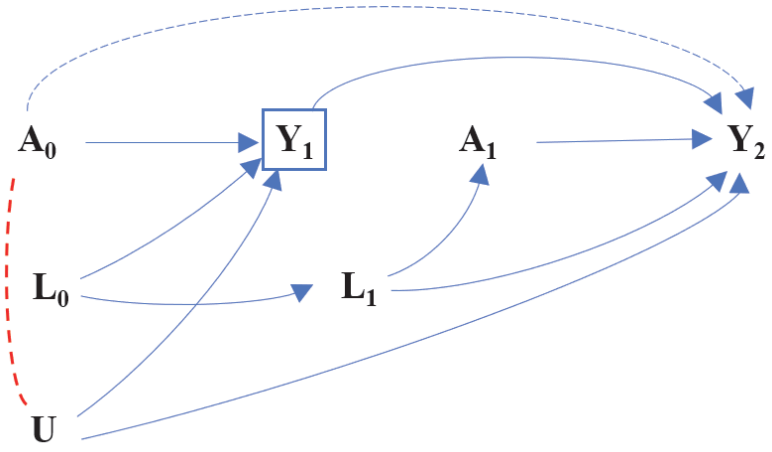

Figure 7.1 Directed acyclic graph of legacy effects with the unmeasured variable

L_0 represents the baseline risk, and A_0 represents the intervention assigned at the start of the trial; due to randomization, they are independent of each other. L_1 represents the risk after the trial (start of post-trial period) and A_1 is the post-trial choice of treatment. Y_1 and Y_2 denote the cardiovascular outcomes at the end of the initial trial and at the end of post-trial follow-up, respectively. An unbiased estimate of legacy effect ($A_0 \rightarrow Y_2$) cannot be obtained in the absence of unmeasured variable U. Conditioning on Y_1 opens the associational path ($A_0 \rightarrow$ U $\rightarrow Y_2$) between A_0 and Y_2.

H Results of Sensitivity Analysis

To examine the robustness of our findings, we undertook a sensitivity analysis of legacy effect by modelling in the following ways:

Model 1. Unadjusted Model

Model 2. Adjusted for baseline Characters (age, gender, race, education, CVD history, BG trial treatment assignment, duration of T2MD) and post-trial medication use (medication of blood glucose control, blood pressure control, statin, and fibrate).

Model 3. Inverse probability weighting (IPW): Individuals were reweighted based on their probability of survival for each specific event. The probability was estimated using baseline age, gender, ethnicity, education, CVD history, clinical center, smoking status, alcohol, baseline medication use, BG trial treatment assignment, baseline HbA1c, systolic blood pressure, TRIG, LDL-C and HDL-C.

Table 7.6 Result of sensitivity analysis

Event	Model 1		Model 2		Model 3	
	Hazard Ratio	P	Hazard Ratio	P	Hazard Ratio	P
Total mortality	0.64(0.45, 0.91)	0.01	0.54(0.30, 0.99)	0.05	0.57(0.35, 0.94)	0.03
CVD mortality	0.78(0.44, 1.38)	0.39	0.59(0.24, 1.47)	0.26	0.82(0.43, 1.55)	0.55
Nonfatal MI	0.85(0.39, 1.84)	0.68	0.52(0.19, 1.45)	0.21	1.00(0.44, 2.30)	0.99
Total stroke	1.00(0.39, 2.6)	0.99	1.33(0.42, 4.21)	0.63	1.16(0.43, 3.16)	0.77
CHF	0.68(0.31, 1.49)	0.33	0.46(0.17, 1.24)	0.12	0.75(0.33, 1.69)	0.50
Major CHD	0.65(0.41, 1.04)	0.07	0.47(0.24, 0.92)	0.03	0.50(0.27, 0.89)	0.02