Supplementary Online Content

Fitzpatrick T, Perrier L, Shakik S, et al. Assessment of long-term follow-up of randomized trial participants by linkage to routinely collected data: a scoping review and analysis. *JAMA Netw Open*. 2018;1(8):e186019. doi:10.1001/jamanetworkopen.2018.6019

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This supplementary material has been provided by the authors to give readers additional information about their work.

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**eTable 1. MEDLINE Search Strategy**

| Database: Ovid MEDLINE(R) <1946 to November Week 4 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 25, 2016> | Search Strategy: |
|---|---|
| 1  | (extension and trial).ti. |
| 2  | randomized trial.mp. [ RCT filter - validated, highly sensitive ] |
| 3  | randomized trial.pt. |
| 4  | random:.mp. |
| 5  | tu.xs. |
| 6  | or/2-5 |
| 7  | ("2 year" adj "follow-up").tw. |
| 8  | ("2$ year" adj "follow-up").tw. |
| 9  | ("3 year" adj "follow-up").tw. |
| 10 | ("3$ year" adj "follow-up").tw. |
| 11 | ("4 year" adj "follow-up").tw. |
| 12 | ("4$ year" adj "follow-up").tw. |
| 13 | ("5 year" adj "follow-up").tw. |
| 14 | ("5$ year" adj "follow-up").tw. |
| 15 | ("6 year" adj "follow-up").tw. |
| 16 | ("6$ year" adj "follow-up").tw. |
| 17 | ("7 year" adj "follow-up").tw. |
| 18 | ("7$ year" adj "follow-up").tw. |
| 19 | ("8 year" adj "follow-up").tw. |
| 20 | ("8$ year" adj "follow-up").tw. |
| 21 | ("9 year" adj "follow-up").tw. |
| 22 | ("9$ year" adj "follow-up").tw. |
| 23 | ("10 year" adj "follow-up").tw. |
| 24 | ("long term" adj "follow-up").tw. |
| 25 | *Follow-Up Studies/ |
| 26 | *Longitudinal Studies/ |
| 27 | (longitudinal adj stud$).tw. |
| 28 | (post adj trial?).tw. |
| 29 | (after adj trial?).tw. |
| 30 | (passive adj surveillance).tw. |
| 31 | or/7-30 |
| 32 | Medical Records/ |
| 33 | Health Records, Personal/ |
| 34 | Medical Record Linkage/ |
| 35 | Medical Records Systems, |
| 36 | Electronic Health Records/ |
| 37 | Health Information Exchange/ |
| 38 | Nursing Records/ |
| 39 | Records as Topic/ |
| 40 | exp Hospital Information Systems/ |
| 41 | exp Registries/ |
| 42 | registry.tw. |
| 43 | registries.tw. |
| 44 | (data adj link$).tw. |
| 45 | (link$ adj2 data).tw. |
| 46 | (death adj certificate?).tw. |
| 47 | "vital stat$ data$".tw. |
| 48 | EHR.tw. |
| 49 | EMR.tw. |
| 50 | (medical adj record?).tw. |
| 51 | (health adj record?).tw. |
| 52 | (patient adj record?).tw. |
| 53 | (nursing adj record?).tw. |
| 54 | (national adj4 index).tw. |
| 55 | (national adj4 register?).tw. |
| 56 | (national adj4 data$).tw. |
| 57 | (administrative adj4 data$).tw. |
| 58 | (administrative adj4 record$).tw. |
| 59 | (population-based adj4 data$).tw. |
| 60 | or/32-59 |
| 61 | 6 and 31 and 60 |
| 62 | 1 or 61 |
| 63 | exp Animals/ not (Humans/ and exp Animals/) |
| 64 | 62 not 63 |
| 65 | limit 64 to english language |
## eTable 2. Summary of Data Abstraction Guide

### Bibliometrics
- Original trial reference
- List of other companion trial references (if applicable)

### Original Trial characteristics
- NCT Number (or other trial registration number, if registered in another country)
- Country(ies) of origin
- Intervention(s) applied, include cointerventions, if applicable.
- Intervention type
- Outcomes originally outlined (include primary and secondary, if applicable)
- Time frame; i.e., calendar dates for which the study was conducted
- Length of intervention (e.g. in months, years - as per original trial reported)
- Average follow-up time (in months), if provided.
- Baseline sample size
- Study inclusion criteria
- Did the original trial use routinely collected (administrative/ vital statistics/ registry) data to measure primary or secondary trial outcomes? If yes, specify.
- Main study findings (i.e., those reported in the abstract)
- Funders (if not stated, specify)
  - Did the original study had industry sponsorship?

### Follow-up trial characteristics
- Was the extension planned as part of the original trial? (Yes/No/Can't tell)
- Was a clear reason given to perform extension?
  - If so, specify; e.g. to determine the long-term benefits of treatment?
- Additional follow-up (e.g. years, months) offered through trial extension.
- Average total follow-up (in months) - or maximum follow-up time when multiple trials were included or where mean/ median are not explicitly stated
- Did the follow-up involve subgroups of the original trial population? If so, briefly describe.
- Sample size used for follow-up study
- Were outcomes reported according to randomization?
- List the outcomes reported by the follow-up study. State primary and secondary outcomes.
- Do the outcomes reported in the follow-up study differ from those reported in the original trial report? Describe.
- Did the authors also report outcomes in an additional population? If yes, specify (e.g. individuals in a registry).
- Main results of follow-up study (i.e., those reported in the abstract)
- What additional information did the trial extension provide? E.g. original intervention effects were sustained/lost. Were there new findings involving other outcomes?
- Were any of the authors of the original study involved in the follow-up study?
Follow-Study Data and Funding Sources

- State the types of routinely collected data used in the follow-up study, e.g. vital statistics, administrative claims data, registry data, etc.
- Did the authors use data other than vital statistics or population registries?
- Was the method of linkage used reported or referenced? If so, specify (e.g. probabilistic, deterministic)
- Do the authors report the % (or number) of study participants successfully linked? If so, record.
- Did the authors report if Research Ethics Board (REB) approval was sought?
  - Please record any mention to ethics and page number.
  - Was REB approval specific to the long-term follow-up study?
- Did the authors have access to details of interventions after the original trial was closed?
  - If yes, specify.
- If they had access to trial intervention data, how did they use it?
- How did the authors state how they treated the analysis? i.e., per-protocol, intention to treat, or as-treated.
- If they had access to post trial treatment or potential confounding variables, please describe whether they included them in any time-varying analyses.
  - Did the authors adjust for any covariates (time-varying or other)?
- Did the authors comment on any challenges they experienced with completing the follow-up study? (e.g. time or cost requirements). If so, please record with page number.
- Funders of follow-up study (if not stated, specify such).
  - Did the follow-up study have industry sponsorship?
- Did the authors provide an estimate of the cost of the extension study? If so, record.
# eTable 3. Complete list of references for the 113 included extension studies and their corresponding original trial reports, according to outcome categorization†

| Extension Study Reference | Original Trial Reference |
|----------------------------|--------------------------|
| **Statistically significant superiority of one treatment observed in trial extension phase** |
| Aasa M, Dellborg M, Herlitz J, Svensson L, Grip L. Risk reduction for cardiac events after primary coronary intervention compared with thrombolysis for acute ST-elevation myocardial infarction (five-year results of the Swedish early decision reperfusion strategy [SWEDES] trial). Am J Cardiol 2010; 106(12): 1685-91. | Svensson L, Aasa M, Dellborg M, Gibson CM, Kirtane A, Herlitz J, et al. Comparison of very early treatment with either fibrinolysis or percutaneous coronary intervention facilitated with abciximab with respect to ST recovery and infarct-related artery epicardial flow in patients with acute ST-segment elevation myocardial infarction: The Swedish Early Decision (SWEDES) reperfusion trial. Am Heart J 2006; 151(4): 798.e1-7. |
| Alehagen U, Aaseth J, Johansson P. Reduced Cardiovascular Mortality 10 Years after Supplementation with Selenium and Coenzyme Q10 for Four Years: Follow-Up Results of a Prospective Randomized Double-Blind Placebo-Controlled Trial in Elderly Citizens, PLoS One 2015; 10(12): e0141641. | Alehagen U, Johansson P, Björnstedt M, Rosén A, Dahlström U. Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens. Int J Cardiol 2013; 167: 1860–6. |
| Arbel Y, Klempfner R, Erez A, Goldenberg I, Benzekry S, Shlomo N, et al. Bezafibrate for the treatment of dyslipidemia in patients with coronary artery disease: 20-year mortality follow-up of the BIP randomized control trial. Cardiovasc Diabetol 2016; 15:11. | The Bezafibrate Infarction Prevention (BIP) Study. Secondary Prevention by Raising HDL Cholesterol and Reducing Triglycerides in Patients with Coronary Artery Disease the Bezafibrate Infarction Prevention (BIP) Study. Circulation 2000; 102: 21-7 |
| Arnsrud Godtman R, Holmberg E, Lilja H, Stranne J, Hugosson J. Opportunistic Testing Versus Organized Prostate-specific Antigen Screening: Outcome After 18 Years in the Göteborg Randomized Population-based Prostate Cancer Screening Trial. Eur Urol 2015; 68(3): 354-60. | Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010; 11(8): 725–32 |
| Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, Harrison LH. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: A 60-year follow-up study. JAMA 2004; 291(17): 2086-91. | Aronson JD and Palmer CE. Experience with BCG Vaccine in the Control of Tuberculosis among North American Indians. Public Health Rep 1946; 61(23): 802-20 |
| Arriagada R, Johansson H, Johansson U, Fornander T, Bergh J. Adjuvant radiotherapy in breast cancer: Results of the Stockholm randomised trial with 30-years of follow-up. European Society for Radiotherapy and Oncology 2010 Meeting Abstract. | Rutqvist LE, Cedermark B, Glas U, Johansson H, Rotstein S, Skoog L, et al. Radiotherapy, chemotherapy, and tamoxifen as adjuncts to surgery in early breast cancer: a summary of three randomized trials. Int J Radiat Oncol Biol Phys 1989; 16(3): 629-39. |
| Extension Study Reference | Original Trial Reference |
|---------------------------|--------------------------|
| Austin J, Williams WR, Ross L, Hutchison S. Five-year follow-up findings from a randomized controlled trial of cardiac rehabilitation for heart failure. Eur J Cardiovasc Prev Rehabil 2008; 15(2): 162-7. | Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. Eur J Heart Fail 2005; 7: 411-7. |
| Bjurstam N, Björneld L, Warwick J, Sala E, Duffy SW, Nyström L, et al. The Gothenburg Breast Screening Trial: First Results on Mortality, Incidence, and Mode of Detection for Women Ages 39–49 Years at Randomization. Cancer 2003; 97(10): 2387-96. | Bjurstam N, Björneld L, Duffy SW, Smith TC, Cahlin E, Eriksson O, et al. The Gothenburg Breast Screening Trial First Results on Mortality, Incidence, and Mode of Detection for Women Ages 39–49 Years at Randomization. Cancer 1997; 80(11): 2091-9. |
| Bogner HR, Morales KH, Post EP, Bruce ML. Diabetes, depression, and death: a randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT). Diabetes Care 2007; 30(12): 3005-10. | Bruce ML, Ten Have TR, Reynolds CF 3rd, Katz II, Schulberg HC, Mulsant BH, et al. Reducing Suicidal Ideation and Depressive Symptoms in Depressed Older Primary Care Patients. A Randomized Controlled Trial. JAMA. 2004; 291(9): 1081-91. |
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| Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006; 24(15): 2268-75. | Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997; 337(14): 949-55. |
| Davies WR, Brown AJ, Watson W, McCormick LM, West NE, Dutka DP, Hoole SP. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP stent trial long-term follow-up. Circ Cardiovasc Interv 2013; 6(3):246-51. | Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, et al. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study. A Prospective, Randomized Control Trial. Circulation 2009; 119 (6): 820-7. |
| Dolan KA, Shearer J, White B, Zhou J, Kaldor J, Wodak AD. Four-year follow-up of imprisoned male heroin users and methadone treatment: mortality, re-incarceration and hepatitis C infection. Addiction 2005; 100(6): 820-8. | Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. Drug Alcohol Depend 2003; 72: 59-65. |
| Ekholm M, Bendahl PO, Fernö M, Nordenskjöld B, Stål O, Rydén L. Two years of adjuvant tamoxifen provides a survival benefit compared with no systemic treatment in premenopausal patients with primary breast cancer: Long-Term follow-up (> 25 years) of the phase III SBII:2pre trial. J Clin Oncol 2016; 34(19): 2232-8. | Rydén L, Jönsson PE, Chebil G, Dufmats M, Fernö M, Jirström K, et al. Two years of adjuvant tamoxifen in premenopausal patients with breast cancer: a randomised, controlled trial with long-term follow-up. Eur J Cancer 2005; 41(2): 256–64. |
| Extension Study Reference                                                                 | Original Trial Reference                                                                 |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Flossmann E, Rothwell PM; British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007; 369: 1603-13. | UK TIA Study: Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991; 54(12): 1044-54. British Doctors Aspirin Study: Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988; 296 (6618): 313-6. |
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| Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy 20-year follow-up of west of Scotland coronary prevention study. Circulation 2016; 133(11): 1073-80. | Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333(20):1301-7. |
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| Gitlin LN, Hauck WW, Dennis MP, Winter L, Hodgson N, Schinfeld S. Long-term effect on mortality of a home intervention that reduces functional difficulties in older adults: results from a randomized trial. J Am Geriatr Soc 2009; 57(3): 476-81. | Gitlin LN, Winter L, Dennis MP, Corcoran M, Schinfeld S, Hauck WW. A Randomized Trial of a Multicomponent Home Intervention to Reduce Functional Difficulties in Older Adults. J Am Geriatr Soc 2006; 54 (5): 809–16. |
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| Goodin DS, Reder AT, Ebers GC, Catter G, Kremenchutzky M, Oger J, et al. Survival in MS: A randomized cohort study 21 years after the start of the pivotal IFN -1b trial. Neurology 2012; 78: 1315-22. | Duquette P, Despault L, Knobler L, Lublin FD, Kelley L, Francis GS, et al. Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial. Neurology 1995; 45(7): 1277-85. |
| Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Lancet 1997; 349: 1493-7. | The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821-28. |
| Extension Study Reference | Original Trial Reference |
|---------------------------|--------------------------|
| Hansen JM, Wildner-Christensen M, Hallas J, Schaffalitzky de Muckadell OB. Effect of a Community Screening for Helicobacter pylori: A 5-Year Follow-Up Study. Am J Gastroenterol 2008; 103(5): 1106-13. | Wildner-Christensen M, Möller Hansen J, Schaffalitzky De Muckadell OB. Rates of Dyspepsia One Year After Helicobacter pylori Screening and Eradication in a Danish Population. Gastroenterology 2003; 125(2): 372–9. |
| Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet 2011; 378: 2013-20. | Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; 361: 2005–16. |
| Holm T, Singnomklao T, Rutqvist LE, Cedermark B. Adjuvant preoperative radiotherapy in patients with rectal carcinoma: Adverse effects during long term follow-up of two randomized trials. Cancer 1996; 78(5): 968-76. | Stockholm Rectal Cancer Study Group. Preoperative Short-term Radiation Therapy in Operable Rectal Carcinoma. A Prospective randomized Trial. Cancer 1990; 66: 49-56. |
| Holme Ø, Løberg M, Kalager M, Brethauer M, Hernán MA, Aas E, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014; 312(6): 606-15. | Hoff G, Grotmol T, Skovlund E, Brethauer M; the Norwegian Colorectal Cancer Prevention Study Group. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009;338: b1846. |
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| Kim LG, P Scott RA, Ashton HA, Thompson SG; Multicentre Aneurysm Screening Study Group. A sustained mortality benefit from screening for abdominal aortic aneurysm. Ann Intern Med 2007; 146(19): 699-706. | Ashton HA, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet 2002; 360: 1531–39. |
| Knatterud GL, Rosenberg Y, Campeau L, Geller NL, Hunninghake DB, Forman SA, et al. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. Circulation 2000; 102(2): 157-65. | The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997; 336(3):153-62. |
| Koh KK. Long-term effectiveness and safety of pravastatin in patients with coronary heart disease: 16 Years of Follow-Up of the LIPID Study. Circulation 2016; 134(13): e294-5. | The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339(19): 1349-57. |

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| Extension Study Reference                                                                 | Original Trial Reference                                                                 |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Kostis JB, Cabrera J, Cheng JQ, Cosgrove NM, Deng Y, Pressel SL, Davis BR. Association Between Chlorthalidone Treatment of Systolic Hypertension and Long-term Survival. JAMA 2011; 306(23): 2588-93. | SHEP Cooperative research group. Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons with Isolated Systolic Hypertension Final Results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991; 265(24): 3255-65. |
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| Labrie F, Candas B, Cusan L, Gomez JL, Bélanger A, Brousseau G, Chevrette E, Lévesque J. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004; 59(3): 311-8. | Tedesco Silva H, Cibrik D, Johnston T, Lackova E, Mange K, Panis C, et al. Everolimus Plus Reduced-Exposure CsA versus Mycophenolic Acid Plus Standard-Exposure CsA in Renal-Transplant Recipients. Am J Transplant 2010; 10: 1401-13. |
| Lim WH, Russ GR, Wong G, Pilmore H, Kanellis J, Chadban SJ. The risk of cancer in kidney transplant recipients may be reduced in those maintained on everolimus and reduced cyclosporine. Kidney Int 2017; 91(4): 954-63. | Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623–30. |
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| Lundström H, Siersma V, Nielsen AB, Brodersen J, Reventlow S, Andersen PK, de Fine Olivarius N. Structured personal care of type 2 diabetes: a 19 year follow-up of the study Diabetes Care in General Practice (DCGP). Diabetologia 2014; 57(6): 1119-23. | Simoons ML, Serruys PW, vd Brand M, Bår F, de Zwaan C, Res J, et al. Improved survival after early thrombolysis in acute myocardial infarction. A Randomised Trial by the Interuniversity Cardiology Institute in The Netherlands. Lancet 1985; 326(8455): 578-81. |
| Maas AC, van Domburg RT, Deckers JW, Vermeer F, Remme WJ, Kamp O. Sustained benefit at 10-14 years follow-up after thrombolytic therapy in myocardial infarction. Eur Heart J 1999; 20(11): 819-26. | Menon V, Li L, Wang X, Greene T, Balakrishnan V, Madero M, et al. Adiponectin and mortality in patients with chronic kidney disease. J Am Soc Nephrol 2006; 17(9): 2599-606. |
| Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). Lancet 2015; 385: 691-7. | Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002; 360: 1267–74. |
| Extension Study Reference | Original Trial Reference |
|---------------------------|--------------------------|
| Nielsen PH, Terkelsen CJ, Nielsen TT, Thuesen L, Krusell LR, Thayssen P, et al. System Delay and Timing of Intervention in Acute Myocardia Infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] Trial). Am J Cardiol 2011; 108(6): 776-81. | Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, et al. Comparison of Coronary Angioplasty with Fibrinolytic Therapy in Acute Myocardial Infarction. N Engl J Med 2003; 349(8): 733-44. |
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| Extension Study Reference                                                                 | Original Trial Reference                                                                                                                                 |
|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
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| Extension Study Reference                                                                 | Original Trial Reference                                                                 |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
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† Individual extension studies may have reported outcomes belonging to multiple categories so the numbers in this table differ from those in Table 3 (Summary of results of trial extension studies), which categorizes all reported analyses (n=155). In this table studies were placed in categories according to a hierarchy in which superiority in the trial extension phase > harms in the trial extension phase > null effects in the trial extension phase > benefits lost in the trial extension phase > analyzed as an observational study. Thus, each study only appears once in the table (n=113).
### eTable 4. Details of participants interventions and outcomes measured in the original and extended trials included in the review

| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|-------------------------|-------------------------|
| **Statistically significant superiority of one treatment observed in trial extension phase** | | | | | |
| Aasa M, 2010. | Svensson L, 2006. | Men and women with ST elevation myocardial infarction. Patients >18 years old presenting within 6 hours after onset of symptoms, with a duration of ≥30 minutes and with ST-segment elevation >2 mm in at least 2 adjacent precordial leads or >1 mm in at least 2 adjacent limb leads were considered for inclusion. Recruited from 7 hospitals and their ambulance organizations. | I: enoxaparin followed by abciximab and transfer to invasive center for optional PCI; C: enoxaparin followed by reteplase; | Primary: ST-segment resolution 120 minutes and TIMI flow at coronary angiography 5 to 7 days after randomization. Secondary: composite of death, stroke, or reinfarction. | Primary: All cause mortality, cardiac death, myocardial infarction. |
| Alehagen U, 2015. | Alehagen U, 2013. | All citizens of a rural Swedish city aged between 70 and 88 years who had previously participated in an epidemiological study and had been continuously followed with medical examinations since 1998. Patients were excluded for the following reasons: Recent myocardial infarction (within 4 weeks), Planned cardiovascular operative procedure within 4 weeks, Hesitation concerning whether the candidate can decide for him/herself to participate in the study or not, or if he/she understands the consequences of participation. Serious disease that substantially reduces survival or when it was not expected that the participant could | I: combination of 200 mg/day of coenzyme Q10 capsules and 200 μg/day of organic selenium yeast tablets; C: placebo | Primary: Cardiovascular mortality; Secondary: All cause mortality and cardiac function. | Primary: cardiovascular mortality; Secondary: to establish if there were different effects on CV-mortality in gender, diabetes, IHD and functional classes as measured by New York Heart Association functional Class (NYHA class) and mortality from other causes. |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|----------------|----------------------------------|-----------------------|-------------------------|------------------------|
|                  |                | cooperate for the full 4 year period and Other factors making participation unreasonable, such as long/complicated transport to the Primary Health Center where the project was managed, or drug/alcohol abuse. | I: 400 mg of bezafibrate per day; C: placebo; Co-I: dietary advice. Also, July 1994 onwards, Colestipol was given concomitantly with the study medication to 165 patients (57 patients in the bezafibrate and 107 in the placebo group) during the study. | Primary: fatal or nonfatal myocardial infarction or sudden death. Secondary: included hospitalization for unstable angina, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. | Fatal or non-fatal myocardial infarction or sudden death. |
| Arbel Y, 2016.   | BIP Study, 2000. | Men and women 45 to 74 years of age, history of MI 6 months but 5 years before enrollment into the study and/or stable angina pectoris confirmed by coronary angiography, and/or radionuclear studies or standard exercise tests. In addition, a lipid profile of serum total cholesterol between 180 to 250 mg/dL, LDL-C #180 mg/dL (#160 mg/dL for patients >50 years), HDL-C #45 mg/dL, and triglycerides #300 mg/dL was required. | I: 400 mg of bezafibrate per day; C: placebo; Co-I: dietary advice. Also, July 1994 onwards, Colestipol was given concomitantly with the study medication to 165 patients (57 patients in the bezafibrate and 107 in the placebo group) during the study. | Primary: fatal or nonfatal myocardial infarction or sudden death. Secondary: included hospitalization for unstable angina, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. | Fatal or non-fatal myocardial infarction or sudden death. |
| Arnsrud Godtman R, 2015. | Hugosson J, 2010. | Men born between 1930 and 1944 (age 50–64, median 56 years) living in the city of Göteborg, Sweden | I: screening group invited for Prostate Specific Antigen testing every 2 years; C: not invited | Prostate-cancer specific mortality | Cumulative prostate cancer incidence and mortality |
| Aronson NE, Aronson JD, 1946. | Indian children and young adults, living on different reservations and communities in various parts of the United States and Alaska, who were free from tuberculosis as indicated by their failure to react, definitely, to a maximum dose (0.005 mg.) of a standardized tuberculin PPD | I: vaccinated intracutaneously with freshly prepared BCG vaccine C: sterile physiological salt solution | Efficacy of BCG vaccine | Efficacy of BCG vaccine |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|-----------------------|-------------------------|-------------------------|
| Arriagada R, 2010. | Rutqvist LE, 1989. | Pre- and postmenopausal women aged below 71 years with a unilateral, operable breast cancer. Surgery consisted of a modified radical mastectomy. Patients were required to have either histologically verified lymph node metastases or a tumor diameter-measured on the surgical specimen exceeding 30 mm. | I1: post-op Radiotherapy; I2: post-op Chemotherapy; C: surgery only | Recurrence free survival, overall survival | Loco-regional recurrence, distant metastases, recurrence free survival, overall survival, secondary malignancies |
| Austin J, 2008. | Austin J, 2005. | Men and women over the age of 60 years with heart failure, New York Heart Association (NYHA) class II or III, and left ventricular systolic dysfunction, confirmed by echocardiography, were eligible for the study. | c: 8-weekly monitoring of clinical status, optimization of pharmacotherapy, and self-care education in a specialist nurse–outpatient clinic (standard care, clinic based care). i: in addition to standard care, twice-weekly 8-week multi-disciplinary cardiac rehab programme, including prescriptive exercise, individualized health education and information, and psychological and social support. (cardiac rehab) | Primary: functional status (NYHA class I–IV), functional performance (6 MWT), perceived exertion (Borg RPE), and health-related quality of life in terms of disease specific (MLHF) and cost utility (EuroQol) questionnaires. Secondary: health care utilisation, in terms of the number and length of stay of hospital admissions arising from heart disease, and prescribed heart failure medication. | Primary: functional status, functional performance, and perceived exertion. HRQL measures, cost-utility questionnaires, EuroQol. Secondary: healthcare use, routine biochemistry, and prescribed heart failure medication, current exercise history, all-cause mortality, survival. |
| Bjurstam N, 2003. | Bjurstam N, 1997. | The entire female population of the city of Gothenburg born between the years 1923 and 1944 inclusive. All women with a history of breast carcinoma prior to randomization were identified and excluded from | i: invitation for screening every 18 months c: one screening around when the study group had their last screening | Primary: breast cancer mortality Secondary: breast cancer incidence | Breast cancer mortality, breast cancer incidence, age-specific breast cancer mortality |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|----------------------|------------------------|------------------------|
| Bogner HR, 2007. | Bruce ML, 2004. | Men and women were recruited using a 2-stage sampling design. The study drew an age-stratified (60-74, 75 years), random sample of patients with an upcoming appointment. Physicians notified sampled patients by mail allowing patients to decline contact. Research associates telephoned the remaining sample to confirm study eligibility: age 60 years or older, ability to give informed consent, Mini-Mental State Examination (MMSE) score of 18 or higher, and ability to communicate in English. With oral consent, eligible patients were screened for depression using the Centers for Epidemiologic Studies Depression scale (CES-D). The study invited all patients with a CES-D score higher than 20 as well as a 5% random sample of patients with lower scores to enroll in the research protocol. | I: Treatment guidelines tailored for the elderly with care management; C: Usual care | Primary: Assessment of suicidal ideation and depression severity (Hamilton Scale) Secondary: all cause and cause-specific mortality; disability (SF12 activities of daily living) | Mortality in patients with or without diabetes |
| Buchwald H, 2002. | Buchwald H, 1992. | Men and women between 30 and 64 years at randomization was the acceptable age range. MI Study: Eligible patients had sustained one and only one electrocardiographically and enzymatically documented, atherosclerotic myocardial infarction (MI) 6-60 months prior to the date of | I: American Heart Association Phase II diet instruction and a partial ileal bypass operation. C: American Heart Association Phase II diet instruction only | Primary: all-cause mortality Secondary: death due to atherosclerosis and morbidity from recurrent myocardial infarction, unstable angina, cerebrovascular accident. Secondary: | Overall mortality |

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| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|----------------|----------------------------------|-----------------------|-------------------------|------------------------|
| Danish Breast Cancer Cooperative Group, 2006. | Overgaard M, 1997. | Premenopausal high-risk patients with breast cancer. High-risk status was defined as consisting of one or more of the following: involvement of axillary lymph nodes, a tumor size of more than 5 cm, and invasion of the cancer to skin or pectoral fascia (pathological stage II or III). A woman was considered premenopausal if she had had amenorrhea for less than five years or had had a hysterectomy before the age of 55. | I: radiotherapy plus systemic chemotherapy; C: chemotherapy alone | Locoregional recurrence, overall survival, disease free survival | Locoregional recurrence and distant metastases |
| Davies WR, 2013. | Hoole SP, 2009. | 1) Patients undergoing elective Percutaneous Coronary Intervention (PCI), 2) baseline cTnI below the lower limit of detection for the assay (<0.04 ng/mL), 3) 18 years of age or older 4) able to give informed consent 5) women could | I: remote ischemic preconditioning (induced by 3 5-minute inflations of a blood pressure cuff to 200 mm Hg around nondominated upper arm, followed by 5-minute | Primary: assess whether remote IPC given approximately 1 hour before elective PCI reduced cardiac troponin I (cTnI) concentration at 24 | MACCE rate |

randomization. Patients with either a transmural or non-transmural MI were accepted. Total plasma cholesterol study: To be eligible, the patient’s total plasma cholesterol at the screening/baseline visit, after at least 6 weeks of dietary therapy, had to equal or exceed 220mg/dl, or if it was between 200 and 2 19 mg/dl, the concurrent LDL-cholesterol level had to equal or exceed 140 mg/dl.

coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, cardiac transplantation, and peripheral vascular surgery, arteriographic changes as a predictor of subsequent clinical coronary events. Combined end point of atherosclerotic coronary heart disease mortality or confirmed nonfatal myocardial infarction.
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|-------------------------|------------------------|
| Dolan KA, 2005.   | Dolan KA, 2003. | Male inmates were eligible to participate if they: (1) were assessed as suitable for MMT by a detailed interview with medical staff which confirmed they had a heroin problem; (2) were serving prison sentences longer than 4 months at time of interview; and (3) were able to provide signed informed consent. | i: Methadone maintenance c: Wait list control | Heroin use, heroin injection and injection of other drugs, syringe sharing, HIV and HCV prevalence, tattooing and sexual risk behavior | Mortality, reincarceration, hepatitis C Seroconversion and HIV seroconversion. |
| Ekholm M, 2016.   | Rydén L, 2005.  | Pre-menopausal women with Stage 2 breast cancer (With and without ER and PR receptors) after breast sparing surgery and radiotherapy by Regional Oncological Centers | I: tamoxifen; C: no treatment | Relapse free survival | All cause mortality and breast cancer related mortality |
| Flossmann E, 2007. | UK TIA Study: Farrell B, 1991. British Doctors | UK TIA: men and women who had a recent transient ischaemic attack (TIA) or minor ischaemic stroke or had potential cardiac sources of embolism who were not anticoagulated. Exclusion: Patients | UK TIA: I: ‘High dose’ aspirin (patients received two 300mg aspirin tablets twice daily); co-I: ‘Low dose’ aspirin | UK-TIA: Primary: survival free of disabling stroke, whilst definitely non-vascular deaths should be censored. | Primary: colorectal cancer. Secondary: other cancers. |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|----------------|----------------------------------|----------------------|------------------------|------------------------|
| **Aspirin Study:** Peto R, 1988. | younger than 40 years of age, cerebrovascular event occurred before 3 months, previously experienced disabling major stroke, attacks were definitely due to something other than arterial thromboembolism, likely to experience adverse events from aspirin (allergy, intolerance, previous abnormal bleeding, alcoholism etc.) and confound analyses by taking aspirin 90 days prior to randomization or having myocardial infarction within 3 months prior to randomization, might have difficulty with follow-up, comply poorly and had severe intercurrent non vascular disease. **BMDAS:** All male doctors resident in the United Kingdom in 1978 who were born this century, who had replied to a questionnaire about their smoking habits that was sent to them in 1951 (as part of another study), and who were still listed in the 1977 Medical Directory. Ineligible: already taking aspirin for various reasons, could not take it, and history of peptic ulcer, stroke, or definite myocardial infarction. | (patients received two 150 mg aspirin tablets in the morning and two placebo tablets in the evening); C: Placebo (patients received two placebo tablets twice daily). **BMDAS:** I: daily aspirin (500mg) unless some contraindication was thought to have developed C: avoid aspirin and products containing aspirin unless some specific indication for aspirin was thought to have developed (no placebo). | Secondary: time to "major stroke, myocardial infarction or vascular death". **BMDAS:** Primary: myocardial infarctions, strokes, and transient ischaemic attacks; Secondary: deaths |
| **Folkesson J, 2005.** | patients aged 79 and under with potentially resectable colorectal cancer (histopathologically proven) | I: reoperative irradiation (2.5 Gy inJive fractions over 1 week) followed by surgery within 1 week; C: surgery alone | Postoperative (short term mortality) and operative complications Primary: overall survival, cancer-specific survival. Secondary: local recurrence rate, and distant metastasis |

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| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|----------------|-----------------------------------|-----------------------|------------------------|------------------------|
| Ford I, 2016.     | Shepherd J, 1995. | Males aged 45-64 years who, at randomization, display at most minor overt evidence of CHD, identified from primary clinics throughout West of Scotland district. Men, who attended the first visit, whose non fasting plasma cholesterol was at least 252 mg/dL with no history of MI and LDL >155 mg/dL | I: pravastatin (40 mg each evening) C: placebo | Primary: nonfatal myocardial infarction or death from coronary heart disease as a first event. Secondary: death from coronary heart disease and nonfatal myocardial infarction. | Mortality, incident cancers, and cumulative number of hospital admissions |
| Frasure-Smith N, 1989. | Frasure-Smith N, 1985. | Male patients post myocardial infarction admitted to coronary care units in Montreal | I: Stress monitoring and psychological intervention after AMI; C: usual care | Stress scores, rehospitalisations, LOHS and mortality | Recurrence of AMI and cardiac mortality |
| Fritz D, 2012.     | de Gans J, 2002. | Men and women 17 years of age or older, had suspected meningitis in combination with cloudy cerebrospinal fluid, bacteria in cerebrospinal fluid on Gram's staining, or a cerebrospinal fluid leukocyte count of more than 1000 per cubic millimeter. | I: dexamethasone sodium phosphate (10 mg given every six hours iv for four days) C: placebo | Primary: score on the Glasgow Outcome Scale Secondary: death, focal neurologic abnormalities (defined as aphasia, cranial-nerve palsy, monoparesis, hemiparesis, and severe ataxia), hearing loss, gastrointestinal bleeding (clinically relevant bleeding with a decreased serum hemoglobin level), fungal infection, herpes zoster, and hyperglycemia (a blood glucose level higher than 144 mg per deciliter [8.0 mmol per | Survival |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|----------------------------------|-----------------------|-------------------------|-------------------------|
| Gitlin LN, 2009. | Gitlin LN, 2006. | Community-living adults (men and women) aged 70 and older who reported difficulty with one or more activities of daily living. | I: Multicomponent Home Intervention (five occupational therapy contacts (four 90-minute visits and one 20-minute telephone contact) and one physical therapy visit(90 minutes)) C: usual care | Instrumental activities of daily living | All cause mortality |
| Gjestad R, 2011. | Dahlgren L, 1989. | Patients were admitted mainly by self-referral. Only women in early phases of alcohol dependence are accepted. Signs of chronic alcoholism (liver cirrhosis, dementia), previous treatment for alcohol problems, and psychotic syndromes are regarded as exclusion criteria, as is use of narcotic drugs. | i: early treatment for women with alcohol addiction at specialized treatment center for women (EWA) c: treatment as usual in regular ward at standard mixed-sex treatment facility (TAU) or the community | Primary and secondary outcomes not explicitly stated; assessed morbidity, mortality, alcohol consumption | All cause mortality |
| Goodin DS, 2012. | Duquette P, 1995. | Young men and women (mean age, 35.5 years) and ambulatory, with Kurtzke Expanded Disability Status Scale (EDSS) scores of 0 to 5.5 (mean, 2.9) | I1: 1.6 million international units (MIU) of interferon beta-1b every other day subQ; I2: 8 MIU; C: placebo | Primary: Annual exacerbation rates, annual change in EDSS and change in MRI lesion area; Secondary: (1) annual exacerbation rates, (2) the proportion of exacerbation-free subjects, (3) the severity of exacerbation as measured by | Primary: survival/mortality (all-cause mortality), Secondary: all-cause mortality |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|----------------|----------------------------------|-----------------------|-------------------------|-------------------------|
| Hall AS, 1997.    | AIRE Study Investigators, 1993. | Men and women 18 years of age or older admitted to coronary care, intensive care, or general medical units with a definite AMI and clinical evidence of heart failure at any time after the index AMI (usually sufficient to justify at least short-term diuretic or vasodilator treatment), were eligible. | I: ramipril on day 3 to day 10 after AMI (occurring on day 1)  c: placebo | Primary: total mortality.  Secondary: progression to heart failure, reinfarction, or stroke. | All-cause mortality |
| Hansen JM, 2008.  | Wildner-Christensen M, 2003. | Men and women aged 40 to 64 (inclusive) years living in the city of Odense, Denmark, and the surrounding municipalities (rural and urban) were identified by their civil registration number in the county’s population register. | I: offered Helicobacter pylori screening and eradication;  C: no invite | Primary: prevalence of dyspepsia;  Secondary: changes in consultation rate at the GP for dyspepsia, number of sick leave days because of dyspepsia, use of ulcer medication and antacids, number of diagnostic procedures for dyspepsia, and resulting diagnoses and quality of life. | Frequency of dyspepsia |
| Heart Protection Study Collaborative Group, 2011. | Collins R, 2003. | Men and women aged about 40–80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) were eligible provided they had a medical | I: 40 mg simvastatin daily;  C: placebo | First major coronary event (i.e., non-fatal myocardial infarction or coronary death) and of first major vascular | Primary: first post-randomisation major vascular event (defined as non-fatal myocardial infarction |

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| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|-----------------------|------------------------|-------------------------|
| Holm T, 1996.     | Stockholm Rectal Cancer Study Group, 1990. | Men and women with biopsy confirmation of rectal adenocarcinoma, resectable tumors as judged by clinical examination, tumors not extending above the sacral promontory (lateral x-ray view), and no signs of distant metastases (physical examination, liver function tests, chest radiograph). | i: radiation therapy plus surgery c: surgery alone | Primary: incidence of pelvic recurrence Secondary: survival | Primary: adverse effects (venous thromboembolism, diseases of the arteries, femoral neck or pelvic fractures, intestinal obstructions, fistulas, diseases of |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|-----------------------|------------------------|------------------------|
| Holme Ø, 2014.   | Hoff G, 2009.   | All residents aged 55-64 years living in the city of Oslo and Telemark County, Norway, who were registered and alive in the national population registry by November 1998 (n=55 736), were eligible | I: flexible sigmoidoscopy screening with or without a single round of faecal occult blood testing (once only); C: no screening | Cumulative incidence and mortality of colorectal cancer after 5, 10, and 15 years. | Colorectal cancer incidence and mortality. |
| Hulse GK, 2003.   | Hulse GK, 2002. | Men and women in psychiatric wards screened for excessive alcohol consumption within 18-65 years of age, given Alcohol Use Disorder Identification Test (AUDIT) - if they scored above 8, they were eligible. Exclusion: had memory problems, apparent organic brain disease, lived outside the metropolitan area, required an interpreter, were insufficiently well to answer questions or were considered too aggressive to be interviewed | I: an information package which detailed safer alcohol consumption patterns and gave comparison scores for the alcohol consumption surveys. i2: motivational interview which was an individual 45-minute treatment based on the non-judgemental approach | Weekly alcohol consumption in standard (10g) drinks (safe, hazardous, harmful) | Survival to first alcohol event (between intervention groups), hospital and mental health morbidity comparisons between intervention and matched groups |
| Jansen AF, 2009. | van Rooij J, 2003. | All successive patients (men and women) with corneal opacities attributed to HED who were scheduled for Penetrating Keratoplasty were considered for enrollment in this study. | I: Oral acyclovir 400 mg twice daily; C: placebo tablets | Recurrence rate of herpetic eye disease–related events and rejection episodes, proven by viral cell culture or polymerase chain reaction. | Primary: Clinically evidence recurrence; Secondary outcomes: visual acuity, graft failure, vascularization |
| Kim LG, 2007.    | Ashton HA, 2002. | Men aged 65–74 years from four centres (Portsmouth, Southampton, Winchester, and Oxford) in the UK | i: invited for screening (for abdominal aortic aneurysm) | Primary: mortality related to abdominal aortic aneurysm | Primary: AAA-related mortality. |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|-------------------------|------------------------|
| Knatterud GL, 2000. | The Post Coronary Artery Bypass Graft Trial Investigators, 1997. | Men and women who were 21 to 74 years of age, had LDL cholesterol levels of no more than 200 mg per deciliter, and had had at least two saphenous-vein coronary bypass grafts placed 1 to 11 years before the start of the study. Of these patients, we deemed eligible those who had LDL cholesterol levels of 130 to 175 mg per deciliter (4.5 mmol per liter) and triglyceride levels below 300 mg per deciliter (3.4 mmol per liter), as measured at any visit to a study physician after the initiation of a Step 1 diet; two patent saphenous-vein grafts (with stenosis of less than 75 percent) in men (one in women); and an ejection fraction of no less than 30 percent. | I1: aggressive-treatment group - lovastatin was initially given in doses of 40 mg per day. i2: moderate treatment group - 2.5 mg per day lovastatin co-I: warfarin or placebo (2x2 factorial design) | Primary: substantial progression of disease. Secondary: grafts with occlusion, grafts with new lesions, grafts with substantial improvement, death, myocardial infarction, cancer, stroke, bypass surgery, angioplasty | All-cause mortality, myocardial infarction, revascularization, composite clinical outcome, other outcomes (stroke, peripheral vascular procedures, cancer). |
| Koh KK, 2016. | LIPID Study Group, 1998. | Men and women who had had an acute myocardial infarction or had a hospital-discharge diagnosis of unstable angina between 3 and 36 months before study entry. For patients to qualify for the study, the plasma total cholesterol level measured four weeks before | i: 40 mg of pravastatin once daily c: matching placebo once daily. | Primary: death from coronary heart disease. Secondary: death from any cause; death from cardiovascular causes; death from CHD or nonfatal myocardial infarction; myocardial | All-cause mortality, cause-specific mortality, cancer incidence |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|----------------|----------------------------------|----------------------|-------------------------|------------------------|
| Kostis JB, 2011.  | SHEP Cooperative research group, 1991. | Men and women aged 60+ with SBP>160 and DBP<90, recruited using mass mailing and community screening techniques | I: Stepped treatment of isolated systolic hypertension: For step 1 of the trial, dose 1 was chlorthalidone, 12.5mg/d, or dose 2 was 25mg/d. For step 2, dose 1 was atenolol, 25mg/d, Dose 2 was 50mg/d; C: placebo | infarction; stroke; non-hemorrhagic stroke; coronary revascularization (coronary angioplasty, coronary-artery bypass surgery, or both); number of days in the hospital; serum lipid levels; and the relation of changes in lipid levels to the occurrence of cardiovascular end points. | Primary: Nonfatal and fatal (total) stroke. Secondary: Cardiovascular and coronary morbidity and mortality, all-cause mortality, and quality of life measures | Primary: CVD mortality. secondary: All cause mortality |
| Küchler T, 2007.  | Kuchler T, 1999. | Male and female patients, recruited from surgical ward of a Hamburg hospital, having surgery for a range of gastrointestinal cancers: esophagus, stomach, liver/gallbladder, pancreas, or colon/rectum | I: psychotherapeutic support in addition to routine care C: routine care in gastrointestinal cancers following surgery | Quality of life, overall survival | Overall survival |
| Labrie F, 2004.   | Labrie F, 1999. | Men aged 45 to 80 years registered in the 1985 electoral rolls in metro Quebec City who were traceable in health registries. Exclusion: men with prostate cancer diagnosis prior I: annual Prostate screening with PSA and DRE; C: no screening invite letter | Death due to prostate cancer | Prostate cancer mortality |

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| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|----------------|----------------------------------|-----------------------|-------------------------|------------------------|
| Lim WH, 2017.    | Tedesco Silva H, 2010. | Men and women aged 18–70 years undergoing primary kidney transplantation were eligible. Key exclusion criteria included, kidneys donated after cardiac death or with a cold ischemia time >40 hours; donor age >65 years; recipients of multiorgan-, ABO-incompatible-, positive T-cell cross-match- or HLA-identical living-related-donor transplants; or most recent anti-HLA Class I panel-reactive antibodies (PRA) >20% by a CDC (complement-dependent cytotoxicity)-based assay or >50% by flow cytometry or ELISA. | I1: Everolimus 1.5 mg (0.75 mg p.o. b.i.d. targeted to 3–8 ng/mL) + RD-CsA.  
I2: Everolimus 3.0 mg (1.50 mg p.o. b.i.d. targeted to 6–12 ng/mL) + RD-CsA.  
C: MPA 1.44 g (720 mg p.o. b.i.d.) + ST-CsA. | Primary: composite efficacy failure (treated biopsy-proven acute rejection, graft loss, death or loss to follow-up).  
Main safety endpoint: renal function (estimated glomerular filtration rate [eGFR], by Modification of Diet in Renal Disease [MDRD]) at Month 12 (last-observation-carried-forward analyses). | Primary: the first NMSC (i.e., basal cell carcinoma [BCC] or squamous cell carcinoma [SCC] of the skin) or any non-skin cancers diagnosed after transplantation.  
Secondary: delayed graft function (defined as requirement for dialysis after transplantation); acute rejection; overall graft loss (defined as death or return to dialysis); eGFR at 1 and 6 months, 1, 2, 3, 5, and 7 years after transplantation (those who lost their grafts or died were censored); discontinuation rate (i.e., discontinued mycophenolic sodium in the MPA group or discontinued everolimus in the everolimus treatment groups), |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|----------------------|------------------------|------------------------|
| Lloyd SM, 2013.  | Shepherd J, 2002. | Men and women aged 70–82 years were recruited if they had either pre-existing vascular disease (coronary, cerebral, or peripheral) or raised risk of such disease because of smoking, hypertension, or diabetes. Their plasma total cholesterol was required to be 4.0–9.0 mmol/L and their triglyceride concentrations less than 6.0 mmol/L. | I: pravastatin (40 mg per day); C: placebo | Primary: a composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke. Secondary: examination of the coronary and cerebrovascular components separately. | Overall mortality, mortality from non-cardiovascular events, cardiovascular events, CHD and stroke |
| Lundström H, 2014. | de Fine Olivarius N, 2001. | All patients aged 40 or older with newly diagnosed diabetes between 1 March 1989 and 28 February 1991 based on hyperglycaemic symptoms or raised blood glucose values measured in general practice, or both, and who were registered with a participating general practitioner. | i: Regular follow up and individualized goal setting in the intervention group, follow up every three months and annual screening for diabetic complications were supported by sending a questionnaire to the general practitioner one month before the next expected consultation. c: routine care (doctor | Primary: mortality, retinopathy, urinary albumin, myocardial infarction, stroke. Secondary: peripheral neuropathy, angina pectoris, intermittent claudication, amputation | Any diabetes-related endpoint, diabetes-related deaths, all-cause mortality, myocardial infarction (MI), stroke, peripheral vascular disease and microvascular disease |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|----------------|----------------------------------|-----------------------|-------------------------|-------------------------|
| Maas AC, 1999.    | Simoons ML, 1985. | Men and women up to 70 years with severe chest pain lasting longer than 20 min with ST segment elevation of >0.2 mv in 1+ precordial leads and/or >0.1mV in 1+ limb leads. Also included patients with 0.2mV ST segment depression in precordial leads indicating posterior wall infarction. | i: treatment with intracoronary streptokinase OR treatment with intravenous + intracoronary streptokinase | Mortality, ventricular fibrillation, pericarditis, cardiogenic shock, bleeding, reinfarction | Mortality/survival rates, reinfarction, subsequent cardiac events |
| Menon V, 2006.    | Peterson JC, 1995. | Men and women aged 18 to 70. Serum creatine level of 1.2 to 7.0 mg/dL for women and 1.4 to 7.0 mg/dL for men or a creatinine clearance less than 70 mL/min; and mean arterial pressure of 125 mm Hg or less. Patients were excluded if they had diabetes requiring insulin, proteinuria of 10 g/d or more, or body weight less than 80% or more than 160% of standard body weight. | c: usual blood pressure goal i: low blood pressure goal STUDY A: usual (1.3g/kg d) or low protein diet (0.58g/kg). STUDY B: low or very-low (0.28g/kg) protein diet. | Rate of decline in glomerular filtration rate and change in proteinuria during follow-up. | All-cause mortality, cardiovascular mortality |
| Molyneux AJ, 2015. | Molyneux AJ, 2002. | Men and women were eligible for the trial if: (1) they had a definite subarachnoid haemorrhage, proven by computed tomography (CT) or lumbar puncture, within the preceding 28 days; (2) they had an intracranial aneurysm, demonstrated by intra-arterial or by CT angiography, which was considered to be responsible for the recent subarachnoid haemorrhage; | i: endovascular coiling c: neurosurgical clipping | Primary: modified Rankin scale (number of patients dependent or dead after one year post treatment). Secondary: prevention of rebleeding from the treated aneurysm, quality of life at 1 year (using a EuroQol measure), the | Death, dependence (measured according to patient-reported modified Rankin scale scores), and recurrent subarachnoid haemorrhage after neurosurgical |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria                                                                 | Original Intervention                                                                 | Original Trial Outcomes                                                                 | Extended Trial Outcomes                                                                 |
|-------------------|-----------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
|                   |                 | (3) they were in a clinical state that justified treatment, at some time, by either neurosurgical or endovascular means; (4) they had an intracranial aneurysm that was judged by both the neurosurgeon and the interventional neuroradiologist to be suitable for either technique on the basis of its angiographic anatomy; (5) there was uncertainty as to whether the ruptured aneurysm should be treated by neurosurgical or endovascular means; and (6) they gave appropriate informed consent, according to the criteria laid down by the local ethics committee. | frequency of epilepsy, cost-effectiveness, and neuropsychological outcomes.          | clipping or endovascular coiling                                                        |
| Nielsen PH, 2011. | Andersen HR, 2003. | Men and women of 18 years or more, the presence of symptoms for at least 30 minutes but less than 12 hours, and cumulative ST-segment elevation of at least 4 mm in at least two contiguous leads. | i: primary angioplasty or fibrinolysis at invasive-treatment centers  c: primary angioplasty or fibrinolysis at referral hospitals | Composite of death from any cause, clinical reinfarction, disabling stroke at 30-days after treatment. | 30 day mortality, long term (8-year) mortality |
| Nyström L, 2002. | Malmo: Andersson I, 1988. | Malmo trial: Women born between 1908 and 1932 (MMST I), women who were born 1933–45 and were living in Malmö between 1978 and 1990 (MMST II). Two County Trial: Women aged 40–49, 50–69, and 70–74 years living in Kopparberg and Östergötland. Stockholm trial: Women in the southern part of Stockholm born between 1917 and 1942. Göteborg trial: All women born | Malmo trial: screen-film mammography alone, in the first two rounds with two views (craniocaudal and oblique) and in subsequent rounds with either two views or the oblique view alone depending on the parenchymal pattern. Two County Trial: offered screening every 2 or 3 years depending on age | Malmo trial: Primary: breast cancer as underlying cause of death. Two county trial: Primary: mortality from breast cancer. Stockholm trial: Primary: prevalence of breast cancer and metastasis. Göteborg trial: breast carcinoma mortality | Breast cancer as underlying cause of death |

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| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|-----------------------|-------------------------|-------------------------|
|                    | Olds DL, 2014.  | Women at less than 29 weeks' gestation, with no previous live births, and with at least 2 sociodemographic risk characteristics (unmarried, <12 years of education, unemployed). | I1: free transport for prenatal care  I2: free transport for prenatal care and developmental screening, referral services at ages 6, 12 and 24 months  I3: Free transport for prenatal care and nurse home visits during pregnancy and 2 postpartum  I4: I3 + home visits through child's 2nd birthday, as well as developmental screens and referrals | Primary: pregnancy induced hypertension, preterm delivery, low birth weight. Secondary: children's injuries, ingestions and immunizations; mothers' reports of children's behavioural problems; tests of children's mental development; mothers' reports of subsequent pregnancy, educational achievement, and labor force participation; and use of welfare derived from state records | All-cause mortality in mothers and preventable-cause mortality in children (sudden infant death syndrome, unintentional injury, and homicide) |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|----------------|----------------------------------|----------------------|------------------------|------------------------|
| Plüss CE, 2011.  | Plüss CE, 2008.| Men and women (<75 years old) with an acute myocardial infarction or patients undergoing coronary artery bypass graft at Danderyd Hospital | I: recurrent case method learning dialogues at their primary healthcare centres: usual care plus stress management program, 5-day stay at patient hotel, cooking sessions with diet counselling; C: usual rehab program: physical training, information/counselling, heart school, outpatient clinic, individual counselling sessions Co-I: all participants who smoked who offered a smoking cessation program | Primary: biochemical risk marker change (e.g. LDL cholesterol) Secondary: exercise performance | Cardiovascular death, myocardial infarction, readmission for cardiovascular disease and days at hospital for cardiovascular reason |
| Puolakka K, 2004. | Mörtnen T, 1999.| Men and women based on the criteria of the American Rheumatism Association for rheumatoid arthritis; age between 18 and 65 years; duration of symptoms of less than 2 years; active disease with three or more swollen joints and at least three of the following: erythrocyte sedimentation rate (ESR), at least 28 mm/h or C-reactive protein (CRP) concentration above 19 mg/L; morning stiffness of 29 min or more; more than five swollen joints and more than ten tender joints | I: Combination drug therapy (DMARDs (sulfasalazine, methotrexate, hydroxychloroquine) plus prednisolone); C: Single drug therapy (DMARDs (sulfasalazine, methotrexate, hydroxychloroquine)) | Primary: induction of remission (as per ACR criteria) Secondary: meaningful clinical response (ACR 50% response criterion—i.e., minimum 50% improvement in tender and swollen joint plus a similar improvement in at least three of five remaining core measures); improvement in each individual core measure; development of radiographic joint | Cumulative duration of all sick leaves and RA-related disability pensions |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|-----------------------|------------------------|------------------------|
| Qu C, 2014..      | Sun Z, 1991.    | All newborns in Qidong County of China (born 1985-90) | I: HBV vaccine; C: no vaccine | Incidence of HBV infection, mortality/ adverse events from vaccination | Primary: mortality from development of hepatic encephalopathy and coagulopathy, PLC incidence; Secondary: Brain tumour incidence |
| Rana MM, 2013.    | The FUTURE II Study Group, 2007. | Women aged 15-26 years who were not pregnant, did not report abnormal results on a Papanicolaou smear, and had had a lifetime number of no more than four sex partners | I: Quadrivalent HPV vaccine (6/11/16/18), 3 doses; C: placebo | Composite end point of cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV-16 or HPV-18 | HPV16/18 associated cervical intraepithelial neoplasia (CIN) Grade 2/3 and invasive cervical carcinoma (ICC) |
| Reichard P, 1988. | SWEDESCREEN: women aged 32-38 participating in population-based screening program; POBASCAM: women aged 30-60 years with a general practitioner; ARTISTIC: women aged 20-64 years attending for routine cervical screening; NTCC: women aged 25–60 years who were not pregnant, had never undergone hysterectomy, had not undergone a pelvic examination in the past year, and had normal results on a Papanicolaou smear | I: intensive control of T1DM C: standard control of T1DM | Primary: HBA1c, retinopathy, microalbuminuria, nerve conduction studies, severe hypoglycemia | Foot ulceration and microcirculation |
| Ronco G, 2014.    | SWEDESCREEN: HPV Screening + Cytology vs. Cytology only POBASCAM: intervention based on cytology and hpv test, control group just based on conventional cytology and no hpv test. ARTISTIC: cervical sample either concealed from or revealed to them | SWEDESCREEN: HPV Screening + Cytology vs. Cytology only POBASCAM: intervention based on cytology and hpv test, control group just based on conventional cytology and no hpv test. ARTISTIC: cervical sample either concealed from or revealed to them | Primary: incidence of CIN2/CIN3+ lesions. POBASCAM: Primary: proportion of histologically confirmed >CIN3 lesions in each study arm. ARTISTIC: primary: proportion of additional lesions in the revealed | Primary: invasive carcinoma of the cervix. Secondary: detection rate |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Ronco G, 2010.    |                 | been treated for CIN in the last 5 years, and who were attending for a new routine cervical screening episode. | NTCC: intervention of conventional cytology vs. HPV test | arm, 3 year detection rate. Secondary: sensitivity and specificity of test, cost effectiveness, psychological effects, attendance rates, test preferences. **NTCC**: Primary: number of women with histologically confirmed pre-invasive lesions and invasive cervical cancer detected after randomisation. | |
| Rosell J, 2013.   | Nordenskjöld B, 2005. | Postmenopausal women younger than 75 years of age who had early stage, axillary lymph node-negative or -positive, invasive disease | I: 5 years of adjuvant treatment with tamoxifen in breast cancer; C: 2 years of treatment | Primary: event-free survival (local-regional recurrence, distant metastasis, contralateral breast cancer, or death) and overall survival. | Hospitalisation for non-fatal and fatal CHD and other forms of cardiac diseases, e.g., heart failure (HF), atrial fibrillation |
| Rousseau MF, 2016. | SOLVD Investigators, 1991. | Men and women with congestive heart failure, ejection fraction < 0.35 already taking drugs other than an angiotensin converting enzyme inhibitor as part of treatment for congestive heart failure. | I: enalapril at an initial dose of 2.5 mg twice daily, gradually increase to 10 mg twice daily unless side effects developed C: placebo | Total mortality. Secondary: incidence of heart failure, rate of heart failure | Primary: total mortality. Secondary: cause-specific mortality |
| Scholefield JH, 2012. | Hardcastle JD, 1996. | Men and women aged 45–74 years who lived in the Nottingham area of the UK (from GP registry) without serious illness | I: FOB screening every 2 years C: no screening | Colorectal cancer (CRC) mortality | CRC mortality |
| Schröder FH, 2014. | Schröder FH, 2009. | Men aged 50-74 at time of randomization. Sweden: 50-54; NED, Italy, Belgium, and Spain: up | I: screening for prostate cancer once every 4 years C: no screening | Mortality from prostate cancer | Primary: Mortality due to prostate |

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| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|-----------------------|-------------------------|-------------------------|
| Secher RG, 2015.  | Petersen L1, 2005. | Men and women aged 18-45 years with first episode of schizophrenia spectrum disorder who had not been given antipsychotic drugs for more than 12 continuous weeks; identified from all inpatient and outpatient mental health services in Copenhagen and Aarhus County | I: Integrated treatment (assertive community treatment with programmes for family involvement and social skills training); C: Standard treatment (contact with a community mental health centre) | Primary: psychotic symptoms (hallucinations, delusions, and thought disorders) and negative symptoms (anhedonia, avolition, affective blunting, and alogia). Secondary: substance abuse, treatment adherence, lower dosage of antipsychotic medication, higher satisfaction with treatment, and reduced burden to the family | Primary: psychotic symptoms (hallucinations, delusions, and thought disorders) and negative symptoms (anhedonia, avolition, affective blunting, and alogia). Secondary: substance abuse, treatment adherence, lower dosage of antipsychotic medication, higher satisfaction with treatment, and reduced burden to the family |
| Sever PS, 2011.   | Sever PS, 2005.  | Men and women 40-79 years; Hypertension (either of: Untreated hypertension with sBP > 160mmHg or dBP > 100mmHg, or both OR Treated hypertension with sBP > 140mmHg or dBP > 90 mmHg, or both); Three or more cardiovascular risk factors, defined as: Left ventricular hypertrophy (by ECHO or ECG), Type 2 diabetes, Peripheral arterial disease, Previous stroke or TIA, Male | I: combination antihypertensive regimen of a CCB (amlodipine) and ACEI (perindopril) C: B-blocker (atenolol) and a thiazide diuretic (bendroflumethiazide). | Primary: nonfatal myocardial infarction, fatal coronary artery disease Secondary: fatal and non-fatal strokes | Primary: all-cause mortality Secondary: CV-related deaths, non-CV-related deaths, deaths from infection or respiratory illness |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria                                                                                                                                                                                                 | Original Intervention                                                                                                                                                                                                 | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|-------------------------|
| Stamler J, 2012.  | Stamler J, 1996. | Men whose risk for coronary heart disease was assessed using measurements of serum cholesterol, diastolic BP, and self-reported cigarette smoking. Men who were in the upper 15% (changed to 10% after one third of the screening was completed) of risk, a serum creatinine 2.0 mg/dl and without evidence of cardiovascular or other life-threatening diseases were included. | I: special intervention (SI) received group and individual counseling on a fat-modified diet; a stepped-care drug treatment program for hypertension (after an initial attempt to control BP by weight reduction, if indicated); and for cigarette smokers, counseling aimed to achieve cessation. C: usual care | Primary: mortality from coronary heart disease Secondary: blood pressure                                                                                      | Primary: CVD Mortality. Secondary: non-fatal CVD outcomes (CHD, MI, CHF, coronary surgery) |
| Stewart JC, 2014. | Unützer J, 2002. | Men and women were selected based on the following 2 strategies. The first strategy relied on referrals of depressed older adults from primary care practitioners, other clinic staff, or patients themselves in response to clinic promotions of the program. The second method consisted of systematic depression screening of English-speaking, | I: IMPACT intervention (access to a depression care manager who was supervised by a psychiatrist and a primary care expert and who offered education, care management, and support of antidepressant management by the | Depression, depression treatments, satisfaction with care, functional impairment, and quality of life | Primary: hard CVD event: a) fatal MI (ICD-10 codes I21-I22 the first-listed cause of death), (b) laboratory evidence of acute MI (creatine kinase-myocardial band isoenzyme value >3.0 ng/ml or |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Stewart S, 2014.  | Stewart S, 2012. | Older adults who used the participating primary care clinics with a 2-item depression screener adapted from the PRIME M.D. study. Exclusion: drinking problem, bipolar or psychosis, in psychiatric treatment, severe cognitive impairment, or at acute risk of suicide. | Patient’s primary care physician or a brief psychotherapy for depression, Problem Solving Treatment in Primary Care; C: usual care | Troponin value >0.3 μg/L, (c) acute MI diagnosis, (d) fatal stroke, or (e) hemorrhagic or non-hemorrhagic stroke diagnosis. Secondary: fatal/nonfatal MI (categories a–c), fatal/nonfatal MI – cardiac enzyme confirmed (categories a and b), fatal/nonfatal stroke (categories d and e), and all-cause mortality. |
| Strandberg TE, 2004.  | 4S Group, 1994. | Men and women aged 35–70 years with previous myocardial infarction or angina pectoris >6 months prior, serum total cholesterol 5.5–8.0 mmol/L, and serum triglycerides 2.5 mmol/L or lower. Excluding: | I: specialized CHF clinic-based intervention (CBI); C: home-based intervention (HBI) | Primary: all-cause, unplanned hospitalization or death during 12- to 18-month follow-up. Secondary: type and duration of hospitalization and healthcare costs. | Primary: event-free survival from all-cause emergency hospitalization or death, all-cause mortality; Secondary: rate of all-cause hospitalization and stay. |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|----------------------|------------------------|------------------------|
| premenopausal women of childbearing potential, secondary hypercholesterolaemia, unstable or Prinzmetal angina, tendon xanthomata, planned coronary artery surgery or angioplasty, MI during the preceding 6 months, antiarrhythmic therapy, congestive heart failure requiring treatment with digitalis, diuretics, or vasodilators, persistent atrial fibrillation, cardiomegaly, haemodynamically important valvular heart disease, history of completed stroke, impaired hepatic function, partial ileal bypass, history of drug or alcohol abuse, poor mental function, other serious disease, current treatment with another investigational drug, or hypersensitivity to HMG-CoA reductase inhibitors. | resuscitated cardiac arrest, silent MI. Tertiary: any coronary event, death or any atherosclerotic event, incidence of myocardial revascularization procedures, incidence of hospital admissions for acute CHD events | Secondary: Cancer incidence |
| Wallentin L, 2016. FRISC II Investigators, 1999. | Men and women with symptoms of ischaemia that were increasing or occurring at rest, or that warranted the suspicion of acute myocardial infarction, with the last episode within 48 h before the start of dalteparin or standard heparin treatment. Exclusion criteria were raised risk of bleeding episodes, anaemia, or indication for or treatment in the past 24 h with thrombolysis, angioplasty in the past 6 months, being on a waiting list for coronary revascularisation, | I: Invasive treatments including coronary angiography within a few days of enrolment, aiming for revascularisation within 7 days of the start of open-label treatment. C: Non-invasive treatment included coronary angiography in patients with refractory or recurrent symptoms, despite maximum medical treatment, or severe | Primary: Mortality and myocardial infarction at 6 months of follow-up. Secondary outcomes: total death, myocardial infarction, symptoms of angina, need for late coronary angiography and revascularisation, bleeding episodes, and stroke. | Primary: composite of death or myocardial infarction. Secondary: all-cause death, cardiac death, and new revascularisation procedures. Additional composite endpoints, such as hospital admissions for ischaemic heart |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|-----------------------|------------------------|------------------------|
|                  |                 | other acute or severe cardiac     | ischaemia on a symptom | disease and any         |                        |
|                  |                 | disease, renal or hepatic         | limited exercise test  | cardiac disease.       |                        |
|                  |                 | insufficiency, known clinically    | before discharge.      |                        |                        |
|                  |                 | relevant osteoporosis, other      | Half of the patients   |                        |                        |
|                  |                 | severe illness, hypersensitivity   | in each group were     |                        |                        |
|                  |                 | to randomised drugs, anticipated  | randomly assigned      |                        |                        |
|                  |                 | difficulties with cooperation or   | long-term treatment    |                        |                        |
|                  |                 | participation in this or another   | with subcutaneous      |                        |                        |
|                  |                 | clinical trial. Patients with     | dalteparin or placebo  |                        |                        |
|                  |                 | previous open-heart surgery,      | for 3 months.         |                        |                        |
|                  |                 | advanced age (eg, >75 years), or   |                      |                        |                        |
|                  |                 | other disorders that made         |                      |                        |                        |
|                  |                 | randomisation to early            |                      |                        |                        |
|                  |                 | revascularisation inappropriate.  |                      |                        |                        |

**Harms observed in trial extension phase**

|                     |                  |                                    |                       |                       |
|---------------------|------------------|------------------------------------|-----------------------|-----------------------|
| Ajeganova S, 2014.  | Svensson B1, 2005.| Men and women diagnosed as        | I: prednisolone 7.5 mg/d; | Primary: rheumatoid   |
|                     |                  | having RA according to the 1987    | co-I: disease-modifying | disease activity score |
|                     |                  | revised criteria of the American   | anti-rheumatic drug    | and joint erosions;   |
|                     |                  | College of Rheumatology (formerly,| (DMARD); C: DMARD     | Secondary: BMD        |
|                     |                  | the American Rheumatism Association),| alone                 |                       |
|                     |                  | were ages 18–80 years, had a       |                       |                       |
|                     |                  | disease duration of 1 year, had    |                       |                       |
|                     |                  | active disease (defined by         |                       |                       |
|                     |                  | Disease Activity Score), and were   |                       |                       |
|                     |                  | started by the treating            |                       |                       |
|                     |                  | rheumatologist on the first DMARD  |                       |                       |
| Heliövaara-Peippo S,| Hurskainen R, 2001.| Women referred by general           | I: levonorgestrel-releasing| Health related quality |
| 2010.              |                  | practitioners or gynaecologists to  | intrauterine system (IUS); | of life               |
|                     |                  | one of the five university hospitals| C: hysterectomy        |                       |
|                     |                  | in Finland because of menorrhagia, |                       |                       |
|                     |                  | between November, 1994, and        |                       |                       |
|                     |                  | November, 1997.                    |                       |                       |
| Hemminki E, 1995.  | Hemminki E, 1991. | Mothers enrolled in the 27 participating | I: routine iron        | Lower urinary tract    |
|                     |                  | maternity centers in Tampere and    | supplementation during  | symptoms, medications  |
|                     |                  | five neighboring                    | pregnancy (100mg daily);| infections and         |
|                     |                  |                                     |                       | subjective adverse     |
|                     |                  |                                     |                       | Next birth, perinatal  |
|                     |                  |                                     |                       | mortality, proportions  |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|-----------------------|-------------------------|-------------------------|-------------------------|
|                  |                 | communities for the first time during a pregnancy were considered for inclusion in the study. | C: selective iron supplementation during pregnancy - if Hb fell below 100g/L after 14 wGA with lab-confirmed anemia, 50 mg ferrous sulfate was prescribed 2x daily for 2 months (or until Hb>110 g/L) | effects, and/or delays in birth | preterm and low birth weight infants, mean gestation length and birth weight. |
| Jones JM, 1989. | Details extracted from: Cuzick J, 1987. | Manchester Christie Trial: randomized 1461 female patients between 1949 and 1955. All patients were treated surgically by a Halsted radical mastectomy. | Two different regimens of kilovoltage radiotherapy were used, initially the so-called quadrate technique and later the peripheral technique I: immediate post-operative DXT after radical mastectomy C: delayed treatment ("watched group"). Randomisation determined by even or odd dates of birth | The data available from a systematic review were limited to all cause mortality. | Deaths and causes of death |
| Killander F, 2014 | Ryden S, 1992. | Postmenopausal (> 5 years after menopause) patients under 71 years of age, with stage I1 breast cancer were included in the trial after modified radical mastectomy; specifically, patients had invasive mammary adenocarcinoma, and T1N+ or T2N0/N+, e.g. stage II with the tumour-node-metastasis (TNM) classification of that time. | I1: radiotherapy (RT), I2: radiotherapy and tamoxifen (RTAM) or I3: tamoxifen without radiotherapy (TAM). | Recurrences, contralateral breast cancer, new primary cancer, cause-specific mortality, all-cause mortality | Overall survival, time to breast cancer death, and fatal and non-fatal late side-effects of radiation. |
| Mortensen FV, 2011. | Jensen LS, 1996. | All patients admitted for elective colorectal surgery between January 1992 and January 1995 were evaluated for inclusion in the study. | I: buffy-coat poor red cells; C: filtered leukocyte depleted red cells | Primary: postoperative wound infection. Secondary: Non-surgical infections, | Primary: cause-specific mortality; Secondary: cause-specific mortality: |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|----------------------|-------------------------|------------------------|
|                    |                 | Exclusion criteria were age less than 18 years, the need for emergency surgery, and the use of immunosuppressive drugs, except steroids. |                      | anastomatic leakage, re-operation and death. | rectal cancer and CVD |
| Onsrud M, 2012.    | Aalders J, 1980. | Women referred to the Norwegian Radium Hospital for primary and/or secondary treatment of stage 1 endometrial carcinoma of the corpus uteri; FIGO stage I cases were excluded | I: Vaginal brachytherapy + external pelvic irradiation C: brachytherapy alone | Primary: Local and remote recurrence of endometrial carcinoma Secondary: survival | Survival, local and distant recurrence and secondary cancers |
| Perez MV, 2012.    | Rossouw JE, 2002. | Postmenopausal women between the ages of 50 and 79 were recruited between 1993 and 1998 at 40 US clinical centers. | I1: women who had not had a hysterectomy were randomized to 0.625 mg/d of conjugated equine estrogens (CEE) plus 2.5 mg/d of medroxyprogesterone acetate (MPA) or placebo i2: women with prior hysterectomy were randomized to 0.625 mg/d of CEE or placebo. | Primary: coronary heart disease (including non-fatal MI and death) Secondary: cancer, fractures | Incident atrial fibrillation |
| Persson PE, 2005.  | Persson PE, 1998. | Men and women operated on with primary THA for arthrosis | I1: Ibuprofen from the day of surgery for 3 weeks; i2: Ibuprofen for 1 week and then placebo for 2 weeks; c: Placebo for 3 weeks. | Primary: Functional grading according to Charnley, the Harris Hip Score and range of motion of the affected joint. Secondary: Pre- and postoperative complications, type of anesthesia, blood loss and blood transfusions. | Primary: revisioning, Secondary: radiographic loosening |
| Radford L, 2011.   | Reid IR, 2006.  | Men and women aged more than 55 years, not receiving therapy for i: 1 g of elemental calcium daily (as citrate). |                      | Primary: time to first clinical fracture at any | Primary: fracture incidence. |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|------------------------------------|-----------------------|------------------------|------------------------|
|                   |                 | osteoporosis or taking calcium supplements, and free of major ongoing disease. Serum creatinine was less than 2.3 mg/dL (0.2 mmol/L), and serum 25-hydroxyvitamin D was greater than 10 g/L (25 nmol/L). Lumbar spine density was not below the age-appropriate normal range. | C: identical placebo in 2 divided doses. | site. Secondary: bone density and the following fracture subgroups: total vertebral fractures, hip fractures, distal forearm fractures, and osteoporotic fractures (comprising all fractures except those of the head, hands, feet, and ankles, and resulting from major trauma). | Secondary: bone mineral density, cardiovascular events (MI, stroke, death) |
| Vessey MP, 1983.  | Swyer GIM, 1954. | Women with their first pregnancy, attending University College hospital | I: stilboestrol varying dose (in total around 11g) C: placebo | Late pregnancy toxaemia and perinatal mortality | Deaths, malignant and non-malignant tumors (mothers) plus a range of urogenital obstetric outcomes in female and male offspring |
| von Bormann B, 2015. | Busch OR, 1993. | Men and women scheduled for a potentially curative resection of cancer of the colon or rectum, did not have severe cardiovascular or respiratory disease, no history of epilepsy after infancy and a hemoglobin concentration above 11.3 g per deciliter. In addition, patients had to have no evidence of metastatic disease, no other cancer except basal cell carcinoma of the skin or in situ carcinoma of the cervix. No history of blood | I: allogeneic transfusion; C: autologous-transfusion | Primary: Colorectal cancer-specific survival rates Secondary: colorectal recurrence | Overall and Colorectal-cancer specific survival |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|-----------------------|------------------------|------------------------|
| Winkel P, 2015.  | Jespersen CM, 2000. | Men and women aged 18 to 85 years who had a discharge diagnosis of myocardial infarction or angina pectoris in 1993-9 and alive in August 1999 were invited by letter. Exclusion criteria included myocardial infarction or unstable angina within the previous three months; percutaneous transluminal coronary angioplasty or coronary bypass surgery within the previous six months; New York Heart Association class IV cardiac failure; impaired renal or hepatic function; active malignancy; intolerance to macrolides; treatment with methylxanthines, carbamazepine, cisapride, astemizole, terfenadine, or coumarin anticoagulants; participation in other clinical trials within the previous month; incapacity to manage own affairs or sign informed consent; breast feeding; and possible pregnancy. | I: oral clarithromycin 500 mg/day; C: placebo treatment | Primary: composite of all cause mortality, myocardial infarction, or unstable angina pectoris during three years' follow-up. Secondary: composite of cardiovascular mortality, myocardial infarction, or unstable angina pectoris. | Primary: All cause mortality, acute myocardial infarction, unstable angina pectoris; Secondary: myocardial mortality, acute myocardial infarction, unstable angina pectoris |

Null effects in original trial also seen in the trial extension phase

| Appel JM, 2012. | Ejlertsen B, 2007. | Women who had completely resected unilateral invasive carcinoma of the breast and no signs of distant metastases as determined by physical examination, chest radiography, and bone scintigraphy (if positive, to I1: CMF (cyclophosphamide 600 mg/m2, methotrexate 40 mg/m2 and 5-fluorouracil 600 mg/m2) i2: CEF (cyclophosphamide 600 | Primary: Symptoms, side effects, and findings on clinical examination, vital status. Secondary: Haemoglobin, white | Survival, incidence of CHF, cardiac impairment |

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| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|-----------------------|-------------------------|-------------------------|
| Beebe GW, 1972.   | Beebe GW, 1964. | Not clearly stated - American army recruits | be confirmed by radiography), or axial bone radiography. Lower axillary clearance (level I and part of level II) in combination with breast-conserving surgery or mastectomy was required. | mg/m², epirubicin 60 mg/m² and 5-fluorouracil 600 mg/m² | blood cell count, and platelet count. |
| Brouwers FP, 2011. | Asselbergs FW, 2004. | All residents of Groningen, Netherlands aged 28-75 were sent a questionnaire and asked to send in a morning urine sample. The key entry criteria of the PREVEND IT were persistent microalbuminuria (a urinary albumin concentration 10 mg/L in 1 early morning spot urine sample and a concentration of 15 to 300 mg/24 hours in 2 24-hour urine samples at least once), a blood pressure 160/100 mm Hg and no use of antihypertensive medication, and a total cholesterol level 8.0 mmol/L, or 5.0 mmol/L in case of previous yocardial infarction, and no use of lipid-lowering medication. The cutoff values for blood pressure and cholesterol were based on guidelines of general practitioners from the Netherlands in 1998. Important exclusion criteria were any of the following: creatinine clearance 60% of the normal age | I1: fosinopril 20 mg; I2: pravastatin 40 mg; C: matching placebo | Cardiovascular mortality and hospitalization for cardiovascular morbidity | Combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Cherry N, 2014.  | Cherry N, 2002.| Women, age 50–69 years, admitted to coronary care units or general medicine wards in participating hospitals, who had survived a first myocardial infarction and were discharged within 31 days of admission. Individuals were recruited from 35 hospitals in England and Wales. Exclusion: previous MI, use of HRT, vaginal bleeding in past 12 months, history of breast/ovarian/endometrial cancer, active thrombophelitis or history of DVT, pulmonary embolism, acute or chronic liver disease, Rotor syndrome, Dubin-Johnson syndrome, or severe renal disease. | I: one tablet of oestradiol valerate (2 mg) daily; C: placebo daily | Primary: reinfarction or cardiac death, and all-cause mortality. Secondary: uterine bleeding, endometrial cancer, stroke or other embolic events, and fractures. | Death (all-cause, cardiac disease, stroke or cancer) and cancer incidence (any, breast or endometrium). |
| Cook NR, 2016.   | The Trials of Hypertension Prevention Collaborative Research Group, 1992. | Healthy men and women, aged 30 through 54 years, who had high normal DBP and were not taking antihypertensive drugs for the prior 2 months. The BP eligibility level was based on three measurements at each of three screening visits (SV), between 10 and 30 days apart, with inclusion limits based on cumulative averages of all readings through that visit, as follows: SV1, 75 through 97 mm Hg; SV2, 77 through 94 mm Hg; and SV3 (baseline), 80 through 89 mm Hg. | I1: Life-style interventions (3 groups: Weight reduction, Sodium reduction and Stress management). I2: Nutritional supplements (2 groups: Calcium and Magnesium, and Fish Oil and Potassium after wash-out period). C: Usual care for Life-style interventions and placebo for Nutritional supplements. | Primary: change in diastolic blood pressure from baseline to final follow-up, measured by blinded observers. Secondary: changes in systolic blood pressure and intervention compliance measures. | Long term mortality |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Cushman WC, 2012. | ALLHAT Collaborative Research Group, 2003. | Men and women 55 years and older with untreated or briefly treated (less than 2 months) high blood pressure - systolic BP 140-180mmHg and/or diastolic BP 90-110 mmHg OR men/women 55+ who took less than 3 antihypertensive medications for at least 2 months with BP of 160/100mmHg. Inclusion also required a risk factor for CHD: prior CVD event (MI, Stroke), left ventricular hypertrophy, history of T2DM, current cigarette smoker, and low HDL. | 1: initial treatment of high-risk hypertension with calcium channel blocker (amlodipine), ACE inhibitor (lisinopril) or alpha-blocker (doxazosin)  c: standard treatment with chlorthalidone | Primary: fatal coronary heart disease, nonfatal myocardial infarction. Secondary: all-cause and cause-specific mortality, stroke, heart failure, cardiovascular disease, end-stage renal disease | Primary: cardiovascular mortality. Secondary: mortality, stroke, CHD, HF, end-stage renal disease |
| Delaney EK, 2008. | Campbell N, 1998. | Men and women with a history of coronary heart disease or prescribed nitrates, were <80 years old and recruited from GP practices | 1: nurse-led secondary prevention clinics which promoted medical and lifestyle aspects of prevention and offered regular follow-up for 1-year; C: usual care | Use of aspirin, BP management, Lipid Management, Smoking | All cause mortality and coronary events |
| Gao YC, 2017. | Rogers SJ, 2010. | Men and women aged 18 and older, classic biliary-type pain, at least 1 episode within the past 6 months, ultrasonographic demonstration of cholecystolithiasis, platelet count 100000, American Society of Anesthesiologists risk grade 1 or 2. | 1: laparoscopic cholecystectomy plus laparoscopic common bile duct exploration (LC LCBD) 2: endoscopic retrograde cholangiopancreatography sphincterotomy plus laparoscopic cholecystectomy (ERCP/S LC). | Primary: efficacy of stone clearance from common bile duct. Secondary: length of hospital stay, cost of index hospitalization, professional fees, hospital charges, morbidity and mortality, and patient acceptance and quality of life scores. | Recurrent common bile duct stone disease or biliary complications |
| Extension Study* | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|----------------------------------|-----------------------|-------------------------|-------------------------|
| Gårdmark T, 2007. | Lundholm C, 1996. | Men and women with primary dysplasia, or stage Tis, stage T1, grade 3 and multiple recurrent stage TaPT1, grade 1 or 2 disease with normal liver and kidney function tests, and no chemotherapy during the prior 6 months. Exclusion criteria were previous or ongoing intravesical treatment with mitomycin C, BCG or radiotherapy, any secondary malignancy except treated carcinoma in situ of the uterine cervix or basal cell carcinoma of the skin, ongoing corticosteroid therapy, leukocytes less than 3,000/mm., thrombocytes less than 100,000/mm., untreated urinary tract infection, urethral stricture preventing cystoscopy, active tuberculosis, pregnancy and expected difficulties during follow-up (for example Karnofsky performance index less than 50, senility, psychotic disease or any other reason that might prevent follow-up. | I: Mitomycin C (40 mg); C: Pasteur strain BCG (120 mg) | Recurrence and progression of superficial bladder carcinoma. | Progression, later treatments and survival in this group of patients with high-risk urinary bladder cancer that was not muscle-invasive. |
| Gibson A, 2008. | Mattick RP, 2003. | Men and women with a current diagnosis of opioid dependence using the criteria in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1994); were aged 18 years or older; lived within commuting distance of the clinic; appeared mentally competent to Patients received buprenorphine or methadone AND either placebo syrup or placebo tablet, as indicated clinically using a flexible dosage regime. During weeks 1–6, patients were dosed daily. From weeks 7–13, buprenorphine | Primary: Retention in treatment, and illicit opioid use as determined by urinalysis. Secondary: Self-reported drug use, psychological functioning, HIV risk behavior, general | Primary: all cause mortality. Secondary: survival and cause-specific mortality |
| Extension Study *       | Original Trial* | Original Study Inclusion Criteria                                                                                                                                                                                                                           | Original Intervention                                                                                      | Original Trial Outcomes                                                                                     | Extended Trial Outcomes                                                                                      |
|------------------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Huttunen JK, 1994.     | Manninen V, 1988.| The screening for participation was conducted in three steps within a period of three to five months. Cholesterol-lowering dietary counseling started three to six weeks prior to the drug treatment. Subjects free of coronary heart disease and other major disability were accepted, including those with mild hypertension and non-insulin-dependent diabetes. At the third pretreatment (baseline) visit, subjects meeting these acceptance criteria who expressed their willingness to participate were randomly allocated either to the gemfibrozil (n = 2046) or to the placebo (n = 2035) group. | I: gemfibrozil therapy 600mg twice daily; C: placebo                                                                                                   | Primary: incidence of heart disease (CHD); Secondary: serum cholesterol level, HDL level and LDL level | Gastrointestinal symptoms, surgery, strokes, cancer incidence, mortality by cause.                        |
| Lentine KL, 2015.      | Brennan DC, 2006.| Only adult candidates for renal transplants from deceased donors were considered for enrollment. Eligibility was determined according to the duration of cold ischemia and other donor and recipient risk factors. One or more of these factors, which put the recipient at high risk for acute rejection or delayed graft function, were required for eligibility. Patients were excluded if they had been receiving immunosuppressive therapy before transplantation; had received an investigational medication within the | I: rabbit antithymocyte globulin (1.5 mg per kilogram of body weight daily) during transplantation (day 0) and on days 1 through 4. Patients assigned to this group were given acetaminophen and diphenhydramine before receiving antithymocyte globulin (1.5 mg per kilogram of body weight given intravenously). Treatment with | Primary: efficacy end point, defined as a composite of the first occurrence of biopsy-proven acute rejection, delayed graft function, graft loss, or death; the incidence of each of these end points was also studied. All episodes of acute rejection were confirmed by biopsy, with histologic characteristics | Primary efficacy endpoint: FDA specified composite triple endpoint of allograft rejection, graft failure, or patient death used in clinical trials of immunosuppression efficacy. Secondary: acute rejection, death-censored graft failure, and all-cause graft loss, evaluated |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|----------------------------------|-----------------------|------------------------|-------------------------|
| *                 |                 | past 30 days; had a known contraindication to the administration of antithymocyte globulin or basiliximab; were suspected or known to have an infection or were seropositive for hepatitis B surface antigen (HBsAg), antibody against hepatitis B core antigen (anti-HBcAg), hepatitis C virus (HCV), or human immunodeficiency virus (HIV); or had had cancer (except nonmelanoma skin cancer) within the previous 2 years. Pregnant women, nursing mothers, and women of childbearing potential who were not using condoms or oral contraceptives were excluded. | antithymocyte globulin was initiated intraoperatively, before graft reperfusion. Subsequent doses were given daily through day 4, for a total dose of 7.5 mg per kilogram. C: basiliximab (20 mg) on days 0 and 4. Basiliximab was given intravenously. Both groups received maintenance immunosuppressive therapy involving cyclosporine (modified), mycophenolate mofetil, and prednisone. | described according to the Banff criteria with the use of microscopy. Delayed graft function was defined as the need for dialysis within the first week after transplantation. Slow graft function was defined as a serum creatinine level exceeding 3.0 mg per deciliter on day 5 that did not require treatment with dialysis. | individually at 10 years post-transplant. |
| Levey AS, 2006.  | Klahr S, 1994.   | Men and women age 18 to 70 years, a serum creatinine concentration of 1.2 to 7.0 mg/dL in women and 1.4 to 7.0 mg/dL in men or a creatinine clearance of less than 70 ml per minute per 1.73 m² of body surface area and a mean arterial pressure 125 mm Hg or less. | I: Low protein diet  C1: Usual protein diet; these groups were further compared between usual or low blood pressure [Study 1];  C2: Low protein diet; these groups were further compared between usual or low blood pressure [Study 2] | Rate of change in glomerular filtration rate | Kidney failure, defined as the requirement for dialysis therapy or kidney transplantation, and a composite of kidney failure and all-cause mortality. |
| Lewinter C, 2014. | Zwisler AD, 2008. | Men and women with CHF, IHD, or HR (high risk of heart disease) who were admitted to the Department of Cardiology of Bispebjerg Hospital. Exclusion criteria: severe or terminal illness, mental or social problems, transfer to another | I: Cardiac rehabilitation  C: Usual Care in cardiac patients | Primary: composite of total mortality, myocardial infarction, or acute first-time readmission due to heart disease. Secondary: | Composite of all cause death, MI and acute hospital admission due to cardiac causes. |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Marcus PM, 2000. | Fontana RS, 1984. | Male outpatients who are at high risk of lung cancer and who met the requirements of the prevalence screening. Participants were excluded if it appeared that the life expectancy was less than 5 years or that pulmonary resection would not be tolerated. Other exclusion criteria include a history of cancer of the respiratory tract, established diagnosis of lung cancer, evidence that either the patient or the referring physician suspected the presence of lung cancer at the time the patient entered the Mayo clinic. | I: patient was part of a close surveillance group, offered roentgenographic and cytologic rescreening every 4 months; Every candidate accepted for prevalence screening was scheduled for chest roentgenography and received assistance in completing a questionnaire. He was given instructions for collecting a 3-day "pooled" specimen of sputum for cytologic examination. Anyone who reported that he was unable to produce sputum spontaneously was offered sputum induction C: was not part of the surveillance group but advised to get the tests at trial entry. | Primary: incidence of lung cancer; Secondary: Survival after treatment | Mortality from lung cancer |
| McNamara HC, 2015. | Norman JE, 2009. | Uncomplicated twin pregnancies recruited from specialized antenatal clinics for women with multiple pregnancy (from 9 hospitals) | I: intravaginal progesterone; C: placebo | Primary: intrauterine death or delivery before 34 week Maternal secondary outcomes: gestation at delivery, method of delivery (spontaneous vaginal delivery, vaginal | Primary: death, congenital anomalies and hospitalisation, routine national child health assessments. Secondary: CDI and HUI |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|-----------------------------------|-----------------------|-------------------------|------------------------|
|                  | Miller AB, 2014. | Miller AB, 1992.                  | Women (50-59 years old) with no history of breast cancer and no mammography in the previous 12 months, recruited from 15 urban centers in Canada | I: annual mammography and physical examination (MP group); C: annual physical examination only (PO group). | breech, forceps or ventouse, or caesarean section, duration of each stage of labour, and safety outcomes such as duration of stay in hospital, maternal satisfaction (by questionnaire). Neonatal secondary outcomes: neonatal unit admission and duration of neonatal unit care. | Rates of referral from screening, rates of detection of breast cancer from screening and from community care, nodal status, tumour size and rates of death from all causes and from breast cancer. | Deaths from breast cancer. |
|                  | Myles PS, 2011.  | Rigg JR, 2002.                    | Men and women (aged 18+) undergoing major abdominal surgery with one of nine defined comorbid states to identify high-risk status | I: intraoperative epidural anaesthesia and postoperative epidural analgesia for 72 h with general anaesthesia (site of epidural selected to provide optimum block); C: Usual care | Death at 30 days or major postsurgical morbidity. | Cancer-free survival |
| Puntoni M, 2016. | Decensi A, 1994. | Men and women under 80 years of age, with non muscle invasive bladder cancer (stage Ta or T1, any grade) resected within the previous 3 years | i: fenretinide 200 mg/day; c: no treatment | Primary: flow cytometric DNA content in epithelial cells obtained after 12 months. Secondary: recurrence | Primary: survival Secondary: cancer survival, bladder cancer survival, prognostic value of circulating VEGF | |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Sandblom G, 2011. | Pedersen KV, 1990. | Men aged 50-69 randomly selected from a population of 9026 in the area of Norrkoping. | I: digital rectal examination by a urologist and a general practitioner; C: no examination | Primary: Prostates having a firm nodular consistency. Secondary: costs, discomfort | Prostate cancer specific mortality, tumour stage, grade, and treatment. |
| Thomsen JL, 2005. | Lauritzen T, 1995. | Any Danish man or woman aged 30-50 years (as of Jan 1, 1991) registered with a general practitioner was included in the study. | i1: health check which included being screened for cardiovascular risk factors, lung and liver function, fitness, sight and hearing and an optional test for the human immunodeficiency virus (HIV); this group received written feedback from the general practitioner. i2: also given a health check and written feedback; in addition, they were given the opportunity to attend their general practitioner to discuss preventive health. c: not invited to participate | Primary: describe the baseline health status of participants including: presence of CVD risk factors, lung and liver function, fitness, sight, hearing and (optionally) their HIV status. Secondary: report on the extent of health advice given as a result of a health check (and on how many healthy people did not require health advice following a health check) and on health goals that participants set following discussion of their health with their general practitioner. The number of referrals to specialists following the health talks was also examined to determine whether the screening would result | Hospital admissions, Ambulatory contacts, Emergency room contacts |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|-------------------------|------------------------|
| Virtamo J, 2014.  | Virtamo J, 2003.| Male smokers aged 50-69 years living in 14 adjoining areas in south western Finland | I1: alpha-tocopherol (50 mg daily), I2: Beta-carotene (20 mg daily); I3: I1 and I2 combination C: placebo daily | in an increase in the number of referrals. | |

**Therapeutic benefits lost in the trial extension phase**

| Clayton PA, 2012. | The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group, 1996. | Men and women receiving their first or second cadaveric renal transplant, were at least 18 years old, and were able to receive oral medication. Patients with a history of malignancy (except successfully treated nonmetastatic basal or squamous cell carcinoma of the skin), serologic evidence of human immunodeficiency virus or hepatitis B, systemic infections requiring continued antibiotic therapy at the time of entry, severe diarrhea, gastrointestinal disorders, or active peptic ulcer disease were excluded from entry, as were pregnant women, nursing mothers, and patients who did not agree to use adequate contraception. | i: Mycophenolate mofetil (MMF), an immunosuppressant, 1.5 g twice daily, MMF 1.0 g twice daily c: azathioprine (AZA) 100-150 mg once daily | Primary: patient and graft survival; graft failure was defined as death or permanent loss of graft function. Secondary: death-censored graft survival, cancer incidence, and estimated kidney function. | Cancer incidence and all cause mortality |

| Henderson RA, 2015. | Fox KA, 2002. | Men and women with suspected cardiac chest pain at rest and had documented evidence of coronary artery disease with at least one of: evidence of ischaemia on electrocardiograph (ST-segment) | i: angiography within 48 h of index episode of cardiac chest pain c: conservative management within 48 h | Primary: a combined rate of death, non-fatal myocardial infarction, or refractory angina at 4 months; and a combined rate of death | All-cause mortality, cardiovascular mortality |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|-----------------------|-------------------------|-------------------------|
| | | depression, transient ST elevation, left bundle branch block [documented previously], or T-wave inversion); pathological Q waves suggesting previous myocardial infarction; or arteriographically proven coronary artery disease on a previous arteriogram. | of the index episode of cardiac chest pain or non-fatal myocardial infarction at 1 year. Secondary: angina, QOL, health-economic evaluations. | | |
| Ishani A, 2006. | Hafström L, 1991. | Men and women with recurrent malignant melanoma of the extremities | I: Surgery plus regional perfusion C: Surgery | Cancer progression and mortality | Mortality |
| Mc Ardle CS, 2010. | Mc Ardle CS, 1986. | Women admitted to teaching hospitals with operable breast cancer with axillary node involvement after surgery and no metastasis, aged 70 years or less | I1: post-op Radiotherapy, I2: post-op chemotherapy I3: both radiotherapy and chemotherapy after surgery for breast cancer | Disease free survival | Primary: cancer specific survival and all cause mortality. Secondary: predictors of cancer mortality |
| Moss SM, 2015. | Moss S, 1999. | Women aged 39–41 years from 23 UK NHS Breast Screening Programme (NHSBSP) units (appendix) were identified from the general practitioners’ (GP) lists of patients held in health authority databases. | i: invited for mammography screening c: no invite for screening | Breast cancer mortality and breast cancer incidence (in situ, invasive, and total incidence). | Breast cancer mortality and breast cancer incidence |
| Roodnat JI, 2014. | Smak Gregoor PJ, 2002. | Men and women that underwent kidney transplantation in university hospitals (This is an open label study). | I1: withdraw cyclosporine from triple drug combo of cyclosporine, prednisone, and MMF i2: withdrawal prednisone from triple drug combo c: standard triple drug combo | Primary: first biopsy-proven acute or chronic rejection between randomization and 24 months after transplantation. Secondary: patient and graft survival, renal function at 1 and 2 years after transplantation, the | Graft and patient survival. |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Bale G, 2008. | Burge PS, 2000. | Men and women aged between 40 and 75 years with mean forced expiratory volume in one second (FEV1) 50% of predicted normal | I: Fluticasone 500 ug BD; C: placebo | incidence of infections and malignancies, and changes in BP and lipid metabolism. | |
| Cygankiewicz I, 2009. | Moss AJ, 2002. | Men and women who were more than 21 years of age (there was no upper age limit) were eligible for the study if they had had a myocardial infarction one month or more before entry, as documented by the finding of an abnormal Q wave on electrocardiography, elevated cardiac-enzyme levels on laboratory testing during hospitalization for suspected myocardial infarction, a fixed defect on thallium scanning, or localized akinesis on ventriculography with evidence of obstructive coronary disease on angiography, and an ejection fraction of 0.30 or less within three months before entry, as assessed | I: implantable defibrillation c: conventional medical therapy | Death from any cause. | All-cause mortality |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Original Trial Inclusion Criteria Or  Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|-------------------------|------------------------------------------------------------|-------------------------|------------------------|
| Dalsgaard EM, 2014. | Griffin SJ, 2001. | General practices in the four study areas within a maximum of 100 miles of the study centres were invited to participate. All patients aged 40-69 years old with newly diagnosed with Type 2 diabetes in were eligible to participate, unless they are found to have: contraindications or intolerance to study medication; a history of alcohol- ism, drug abuse, psychosis or other emotional problems that are likely to invalidate informed consent or adherence to treatment; malignant disease with a poor prognosis; or are pregnant or lactating. | I: Intensive multifactorial diabetes treatment, including prescription of aspirin, lifestyle advice (concerning diet, physical activity and tobacco consumption) and stepwise increases in drug treatment of blood glucose, blood pressure and lipids according to strict targets. C: conventional diabetes care - standard care according to broadly similar national recommendations for the management of Type 2 diabetes and prevention of cardiovascular disease. | Primary: All-cause mortality, Cardiovascular mortality/morbidity, Nonfatal myocardial infarction, nonfatal stroke, amputations, hospitalization for angina/congestive heart failure/coronary revascularization, peripheral revascularization. Secondary: development of renal impairment, diabetic ulcers, blindness, reduced visual acuity, macular oedema, retinopathy, health status, health utility, quality of life, patient satisfaction, health service costs, patient costs | Change in cardiovascular risk factors (HbA1c, (mmol/mol (%)), cholesterol (mmol/l), blood pressure (mmHg), BMI and smoking status (current/former or never smoker)) from baseline to follow-up and the proportion of people meeting treatment targets; HbA1c ≤53 mmol/mol (7.0%), cholesterol ≤5.0 mmol/l and blood pressure ≤140/90mmHg. |
| Korpelainen R, 2010. | Korpelainen R, 2006. | A birth cohort of elderly women (born 1924-7, aged 70-73) who were residents of Oulu, Finland in Nov 1997 with hip BMD at least 2 SD below the reference value were included. Exclusion criteria: use of walking aid other than a stick, bilateral hip joint replacement, unstable chronic illness, medication | I: 30 months either of supervised and home-based impact exercise training C: no intervention. | Primary: femoral neck, trochanter and total hip BMD. Secondary: bone density measures at the radius and calcaneum | Fractures and death |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|----------------------------------|-----------------------|------------------------|------------------------|
| Kümler T, 2010.   | Køber L, 1995.  | Men and women with an enzyme confirmed acute myocardial infarction with wall motion index of less than or equal to 1.2, 6 days after MI. | i: trandolapril c: placebo | All-cause mortality | All-cause mortality by wall motion index class, all-cause mortality by HF, survival by WMI, prognostic effect of WMI and HF |
| Nelson MR, 2015.  | Wing LM, 2003.  | Men and women aged 65+. Average systolic blood pressure of at least 160 mm Hg or an average diastolic blood pressure of at least 90 mm Hg (if the systolic blood pressure was at least 140 mm Hg); the absence of recent cardiovascular events (within the previous six months); and willingness to give informed consent. | i: ACE-inhibitor c: diuretic agents (The ACE inhibitor enalapril and the diuretic hydrochlorothiazide were recommended as initial therapy; however, the choice of the specific agent and dose was made by the family practitioner.) | Primary: all cardiovascular events and all-cause mortality. Secondary: cause-specific cardiovascular events - initial and subsequent, fatal and nonfatal | Any first cardiovascular events such as stroke, myocardial infarction, heart failure, and any cardiovascular mortality and all-cause mortality |
| Novak M, 2013.    | Wilhelmsen L, 1986. | All men living in Goteborg and born 1915-1922 and 1924-1925. | i: antihypertensive treatment in subjects with screening blood pressure above 175 mmHg systolic or 115 mmHg diastolic, dietary advice to men with serum cholesterol levels above 260 mg per 100 ml, advice to stop smoking to subjects who smoked more than 15 cigarettes per day. C: no advice given | Incidence of non-fatal and fatal myocardial infarction, stroke and the total death rate in the intervention group compared with two control groups | Type 2 diabetes |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|------------------|-----------------|----------------------------------|-----------------------|-------------------------|-------------------------|
| Regieli JJ, 2009. | Jukema JW, 1995. | All male patients who, from a review of the records at the participating centers, were scheduled to undergo coronary arteriography were considered for entry into the study; with serum cholesterol 4 - 8 mmol/l | I: Pravastatin 40 mg daily; C: placebo | Primary: 1) change in average mean segment diameter and 2) change in average minimum obstruction diameter; Secondary: Clinical events (MI, CHD death, PTCA or CABG, Stroke/ TIA; death) | Death from ischemic heart disease, all-cause mortality |
| Sharma A, 2012.  | Menon U, 2009.  | Post-menopausal women aged 50–74 years whose details were obtained from the registers of the participating 27 Primary Care Trusts. Women were excluded if they had a history of bilateral oophorectomy, active malignancy (women with a past history of malignancy were eligible if they had no documented persistent or recurrent disease and had not received treatment for >12 months), previous history of ovarian cancer, participation in other ovarian cancer screening trials, or increased risk of familial ovarian cancer. High-risk women were eligible for a separate trial: the United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS). | I1: annual CA125 screening (interpreted using a risk of ovarian cancer algorithm) with transvaginal ultrasound scan as a second-line test (multimodal screening [MMS]); I2: annual screening with transvaginal ultrasound (USS); C: usual care | Ovarian cancer mortality. | Ovarian epithelial ovarian cancer (EOC) and slow growing borderline or Type I and aggressive Type II EOC |
| Smelov V, 2015.  | Elfgren K, 2005. | Females 32 to 38 years, sexually active, who were recruited for screening in 5 major regions in Sweden; women with PAP smear taken in past 18 months were ineligible | I: Screening for HPV persistence and typing; C: HPV test taken but not performed (sample frozen) | Intraepithelial neoplasia grade 2 or 3 | CIN 2 and CIN3 risk according to HPV type |
| Extension Study * | Original Trial* | Original Study Inclusion Criteria | Original Intervention | Original Trial Outcomes | Extended Trial Outcomes |
|-------------------|-----------------|-----------------------------------|-----------------------|-------------------------|-------------------------|
| White MC, 2005.   | White MC, 2002. | Male and female jail inmates with latent TB infection | i: education every 2 weeks in jail. co-i: incentive to be provided at the first visit to a TB clinic c: no intervention | Primary: first visit to TB clinic after 1 month from prison release Secondary: completion of a first course of therapy | Primary: rate of completed therapy. Secondary: incidence of TB |

† Individual extension studies may have reported outcomes belonging to multiple categories so the numbers in this table differ from those in Table 3 (Summary of results of trial extension studies), which categorizes all reported analyses (n=155). In this table studies were placed in categories according to a hierarchy in which superiority in the trial extension phase > harms in the trial extension phase > null effects in the trial extension phase > benefits lost in the trial extension phase > analyzed as an observational study. Thus, each study only appears once in the table (n=113).* References listed alphabetically by first author surname. For full references see Supplementary Table 3.