Comparative Effectiveness of Exercise and Drug Interventions on Mortality Outcomes: A meta-epidemiological study

Supplementary Table

Coronary Heart Disease

Intervention	Publication	Pairwise meta-analysis	Trial and patient population characteristics
Exercise	Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD001800.	Number of included trials: 34 Pairwise effect estimate (95% CI): 0.89 (0.78, 1.02) I^2: 0.0%	*Eligibility criteria*: Randomized controlled trials of men and women of all ages who have had coronary heart disease. *Included patients*: Patients who have had a myocardial infarction, or who had undergone revascularization, or who have angina pectoris or coronary artery disease defined by angiography. 64% of trials included only patients with myocardial infarction. *Age distribution*: Range from 46 to 84 years. *Trial follow-up duration*: 24 months (median). *Blinding*: Trial participants not blinded; 3 trials had blinded assessors.
Statins	Naci H, Brugts JJ, Fleurence R, Tsoi B, Toor H, Ades AE. Comparative benefits of statins for the primary and secondary prevention of all-cause mortality and major coronary events. Eur J Prev Cardiol. 2013 Aug;20(4):641-57.	Number of included trials: 43 Pairwise effect estimate (95% CI): 0.82 (0.77, 0.88) I^2: 0.0%	*Eligibility criteria*: Placebo-controlled or active-comparator randomized controlled trials of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin in adults with coronary heart disease. *Included patients*: Patients with established coronary heart disease, as defined by trial investigators. *Age distribution*: Range from 47 to 76 years. *Trial follow-up duration*: 116 weeks (mean). *Blinding*: 19 trials had double blinding.
Beta-blockers	Freemantle N, Cleland J, Young P, Mason J, Harrison J. β Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ 1999;318:1730	Number of included trials: 80 Pairwise effect estimate (95% CI): 0.87 (0.83, 0.93) I^2: 0.0%	Eligibility criteria: Randomized controlled trials of beta-blockers in patients with acute or past myocardial infarction. *Included patients*: patients who had myocardial infarction. *Age distribution*: Not reported. *Trial follow-up duration*: 51 trials in acute treatment with follow-up of 6 weeks; and 31 trials with long-term treatment ranging with follow-up ranging from 6 to 48 months.

			Blinding: 46 trials had double-blinding.
ACE-inhibitors	Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. J Am Coll Cardiol. 1999;33(3):598-604	Number of included trials: 15 Pairwise effect estimate (95%CI): 0.83 (0.71, 0.97) I^2: 39.5%	*Eligibility criteria*: Randomized controlled trials of ACE inhibitor therapy following MI. *Included patients*: men and women of all ages in patients with a history of myocardial infarction within the prior 14 days. *Age distribution*: Range from 54 to 67 years. *Trial follow-up duration*: Ranged from 2 months to 42 months, with the majority of trials following patients up for a period between 3 and 12 months. *Blinding*: All included trials were double-blinded.
Antiplatelets	Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71	Number of included trials: 27 Pairwise effect estimate (95% CI): 0.83 (0.75, 0.93) I^2: 22.5%	*Eligibility criteria*: Randomized controlled trials of an antiplatelet regimen versus control or of one antiplatelet regimen versus another in high-risk patients. *Included patients*: Patients with acute myocardial infarction or previous myocardial infarction. *Age distribution*: Not reported. *Trial follow-up duration*: Ranged from 7 days to 72 months (mean ~16 months). *Blinding*: Not specified; trials were "unconfounded" as described by investigators.

Stroke

Intervention	Publication	Pairwise meta-analysis	Trial and patient population characteristics
Exercise	Brazzelli M, Saunders DH, Greig CA, Mead GE. Physical fitness training for stroke patients. Cochrane Database of Systematic Reviews 2011, Issue 11. Art. No.: CD003316.	Number of included trials: 3 Pairwise effect estimate (95% CI): 0.27 (0.05, 1.39) I^2: 0.0%	*Eligibility criteria*: Randomized trials comparing either cardiorespiratory training or resistance training, or both, with no intervention, a non-exercise intervention, or usual care in stroke survivors. *Included patients*: Adult stroke survivors who were considered suitable for exercise training. The majority of patients were ambulatory stroke survivors but one trial included non-ambulatory patients as well. *Age distribution*: 64 (mean). *Trial follow-up duration*: Range from 12 weeks to 12 months. *Blinding*: Assessors were blinded.
Anticoagulants	Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev. 2008;(4):CD000024.	Number of included trials: 10 Pairwise effect estimate (95% CI): 1.01 (0.85, 1.20) I^2: 22.8%	*Eligibility criteria*: Randomized trials comparing early anticoagulant therapy (started within two weeks of stroke onset) with control in patients with acute presumed or confirmed ischemic stroke. *Included patients*: Patients undergoing early treatment of acute ischemic stroke within 14 days after stroke. *Age distribution*: Range from 28 to 92 years with a significant share over 70 years. *Trial follow-up duration*: >1 month. *Blinding*: Predominantly double-blinded.
Antiplatelets	Sandercock PAG, Counsell C, Gubitz GJ, Tseng M-C. Antiplatelet therapy for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD000029.	Number of included trials: 14 Pairwise effect estimate (95% CI): 0.92 (0.86, 0.99) I^2: 2.2%	*Eligibility criteria*: Randomized trials comparing antiplatelet therapy (started within 14 days of the stroke) with control in patients with definite or presumed ischemic stroke. *Included patients*: Patients within two weeks of onset of presumed ischemic stroke. *Age distribution*: Majority of patients were elderly, with a significant proportion of participants over 70 years of age. *Trial follow-up duration*: Follow up ranged from 10 days to 6 months with the majority of trials reporting at 3 months. *Blinding*: Participants were blinded in all trials except for one

			(where only assessors were blinded).
Anticoagulants vs. antiplatelets	Berge E, Sandercock P. Anticoagulants versus antiplatelet agents for acute ischaemic stroke. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD003242.	Number of included trials: 3 Pairwise effect estimate (95% CI): 1.10 (1.01, 1.21) I^2: 0.0%	*Eligibility criteria*: Randomized controlled trials comparing anticoagulants with antiplatelet agents, or anticoagulants and antiplatelet agents with antiplatelet agents alone, given within 14 days of onset of presumed or confirmed ischemic stroke. *Included patients*: Patients within 14 days of onset of acute ischemic stroke. *Age distribution*: Range from 10 days to 6 months, with the majority of trials following patients up until 3 months. *Trial follow-up duration*: Two trials had a follow-up duration of 6 months and one trial had a follow-up duration of 3 months. *Blinding*: Two trials were double-blinded while only the assessors were blinded in one trial.

Heart Failure

Intervention	Publication	Pairwise meta-analysis	Trial and patient population characteristics
Exercise	Davies EJ, Moxham T, Rees K, Singh S, Coats AJ, Ebrahim S, Lough F, Taylor RS. Exercise based rehabilitation for heart failure. Cochrane Database Syst Rev(4): 2011 CD003331.	Number of included trials: 16 Pairwise effect estimate (95% CI): 0.81 (0.64, 1.02) I^2: 6.4%	*Eligibility criteria*: Randomized controlled trials of exercise-based interventions in adults of all ages with evidence of chronic systolic heart failure. *Included patients*: Patients with heart failure or left-ventricular dysfunction, with all of the included trials including patients with NYHA class II-III. *Age distribution*: Range from 43 to 72 years. *Trial follow-up duration*: While a number of trials had follow-up shorter than 12 months, over 70% of trial participants were included in trials with follow-up durations longer than 12 months. *Blinding*: Only two trials had blinded outcome assessment.
ACE-inhibitors	Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moyé L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet. 2000 May 6;355(9215):1575-81.	Number of included trials: 5 Pairwise effect estimate (95% CI): 0.78 (0.71, 0.86) I^2: 0.0%.	*Eligibility criteria*: Randomized controlled trials with individual-patient level data that assessed ACE inhibitors in patients with left-ventricular dysfunction or heart failure. *Included patients*: patients with heart failure or left-ventricular dysfunction, with 54% of patients had a history of myocardial infarctions. *Age distribution*: 61 years (mean). *Trial follow-up duration*: Mortality outcomes were available up to four years; data at one year were used to ensure consistency with other interventions. *Blinding*: All trials were double-blinded.
Beta-blockers	Chatterjee S, Biondi-Zoccai G, Abbate A, D'Ascenzo F, Castagno D, Van Tassell B,	Number of included trials: 21 Pairwise effect estimate (95% CI): 0.71 (0.64, 0.80) I^2: 34.4%	*Eligibility criteria*: Randomized trials comparing β blockers with control or other β blockers in heart failure. *Included patients*: Patients with heart failure or left ventricular

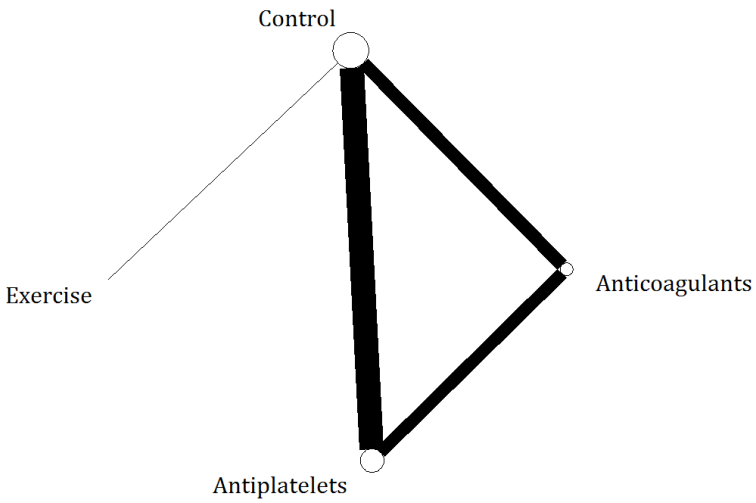
	Mukherjee D, Lichstein E. Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMJ 2013;346:f55		ejection dysfunction, with 57% of patients with ischemic heart failure with the rest with left ventricular rejection dysfunction. *Age distribution*: 61 years (median). *Trial follow-up duration*: 12 months (median). *Blinding*: All trials had double blinding.
Diuretics	Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003838.	Number of included trials: 3 Pairwise effect estimate (95% CI): 0.24 (0.07, 0.84) I^2: 0.0%	*Eligibility criteria*: Double-blinded randomized controlled trials of diuretic therapy comparing one diuretic with placebo, or one diuretic with another active agent (e.g. ACE inhibitors, digoxin) in patients with chronic heart failure. *Included patients*: Adults with chronic heart failure (NYHA Class II-IV). *Age distribution*: 59 years (mean). *Trial follow-up duration*: 23 weeks (average). Blinding: All trials had double blinding.
ARBs	Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. Cochrane Database of Systematic Reviews 2012, Issue 4. Art. No.: CD003040.	Number of included trials: 19 <u>Comparison of ARBs vs. control</u> Pairwise effect estimate (95% CI): 0.94 (0.80, 1.10) I^2: 23.2% <u>Comparison of ARBs vs. ACE inhibitors</u> Pairwise effect estimate (95% CI): 0.86 (0.53, 1.40) I^2: 38.9%	*Eligibility criteria*: Double blind randomized controlled trials in men and women of all ages who have symptomatic heart failure and left ventricular systolic dysfunction or preserved ejection fraction. *Included patients*: Patients with class NYHA II-IV. *Age distribution*: Mean age was 64 for the comparison of ARBs vs. control; and 70 for the comparison of ARBs vs. ACE inhibitors. *Trial follow-up duration*: Average follow-up duration was 67 weeks for the comparison of ARBs vs. control; and 56 weeks for the comparison of ARBs and ACE inhibitors. *Blinding*: 8 out of 11 trials comparing ARBs vs. control had double blinding. 6 out of 8 trials comparing ARBs vs. ACE inhibitors had double blinding.

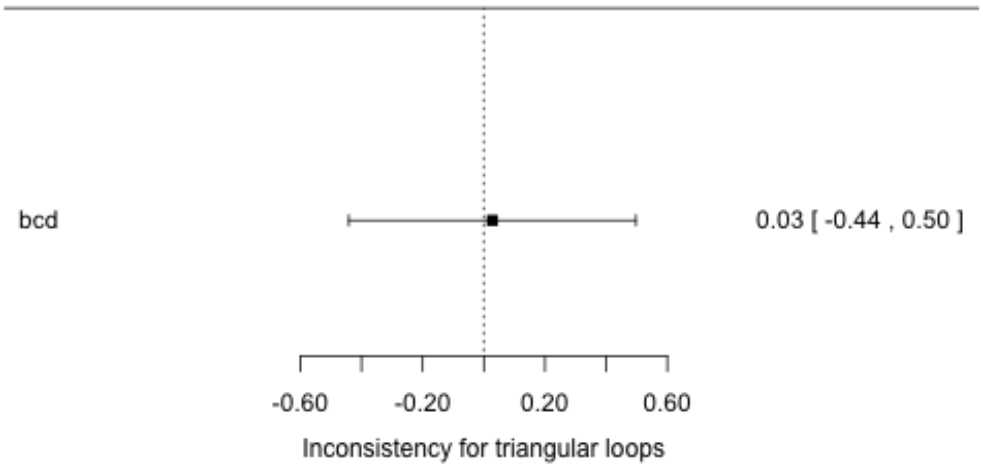
Pre-diabetes

Intervention	Publication	Pairwise meta-analysis	Trial and patient population characteristics
Pre-diabetes	Hopper I, Billah B, Skiba M, Krum H. Prevention of diabetes and reduction in major cardiovascular events in studies of subjects with prediabetes: meta-analysis of RCTs. Eur J Cardiovasc Prev & Rehabil.2010:18(6) 813–823.	Number of included trials: 10 <u>Comparison of exercise vs. control</u> Pairwise effect estimate (95% CI): 0.77 (0.52, 1.14) I^2: 0.0% <u>Comparison of AGIs vs. control</u> Pairwise effect estimate (95% CI): 1.99 (0.36, 10.87) I^2: 0.0% <u>Comparison of thiazolidinediones vs. control</u> Pairwise effect estimate (95% CI): 5.02 (0.24, 105.31) I^2: 0.0% <u>Comparison of biguanides vs. control</u> Pairwise effect estimate (95% CI): 0.28 (0.05, 1.70) I^2: 0.0% <u>Comparison of ACE inhibitors vs. control</u> Pairwise effect estimate (95% CI): 0.91 (0.78, 1.06) I^2: 0.0% <u>Comparison of glides vs. control</u> Pairwise effect estimate (95% CI): 1.00 (0.85, 1.17) I^2: 0.0% <u>Comparison of biguanides vs. exercise</u> Pairwise effect estimate (95% CI): 0.42 (0.06, 2.89) I^2: 0.0% <u>Comparison of AGIs vs. exercise</u> Pairwise effect estimate (95% CI): 13.33 (0.75, 236.92) I^2: 0.0%	*Eligibility criteria*: Randomized controlled trials reporting mortality benefits of pharmacological or non-pharmacological interventions in pre-diabetes. *Included patients*: Patients with impaired glucose tolerance and impaired fasting glucose. *Age distribution*: 52 years (mean) with a range from 45 to 64 years. *Trial follow-up duration*: Range from 2.8 to 6 years. *Blinding*: Not reported.

Statistical evaluation of inconsistency between direct and indirect evidence

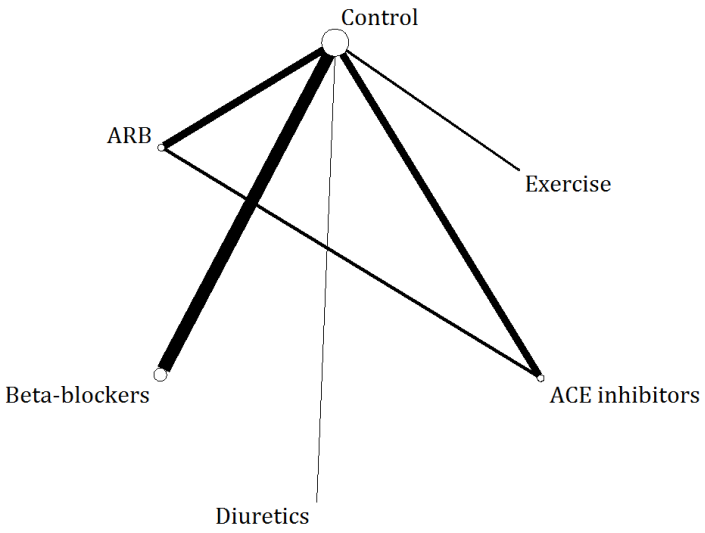
1. Stroke

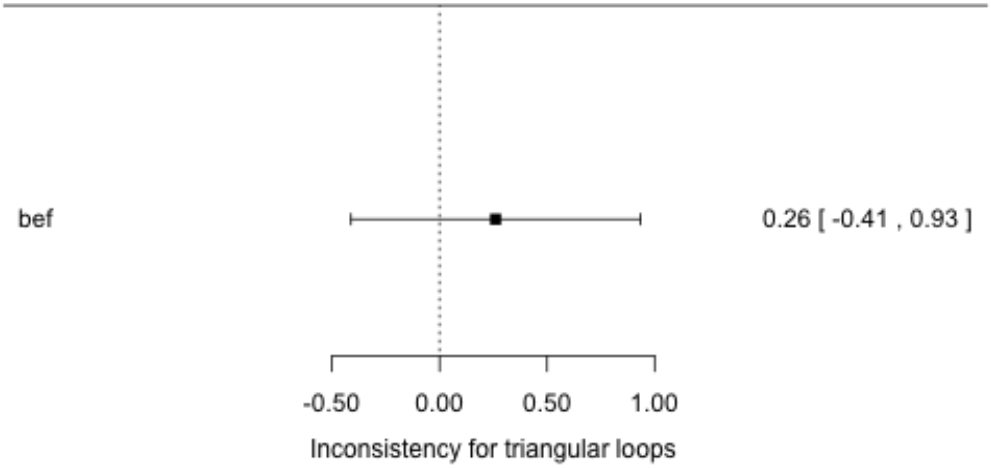




a: exercise; b: anticoagulants; c: antiplatelets; d: control

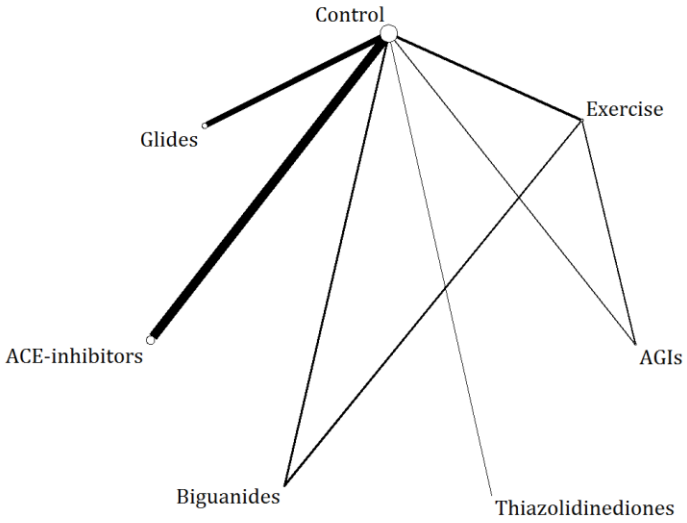
2. Heart Failure

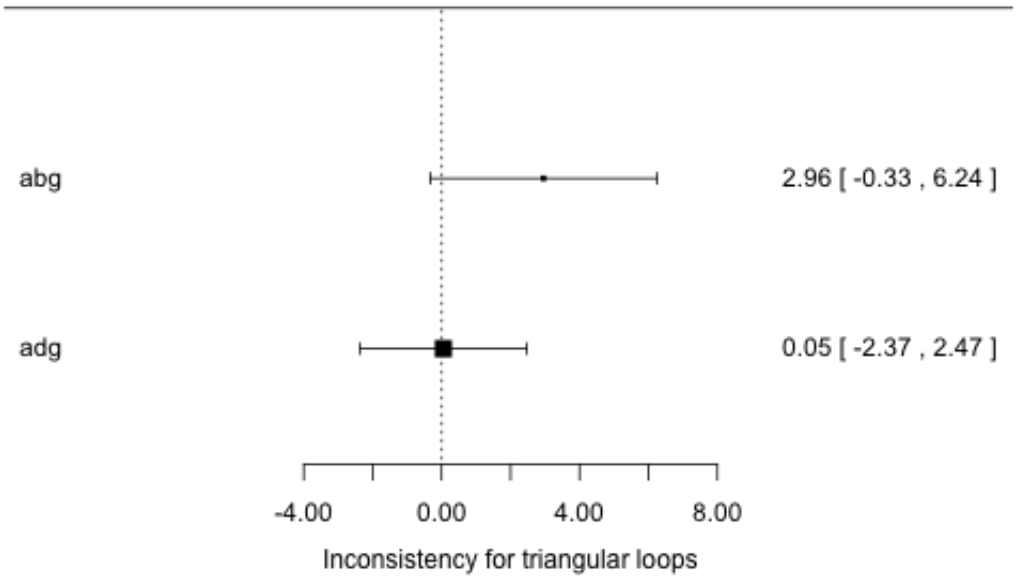




a: exercise; b: ACE inhibitors; c: diuretics; d: beta-blockers; e: ARBs; f: control

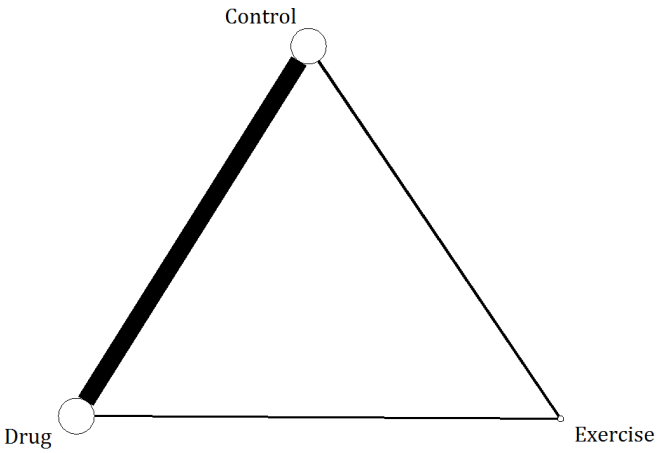
3. Pre-diabetes

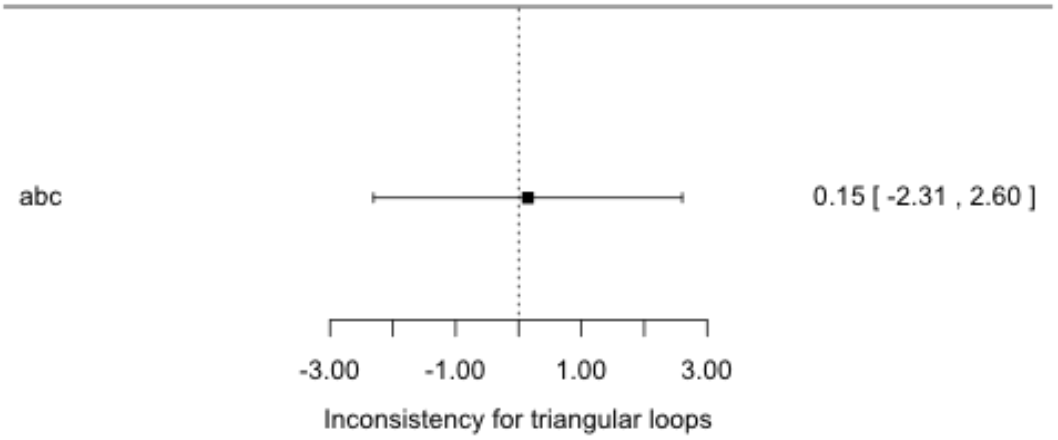




a: exercise; b: AGIs; c: thiazolididiones; d: biguanides; e: ACE inhibitors; f: glides; g: control

4. Pre-diabetes (sensitivity analysis)





a: exercise; b: drug; c: control