Diminishing Returns in Cardiovascular Disease Research: Systematic Review and Meta-analysis

By

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Abstract

If “usual care” improves with time, it becomes increasingly difficult for new therapies to demonstrate additional benefit. Our objective then was to determine, by systematic review of randomized trials, whether the absolute cardiovascular risk reduction attributed to community-implemented preventive therapies has changed over time. Data sources included MEDLINE and Cochrane Central Register of Controlled Trials from inception until 31 December 2015. We examined randomized controlled trials focusing on primary or secondary prevention of atherosclerotic cardiovascular disease (myocardial infarction or stroke) published in 6 leading medical journals. Eligible studies examined a community-implemented intervention, had ≥ 1000 patient-years of observation, and a primary outcome that included at least one of: mortality (all-cause or cardiovascular), stroke, or myocardial infarction. Paired reviewers independently screened articles and extracted data. The period of eligible studies was broken into 9-year quintiles for analysis of time trends. The primary outcome was absolute risk reduction in all-cause mortality. We also examined absolute difference in cardiovascular mortality, stroke/TIA (transient ischemic attack), and myocardial infarction/acute coronary syndrome (MI/ACS).

A total of 170 studies met the inclusion criteria. Absolute risk reduction for all-cause mortality fell steadily from 3.42 deaths per 100 patient-years in 1971-1979 to 0.16 deaths per 100 patient-years in 2007-2015. Similar falls were observed for absolute risk reduction in MI/ACS (5.42 to 0.37 deaths per 100 patient-years). Cardiovascular mortality (1.34 to 0.11 deaths per 100 patient-years), and stroke/TIA (1.51 to 0.05 deaths per 100 patient-years) showed similar falls from 1980-1988 to 2007-2015. This shows that the absolute additive benefit from new therapies targeting the prevention of atherosclerotic cardiovascular disease continues to diminish with

time. As usual care improves, effective new therapeutics will face ever greater hurdles to demonstrating statistical and clinical significance.

Preface

The following team members contributed to the development and data extraction for this project:

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Betsy Thomas

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Dr. Ricky Turgeon

Dedication

For my brothers and sister in arms who support me in all my endeavors (whether they understand them or not). *Militi Succurrimus.*

Also for my father, Charles David Barrington, for instilling his work ethic in me and for his endless support.

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Chapter 1 - Introduction

Statement of the Problem

The concept of diminishing returns, which examines why increasing input into a system, at some point results in diminished output, was first put forth in terms of economic problems. However, it has many parallels in medicine[1] , with each successive intervention providing less benefit than its predecessor. This concept has been explored in terms of the diminishing benefit of diagnostic testing with respect to myocardial infarctions. Investigators found that the added benefit of each successive test was decreased[2], asking the question of when is there so little information gained that the process becomes inefficient. We can look at the concept of diminishing returns with respect to cardiovascular disease research in this way, and the benefit gained with each new intervention developed.

Heart disease remains the number one cause of death in the United States[3,4]. However age specific cardiovascular mortality and morbidity have been falling steadily for decades[5]. From its peak in mortality rate in 1960[6], the change is large – with age specific mortality rates now perhaps ¼ of what they were in 1970[7]. From 1969 to 2010 there was a 41% decrease in age adjusted mortality due to cardiovascular disease in the US, this has been widely attributed to advances and changes in prevention, diagnosis, and treatment[3]. This includes the advent of coronary intensive care units, increases in focused cardiac rehabilitation, and improvements in primary and secondary prevention[6].

In recent years there has been a trend towards the publication of cardiovascular disease trials where the objective is not focused on improvements in mortality outcomes, but rather a

focus on non-inferiority trials[8]. In these the goal is not to show a significantly superior intervention over another, but rather the goal is to show an intervention is therapeutically similar to another, usually pre-existing, intervention[9]. These interventions, tested against an active control, are examined using a margin of inferiority[9]. The increase in these in recent years of noninferiority trials could indicate that trialists know the difficulty they will experience in showing superiority, and the use of a non-inferiority model provides the means to deliver new interventions in a meaningful way.

The large decline in mortality from CHD has been estimated across various countries as 44-76% due to changes in patient risk factors for disease, and relative risk reductions of 23-47% from various treatments[6]. We feel that this will mean that any new intervention trying to prove it's worth by RCT will have a tougher time doing so because the absolute risk reduction will be less. We hypothesize that this will mean RCTs from 1970 to present will show diminishing absolute risk reduction over time.

Objective

To determine, by systematic review of randomized trials, whether the absolute cardiovascular risk reduction attributed to community-implemented preventive therapies has changed over time.

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Chapter 2 - Cardiovascular Risk Reduction in Randomized Trials Over Time: A Systematic Review and Meta-analysis

Introduction

Heart disease continues to be the number one cause of death world-wide, with over 17 million deaths due to cardiovascular disease in 2016[1] . However age-standardized rates of cardiovascular mortality and morbidity have been in decline for decades[2]. After reaching a peak in the late 1960's[3], at around 500 deaths per 100,000 patient-years, age-adjusted death rates from coronary heart disease have steadily fallen to less than a quarter of what they once were[2]. This is presumably due, in large part, to the introduction of antihypertensives, statins, antiplatelets, certain diabetes therapies, improvements in acute care management, and a variety of other medical and public health interventions aimed at cardiovascular risk reduction.

When equally effective therapeutics are sequentially added to a treatment regimen, each successive agent conveys less absolute benefit. If, for instance, improvements in usual care cause the baseline annual mortality rate to fall from 5% to 2.5%, the absolute benefit from adding an intervention reducing risk by 20% falls from 1% to 0.5%. Mechanisms of action of new drugs can also interact, or overlap, with drugs that are already in use. It would be more challenging, for instance, for a new lipid lowering agent to demonstrate benefit when a statin is already in use.

To determine if the benefit from new therapies is diminishing, we systematically searched, over all years of electronically available data, the 6 medical journals most likely to publish major cardiovascular trials. We identified randomized trials examining community-implemented therapies for the prevention of atherosclerotic cardiovascular disease (myocardial infarction and stroke) and determined how absolute risk reduction for mortality, and cardiovascular morbidity, changed over time.

Methods

This review followed guidance published by the Cochrane Collaboration[4] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement[5]. The study protocol is available in eAppendix1.

Data Sources and Searches

An experienced medical librarian developed the search strategy (eAppendix1) and conducted a search of CENTRAL (Cochrane Central Register of Controlled Trials) and MEDLINE from 1946 to Dec 31, 2015. Our search was limited to 6 major medical journals, all of which are indexed in MEDLINE. These journals include the Journal of the American Medical Association, the New England Journal of Medicine, the Lancet, the British Medical Journal, Annals of Internal Medicine, and Circulation.

Eligibility Criteria

Studies were included if they:

1) Described a randomized trial with original research (i.e. were not a subgroup or re-analysis analysis of previously published work)
2) Targeted atherosclerotic conditions (as primary or secondary prevention).
3) Had a primary outcome that included at least one of all-cause death, cardiovascular death, myocardial infarction / acute coronary syndrome (MI/ACS), or stroke / transient ischemic attack (stroke/TIA).
4) Examined interventions implementable by community providers (i.e. we excluded surgeries and procedures, but included interventions started in hospital and continued on discharge).

Studies were excluded if:

1) The study mandated all patients have congestive heart failure or atrial fibrillation (which suggested a different disease process and therapeutic intention)

2) The study had fewer than 1000 patient-years of observation (to avoid studies that were underpowered, or enrolling populations at unusually high risk)[6 7] .

Study Selection and Data Extraction

Dual review of titles, abstracts, and full papers to assess eligibility was performed by the primary author (CB) paired with one of 5 co-authors (CF, RA, CS, DC, and RT). Disagreements were resolved by discussion, or by third party adjudication when necessary. Dual data extraction into a standardized template was performed by those 6 authors, with a 7th author (SG) adjudicating any discrepancies.

The primary outcome was the absolute risk reduction for all-cause mortality. Secondary outcomes included absolute risk reductions for cardiovascular mortality, MI/ACS, and stroke. When stroke was presented with or without TIA, we chose without TIA, given it is the more clinically meaningful outcome. We recorded the date of publication, the number of patients randomized, the number of patient-years of observation, and patient descriptors including mean age, percent male, percent smoker, percent diabetic, percent hypertensive, and mean systolic / diastolic blood pressure. We also captured study methodology, including type of intervention, type of comparator, assumed relative risk reduction when powering, and select inclusion and exclusion criteria. The inclusion criteria captured were hypertension, diabetes, stable coronary artery disease, acute coronary syndrome / myocardial infarction, abnormal lipids, chronic kidney disease, and high cardiovascular risk. Exclusion criteria captured were the presence of an upper age limit, and a lower limit for glomerular filtration / renal impairment (not including dialysis).

Data Synthesis and Analysis

The period of eligible studies was broken evenly into quintiles of time. Within each quintile, studies were pooled for determining outcomes and study characteristics. If unstated, patient-years of observation for each study was calculated using the average follow-up time in each of the treatment and control arms of the study, multiplied with the number of participants in that arm. The differences in absolute risk reduction over time were examined graphically, and by analysis of variance to determine significance of the change over time. The reporting quality of the included trials was assessed using the JADAD scoring tool[8] .

Results

The search protocol yielded 8,676 records (8,126 after de-duplication) of which 7,728 were removed during dual review of titles and abstracts. Full papers were reviewed for 398 studies and 170 randomized controlled trials met our inclusion criteria (Figure 1).

Study Characteristics

Since the first eligible study was published in 1971, the years under study were broken down evenly into 9-year quintiles spanning the time periods 1971-1979, 1980-1988, 1989-1997, 1998-2006, and 2007-2015. Both the number of trials, the number of enrolled subjects within each trial, and the number of patient-years of observation increased over time. Characteristics of the studies contributing to each time quintile are shown in Table 1, and demonstrate a shift over time towards enrolment of fewer smokers (62.9% of study participants in 1970-1979 falling to 19.4% in 2007-2015) and more patients labelled as diabetic (1.5% rising to 47.3%). The majority of studies compared introduction of a drug (90.6% across all quintiles) to placebo or usual care (91.6%). Study quality, as measured by JADAD, increased over time.

All-cause Mortality

The absolute risk reduction for all-cause mortality fell over time from 3.42 deaths per 100 patient-years in 1970-1979 to 0.16 deaths per 100 patient-years in 2007-2015, a fall of 95% (Table 1, Figure 2). Analysis of variance using the Kruskal-Wallis test shows differences over time to be statistically significant ($p = 0.0014$).

Other Cardiovascular Outcomes

There were no eligible studies reporting cardiovascular death or stroke within the earliest quintile (1971-1979). Rates for each of these outcomes over time, plus rates for MI/ACS are given in Table 1 and depicted in Figure 3. The clear diminishment for each over time is substantial (absolute risk reduction falling by 92% for cardiovascular mortality, 93% for MI/ACS, and 97% for stroke) and statistically significant via the Kruskal-Wallis test for analysis of variance (cardiovascular death $p = 0.0028$; MI/ACS $p = 0.0026$; stroke $p = 0.0002$).

Enrolled Subjects and Assumed Benefit in Study Powering

Specifics for each time quintile are given in Table 1. The number of subjects enrolled in each trial increased over time from a mean of 1034 (SD 532) in 1971-1979 to 9147 (SD 6838) in 2007-2015. The benefit (relative risk reduction) assumed during powering for the primary outcome decreased from 43% in 1980-1988 to 21% in 2007-2015.

Control Event Rate

All-cause mortality in controls fell from 6.78 deaths per 100 patient-years in 1971-1979 to 2.97 deaths per 100 patient-years in 2007-2015, a 56 percent reduction ($p = 0.0074$ via Kruskal-Wallis). Control event rates for other outcomes are given in Table 1 and demonstrate similar reductions in the rate of cardiovascular death ($p < 0.0001$), MI/ACS ($p = 0.0033$), and stroke ($p = 0.015$).

Discussion

From 1971 to 2015, studies exploring interventions for the prevention of atherosclerotic cardiovascular disease have become more numerous, assumed less benefit when powering, enrolled more participants labeled as hypertensive or diabetic, and increased the number of participants and patient-years of observation. Over the same time period the absolute risk reduction for all-cause mortality in such trials has fallen 95.3% (from 3.42 deaths per 100 patient-years in 1971-1978 to 0.16 deaths per 100 patient-years in 2008-2015). Similar reductions in absolute risk reduction have occurred for cardiovascular mortality, MI/ACS, and stroke.

These findings are consistent with previous predictions of the inevitability of diminishing returns when multiple therapeutics are introduced to prevent the same condition[9] , and with the observation that the mortality rate from cardiovascular disease is leveling off in recent years. [1, 10] . Our findings are also numerically consistent with the over 75% fall in age-adjusted death rates from coronary heart disease since the late 1960's reported by the NIH[2] . If the relative risk reduction of new therapies remained the same over time, a greater than 75% fall in baseline risk would result in a similar reduction, as we have observed, in the absolute risk reduction provided by new therapies.[10] Our finding that the number of patient-years of observation is increasing over time, is itself a corroboration of our findings, in that trialists themselves are planning to detect smaller absolute differences between groups as time goes on.

Limitations

Although we speculate that diminishing baseline risk is primarily responsible for the falling absolute risk reductions, it is also possible that other changes in study populations contribute. If diabetics are less responsive to therapies, for instance, the increasing proportion of diabetics in

cardiovascular trials might lead to lower absolute risk reductions. Outcome definition could also contribute. If the criteria for diagnosing stroke or MI has become more restrictive (e.g. requiring cardiac enzyme changes to diagnose MI, or excluding TIA from the definition of stroke), we might observe fewer outcomes and lower absolute risk reduction as a result. We have also examined all eligible studies, whether or not those studies were statistically significant. If each therapy under study had a lower likelihood of providing benefit over time (e.g. opening up new classes of chemicals), if the relative risk reduction of new therapies is also diminishing, or if there was a greater desire of the major journals to publish negative studies, that might also contribute to the observed reduction in mean absolute risk reduction.

Our conclusions are also limited to atherosclerotic cardiovascular disease. If new therapeutic areas are opened, we would expect to initially see large absolute risk reductions for those conditions. When warfarin first became available, for instance, it introduced a large absolute risk reduction for stroke in patients with atrial fibrillation or valvular heart disease.

Conclusion

The absolute additive benefit of new therapies for the prevention of atherosclerotic cardiovascular disease is diminishing. As time goes on, trialists will be increasingly challenged to demonstrate statistical and clinical significance for new therapeutics.

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Figure 1: PRISMA Flow Diagram

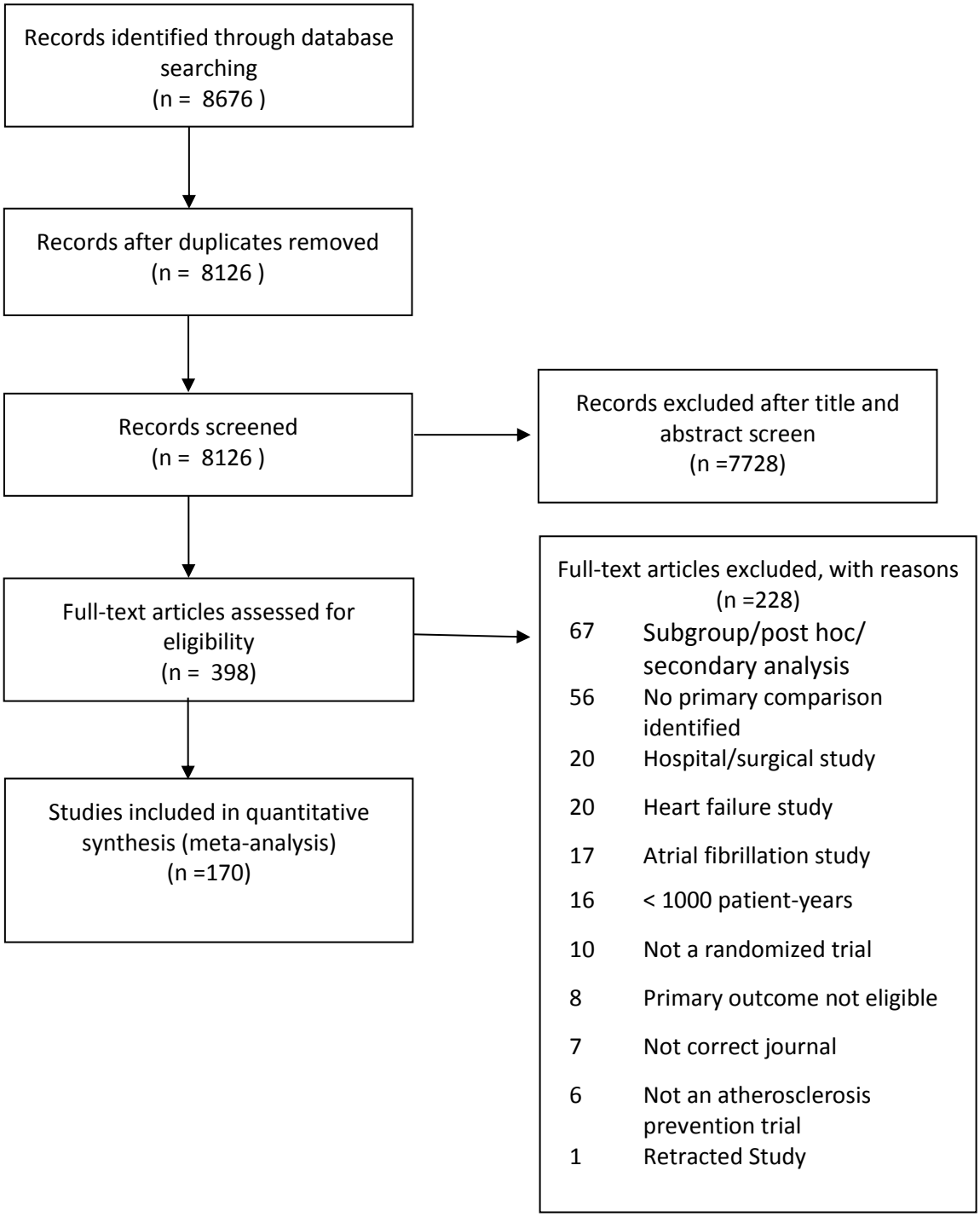

Figure 2: Absolute Risk Reduction in All-Cause Mortality

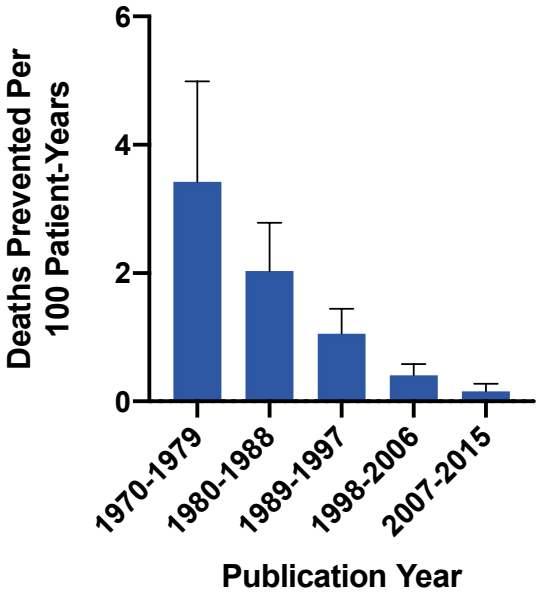

Figure 3: Absolute Risk Reduction in Cardiovascular Death, Myocardial Infarction, and Stroke/Transient Ischemic Attack

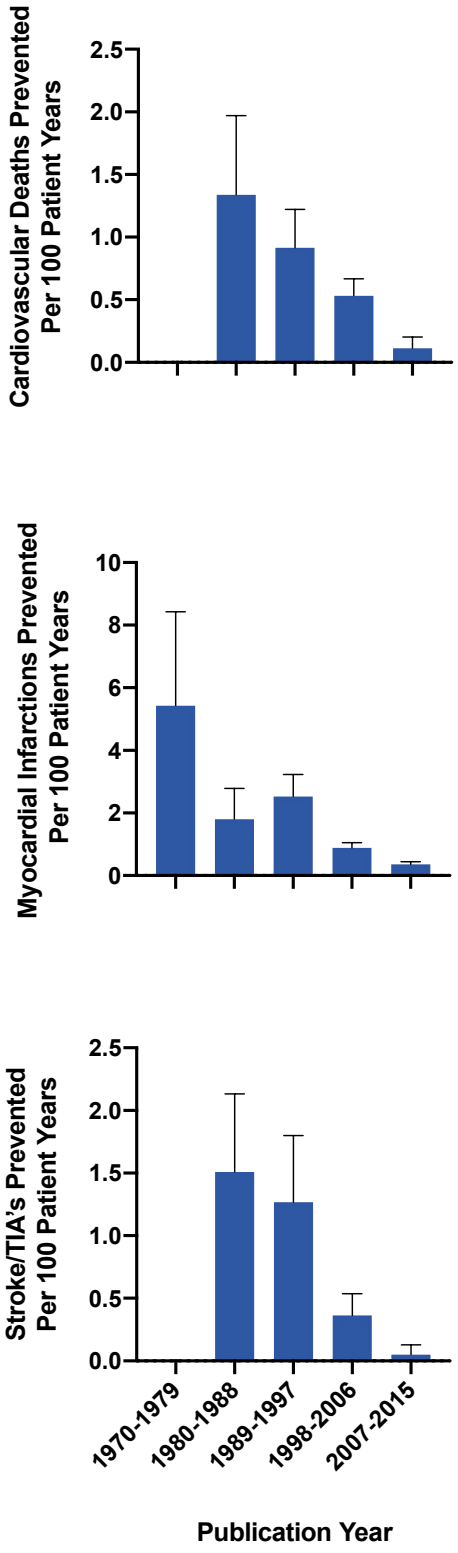

Table 1: Study Characteristics					
Quintiles	**1971-1979**	**1980-1988**	**1989-1997**	**1998-2006**	**2007-2015**
Number of Studies	4	11	22	70	63
Study N, Mean(SD)	1034 (533)	3597 (4811)	4302 (5561)	9257 (9475)	9147 (6838)
Patient Years Observed, Mean(SD)	2526.6 (1219.4)	15223.7 (24786.6)	15298.4 (23965.4)	48402.3 (80447.4)	36443.9 (32243.5)
Baseline Characteristics, Mean(SD)					
Age, Mean(SD), years	54.3 (1.5)	58.8 (7)	63.5 (5.5)	62.8 (5)	63.3 (4.7)
% Male, Mean(SD)	87 (8.8)	72.4 (28.7)	71.8 (20.1)	58.7 (28.4)	63.8 (20.1)
% Smoker, Mean(SD)	62.9 (3.1)	35.4 (13.4)	31.3 (21)	19.6 (9.6)	19.4 (14.5)
% Diabetic, Mean(SD)	1.5 (2.6)	4 (5.5)	12.2 (8.3)	27.7 (25.8)	47.3 (35.9)
% Hypertension, Mean(SD)	19.5	63.7 (45.4)	54.1 (27.3)	61.7 (24.1)	72.8 (16.2)
Blood Pressure (mmHg)					
Systolic, Mean(SD)	142.0 (1.4)	154.1 (26.8)	150.9 (22.9)	144.8 (14.2)	138.5 (9.1)
Diastolic, Mean(SD)	87.5 (4.2)	95.0 (10.6)	84.3 (7.3)	83.7 (7.8)	79.2 (4.7)
Inclusion Criteria					
Hypertension, No(%)	-	4 (36.4)	4 (18.2)	14 (20)	7 (11.1)
Diabetes, No(%)	-	-	-	11 (15.7)	19 (30.2)
Coronary Artery Disease, No(%)	3 (75)	3 (27.3)	3 (13.6)	15 (21.4)	10 (15.9)
MI/ACS, No(%)	1 (25)	1 (9.1)	6 (27.3)	5 (7.1)	8 (12.7)
Abnormal Lipids, No(%)	-	-	2 (9.1)	12 (17.1)	9 (14.3)
Chronic Kidney Diseases, No(%)	-	-	-	3 (4.3)	6 (9.5)
High Risk, No(%)	-	-	3 (13.6)	24 (34.3)	31 (49.2)
Exclusion Criteria					
Upper Age Limit, No(%)	2 (50)	7 (63.6)	11 (50)	38 (54.3)	20 (31.7)
Lower GFR Limit, No(%)	1 (25)	1 (9.1)	6 (27.3)	25 (35.7)	27 (42.9)
Study Intervention					
Drug, No(%)	4 (100)	11 (100)	19 (86.4)	61 (87.1)	50 (79.4)
Diet, No(%)	-	-	1 (4.5)	2 (2.9)	2 (3.2)
Exercise, No(%)	-	-	-	1 (1.4)	-
Smoking Cessation, No(%)	-	-	-	-	-
Care Team Intervention, No(%)	-	-	-	-	-
Patient Education, No(%)	-	-	-	-	-
Other, No(%)	-	-	1 (4.5)	1 (1.4)	3 (4.8)
Comparator					
Placebo, No(%)	4 (100)	6 (54.5)	17 (77.3)	44 (62.9)	36 (57.1)
Usual Care / No Treatment, No(%)	-	4 (36.4)	3 (13.6)	17 (24.3)	20 (31.7)
Wait List, No(%)	-	-	-	-	-

Active Control, No(%)	-	1 (9.1)	2 (9.1)	9 (12.9)	6 (9.5)
Other, No(%)	-	-	-	-	1 (1.6)
Quality Assessment JADAD Score (0-5), Mean(SD)	3 (0.8)	3 (0.8)	4 (1.4)	4 (1.1)	4 (1.0)
Control Event Rate, Mean(SD) **(Per 100 Patient-Years)**					
All-Cause Mortality, Mean(SD)	6.8 (5.6)	4.3 (2.9)	3.3 (1.7)	2.7 (2.1)	3.0 (3.9)
Cardiovascular Mortality, Mean(SD)	-	2.9 (2.5)	2.0 (1.2)	1.4 (1.5)	1.2 (1.3)
Myocardial Infarctionn, Mean(SD)	5.1 (3.7)	2.7 (2.4)	2.4 (1.8)	1.8 (1.6)	1.4 (1.5)
Stroke / TIA, Mean(SD)	-	1.6 (2.2)	2.0 (2.2)	1.6 (1.8)	0.9 (0.8)
Absolute Risk Reduction (Per 100 Patient-Years) Mean(SD)					
Mortality, Mean(SD)	3.4 (3.1)	2.0 (2.5)	1.1 (1.8)	0.4 (1.4)	0.2 (0.9)
Cardiovascular Mortality, Mean(SD)	-	1.3 (1.9)	0.9 (1.4)	0.5 (1.0)	0.1 (0.7)
Myocardial Infarctionn, Mean(SD)	5.4 (4.2)	1.8 (2.8)	2.5 (3.1)	0.9 (1.3)	0.4 (0.6)
Stroke / TIA, Mean(SD)	-	1.5 (1.9)	1.3 (2.3)	0.4 (1.4)	<0.1 (0.6)

eAppendix:

Appendix 1: STUDY PROTOCOL

Databases and Search Strategy:
CENTRAL & Medline using Cochrane Collaboration RCT filter and terms of interest (see Appendix 2)

Time Frame: Jan 1 1946 – Dec 31 2015 Inclusive

Study Inclusion Criteria:

1. Randomized trial
2. Original research (i.e. not a subgroup analysis of a prior publication)
3. Intervention targets an atherosclerotic condition, such as primary or secondary prevention of stroke or MI/ACS.
4. Primary outcome contains at least one major adverse cardiovascular event including all-cause mortality, cardiovascular mortality, MI/ACS, or stroke.
5. Intervention is implementable in the community (i.e. excludes surgeries and procedures) and the bulk of the study follow-up occurred while out of hospital (i.e. an intervention can be started in hospital, but studies looking only at inpatient outcomes are not eligible).

Study Exclusion Criteria:

1. Pediatric focus (exclusively enrolls patients <=18 years of age).
2. All patients are mandated to have atrial fibrillation or heart failure (since those studies are unlikely to be targeting atherosclerosis).
3. Fewer than 1000 patient-years of observation (which would suggest enrollment of unusually high-risk populations or studies that are underpowered).
4. A primary outcome is not identified

Data to be collected:

A) Citation

a. Short title (in Format 1st author/date e.g. Barrington, 2016)
b. Date
c. Full Citation (Vancouver Style)
d. Journal
    i. NEJM
    ii. Lancet
    iii. JAMA
    iv. Annals of Int Med
    v. BMJ
    vi. Circulation

B) Study Inclusion Criteria

a. Hypertension

b. Diabetes
c. Stable coronary artery disease
d. Acute coronary syndrome / MI
e. Elevated Lipids
f. Chronic Kidney Disease
g. High cardiovascular disease risk

C) Study Exclusion Criteria

a. Includes upper age limit (yes/no)
b. Exclusion for renal impairment (other than dialysis) (yes/no)

D) Study Population

a. Type (Primary prevention, secondary prevention, or mixed)
b. Number (Total, Control, Intervention)
c. Mean age
d. % Male
e. % Current smoker
f. % Labelled as diabetic
g. % Labelled as hypertensive
    i. Mean Systolic BP
    ii. Mean Diastolic BP

E) Intervention

a. Treatment name
b. Treatment type
    i. Drug
    ii. Diet
    iii. Exercise
    iv. Smoking cessation
    v. Vitamins / herbal supplements
    vi. Care team reorganization
    vii. Provider education
    viii. Other

F) Comparator

a. Comparator name
b. Comparator type
    i. Placebo
    ii. Usual Care/No treatment
    iii. Wait list
    iv. Other

G) Primary Outcome

a. Definition (free text) as given in the study
b. Statistical significance (yes / no) and p-value

H) Cardiovascular Outcomes

- **a.** Total Mortality
  - i. Treatment
    1. Number enrolled
    2. Number with Event
  - ii. Control
    1. Number enrolled
    2. Number with event
- **b.** Cardiovascular Mortality
  - i. Treatment
    1. Number enrolled
    2. Number with Event
  - ii. Control
    1. Number enrolled
    2. Number with event
- c. MI/ACS
  - i. Treatment
    1. Number enrolled
    2. Number with Event
  - ii. Control
    1. Number enrolled
    2. Number with event
- d. Stoke (excluding TIA if presented separately)
  - i. Treatment
    1. Number enrolled
    2. Number with Event
  - ii. Control
    1. Number enrolled
    2. Number with event

I) Methods

- a. % Benefit assumed for sample size calculation

Appendix 2: Search Strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 27 July 2016
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1 exp Myocardial Infarction/ (156931)

2 exp Myocardial Ischemia/ (385374)

3 ((cardiac or heart or myocardial) adj (infarct$ or isch$)).tw. (176511)

4 (AMI or MI).tw. (44679)

5 post-infarct$.tw. (2812)

6 heart attack?.tw. (4143)

7 exp cerebrovascular disorders/ (312092)

8 (poststroke or stroke or strokes).tw. (162862)

9 (apoplex$ or brain vascul$ or cerebral vascul$ or cerebrovascul$ or cva or cvas or tia or tias).tw. (55592)

10 ((brain$ or cerebell$ or cerebr$ or intercerebr$ or intracerebr$ or intracran$ or cortical or hemispher$ or infratentorial or intraventricular or MCA or subarachnoid or supratentorial or transient or vertebrobasilar) adj4 (accident$ or aneurysm? or bleed$ or emboli$ or h?ematoma$ or h?emorrhag$ or infarct$ or isch?emi$ or occlus$ or rupture$ or thrombo$ or vasospasm?)).tw. (151942)

11 or/1-10 (818870)

12 "new england journal of medicine".jn. (73866)

13 lancet.jn. (131641)

14 jama.jn. (67993)

15 "journal of the american medical association".jn. (10842)

16 "annals of internal medicine".jn. (30330)

17 bmj.jn. (64643)

18 british medical journal.jn. (47124)

19 british medical journal clinical research ed.jn. (13560)

20 circulation.jn. (40849)

21 or/12-20 (480848)

22 randomized controlled trial.pt. (424993)

23 controlled clinical trial.pt. (91267)

24 randomized.ab. (321594)

25 placebo.ab. (162626)

26 clinical trials as topic/ (178344)

27 randomly.ab. (226282)

28 trial.ti. (140773)

29 or/22-28 (969652)

30 animals/ not (humans/ and animals/) (4248969)

31 29 not 30 (887462)

32 11 and 21 and 31 (5469)

33 remove duplicates from 32 (5345)

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Database: Cochrane CENTRAL via Cochrane Register of Studies Online
Search Date: 27 July 2016

#1 MESH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES 8398
#2 MESH DESCRIPTOR Myocardial Ischemia EXPLODE ALL TREES 20892
#3 myocardial next (infarct* or isch*):ti,ab 17816
#4 (ami or mi):ti,ab 5843
#5 MESH DESCRIPTOR Cerebrovascular Disorders EXPLODE ALL TREES 9074
#6 (poststroke or stroke or strokes):ti,ab 25135
#7 (apoplex* or brain vascul* or cerebral vascul* or cerebrovascul* or cva or cvas or tia or tias):ti,ab 3778
#8 (brain* or cerebell* or cerebr* or intercerebr* or intracerebr* or intracran* or cortical or hemispher* or infratentorial or intraventricular or MCA or subarachnoid or supratentorial or

transient or vertebrobasilar) near3 (accident* or aneurysm* or bleed* or emboli* or haematoma* or hematoma* or haemorrhag* or hemorrhag* or infarct* or isch*emi* or occlus* or rupture* or thrombo* or vasospasm*):ti,ab 8817
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 60770
#10 ("new england journal of medicine"):SO 4085
#11 nejm:so 19
#12 "n engl j med":so 18
#13 lancet:so 8583
#14 "journal of the american medical association":so 352
#15 jama:so 3031
#16 "annals of internal medicine":so 1556
#17 "ann intern med":so 8
#18 "british medical journal":so 2970
#19 bmj:so 3149
#20 circulation:so 9772
#21 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 33377
#22 #9 AND #21 8355
#23 #9 AND #21 NOT INMEDLINE 3299

Appendix 3: Included and excluded full review studies.

Randomized Controlled Trials Included in Review

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Chapter 3 - Conclusion

Overview of Research and Objectives

The aim of this project was to determine if the additive benefit conveyed by new cardiovascular preventive therapies is diminishing with time. A systematic review of randomized trials published in 6 major medical journals, over all years of publication, was conducted to determine changes over time in absolute risk reduction for all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke/transient ischemic attack.

Summary of Findings:

The absolute risk reduction (ARR) in terms of mortality was found to have declined significantly from 1971-1979 to 2007-2015. ARR was reduced from 3.42 deaths avoided per 100 patient-years down to 0.16 deaths avoided per 100 patient-years, with a p-value of 0.0014. Cardiovascular mortality, myocardial infarction, and stoke/transient ischemic attack all showed similar trends in term of decline with the following p-values: 0.0028, 0.0026, 0.0002 respectively.

Implications for Practice:

While the outcome of our review may seem disheartening to clinicians, new therapies are likely not finding lesser benefit because they are less useful than previous interventions, but rather because “usual care” has improved so greatly over time – making it increasingly difficult

for new treatments to provide added value. For those that want to introduce new products, the cup may be half full, since this is becoming more difficult. But for the public, who are receiving the benefit of decades of improvements in prevention and public health initiatives (such as successful smoking cessation efforts), the cup is half full in terms of the great strides we have made.

Importantly, the diminishing absolute risk reduction shown by new therapies does not mean those therapies would not have been just as effective as the older therapies had they been introduced at the same period time. Although the development of new therapies may have less impact on the general population; those therapies could still benefit individual patients. For example, certain medications may not be effective for some individuals, or poorly tolerated[1]. Having a wider selection of available interventions helps to find options for patients that are effective, but have greater tolerability or convenience.

Implications for Future Research:

In 2013 ischemic heart disease accounted for 88.1 billion dollars of health care spending in the United States.[2] In Canada the major driving force behind cardiovascular research is funding from the public and charitable sectors with around 90 million dollars in cardiovascular research spending in 2000.[3] In 2008, the US spent around 4.8 billion dollars on cardiovascular disease research, substantially more than in Canada.[3] It can be difficult to quantify the value in terms of dollars on the benefit of new therapies. A study conducted in 2006 concluded that although the cost was high, the return on that investment was also high.[4] What happens now in terms of the value added in funding new research? With the finding that the return on investment

may not be as high, how do we value new cardiovascular disease research, and who should pay for that funding?

The search terms should be updated to include recent years and this information added to the data set. This would ensure that the most recent understanding of the changes in cardiovascular disease risk reduction over time.

Given the increase in patients enrolled over time, trialists are already expecting to find diminishing absolute differences. There is potential for more pragmatic studies, such as safety studies, or studies looking at ways to use the current tools we have more effectively. For instance, should we use less aggressive blood pressure targets in the elderly? And we should also consider looking at ways to more broadly apply the interventions we already have more equitably to all populations.

Limitations:

The scope of the project is such that the large volume of information available requires lengthy processing, and leads to our findings being slightly out of date (i.e. our search ending in Dec 2015 rather than 2019). It is also a time series, and other changes that occur over time might be responsible for the diminishing absolute benefit we observed rather than the improvement in usual care we assume to be responsible.

Conclusions:

The absolute additive benefit of new therapies is decreasing over time. Trialists will have a more difficult time proving the worth of their therapies and providers and payors will increasingly need to weigh the cost/benefit of new opportunities.

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