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Management of Cardiovascular Disease Risk Factors in Older Adults With Type 2 Diabetes Mellitus: 2002 - 2012 Literature Review

Gerardo Moreno, MD, MSHS[1] and **Carol M. Mangione, MD, MSPH**[2,3]

[1]Department of Family Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA

[2]Department of Medicine, David Geffen School of Medicine at UCLA Los Angeles, CA

[3]Department of Health Policy and Management, UCLA Fielding School of Public Health, Los Angeles, CA

Abstract

Diabetes Mellitus type 2 (DM) is one of the most common chronic conditions among older adults and is often present with co-morbidities and geriatric syndromes. The management of cardiovascular disease risk factors in older adults with DM is of important significance to clinicians. The literature was reviewed from 2002-2012 to provide an American Geriatrics Society (AGS) expert panel with an evidence base for updating and making new recommendations for improving the care of the older adult with DM. This review includes only the domains of the management of blood pressure, lipid control, glycemic control, and use of aspirin.

Over the last ten years, new randomized clinical trial (RCT) evidence designed to study the impact of different blood pressure treatment targets did not find that intensive blood pressure control (<130 mmHg) reduced myocardial infarction and mortality. There are increased risks of side effects with achieving a blood pressure of < 120 mmHg. Statin class lipid lowering drugs are effective in reducing cardiovascular events among middle aged and older adults but data on niacin and fibrates is limited. Lipid lowering trials of statins and other lipid lowering agents do not evaluate the cardiovascular effects of treating lipids to different low density lipoprotein (LDL) cholesterol targets. There were no randomized clinical trials of lipid lowering drugs that enrolled significant numbers of adults age 80 years and above with or without DM. Three major RCTs that investigated intensive glycemic control did not find reductions in primary cardiovascular endpoints and one study reported increased mortality with a hemoglobin A1C < 6%. Two recent published RCTs were designed to study the cardiovascular benefits of aspirin use by patients with DM. Both trials failed to significantly reduce primary cardiovascular endpoints with aspirin compared to control groups. Overall, RCTs enrolled very few adults greater than 80 years of age or with significant co-morbidities. More research is needed for clinicians to effectively tailor care to older adults with DM because of heterogeneity in health status, co-morbidities, duration of disease, frailty and functional status, and differences in life expectancy.

Introduction

During the last ten years, we have seen new high quality evidence for the management and prevention of cardiovascular disease in older adults with diabetes mellitus (DM). During this same time, we also witnessed a treatment paradigm that has shifted away from disease

Corresponding author: Gerardo Moreno MD, MSHS, 10880 Wilshire Blvd, Suite 1800, Los Angeles, CA 90024, P: (310) 739 – 0567, F: (310) 794 – 3938, gemoreno@mednet.ucla.edu.

focused treatment goals to patient centered treatment recommendations. The evidence base for the prevention and management of cardiovascular disease (CVD) has grown for middle-aged adults but remains scant, at best, for older adults aged ≥ 80 years of age. Although the majority of older adults are healthy, older adults with DM are a highly heterogeneous population and research is generally not generalizable to those with poor functional status, complex comorbidities, and limited life expectancy.

The updated clinical guideline recommendations published by the American Geriatrics Society (AGS) provide guidance to clinicians who care for older adults with DM.[1] This report complements the guideline and provides detail about important studies, with an emphasis on randomized clinical trials (RCTs) between 2002 and 2012. The purpose of this report is to review the prevention and management of CVD literature for older adults with DM. In particular, we focus on blood pressure control, management of lipids, role of aspirin, and glycemic control.

Methods

Existing peer-reviewed literature and guidelines on each DM topic were identified. We searched PubMed for relevant studies published in the peer-reviewed literature and limited this search to the English language literature from 2002 to 2012. Terms searched included “diabetes mellitus,” “diabetes geriatrics,” “diabetes complications,” and “hypertension and diabetes” with the search limits to “randomized controlled trials,” “meta-analysis,” and “systematic reviews.” We reviewed randomized clinical trials and systematic reviews or meta-analyses for aspirin use, glycemic control, hypertension management, and lipid management. For many of the topic areas reviewed and updated, limited data that were specific to older adults with DM were found, but for some of the domains under consideration, there were data from studies of older adults or of persons of all ages with DM. For a number of these domains, the expert panel decided whether it was reasonable to extrapolate the findings to older adults with DM. Existing published clinical guidelines from all relevant societies, the Cochrane Collaboration, and the Adult Treatment Panel III report from the National Cholesterol Education Program were also carefully reviewed for each DM domain. The references in the guidelines and peer-reviewed papers were also searched and reviewed. Evidence tables were then constructed that summarize the new evidence from RCTs and systematic reviews for each DM topic and that provide an updated overview of some of the most important aspects of care that either differ significantly or deserve special emphasis compared with the care provided to younger persons with diabetes. This review is an updated overview of some of the aspects of care that either differ significantly or deserve special emphasis compared with care provided to younger persons with diabetes. We do not address studies that target the control of multiple risk factors because they were found to be limited.[2, 3]

Results

Research on blood pressure management

Older adults with DM have a high prevalence of hypertension and complications from hypertension are independent from those of hyperglycemia. Until recently, except for the 2003 *AGS Guidelines for Improving the Care of the Older Adult with Diabetes Mellitus*, most clinical care guidelines recommended that patients with DM attain a goal blood pressure of < 130/80 mmHg.[1] The recommendations were based mostly on interpretations of benefit from retrospective subanalysis of RCTs of hypertensive middle age and older adults with and without DM.[4-7] In this review, three important RCTs of blood pressure control among middle age and older adults with DM were published in the last 10 years (Table 1).[8-10] RCTs of older adults with DM and hypertension remain limited during this last

decade. Of major significance, the Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD) compared intensive blood pressure treatment (target of < 120 mmHg SBP) with a standard treatment with a goal of 140 mmHg among middle age and older adults (ages 40-79) with DM and a high risk of cardiovascular disease.[8] ACCORD did not find statistically significant reductions in the primary outcome, MI or all cause mortality, but did find a modest statistically significant reduction in the intensive treatment arm for the secondary outcome of stroke (number needed to treat (NNT) was 89 over five years) and concerning rates of serious adverse events. A United Kingdom Prospective Diabetes Study (UKPDS) follow-up study on the long-term benefits after tight blood pressure control determined that there were no macrovascular benefits if tight blood pressure control is not sustained.[9]

Recent large subgroup post hoc analysis of the International Verapamil SR-Trandolapril Study (INVEST) and the Ongoing Telmistsartan Alone and in Combination With Ramipril Global Endpoint Trail (ONTARGET) also provide important findings.[11, 12] The INVEST researchers concluded that blood pressure control < 130/80 mmHg was not associated with better cardiovascular outcomes compared to usual control of 140-130 mmHg among patients ≥ 55 years old (mean age 66 ± 6 years). The ONTARGET study (mean age 66 ± 7 years and 57% with age ≥ 65 years) conclusions were similar except for the risk of stroke.[11] A third analysis of the large Veterans Affairs Diabetes Trail (VADT) reported increased cardiovascular risks with a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of < 70 mmHg (average age of patients was 60±9 years).[13] Two meta-analyses pooled studies of patients with DM to examine the effect of intensive blood pressure control (< 130mmHg) and did not show benefits for MI or mortality compared to a blood pressure of < 140 mmHg.[14, 15] The meta-analyses found an association between lower blood pressure and risk of stroke but this was in the setting of increased serious adverse events.[14, 15]

Research on control of lipids

Numerous randomized clinical trials have demonstrated the benefits of the statin class of lipid lowering agents in the primary and secondary prevention of CVD and reducing cardiovascular morbidity and mortality. For older adults with DM, the benefits of statins have been extrapolated from trials of adults without DM and trials of adults with and without DM.

Subgroup analysis of the Scandinavian Simvastatin Survival Study (4S),[16] the Cholesterol and Recurrent Events (CARE) Trail,[17] the Long-term Intervention with Pravastatin in ischemic Disease (LIPID) trail,[18] and the Heart Protection Study (HPS)[19] demonstrated the secondary prevention benefits of statins in reducing CVD events in older adults in general. The age range for these trials was 35 to 79 years. A meta-analysis by Afilalo et al. (2008) of nine secondary prevention trials with statins in patients aged 65 to 82 years of age also found CVD benefits.

Primary prevention studies of statins in older adults include subanalysis of the Cardiovascular Health Study (CHS),[20] and the Air Force/Texas Coronary Atherosclerosis Study (AFCAPS/TexCAPS).[21] The Heart Protection Study (HPS) was one of the first studies that included adults with DM. More recent (2002-2012) studies[22] of statins versus placebo (Table 2) that were reviewed include the Collaborative Atorvastatin Diabetes Study (CARDS),[23] Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA),[24] and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN).[25] Table 3 lists RCTs of high dose statins versus low dose statins for adults with and without DM.[2, 26, 27] These reductions in cardiovascular outcomes shown in these trials suggest benefits to older adults. Table 4 lists two RCTs reviewed of statins plus fibrates and niacin, and that did not show reductions in

primary cardiovascular outcomes from the intensive therapy.[28, 29] Finally, we reviewed two large meta-analysis of 18,686 and 5,963 people with DM that found significant reductions of cardiovascular events and all cause moratlity.[30, 31]

Randomized clinical trials that examined the effect of statins on CVD endpoints and mortality have largely excluded adults > 80 years of age. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study conducted in 2002 remains one of the few RCTs that was designed to examine the benefits of statins in older adults with and without DM aged 70-82 years.[32] This was a primary and secondary prevention trial that found a 15% reduction in CVD endpoints among those in the statin group. Between 2002 and 2012, there were no randomized clinical trials of lipid lowering medication that enrolled a large number of older adults age 80 or above.

Research on glycemic control

Epidemiologic evidence suggests that uncontrolled glycemia is associated with higher risks of cardiovascular disease.[33] The UKPDS has established the evidence base for the benefits of tight glycemic control for the prevention of microvascular disease. The UKPDS has poor generalizabilty to older adults because patients enrolled were < 65 years of age and newly diagnosed with DM. The UKPDS 10 year post-trial follow-up study found new significant risk reductions for MI and mortality – referred to as the "legacy effect."[34] There was no older adult subgroup analysis conducted.

We did not find any RCTs on glycemic control that are applicable to all older adults with DM. In particular, RCTs conducted from 2002-2012 along with previous trials did not include many older adults with ≥ 80 years of age, poor health status, or many co-morbidities. The three large RCTs that were reviewed (ACCORD, ADVANCE, and VADT) included patients with long-standing diabetes ranging from 8 to 11.5 years, prior cardiovascular event, or with risk factors for cardiovascular disease (Table 5). This is different than the younger and newly diagnosed DM population enrolled in the UKPDS. The ACCORD and ADVANCE compared intensive glycemic control (A1C < 6% or < 6.5%) versus less intensive therapy and none of the studies reported reductions in macrovascular events. The VADT intensive therapy arm had a goal of an absolute reduction of 1.5% (or an A1C < 6%) compared to the standard therapy arm. In the ACCORD trial, hypoglycemia was more common in older adults and increased mortality was found in the intensive glucose control group compared to the less intensive usual care.[35, 36] The RCTs reviewed do not provide supportive evidence that intensive glycemic control (A1C < 6% or 6.5%) is beneficial in older adults.[35-38]

Five meta-analyses were published that pooled data from 4-13 trials and examined the effect of intensive glucose control and macrovascular outcomes.[39-43] All of these included the UKPDS study and also did not show any significant reductions in cardiovascular death or all cause mortality. Results from all of these studies suggested that intensive glucose control reduced myocardial infarction but significantly increased events of severe hypoglycemia.

Research on use of aspirin for primary prevention

Until recently, clinical recommendations for the use of aspirin by older adults with DM are largely a result of extrapolation of findings from study populations with and without DM. Randomized controlled trials for the prevention of cardiovascular events with aspirin have been conducted in three main patient populations. These include patients with DM, patients with and without DM, and patients without DM. Two decades ago, The Early Treatment of Diabetic Retinopathy (ETDRS) trial only enrolled patients with type 1 and 2 DM but also included some patients with a history of stoke and coronary heart disease. In the ETDRS,

aspirin resulted in a 15% reduction in fatal plus nonfatal MI (RR 0.85, 95% CI 0.73–1.00). During the last 10 years, only two RCTs designed to study the cardiovascular benefits of aspirin use by patients with diabetes have been published (Table 6). One Japanese trial enrolled 2,539 patients with a mean age of 65 ± 10 years and type 2 DM. Among those, 1,365 were older than 65 years of age (719 in the aspirin group and 644 in the placebo group).[44] A second trial (2 × 2 factorial with an antioxidant) from the U.K. randomized 1,276 patients with type 1 or 2 DM to aspirin versus placebo.[45] Six hundred and seventy five patients were > 60 years of age. Both trials failed to significantly reduce CVD endpoints with aspirin compared to control groups (Table 4). [46]

Six RCTs of middle aged adults with and without DM have examined the primary prevention benefits of aspirin on the reduction of CVD events using subgroup analysis. These are the British Medical Doctors (BMD) study,[47] the Physicians Health Study (PHS),[48] the Thrombosis Prevention Trial (TPT),[49] the Hypertension Optimal Treatment (HOT) study,[5] the Primary Prevention Project (PPP)[50] and the Women's Health Study (WHS).[51] Four of these trials were published between 1988 and 1998. In the last ten years, the two newer trials, the Primary Prevention Project (PPP) and the Women's Health Study (WHS) also examined the benefits of aspirin among a subgroup of patients with DM and were published in 2003 and 2005 repsectively.[50, 51] Among patients with DM in the PPP trial, aspirin was associated with a nonsignificant reduction in the main endpoint (RR 0.90, 95% CI 0.50- 0.90) and total CVD events (RR 0.89, 95% CI 0.62-1.26). Similarly, no reductions in CVD events were reported in the WHS for patients overall and for the subgroup with DM. The study did find a reduction in stroke (RR 0.45, 95% CI 0.25-0.82) with aspirin for women with DM.

Five meta-analyses have been performed in attempt to clarify the risk and benefits of aspirin use among adults with DM.[52-56] All of the meta-analyses did not find statistically significant reductions in CVD events, all cause mortality, cardiovascular mortality, stroke, and MI after pooling DM data from 4 to 9 trails. The meta-analyses by Zhang et al. and De Berardis et al. found sex specific effects of aspirin on MI and stroke.[52, 53] De Berardis et al reported a 43% reduction in MI for men (0.57; 95% CI 0.34 to 0.94), but not in women (1.08; 95% CI 0.71 to 1.65; P for interaction=0.056) and did not include the newer RCTs (e.g. POPADAD and JAPAD) designed for adults with type 2 DM. Meat-regressions by Zhang et al. included the newer trials and found statistically significant association between male percentage and the incidence of MI (p = <0.001) or stroke (p = <0.001), suggesting sex-specific reductions of aspirin on MI in men with DM and stroke in women with DM. A sixth meta-analysis by the Anti-Thrombotic Trialists' collaborators included six trials of aspirin for primary prevention in the general population and found similar effects of aspirin on major CVD events in those with DM (RR 0.88, 95% CI 0.67-1.15) compared to those without DM (RR 0.87, 95% CI 0.79-0.96).[57] Recent trials (e.g. POPADAD and JAPAD) were not included in this meta-analysis.[44, 45] The overall results however are inconsistent and when all the evidence is examined together, the benefits of aspirin for adults with DM is inconclusive.

Ongoing trials will add to this evidence base and help clarify the role of aspirin for primary prevention of CVD among middle aged and older adults with DM. Two trials in the U.K designed for persons with diabetes, the A Study of cardiovascular Events in Diabetes (ASCEND) and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCPET-D) are ongoing. The ASCEND trial randomized 15,480 persons age ≥ 40 years of age and the ACCEPT-D trial's target enrollment is 5,170 persons aged ≥ 50 years of age to be randomized to receive aspirin plus a statin or a statin alone.[58] One ongoing trial in the U.S., the Aspirin in Reducing Events in the Elderly (ASPREE) trial will also help to elucidate the role of aspirin in primary prevention for

persons 65 years and older. Until more evidence is available, the AGS does not recommend the use of aspirin for older adults with DM.

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Table 1

Randomized clinical trials (RCTs) conducted between 2002 – 2012 to study blood pressure control in older adults with diabetes mellitus type 2 (DM)

Study (Author, Year) Country	Sample Size, Participants,	Treatment	Design, Length	Primary Outcome(s)	Results
ACCORD (Cushman et al., 2010) U.S. & Canada	N = 10,251 (4,733 for blood pressure control study) Mean age 62 ± 7 Adults 40 – 79 years 1617 were ≥65 years Patients with type 2 DM for 10 years, mean baseline SBP 139 mmHg, and 37% had cardiovascular disease (CVD)	Intensive therapy of blood pressure <120 mmHg versus standard therapy of blood pressure <140mmHg	Randomized clinical trial (RCT), mean duration 4.7 years	Primary composite (nonfatal MI, nonfatal stroke, or cardiovascular [CV] death)	No significant difference in CV or all cause death Nonsignificant reduction in primary outcome (298 events versus 237 events; P=0.20) Significant reduction in stroke (36 versus 62 events; P=0.01) No age interaction for primary outcome (age ≥65 years)
ADVANCE (Patel et al., 2007) Various countries	N=11,140 Mean age 62 ± 6.9 55 years or older 6601 were ≥65 years Patients with type 2 DM for 8 years, mean entry blood pressure 145 mmHg and 32% with CVD	Combination of perindopril and indapamide versus placebo Mean SBP reduction was 5.6 mmHg and DBP was 2.2 mmHg	RCT, mean duration 4.3 years Not designed for treating to target blood pressure	Composite of combined major macrovascular events (CV death, nonfatal MI or stroke) and major microvascular events (new or worse nephropathy, or retinopathy)	Nonsignificant reduction in macrovascular events (480 versus 520;P=16) Reduction in cardiovascular death (211 versus 257 events; HR 0.82, P=0.03) Reduction in composite outcome (536 versus 592 events) for adults ≥65 years
UKPDS (Holman et al., 2008) U.K.	N=1,148 for blood pressure study (884 for post-trial monitoring) Mean age 56.4 ± 8.1 at 10 year follow-up Adults 26 – 65 years Patients with new type 2 DM and 7.5% with CVD	Tight blood pressure <150 mmHg versus less-tight blood pressure <180mmHg Differences disappeared after 2 years	RCT, mean duration 15.4 years (8 yrs post-trial)	Any DM related endpoint (includes death from any cause, macrovascular and microvascular complications)	No reductions for Stroke, MI or death from any cause Significant reduction for peripheral vascular disease (141 versus 82 events; P=0.02)

ACCORD = Action to Control Cardiovascular Risk in Diabetes

ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation. Industry sponsored.

UKPDS = United Kingdom Prospective Diabetes Study

SBP= systolic blood pressure; DBP = diastolic blood pressure

Table 2

Randomized clinical trials (RCTs) of statins for older adults with and without diabetes mellitus type 2 (DM) (2002 – 2012)

Study (Author, Year) Country	Sample Size, Participants,	Treatment	Design, Length	Primary Outcome(s)	Results
CARDS study (Colhoun et al., 2004) U.K. & Ireland	N=2838 Mean age 61.8 ± 8.3 Aged 40 – 75 years 1751 were > 60 years Patients with type2-DM Without cardiovascular disease (CVD)	Atorvastatin 10 mg versus placebo	Randomized clinical trial (RCT), mean duration 3.9 years	Primary endpoint (first event for acute coronary events, coronary revascularizations, and stroke)	Treatment reduced risk (37%) of first CVD events
ASPEN (Knopp et al. 2006) U.S. and multiple countries	N=2410 Mean age 61 ± 8 Adults 40 – 75 year 910 were ≥ 65 years Patients with type 2 DM, 69% with no prior vascular disease	Atorvastatin 10 mg versus placebo	RCT, mean duration 4 years	Composite primary end point	Non-significant results
ASCOT-LLA (Sever et al., 2005) U.K.	N=2,532 Mean age 63.8±8.4 Aged 40-79 years 1716 were > 60 years Patients with type 2 DM, having at least 3 CV risk factors	Atorvastatin 10 mg versus placebo	RCT, mean duration 3.3 years	CV events and procedures	Treatment reduced risk of major CVD events and procedures Non-significant results for subgroup of age > 60 years
MEGA (Nakamura et al., 2006) Japan	N=7,832 Mean age 58±7 Aged 40-70 years Patients with high lipids without CVD, 31% with DM	Pravastatin 10-20mg and diet versus diet	RCT, mean duration 5.3 years	First occurrence of coronary heart disease	Coronary heart disease events lower in treatment group (66 versus 101 events, P=0.01) Tests for interaction for age (< 60 versus ≥ 6 years) and for DM was not significant

CARDS = Collaborative Atorvastatin Diabetes Study

ASPEN = Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus

ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm

MEGA = Mangement of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese

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Table 3

Randomized clinical trials (RCTs) of high dose versus low dose statins for adults with and without diabetes mellitus type 2 (DM) (2002 – 2012)

Study (Author, Year) Country	Sample Size, Participants,	Treatment	Design, Length	Primary Outcome(s)	Results
TNT study (Shepherd et al., 2006) U.K.	N=1501 Mean age 62.8±8.0 Adults 35 – 75 year 600 were ≥ 65 years 10,001 patients with coronary heart disease (CHD) randomized and 15% with DM	Atorvastin 80mg/day versus Atorvastin 10mg/day	Randomized clinical trial (RCT), mean duration 4.9 years	Major cardiovascular (CV) event composite	Intensive therapy reduced major CVD events by 25% compared with less intensive Significant reduction in all age groups
SANDS (Howard et al., 2008) U.S.	N=548 Mean age 56 American Indian adults with type 2 DM and no cardiovascular disease (CVD), 38% taking lipid-lowering drugs, and 73% undergoing antihypertensive treatment	Treatment of LDL-c (≤ 70 mg/dL versus ≤ 100 mg/dL) and blood pressure (≤ 115 mmHg versus ≤ 130 mmHg)	RCT, median duration 3 years	Progression of Atherosclerosis; secondary outcomes were clinical events (e.g. CVD events)	Aggressive treatment resulted in regression of carotid intimal medial thickness Clinical outcomes did not differ significantly between groups
PROVE IT TIMI (Cannon, et al, 2004) US and 8 total countries	N=4162 Mean age 58 1230 were ≥ 65 years All hospitalized for acute coronary syndromes; 18% (n=734) with DM	Atorvastatin 80 mg daily versus Pravastatin 40mg	RCT, mean duration 2 years	Primary end-point of death from any cause or a major CV event	16%reduction in the atorvastatin group compared to the pravastatin group (P=0.005) Tests for interaction for age (< 65 versus ≥ 65 years) and for DM was not significant

TNT = Treating to New Targets study

SANDS = Stop Atherosckerosis in Native Diabetics Study

PROVE-IT TIMI= Pravastatin or Atorvastatin Evalaution and Infection Therapy-Thrombolysis im Myocardial Infarction 22

Table 4

Randomized clinical trials (RCTs) of statins plus fibrates and niacin for adults with and without diabetes mellitus type 2 (DM) (2002 – 2012)

Study (Author, Year) Country	Sample Size, Participants,	Treatment	Design, Length	Primary Outcome(s)	Results
ACCORD (Ginsberg, 2010) U.S.	N = 5518 Mean age 62 ± 7 Adults 40 – 79 years 1858 were ≥ 65 years Patients with type 2 DM	Simvastatin + Fenofibrate versus Simvastatin + Placebo	Randomized clinical trial (RCT), mean duration 4.7 years	Major fatal or nonfatal cardiovascular (CV) event	No significant difference No interaction between age and treatment
AIM-HIGH (Boden et al., 2011) U.S.	N=3414 Mean age 64.9±9 45 yrs or older 46% were ≥ 65 yrs All patients with vascular disease and atherogenic dyslipidemia; 38% of with DM type 1 or 2	Extended-release niacin 1500-2000 mg/day plus simvastatin versus placebo plus simvastatin	RCT, mean duration 3 years	Primary composite endpoint	No significant difference No interaction between age and treatment

ACCORD = Action to Control Cardiovascular Risk in Diabetes

AIM-HIGH = Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides

Table 5

Major randomized clinical trials (RCTs) conducted between 2002 - 2012 to study glycemic control in adults with diabetes mellitus type 2 (DM)

Study (Author, Year) Country	Sample Size, Participants,	Treatment	Design, Length	Primary Outcome(s)	Results
ACCORD (Gerstein, 2008) U.S.	N = 10,251 Mean age 62 ± 2 Adults 40 – 79 years 3472 were ≥65 years Patients with type 2 DM for 10 years, mean baseline A1C 8.1%, and 35% with Known cardiovascular disease (CVD)	Intensive therapy A1C <6% versus standard therapy A1C 7-7.9%	Randomized clinical trial (RCT), mean duration 3.5 years	Primary composite (nonfatal MI, nonfatal stroke, cardiovascular (CV) death)	No significant difference in CV events (352 versus 371) Increased mortality in intensive group (257 versus 203) No age interaction with treatment
VADT (Duckworth, 2009) U.S.	N = 1,791 Mean age 60 ± 4 41 years or older Patients with type 2 DM for 11.5 years mean baseline A1C 9.4%, and 40% with CVD	Intensive therapy A1C <6% (or absolute reduction of 1.5%) versus standard therapy	RCT, mean duration 5.6 years	Composite of major CV event (MI, stroke , CV death, CHF, vascular disease surgery CAD inoperable, amputation for ischemic gangrene)	No significant difference in CV events or mortality Significant reduction in albuminuria No age subgroup analysis done
ADVANCE (Patel, 2008) Various countries	N = 11,140 Mean age 66 ± 6 55 years or older 6601 were ≥65 years Patients with type 2 DM for 8 years, mean baseline A1C 7.5%, and 32% with CVD	Intensive therapy A1C <6.5% versus standard therapy	RCT, mean duration 5.5 years	Composite of combined major macrovascular events (CV death, nonfatal MI or stroke) and major microvascular events (new or worse nephropathy, or retinopathy)	Significant decrease in composite outcome (1009 versus 1116) No differences in macrovascular events (557 versus 590) or mortality (498 versus 533) No interaction by age
UPKDS (Holman, 2008) U.K.	N = 3,277 (for post-trial monitoring) Mean age 65 ± 8 at 10 year follow-up Adults 26 – 65 years Patients with new type 2 DM and 7.5% with CVD	Intensive therapy (sulfonylurea or insulin; metformin) versus conventional therapy	RCT, 10-year post-trial monitoring	Any diabetes-related endpoint (includes death from any cause, macrovascular and microvascular complications)	Reductions in death and MI for both treatments sustained from post trial (“legacy effect”) No age subgroup analysis done

ACCORD = Action to Control Cardiovascular Risk in Diabetes

VADT = Veterans Affairs Diabetes Trail

ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; Industry sponsored.

UKPDS = United Kingdom Prospective Diabetes Study

Table 6

Randomized clinical trials (RCTs) designed to study aspirin in patients with mellitus type 2 only (2002 – 2012)

Study (Author, Year) Country	Sample Size, Participants,	Treatment	Design, Length	Primary Outcome(s)	Results
JAPAD (Ogawa et al, 2008) Japan	N = 2539 Adults 30 – 85 years Mean age 65 ± 10 1365 were ≥ 65 years Patients with type 2 diabetes	Aspirin 81 mg or 100 mg daily n=1262 Placebo n=1277	Randomized clinical trial (RCT), mean duration 4.4 years	Atherosclerotic events (fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease). Secondary endpoint included death from any cause.	No significant difference in composite endpoint (68 versus 86 events, P=0.16), or death from any cause (34 versus 38 events, P=67) In subgroup analysis (age ≥65 years), aspirin had 45 events versus 59 for placebo (HR 0.68; 95% CI 0.46 – 0.99; P=0.047). P interaction 0.27
POPADAD (Belch et al, 2008) U.K.	N = 1276 Adults 40 and up Mean age 60 ± 10 675 were > 60 years Patients with type 2 or 1 diabetes	Aspirin 100 mg daily n=638 Placebo n=638	RCT(2 × 2 factorial with antioxidant), mean duration 6.7 years	Death from coronary heart disease (CHD) or composite of stroke, non-fatal MI or stroke or above ankle amputation for critical limb ischemia	No significant difference in composite endpoint (116 versus 117 events, P=0.86) In subgroup analysis (age >60 years), no significant difference between groups

POPADAD = The Prevention of Progression of Arterial Disease and Diabetes

JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes

CHD = coronary heart disease

RCT = randomized controlled trial

MI = myocardial infarction

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