UCLA
UCLA Previously Published Works

Title

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

Permalink

https://escholarship.org/uc/item/9fk8w61x

Journal

Journal of the American Geriatrics Society, 61(11)

ISSN

0002-8614

Authors

Moreno, Gerardo
Mangione, Carol M

Publication Date

2013-11-01

DOI

10.1111/jgs.12513

Peer reviewed

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

Gerardo Moreno, MD, MSHS,* and Carol M. Mangione, MD, MSPH[†‡]

Type 2 diabetes mellitus (DM) is one of the most common chronic conditions in older adults and is often accompanied by comorbidities and geriatric syndromes. The management of cardiovascular disease risk factors in older adults with DM is important to clinicians. The literature was reviewed from 2002 to 2012 to provide an American Geriatrics Society expert panel with an evidence base for updating and making new recommendations for improving the care of older adults with type 2 DM. This review includes only the domains of the management of blood pressure, lipid control, glycemic control, and use of aspirin. Over the last 10 years, new randomized controlled trials (RCT) designed to study different blood pressure treatment targets did not find evidence that intensive systolic blood pressure control (<130 mmHg) resulted in lower rates of myocardial infarction and mortality than less-intensive control. There are risks of side effects with achieving systolic blood pressure of less than 120 mmHg. Lipid-lowering statins are effective in reducing cardiovascular events in middle-aged and older adults, but data on niacin and fibrates is limited. Trials of statins and other lipid-lowering agents do not evaluate the cardiovascular effects on outcomes from treating lipids to different low-density lipoprotein cholesterol targets. No RCTs of lipid-lowering drugs enrolled significant numbers of adults aged 80 and older with or without DM. Three major RCTs that investigated intensive glycemic control did not find reductions in primary cardiovascular endpoints, and one study reported greater mortality with glycosylated hemoglobin of less than 6%. Two recently published RCTs were designed to study the cardiovascular benefits of aspirin use by individuals with DM. Neither trial found significantly fewer primary cardiovascular endpoints with aspirin than in control groups. Overall, RCTs enrolled few adults aged 80 and older or with significant comorbidities. More research is needed for clinicians to effectively customize care to older adults with DM because of heterogeneity in health status, comorbidities, duration of disease, frailty and functional status, and differences in life expectancy. **J Am Geriatr Soc 61:2027–2037, 2013.**

Key words: diabetes mellitus; statin; review.

New high-quality evidence from studies of the management and prevention of cardiovascular disease (CVD) in older adults with diabetes mellitus (DM) has been published in the last 10 years. During this same time, the treatment paradigm has shifted away from disease-focused treatment goals to patient-centered treatment recommendations. The evidence base for the prevention and management of CVD has grown for middle-aged adults but remains scant, at best, for individuals aged 80 and older. 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 that the American Geriatrics Society (AGS) has published provide guidance to clinicians who care for older adults with DM.[1] This report complements the recommendations and provides detail about important studies, with an emphasis on randomized controlled 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, blood pressure control, management of lipids, the role of aspirin in primary prevention, and glycemic control are focused on.

METHODS

Existing peer-reviewed literature and guidelines on each DM topic were identified. PubMed was searched for

From the *Departments of Family Medicine, †Medicine, David Geffen School of Medicine, and ‡Health Policy and Management, Fielding School of Public Health, University of California at Los Angeles, Los Angeles, California.

Address correspondence to Gerardo Moreno, MD, MSHS, 10880 Wilshire Blvd, Suite 1800, Los Angeles, CA 90024. E-mail: gemoreno@mednet.ucla.edu

relevant studies published in the peer-reviewed literature; the search was limited 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 set to include only "randomized controlled trials," "meta-analysis," and "systematic reviews." RCTs and systematic reviews or meta-analyses were reviewed for aspirin use, glycemic control, hypertension management, and lipid management. For many of the topic areas reviewed and updated, limited data 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, 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 for each DM topic and that provide an updated overview of some of the most important aspects of care that differ significantly from the care provided to younger persons with DM or deserve special emphasis. This review is an updated overview of some of the aspects of care that differ significantly from care provided to younger persons with DM or deserve special emphasis. Studies that target the control of multiple risk factors are not addressed 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 of 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 individuals with DM attain a goal blood pressure of less than 130/80 mmHg.[1] The recommendations were based mostly on interpretations of benefit from a retrospective subanalysis of RCTs of hypertensive middle-aged and older adults with and without DM.[4–7] Three important RCTs of blood pressure control in middle-aged and older adults with DM published in the last 10 years were included in this review (Table 1).[8–11] RCTs of older adults with DM and hypertension were limited during the decade that this review covers (2002–2012). The Action to Control Cardiovascular Risk in Diabetes—Blood Pressure (ACCORD-BP) compared intensive blood pressure treatment (target of <120 mmHg systolic blood pressure) with standard treatment with a goal of 140 mmHg in middle-aged and older adults (40–79) with DM and a high risk of CVD.[8] ACCORD-BP did not find statistically significant reductions in primary outcomes, myocardial infarction (MI), or all-cause mortality but found modestly statistically significantly fewer in the intensive treatment arm of the secondary outcome of stroke (number needed to

treat (NNT) was 89 over 5 years) and troubling 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 was not sustained.[10]

Recent large subgroup post hoc analysis of the International Verapamil SR-Trandolapril Study (INVEST) and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) also had important findings.[12,13] The INVEST researchers concluded that controlling blood pressure to less than 130/80 mmHg was not associated with better cardiovascular outcomes than usual control of 140 to 130 mmHg in individuals aged 55 and older (mean age 66 ± 6). ONTARGET (mean age 66 ± 7 and 57% aged ≥65) conclusions were similar except for the risk of stroke.[12] A third analysis of the large Veterans Affairs Diabetes Trial (VADT) reported greater cardiovascular risks with a systolic blood pressure of 140 mmHg or greater or a diastolic blood pressure of less than 70 mmHg (average age of participants was 60 ± 9).[14] Two meta-analyses pooled studies of individuals with DM examined the effect of intensive blood pressure control (<130 mmHg) and did not show benefits for MI or mortality over a blood pressure of less than 140 mmHg.[15,16] The meta-analyses found an association between lower blood pressure and risk of stroke, but this was in the setting of more serious adverse events.[15,16]

Research on Control of Lipids

Numerous RCTs have demonstrated the benefits of statins 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,[17] the Cholesterol and Recurrent Events Trial,[18] the Long-term Intervention with Pravastatin in Ischemic Disease trial,[19] and the Heart Protection Study[20] 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. A meta-analysis of nine secondary prevention trials with statins in individuals aged 65 to 82 also found CVD benefits.

Primary prevention studies of statins in older adults include subanalysis of the Cardiovascular Health Study,[21] and the Air Force/Texas Coronary Atherosclerosis Study.[22] The Heart Protection Study was one of the first studies that included adults with DM. More-recent (2002–2012) studies[23] comparing statins with placebo (Table 2) that were reviewed include the Collaborative Atorvastatin Diabetes Study,[24] Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm,[25] and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus.[26] Table 3 lists RCTs of high- and low-dose statins for adults with and without DM.[2,27,28] The differences in cardiovascular outcomes shown in these trials suggest benefits to older adults. Table 4 lists two RCTs of statins plus fibrates and

Table 1. Randomized Clinical Trials (RCTs) Conducted Between 2002 and 2012 to Study Blood Pressure Control in Older Adults with Type 2 Diabetes Mellitus (DM)

Study (Author, Ref.) Country	Sample Size	Age, Mean (Range)	Participants	Treatment	Design	Length, Years, Mean	Primary Outcome(s)	Results
Action to Control Cardiovascular Risk in Diabetes (Cushman et al., 8) United States, Canada	10,251 (4,733 for blood pressure control study) (1,617 aged ≥65)	62 ± 7 (40–79)	Type 2 DM for 10 years, mean baseline systolic blood pressure 139 mmHg, 37% with CVD	Intensive therapy of blood pressure < 120 mmHg versus standard therapy of blood pressure <140 mmHg	RCT	4.7	Primary composite (nonfatal MI, nonfatal stroke, or CV death)	No significant difference in CV or all-cause death, nonsignificantly fewer primary outcomes (298 vs 237 events; $P = .20$), significantly less stroke (36 vs 62 events; $P = .01$), no age interaction for primary outcome (aged ≥65)
Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (Patel et al., 2009) Various countries	11,140 (6,601 aged ≥65)	62 ± 6.9	Aged ≥55 with type 2 DM for 8 years, mean entry blood pressure 145 mmHg, 32% with CVD	Combination of perindopril and indapamide versus placebo. Mean blood pressure difference was 5.6 mmHg systolic and 2.2 mmHg diastolic	RCT, not designed for treating to target blood pressure	4.3	Composite of combined major macrovascular events (CV death, nonfatal MI, or stroke) and major microvascular events (new or worse nephropathy, retinopathy)	Nonsignificantly fewer macrovascular events (480 vs 520; $P = .16$), fewer CV deaths (211 vs 257; hazard ratio=0.82, $P = .03$), fewer composite outcomes (536 vs 592) for adults aged ≥65
United Kingdom Prospective Diabetes Study (Holman et al., 10) United Kingdom	1,148 for blood pressure study (884 for posttrial monitoring)	56.4 ± 8.1 at 10-year follow-up (26–65)	New type 2 DM, 7.5% with CVD	Tight blood pressure <150 mmHg versus less-tight blood pressure <180 mmHg Differences disappeared after 2 years	RCT	15.4 (8 years posttrial)	Any DM-related endpoint (includes death from any cause, macrovascular and microvascular complications)	No fewer stroke, MI, or death from any cause; significantly less peripheral vascular disease (141 vs 82; $P = .02$)

CVD = cardiovascular disease; CV = cardiovascular; RCT = randomized controlled trial; MI = myocardial infarction.

Table 2. Randomized Clinical Trials (RCTs) of Statins for Older Adults with and without Type 2 Diabetes Mellitus (DM) (2002–2012)

Study (Author, Ref.) Country	Sample Size	Age, Mean (Range)	Participants	Treatment	Design	Length, Years, Mean	Primary Outcome(s)	Results
Collaborative Atorvastatin Diabetes Study (Colhoun et al., 24) United Kingdom, Ireland	2,838 (1,751 aged ≥60)	61.8 ± 8.3 (40–75)	Type 2 DM without CVD	Atorvastatin 10 mg versus placebo	RCT	3.9	Primary endpoint (first event for acute coronary events, coronary revascularization, and stroke)	Less risk (37%) of first CVD events with treatment
Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (Knopp et al., 26) U.S. and multiple countries	2,410 (910 aged ≥65)	61 ± 8 (40–75)	Type 2 DM, 69% with no prior vascular disease	Atorvastatin 10 mg versus placebo	RCT	4	Composite primary endpoint	Nonsignificant
Anglo-Scandinavian Cardiac Outcomes Trial –lipid-lowering arm (Sever et al., 25) United Kingdom	2,532 (1,716 aged ≥60)	63.8 ± 8.4 (40–79)	Type 2 DM with ≥3 CV risk factors	Atorvastatin 10 mg versus placebo	RCT	3.3	CV events and procedures	Less risk of major CVD events and procedures with treatment, nonsignificant for subgroup aged ≥60
Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (Nakamura et al., 23) Japan	7,832	58 ± 7 (40–70)	High lipids without CVD, 31% with DM	Pravastatin 10–20 mg and diet versus diet	RCT	5.3	First occurrence of coronary heart disease	Fewer coronary heart disease events in treatment group (66 vs 101, P = .01), tests for interaction for age (<60 vs ≥60) and for DM not significant

CVD = cardiovascular disease; CV = cardiovascular.

Table 3. Randomized Clinical Trials (RCTs) of High-Versus Low-Dose Statins for Adults with and without Type 2 Diabetes Mellitus (DM) (2002–2012)

Study (Author, Ref.) Country	Sample Size	Age, Mean (Range)	Participants	Treatment	Design	Length, Years, Mean	Primary Outcome	Results
Treating to New Targets study (Shepherd et al., 28) United Kingdom	1,501 (600 aged ≥65)	62.8 ± 8.0 (35–75)	Individuals with coronary heart disease and DM	Atorvastatin 80 versus 10 mg/d	RCT	4.9	Major CV event composite	25% fewer major CVD events with intensive therapy than with less-intensive, significant in all age groups
Stop Atherosclerosis in Native Diabetics Study (Howard et al., 2) United States	548	56	American Indian adults with type 2 DM and no CVD, 38% taking lipid-lowering drugs, and 73% undergoing antihypertensive treatment	Treatment of low-density lipoprotein cholesterol (≤70 vs ≤100 mg/dL) and blood pressure (≤115 vs ≤130 mmHg)	RCT	3	Progression of atherosclerosis; secondary outcomes were clinical events (e.g., CVD events)	Regression of carotid intimal medial thickness with aggressive treatment, clinical outcomes not significantly different between groups
Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (Cannon, et al., 27) United States and 8 total countries	4,162 (1,230 aged ≥65)	58	All hospitalized for acute coronary syndromes; 18% (n = 734) with DM	Atorvastatin 80 mg/d versus pravastatin 40 mg/d	RCT	2	Primary endpoint of death from any cause or a major CV event	16% fewer events in atorvastatin group than in pravastatin group (P = .005), tests for interaction for age (<65 vs ≥65) and for DM not significant

CVD = cardiovascular disease; CV = cardiovascular.

Table 4. Randomized Clinical Trials (RCTs) of Statins Plus Fibrates and Niacin for Adults with and without Type 2 Diabetes Mellitus (DM) (2002–2012)

Study (Author, Ref.) Country	Sample Size	Age, Mean (Range)	Participants	Treatment	Design	Length, Years, Mean	Primary Outcome	Results
Action to Control Cardiovascular Risk in Diabetes (Ginsberg, 29) United States	5,518 (1,858 aged ≥65)	62 ± 7 (40–79)	Type 2 DM	Simvastatin plus fenofibrate versus simvastatin plus placebo	RCT	4.7	Major fatal or nonfatal cardiovascular event	No significant difference, no interaction between age and treatment
Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides (Boden et al., 30) United States	3,414 (46% aged ≥65)	64.9 ± 9 (≥45)	Vascular disease and atherogenic dyslipidemia; 38% with type 1 or 2 DM	Extended-release niacin 1,500–2,000 mg/d plus simvastatin versus placebo plus simvastatin	RCT	3	Primary composite endpoint	No significant difference, no interaction between age and treatment

niacin that did not show fewer primary cardiovascular outcomes with the intensive therapy.[29,30] Finally, two large meta-analyses of 18,686 and 5,963 people with DM that found significant reductions in cardiovascular events and all cause mortality were reviewed.[31,32]

RCTs that have examined the effect of statins on CVD endpoints and mortality have largely excluded adults aged 80 and older. The Prospective Study of Pravastatin in the Elderly at Risk conducted in 2002 was a RCT designed to examine the benefits of statins in older adults with and without DM aged 70 to 82.[33] This was a primary and secondary prevention trial that found a 15% fewer CVD endpoints in the statin group. Between 2002 and 2012, there were no RCTs of lipid-lowering medication that enrolled a large number of adults aged 80 and older.

Research on Glycemic Control

Epidemiological evidence suggests that uncontrolled glycemia is associated with greater risk of CVD.[34] The UKPDS has established the evidence base for the benefits of tight glycemic control for the primary prevention of microvascular disease. The UKPDS has poor generalizabilty to older adults because participants were younger than 65 and newly diagnosed with DM. The UKPDS 10-year posttrial follow-up study found significant risk reductions for MI and mortality. This is referred to as the "legacy effect" because benefits remained many years after the differences in HbA1c levels between the intensive therapy and conventional therapy groups disappeared.[35] No older adult subgroup analysis was conducted.

No RCTs on glycemic control applicable to all older adults with DM were found. In particular, RCTs conducted from 2002 to 2012 did not include many participants aged 80 and older, with poor health status, or with many comorbidities. The three large RCTs reviewed (ACCORD-BP, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and VADT) included participants who had had DM for 8 to 11.5 years, a prior cardiovascular event, or risk factors for CVD (Table 5). This is different from the younger, more-recently diagnosed DM population enrolled in the UKPDS. ACCORD-BP and ADVANCE compared intensive glycemic control (glycosylated hemoglobin (HbA1c) <6% or <6.5%) with less-intensive therapy, and neither reported fewer macrovascular events with intensive control. The VADT intensive therapy arm had a goal of an absolute reduction of 1.5% (or HbA1c <6%) compared to the standard therapy arm. In the ACCORD-BP trial, hypoglycemia was more common in older adults, and greater mortality was found in the intensive glucose control group than in the less-intensive usual care group.[36,37] The RCTs reviewed do not provide supportive evidence that intensive glycemic control (HbA1c <6% or <6.5%) is beneficial for the prevention of macrovascular events in older adults.[36–39]

Five meta-analyses were published that pooled data from four to 13 trials and examined the effect of intensive glucose control and macrovascular outcomes.[40–44] All of these included the UKPDS study and also did not show significant less cardiovascular or all-cause mortality. Results from all of these studies suggested that intensive

Table 5. Major Randomized Clinical Trials (RCTs) Conducted Between 2002–2012 to Study Glycemic Control in Adults with Type 2 Diabetes Mellitus (DM)

Study (Author, Ref.) Country	Sample Size	Age, Mean (Range)	Participants	Treatment	Design	Length, Years, Mean	Primary Outcome	Results
Action to Control Cardiovascular Risk in Diabetes (Gerstein, 36) United States	10,251 (3,472 aged ≥65)	62 ± 2 (40–79)	Type 2 DM for 10 years, mean baseline HbA1c 8.1%, 35% with known CVD	Intensive therapy (HbA1c <6%) versus standard therapy (HbA1c 7–7.9%)	RCT	3.5	Primary composite (nonfatal MI, nonfatal stroke, cardiovascular (CV) death)	No significant difference in CV events (352 vs 371), greater mortality in intensive group (257 vs 203), no age interaction with treatment
Veterans Affairs Diabetes Trial (Duckworth, 38) United States	1,791	60 ± 4 (≥41)	Type 2 DM for 11.5 years, mean baseline HbA1c 9.4%, 40% with CVD	Intensive therapy (HbA1c <6%, or absolute reduction of 1.5%) versus standard therapy	RCT	5.6	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, significantly less albuminuria, no age subgroup analysis done
Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (Patel, 39) Various countries	11,140 aged >55, 6,601 aged ≥65	66 ± 6	Type 2 DM for 8 years, mean baseline HbA1c 7.5%, 32% with CVD	Intensive therapy (HbA1c <6.5%) versus standard therapy	RCT	5.5	Composite of combined major macrovascular events (CV death, nonfatal MI or stroke) and major microvascular events (new or worse nephropathy, or retinopathy)	Significantly fewer composite outcomes (1,009 vs 1,116), no difference in macrovascular events (557 vs 590) or mortality (498 vs 533), no age interaction
United Kingdom Prospective Diabetes Study (Holman, 10) United Kingdom	3,277 (for posttrial monitoring)	65 ± 8 at 10-year follow-up (26–65)	New type 2 DM, 7.5% with CVD	Intensive therapy (sulfonylurea or insulin; metformin) versus conventional therapy	RCT	10-year posttrial monitoring	Any diabetes-related endpoint (including death from any cause, macrovascular and microvascular complications)	Less death and MI for both treatments sustained from posttrial (legacy effect), no age subgroup analysis

HbA1c = glycosylated hemoglobin; CVD = cardiovascular disease; CV = cardiovascular.

Table 6. Randomized Clinical Trials (RCTs) Designed to Study Aspirin in Individuals with Type 2 Diabetes Mellitus (DM) (2002–2012)

Study (Author, Ref.) Country	Sample Size	Age, Mean (Range)	Participants	Treatment	Design	Length, Years, Mean	Primary Outcome	Results
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (Ogawa et al., 45) Japan	2,539 (1,365 aged ≥65)	65 ± 10 (30–85)	Type 2 DM	Aspirin 81 or 100 mg/d (n = 1,262), placebo (n = 1,277)	RCT	4.4	Atherosclerotic events (fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, peripheral arterial disease), secondary endpoint death from any cause	No significant difference in composite endpoint (68 vs 86 events, $P = .16$) or death from any cause (34 vs 38 events, $P = .67$), 45 events with aspirin versus 59 with placebo in subgroup analysis (aged ≥65) (hazard ratio = 0.68, 95% confidence interval = 0.46–0.99, $P = .047$), P interaction = .27
Prevention of Progression of Arterial Disease and Diabetes (Belch et al., 46) United Kingdom	1,276 (675 aged ≥60)	60 ± 10 (≥40)	Type 1 or 2 DM	Aspirin 100 mg/d (n = 638), placebo (n = 638)	RCT (2 × 2 factorial with antioxidant)	6.7	Death from coronary heart disease or composite of stroke, nonfatal myocardial infarction or stroke, or above-ankle amputation for critical limb ischemia	No significant difference in composite endpoint (116 vs 117 events, $P = .86$), no significant difference between groups in subgroup analysis (aged ≥60)

glucose control reduced MI but significantly increased severe hypoglycemia events.

Research on Use of Aspirin for Primary Prevention

Until recently, clinical recommendations for the use of aspirin by older adults with DM have been 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 populations: individuals with DM, individuals with and without DM, and individuals without DM. Two decades ago, the Early Treatment of Diabetic Retinopathy Study (ETDRS) enrolled participants with type 1 and 2 DM and some individuals with a history of stoke and coronary heart disease. In the ETDRS, aspirin resulted in a 15% fewer fatal plus nonfatal MIs (relative risk (RR) = 0.85, 95% confidence interval (CI) = 0.73–1.00). Only two RCTs designed to study the cardiovascular benefits of aspirin use by individuals with DM have been published during the last 10 years (Table 6). One Japanese trial enrolled 2,539 participants with a mean age of 65 ± 10 and type 2 DM, 1,365 of whom were aged 65 and older (719 in the aspirin group, 644 in the placebo group).[45] A second trial (two by two factorial with an antioxidant) from the United Kingdom randomized 1,276 participants with type 1 or 2 DM to aspirin or placebo,[46] 675 of whom were aged 60 and older. Neither trial found significantly fewer CVD endpoints with aspirin than in the control group (Table 4).[47]

Six RCTs of middle-aged adults with and without DM examined the primary prevention benefits of aspirin on the reduction of CVD events using subgroup analysis: the British Medical Doctors study,[48] the Physicians Health Study,[49] the Thrombosis Prevention Trial,[50] the Hypertension Optimal Treatment study,[5] the Primary Prevention Project (PPP),[51] and the Women's Health Study (WHS).[52] Four of these trials were published between 1988 and 1998. In the last 10 years, the two newer trials, the PPP and the WHS also examined the benefits of aspirin in a subgroup of participants with DM and were published in 2003 and 2005, respectively.[51,52] In individuals with DM in the PPP trial, aspirin was associated with nonsignificantly fewer main endpoints (RR = 0.90, 95% CI = 0.50–0.90) and total CVD (RR = 0.89, 95% CI = 0.62–1.26) events. Similarly, fewer CVD events were not reported in the WHS for participants overall and for the subgroup with DM. The study found less stroke (RR = 0.45, 95% CI = 0.25–0.82) with aspirin for women with DM.

Five meta-analyses have been performed in an attempt to clarify the risk and benefits of aspirin use in adults with DM.[53–57] None of the meta-analyses found statistically significantly fewer CVD events or less all-cause mortality, cardiovascular mortality, stroke, or MI after pooling DM data from four to nine trails. Two meta-analyses found sex-specific effects of aspirin on MI and stroke.[53,54] One reported 43% fewer MIs for men (relative risk (RR) = 0.57, 95% CI = 0.34–0.94) but not women (RR = 1.08, 95% CI = 0.71–1.65; P for interaction = .06) and did not include the newer RCTs (e.g., Prevention of Progression of Arterial Disease and Diabetes (POPADAD) and Japanese Primary Prevention of Atherosclerosis With

Aspirin for Diabetes (JPAD)) designed for adults with type 2 DM.[54] Meta-regressions in the other included the newer trials and found a statistically significant association between sex and the incidence of MI (P < .001) and stroke (P < .001), suggesting sex-specific reductions with aspirin in MI in men with DM and stroke in women with DM.[53] 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 (RR = 0.88, 95% CI = 0.67–1.15) and without (RR = 0.87, 95% CI = 0.79–0.96) DM.[58] Recent trials (e.g., POPADAD and JAPAD) were not included in this meta-analysis,[45,46] although the overall results from the studies reviewed are inconsistent, and when all the evidence is examined together, the benefits of aspirin for primary prevention in 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 in middle-aged and older adults with DM. Two trials in the United Kingdom designed for persons with DM, A Study of Cardiovascular Events in Diabetes and Aspirin, which randomized 15,480 persons aged 40 and older, and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes, with a target enrollment of 5,170 participants aged 50 and older to be randomized to receive aspirin plus a statin or a statin alone,[59] are ongoing. One ongoing trial in the United States, Aspirin in Reducing Events in the Elderly, will also help to elucidate the role of aspirin in primary prevention for persons aged 65 and older.

REFERENCES

1. Brown AF, Mangione CM, Saliba D et al. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51 (5 Suppl Guidelines):S265–S280.

2. Howard BV, Roman MJ, Devereux RB et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: The SANDS randomized trial. JAMA 2008;299:1678–1689.

3. Gaede P, Vedel P, Parving HH et al. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: The Steno type 2 randomised study. Lancet 1999;353:617–622.

4. Schrier RW, Estacio RO, Esler A et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086–1097.

5. Hansson L, Zanchetti A, Carruthers SG et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998;351:1755–1762.

6. 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;265:3255–3264.

7. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998a;317:703–713.

8. Cushman WC, Evans GW, Byington RP et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585.

9. Patel A. ADVANCE Collaborative Group, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. Lancet 2007;370:829–840.

10. Holman RR, Paul SK, Bethel MA et al. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 2008a;359:1565–1576.

11. Ninomiya T, Zoungas S, Neal B et al. Efficacy and safety of routine blood pressure lowering in older patients with diabetes: Results from the ADVANCE trial. J Hypertens 2010;28:1141–1149.

12. Sleight P, Redon J, Verdecchia P et al. Prognostic value of blood pressure in patients with high vascular risk in the ongoing telmisartan alone and in combination with Ramipril Global Endpoint Trial study. J Hypertens 2009;27:1360–1369.

13. Cooper-DeHoff RM, Gong Y, Handberg EM et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010;304:61–68.

14. Anderson RJ, Bahn GD, Moritz TE et al. Blood pressure and cardiovascular disease risk in the Veterans Affairs Diabetes Trial. Diabetes Care 2011;34:34–38.

15. McBrien K, Rabi DM, Campbell N et al. Intensive and standard blood pressure targets in patients with type 2 diabetes mellitus: Systematic review and meta-analysis. Arch Intern Med 2012;172:1296–1303.

16. Bangalore S, Kumar S, Lobach I et al. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: Observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011;123:2799–2810, 9 p following 2810.

17. Miettinen TA, Pyorala K, Olsson AG et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: Findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 1997;96:4211–4218.

18. Sacks FM, Pfeffer MA, Moye LA et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–1009.

19. The Long-Term Intervention With Pravastatin In Ischemic 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 1998b;339:1349–1357.

20. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. Lancet 2002;360:7–22.

21. Lemaitre RN, Psaty BM, Heckbert SR et al. Therapy with hydroxymethylglutaryl coenzyme a reductase inhibitors (statins) and associated risk of incident cardiovascular events in older adults: Evidence from the Cardiovascular Health Study. Arch Intern Med 2002;162:1395–1400.

22. Downs JR, Clearfield M, Weis S et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615–1622.

23. Nakamura H, Arakawa K, Itakura H et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): A prospective randomised controlled trial. Lancet 2006;368:1155–1163.

24. Colhoun HM, Betteridge DJ, Durrington PN et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696.

25. Sever PS, Poulter NR, Dahlof B et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial—lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005;28:1151–1157.

26. Knopp RH, d'Emden M, Smilde JG et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care 2006;29:1478–1485.

27. Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–1504.

28. Shepherd J, Barter P, Carmena R et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: The Treating to New Targets (TNT) study. Diabetes Care 2006;29:1220–1226.

29. Ginsberg HN, Elam MB, Lovato LC et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574.

30. Boden WE, Probstfield JL, Anderson T et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255–2267.

31. Kearney PM, Blackwell L, Collins R et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: A meta-analysis. Lancet 2008;371:117–125.

32. Collins R, Armitage J, Parish S et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. Lancet 2003;361:2005–2016.

33. Shepherd J, Blauw GJ, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. Lancet 2002;360:1623–1630.

34. Selvin E, Marinopoulos S, Berkenblit G et al. Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–431.

35. Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008b;359:1577–1589.

36. Gerstein HC, Miller ME, Byington RP et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559.

37. Gerstein HC, Miller ME, Genuth S et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–828.

38. Duckworth W, Abraira C, Moritz T et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139.

39. Patel A, MacMahon S, Chalmers J et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572.

40. Ray KK, Seshasai SR, Wijesuriya S et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mel-litus: A meta-analysis of randomised controlled trials. Lancet 2009;373:1765–1772.

41. Turnbull FM, Abraira C, Anderson RJ et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–2298.

42. Mannucci E, Monami M, Lamanna C et al. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: A meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2009;19:604–612.

43. Kelly TN, Bazzano LA, Fonseca VA et al. Systematic review: Glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med 2009;151:394–403.

44. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: Meta-analysis of randomised controlled trials. BMJ 2011;343:d4169.

45. Ogawa H, Nakayama M, Morimoto T et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: A randomized controlled trial. JAMA 2008;300:2134–2141.

46. Belch J, MacCuish A, Campbell I et al. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial: Factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840.

47. ET-DRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. JAMA 1992;268:1292–1300.

48. Peto R, Gray R, Collins R et al. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988;296:313–316.

49. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129–135.

50. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: Randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 1998c;351:233–241.

51. Sacco M, Pellegrini F, Roncaglioni MC et al. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: Results of the Primary Prevention Project (PPP) trial. Diabetes Care 2003;26:3264–3272.

52. Ridker PM, Cook NR, Lee IM et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293–1304.

53. Zhang C, Sun A, Zhang P et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pract 2010;87:211–218.

54. De Berardis G, Sacco M, Strippoli GF et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: Meta-analysis of randomised controlled trials. BMJ 2009;339:b4531.

55. Calvin AD, Aggarwal NR, Murad MH et al. Aspirin for the primary prevention of cardiovascular events: A systematic review and meta-analysis comparing patients with and without diabetes. Diabetes Care 2009;32:2300–2306.

56. Stavrakis S, Stoner JA, Azar M et al. Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Am J Med Sci 2011;341:1–9.

57. Pignone M, Alberts MJ, Colwell JA et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: A position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Diabetes Care 2010;33:1395–1402.

58. Baigent C, Blackwell L, Collins R et al. Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–1860.

59. De Berardis G, Sacco M, Evangelista V et al. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): Design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. Trials 2007;8:21.