PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
1.1 BMI and Associated Risk Factors of T2DM																												
23867023	Casagrande 2013	Utility of the U.S. Preventive Services Task Force criteria for diabetes screening	2013	Cross-sectional study-observational	USA	NHANES survey			Data from 2003-2010	The goals of this study were to determine the sensitivity and specificity of the USPSTF screening criteria and to determine the prevalence of cardiovascular risk factors and comorbidity among undiagnosed individuals by USPSTF criteria.	7189	7189 adults who participated in NHANES survey from 2003-2010		>=20 years of age and undiagnosed diabetes						Sensitivity and specificity of USPSTF diabetes screening criteria; prevalence of cardiovascular risk factors and comorbidity among undiagnosed individuals.	4% had undiagnosed diabetes. Those with undiagnosed diabetes who were identified (sensitivity) using BP >135/ 80 mmHg as the screening standard was 44.4%; among individuals without undiagnosed diabetes, 74.8% had BP ≤135/80 mmHg (specificity). For those with undiagnosed diabetes, the prevalence of HbA1c 7.0%–o8.0% was 10.6% for those with BP ≤135/80 mmHg and 14.3% for those with BP 4135/80 mmHg; and 12.8% and 9.4% for HbA1c ≥8.0%, respectively. Elevated low-density lipoprotein (100–160 mg/dL) was similar by BP cut-point (52%–53%). For those with BP ≤135/80 mmHg, 16.7% had a history of cardiovascular disease and 22.9% had chronic kidney disease.				The USPSTF screening recommendations result in missing more than half of those who have undiagnosed diabetes, and a substantial proportion of these people have increased low-density lipoprotein and other cardiovascular risk factors.	Low	Screening	1.1; 1.2
24082791	Colosia 2013	Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review	2013	Observational	USA				Studies reported in English from January 1, 2001 to February 16, 2012.	Knowing the proportion of the T2DM population at addi- tional risk of complications from hypertension and obesity is an important public health measure to determine public and private resource requirements to reduce these risk factors or to care for patients after cardiovascular events. This systematic literature review was conducted to determine the rates of hypertension and/or obesity among patients with T2DM as reported in observational studies.	A total of 2688 studies were reviewed. Out of those 78 studies were included in the analysis.	Type 2 diabetes patients							Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus	61 studies reported hypertension prevalence, 44 reported obesity prevalence, and 12 reported the prevalence of hypertension with obesity. The continental regions with the most observational studies of hypertension or obesity prevalence were Europe (n = 30) and Asia (n = 26). Hypertension rates typically were high in all regions; most studies presented rates above 50%, and many presented rates above 75%. Obesity rates exceeded 30% in 38 of 44 studies and 50% in 14 of 44 studies, especially those assessing central obesity (based on waist circumference). Among obese adults, hypertension rates were at or above 70% in Asia and above 80% in Europe; rates were lower in North and South America but still above 30%.				Around the world, hypertension and obesity, separately or together, are common comorbidities in adults with T2DM.	Low	Hypertension	1.1; 1.2
23972041	Waugh 2013	Screening for type 2 diabetes: a short report for the National Screening Committee	2013	Systematic review	USA					The aim of this review was to provide an update for the UK National Screening Committee (NSC) on screening for T2DM.															Systematic Review	Screening	1.1; 1.2; 1.3; 1.4
21146762	Ackermann 2011	Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c National Health and Nutrition Examination Survey 2005-2006	2011	Observational cross-sectional	USA	NHANES survey				To estimate composite risks of developing diabetes and cardiovascular disease (CVD) for adults with different hemoglobin A1c test results and to compare those risks with those of adults who met the 2003 ADA definition for prediabetes.	1798	Civilian, noninstitutionalized U.S. population with no prior diagnosis of diabetes or CVD				Laboratory (using A1c testing to predict type 2 diabetes and CVD)		2003 American Diabetes Association for prediabetes		7.5-year probability of type 2 diabetes; 10-year probability of general CVD event	Among adults meeting the 2003 ADA definition for prediabetes, the probabilities for incident type 2 diabetes (over 7.5 years) and CVD (over 10 years) were 33.5% and 10.7%, respectively. Use of A1c alone, in the range of 5.5% to <6.5%, would identify a population with comparable risks for diabetes (32.4% [SE=1.2%]) and CVD (11.4% [SE=0.6%]). A slightly higher cutoff (≥5.7%) would identify adults with risks of 41.3% (SE=1.5%) for diabetes and 13.3% (SE=0.8%) for CVD-risks that are comparable to people enrolled in the Diabetes Prevention Program.	Not significant difference			A1c based testing should be considered in clinical settings to identify patients at risk for developing type 2 diabetes and CVD.	Low	Screening	1.1; 1.2
	Li 2008	The long-term effect of lifestyle interventions to prevent diabetes in the China Da Quing diabetes prevention study: a 20-year follow-up study.	2008	Randomized Controlled Trial	China	Clinical		6 years	20 years	To assess whether intensive lifestyle intervention has a long-term effect on the risk of diabetes, diabetes-related macrovascular and microvascular complications, and mortality.	577	Adults with impaired glucose tolerance		Control age: 46.6 years; sex male 57%; Combined intervention: 44.7 years; sex male 53%	438(274)	3 lifestyle intervention groups (diet, exercise, or diet plus exercise)		138(92)		Primary: diabetes iincidence, CVD incidence, CVD mortality, all-cause mortality	Compared with control participants, those in the combined lifestyle intervention groups had a 51% lower incidence of diabetes (hazard rate ratio (HRR) 0.49; 95% CI 0.33-0.73) during the active intervention period and a 43% lower incidence (0.57-0.41-0.81) over the 20 year period, controlled for age and clustering by clinic. The average annual incidence of diabetes was 7% for intervention participants vs 11% in control participants, with 20-year cumulative incidence of 80% in the intervention groups and 93% in the control group. Participants in the intervention group spent an average of 3.6 fewer years with diabetes than those in the control group. There was no significant difference between the intervention and control groups in the rate of first CVD events (HRR 0.98; 95% CI 0.71-1.37), CVD mortality (0.83; 0.48-1.40), and all-cause mortality (0.96; 0.65-1.41), but our study had limited statistical power to detect differences for these outcomes.				Group-based lifestyle interventions over 6 years can prevent or delay diabetes for up to 14 years after the active intervention. However, whether lifestyle intervention also leads to reduced CVD and mortality remains unclear.	Low		1.1; 1.2
15562189	Gregg 2004	Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the U.S.	2004	Cross-sectional study-observational	USA	NHANES survey data 1960-2000				To examine trends in the prevalence of diagnosed and undiagnosed diabetes and the proportion of total cases previously diagnosed, according to obesity status in the U.S. over the past 40 years.		U.S. population adults aged 20–74 years									In the U.S. population aged 20–74 years between 1976–1980 and 1999–2000, significant increases in the prevalence of diagnosed diabetes (3.3–5.8%, probability >99.9%) were accompanied by nonsignificant increases in undiagnosed diabetes (2.0–2.4%, 66.6%). This resulted in an increase in total diabetes (5.3– 8.2%, >99.9%) and a modest nonsignificant increase in the proportion of cases that were diagnosed (62–70%, 62.4%). However, these trends varied considerably by BMI level. In individuals with BMI >=35 kg/m2, diagnosed diabetes increased markedly (from 4.9% in 1960, to 8.6% during 1976 –1980, to 15.1% in 1999 –2000, probability >99.9%), whereas undiagnosed diabetes declined considerably (12.5% during 1976 –1980 to 3.2% in 1999 –2000, probability of increase 4.5%) Therefore, the proportion of total diabetes cases that were diagnosed increased from 41 to 83% (probability 99.9%) among individuals with BMI >=35 kg/m2. By comparison, changes in prevalence within BMI strata <35 kg/m2 were modest and there was no increase in the percent of total cases that were diagnosed.				National surveys over the last several decades have found large increases in diagnosed diabetes, particularly in overweight and obese individuals, but this has been accompanied by large decreases in undiagnosed diabetes only among individuals with BMI > or =35 kg/m2. This suggests that improvements in diabetes awareness and detection are most prominent among this subgroup.	Low	Diagnosis	1.1
1.2 Cardiovascular Risk																												
23867023	Casagrande 2013	Utility of the U.S. Preventive Services Task Force criteria for diabetes screening	2013	Cross-sectional study-observational	USA	NHANES survey			Data from 2003-2010	The goals of this study were to determine the sensitivity and specificity of the USPSTF screening criteria and to determine the prevalence of cardiovascular risk factors and comorbidity among undiagnosed individuals by USPSTF criteria.	7189	7189 adults who participated in NHANES survey from 2003-2010		>=20 years of age and undiagnosed diabetes						Sensitivity and specificity of USPSTF diabetes screening criteria; prevalence of cardiovascular risk factors and comorbidity among undiagnosed individuals	4% had undiagnosed diabetes. Those with undiagnosed diabetes who were identified (sensitivity) using BP >135/ 80 mmHg as the screening standard was 44.4%;among individuals without undiagnosed diabetes, 74.8% had BP ≤135/80 mmHg (specificity).For those with undiagnosed diabetes, the prevalence of HbA1c 7.0%–o8.0% was 10.6% for those with BP ≤135/80 mmHg and 14.3% for those with BP 4135/80 mmHg; and 12.8% and 9.4% for HbA1c ≥8.0%, respectively. Elevated low-density lipoprotein (100–160 mg/dL) was similar by BP cut-point (52%–53%). For those with BP ≤135/80 mmHg, 16.7% had a history of cardiovascular disease and 22.9% had chronic kidney disease.				The USPSTF screening recommendations result in missing more than half of those who have undiagnosed diabetes, and a substantial proportion of these people have increased low-density lipoprotein and other cardiovascular risk factors.	Low	Screening	1.1; 1.2
24082791	Colosia 2013	Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review	2013	Observational	USA				Studies reported in English from January 1, 2001 to February 16, 2012.	Knowing the proportion of the T2DM population at addi- tional risk of complications from hypertension and obesity is an important public health measure to determine public and private resource requirements to reduce these risk factors or to care for patients after cardiovascular events. This systematic literature review was conducted to determine the rates of hypertension and/or obesity among patients with T2DM as reported in observational studies.	A total of 2688 studies were reviewed. Out of those 78 studies were included in the analysis.	Type 2 diabetes patients							Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus	61 studies reported hypertension prevalence, 44 reported obesity prevalence, and 12 reported the prevalence of hypertension with obesity. The continental regions with the most observational studies of hypertension or obesity prevalence were Europe (n = 30) and Asia (n = 26). Hypertension rates typically were high in all regions; most studies presented rates above 50%, and many presented rates above 75%. Obesity rates exceeded 30% in 38 of 44 studies and 50% in 14 of 44 studies, especially those assessing central obesity (based on waist circumference). Among obese adults, hypertension rates were at or above 70% in Asia and above 80% in Europe; rates were lower in North and South America but still above 30%.				Around the world, hypertension and obesity, separately or together, are common comorbidities in adults with T2DM.	Low	Hypertension	1.1; 1.2
23972041	Waugh 2013	Screening for type 2 diabetes: a short report for the National Screening Committee	2013	Systematic review	USA					The aim of this review was to provide an update for the UK National Screening Committee (NSC) on screening for T2DM.															Systematic Review	Screening	1.1; 1.2; 1.3; 1.4
22010971	Rahman 2012	Effect of screening for Type 2 diabetes on population-level self-rated health outcomes and measures of cardiovascular risk: 13-year follow-up of the Ely cohort	2012	Cohort study-observational	United Kingdom	National register			13 years	There is continuing uncertainty regarding the overall net benefits of population-based screening for Type 2 diabetes. We compared clinical measures, prescribed medication, cardiovascular morbidity and self-rated health in individuals without diabetes in a screened vs. an unscreened population.	3390	people aged 40–65 years, free of known diabetes							Self-rated health outcomes and measures of cardiovascular risk	Of 3390 eligible individuals without diabetes, 1442 (43%) attended for health assessment, with no significant difference in attendance between groups. Thirteen years after the commencement of screening, self-rated functional health status and health utility were identical between the screened and unscreened populations. Clinical measures, self-reported medication and cardiovascular morbidity were similar between the two groups.				Screening for diabetes is not associated with long-term harms at the population level. However, screening has limited long-term impact on those testing negative; benefits may largely be restricted to those whose diabetes is detected early through screening.	Low		1.2; 1.3
21146762	Ackermann 2011	Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c National Health and Nutrition Examination Survey 2005-2006	2011	Observational cross-sectional	USA	NHANES survey				To estimate composite risks of developing diabetes and cardiovascular disease (CVD) for adults with different hemoglobin A1c test results and to compare those risks with those of adults who met the 2003 ADA definition for prediabetes.	1798	Civilian, noninstitutionalized U.S. population with no prior diagnosis of diabetes or CVD				Laboratory (using A1c testing to predict type 2 diabetes and CVD)		2003 American Diabetes Association for prediabetes		7.5-year probability of type 2 diabetes; 10-year probability of general CVD event	Among adults meeting the 2003 ADA definition for prediabetes, the probabilities for incident type 2 diabetes (over 7.5 years) and CVD (over 10 years) were 33.5% and 10.7%, respectively. Use of A1c alone, in the range of 5.5% to <6.5%, would identify a population with comparable risks for diabetes (32.4% [SE=1.2%]) and CVD (11.4% [SE=0.6%]). A slightly higher cutoff (≥5.7%) would identify adults with risks of 41.3% (SE=1.5%) for diabetes and 13.3% (SE=0.8%) for CVD-risks that are comparable to people enrolled in the Diabetes Prevention Program.	Not significant difference			A1c based testing should be considered in clinical settings to identify patients at risk for developing type 2 diabetes and CVD.	Low	Screening	1.1; 1.2
20042775	American Diabetes Association 2010	Diagnosis and classification of diabetes mellitus	2010	Reference	USA	Ambulatory care																			Reference	Diagnosis	1.2; 1.4
	Li 2008	The long-term effect of lifestyle interventions to prevent diabetes in the China Da Quing diabetes prevention study: a 20-year follow-up study.	2008	Randomized Controlled Trial	China	Clinical		6 years	20 years	To assess whether intensive lifestyle intervention has a long-term effect on the risk of diabetes, diabetes-related macrovascular and microvascular complications, and mortality.	577	Adults with impaired glucose tolerance		Control age: 46.6 years; sex male 57%; Combined intervention: 44.7 years; sex male 53%	438(274)	3 lifestyle intervention groups (diet, exercise, or diet plus exercise)		138(92)		Primary: diabetes iincidence, CVD incidence, CVD mortality, all-cause mortality	Compared with control participants, those in the combined lifestyle intervention groups had a 51% lower incidence of diabetes (hazard rate ratio (HRR) 0.49; 95% CI 0.33-0.73) during the active intervention period and a 43% lower incidence (0.57-0.41-0.81) over the 20 year period, controlled for age and clustering by clinic. The average annual incidence of diabetes was 7% for intervention participants vs 11% in control participants, with 20-year cumulative incidence of 80% in the intervention groups and 93% in the control group. Participants in the intervention group spent an average of 3.6 fewer years with diabetes than those in the control group. There was no significant difference between the intervention and control groups in the rate of first CVD events (HRR 0.98; 95% CI 0.71-1.37), CVD mortality (0.83; 0.48-1.40), and all-cause mortality (0.96; 0.65-1.41), but our study had limited statistical power to detect differences for these outcomes.				Group-based lifestyle interventions over 6 years can prevent or delay diabetes for up to 14 years after the active intervention. However, whether lifestyle intervention also leads to reduced CVD and mortality remains unclear.	Low		1.1; 1.2
	U.S. Preventive Services Task Force 2008	Screening for type 2 diabetes mellitus in adults	2008	Systematic review	USA																				Systematic Review	Screening	1.2; 1.3
1.3 Screening																												
23972041	Waugh 2013	Screening for type 2 diabetes: a short report for the National Screening Committee	2013	Systematic review	USA					The aim of this review was to provide an update for the UK National Screening Committee (NSC) on screening for T2DM.															Systematic Review	Screening	1.1; 1.2; 1.3; 1.4
22010971	Rahman 2012	Effect of screening for Type 2 diabetes on population-level self-rated health outcomes and measures of cardiovascular risk: 13-year follow-up of the Ely cohort	2012	Cohort study-observational	United Kingdom	National register			13 years	There is continuing uncertainty regarding the overall net benefits of population-based screening for Type 2 diabetes. We compared clinical measures, prescribed medication, cardiovascular morbidity and self-rated health in individuals without diabetes in a screened vs. an unscreened population.	3390	people aged 40–65 years, free of known diabetes							Self-rated health outcomes and measures of cardiovascular risk	Of 3390 eligible individuals without diabetes, 1442 (43%) attended for health assessment, with no significant difference in attendance between groups. Thirteen years after the commencement of screening, self-rated functional health status and health utility were identical between the screened and unscreened populations. Clinical measures, self-reported medication and cardiovascular morbidity were similar between the two groups.				Screening for diabetes is not associated with long-term harms at the population level. However, screening has limited long-term impact on those testing negative; benefits may largely be restricted to those whose diabetes is detected early through screening.	Low		1.2; 1.3

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
15797851	Simmons 2012	Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial	2012	Randomized Controlled Trial	United Kingdom		The investigators assessing outcomes and analysing data were masked to group assignment.			Effects of a population-based stepwise screening programme on mortality.	20184	individuals aged 40–69 years (mean 58 years), at high risk of prevalent undiagnosed diabetes, on the basis of a previously validated risk score								The primary outcome was all-cause mortality.	Of 16047 high-risk individuals in screening practices, 15089 (94%) were invited for screening during 2001–06, 11 737 (73%) attended, and 466 (3%) were diagnosed with diabetes. 4137 control individuals were followed up. During 184 057 person-years of follow up (median duration 9·6 years [IQR 8·9–9·9]), there were 1532 deaths in the screening practices and 377 in control practices (mortality hazard ratio [HR] 1·06, 95% CI 0·90–1·25). We noted no significant reduction in cardiovascular (HR 1·02, 95% CI 0·75–1·38), cancer (1·08, 0·90–1·30), or diabetes-related mortality (1·26, 0·75–2·10) associated with invitation to screening.				In this large UK sample, screening for type 2 diabetes in patients at increased risk was not associated with a reduction in all-cause, cardiovascular, or diabetes-related mortality within 10 years. The benefits of screening might be smaller than expected and restricted to individuals with detectable disease.	High	Universal Screening	1.3
	U.S. Preventive Services Task Force 2008	Screening for type 2 diabetes mellitus in adults	2008	Systematic review	USA																					Systematic Review	Screening	1.2; 1.3
1.4 Diagnostic Testing for T2DM and 1.5 Diagnosis of T2DM																												
23972041	Waugh 2013	Screening for type 2 diabetes: a short report for the National Screening Committee	2013	Systematic review	USA					The aim of this review was to provide an update for the UK National Screening Committee (NSC) on screening for T2DM.																Systematic reivew	Screening	1.1; 1.2; 1.3; 1.4
20042775	American Diabetes Association 2010	Diagnosis and classification of diabetes mellitus	2010	Reference	USA	Ambulatory care																				Reference	Diagnosis	1.2; 1.4
20067953	Cowie 2010	Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988-2006	2010	Cross-sectional study-observational	USA	NHANES Survey			2003-2006	We examined prevalences of previously diagnosed diabetes and undiagnosed diabetes and high risk for diabetes using recently suggested A1C criteria in the U.S. during 2003-2006. We compared these prevalences to those in earlier surveys and those using glucose criteria.	14611	U.S. civilian non- institutionalized population aged>=12 years.								Prevalence of Diabetes and High Risk for Diabetes Using A1C Criteria	Using A1C criteria, the crude prevalence of total diabetes in adults aged >=20 years was 9.6% (20.4 million), of which 19.0% was undiagnosed (7.8% diagnosed, 1.8% undi- agnosed using A1C >=6.5%). Another 3.5% of adults (7.4 million) were at high risk for diabetes (A1C 6.0 to <6.5%). Prevalences were disproportionately high in the elderly. Age-/sex- standardized prevalence was more than two times higher in non-Hispanic blacks and Mexican Americans versus non-Hispanic whites for diagnosed, undiagnosed, and total diabetes (P < 0.003); standardized prevalence at high risk for diabetes was more than two times higher in non-Hispanic blacks versus non-Hispanic whites and Mexican Americans (P < 0.00001). Since 1988–1994, diagnosed diabetes generally increased, while the percent of diabetes that was undiagnosed and the percent at high risk of diabetes generally decreased. Using A1C criteria, prevalences of undiagnosed diabetes and high risk of diabetes were one-third that and one-tenth that, respectively, using glucose criteria.				Although A1C detects much lower prevalences than glucose criteria, hyperglycemic conditions remain high in the U.S., and elderly and minority groups are disproportionately affected.	Low	Diagnosis	1.4
20371663	Kumar 2010	Utility of glycated hemoglobin in diagnosing type 2 diabetes mellitus: a community-based study.	2010	Cross-sectional study-observational	India	Community		16 months	16 months	The objective of the study was to assess the validity of HbA1c as a screening and diagnostic test in individuals with newly detected diabetes mellitus.	1972	subjects aged 20 yr or older					Intervention included an oral glucose tolerance test and glycated hemoglobin in all the subjects.			Utility of HbA1c as a diagnostic method in newly detected diabetes mellitus subjects was evaluated.	Using World Health Organization criteria for diagnosis of diabetes mellitus, 134 (6.7%) had newly detected diabetes mellitus, 192 (9.7%) known diabetes mellitus, 329 (16.6%) prediabetes, and 1317 (69.4%) were normal of 1972 people screened. Using only the ADA criteria, 38% people were underdiagnosed. An HbA1c level of 6.1% had an optimal sensitivity and specificity of 81% for diag- nosing diabetes. A HbA1c level of 6.5% (+/-2 SD) and 7% (+/-2.7 SD) had sensitivity and specificity of 65 and 88% and 42 and 92%, respectively, with corresponding positive predictive value and negative predic- tive value of 75.2 and 96.5% and 90.4and 94.4%, respectively, for diagnosis of newly detected diabetes mellitus.				A HbA1c cut point of 6.1% has an optimal sensitivity and specificity of 81% and can be used as a screening test, and a cut point of 6.5% has optimal specificity of 88% for diagnosis of diabetes.	Moderate	Diagnosis	1.4
18997198	Olson 2010	Screening for Diabetes and Pre-Diabetes With Proposed A1c-Based Diagnostic Criteria	2010	Cross-sectional study-observational	USA	Reaarch studies, surveys				An International Expert Committee (IEC) and the American Diabetes Asso- ciation (ADA) proposed diagnostic criteria for diabetes and pre-diabetes based on A1C levels. Hypothesis that screening for diabetes and pre-diabetes with A1C measurements would differ from using oral glucose tolerance tests (OGTT).		Non-Hispanic white or black adults without known diabetes who had A1C and 75-g OGTT measurements were included from the prospective Screening for Impaired Glucose Tolerance study (n = 1,581), and from the National Health and Nutrition Examination Survey (NHANES) III (n = 2014), and NHANES 2005–2006 (n = 1,111).									OGTTs revealed pre-diabetes in 35.8% and diabetes in 5.2% of combined study subjects. A1C provided receiver operating characteristic (ROC) curve areas for diabetes of 0.79 – 0.83, but ROC curve areas were <=0.70 for dysglycemia or pre-diabetes. The proposed criteria missed 70% of individuals with diabetes, 71–84% with dysglycemia, and 82–94% with pre- diabetes. Compared with the IEC criteria, the ADA criteria for pre-diabetes resulted in fewer false-negative and more false-positive result. There were also racial differences, with false-positive results being more common in black subjects and false-negative results being more common in white subjects. With use of NHANES 2005–2006 data, near 5.9 million non-Hispanic U.S. adults with unrecognized diabetes and 43–52 million with pre-diabetes would be missed by screening with A1C.				The proposed A1C diagnostic criteria are insensitive and racially discrepant for screening, missing most Americans with undiagnosed diabetes and pre-diabetes.	Low	Screening	1.4
19502545	International Expert Committee 2009	International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes	2009	Consensus Report	USA					An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes in nonpregnant individuals.																Low	Diagnosis	1.4
16801588	Droumaguet 2006	Use of HbA1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR)	2006	Cohort study-observational	France					Early identification of subjects at high risk for diabetes is essential, and random HbA(1c) (A1C) may be more practical than fasting plasma glucose (FPG). The predictive value of A1C, in comparison to FPG, is evaluated for 6-year incident diabetes.				1,383 men and 1,437 women, aged 30 – 65 years, were volunteers for a routine health check-up.						Incidence of diabetes	At 6 years, 30 women (2.1%) and 60 men (4.3%) had developed diabetes. Diabetes risk increased exponentially with A1C in both sexes (P< 0.001). After stratifying on FPG, A1C predicted diabetes only in subjects with impaired fasting glucose (IFG) (FPG >=6.10 mmol/l): the odds ratio (95% CI) for a 1% increase in A1C was 7.20 (3.00–17.00). In these subjects, an A1C of 5.9% gave an optimal sensitivity of 64% and specificity of 77% to predict diabetes.				A1C predicted diabetes, even though the diagnosis of diabetes was based on FPG, but it was less sensitive and specific than FPG. It could be used as a test if fasting blood sampling was not available or in association with FPG. In subjects with IFG, A1C is better than glucose to evaluate diabetes risk, and it could be used to select subjects for intensive early intervention.	Low	Diagnosis	1.4
4. Glycemic Control and A1c Goals																												
24214280	Hemmingsen 2013	Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus	2013	Systematic review	Denmark					To assess the effects of targeted intensive glycaemic control compared with conventional glycaemic control in patients with T2D.	Patients with type 2 diabetes						intensive glycaemic control		conventional glycaemic control					Although we have been able to expand the number of participants by 16% in this update, we still find paucity of data on outcomes and the bias risk of the trials was mostly considered high. Targeting intensive glycaemic control compared with conventional glycaemic control did not show significant differences for all-cause mortality and cardiovascular mortality. Targeting intensive glycaemic control seemed to reduce the risk of microvascular complications, if we disregard the risks of bias, but increases the risk of hypoglycaemia and serious adverse events.	Systematic Review	Glycaemic Control	4
22696371	Callaghan 2012	Enhanced glucose control for preventing and treating diabetic neuropathy	2012	Systematic review	USA			At least 1 year of interventi on		To examine the evidence for enhanced glucose control in the prevention of distal symmetric polyneuropathy in people with type 1 and type 2 diabetes.	1228 with type 1 diabetes and 6669 with type 2 diabetes	Type 1 and type 2 diabetes					Enhanced glucose control				A meta-analysis of the two studies that reported the primary outcome (incidence of clinical neuropathy) with a total of 1228 participants with type 1 diabetes revealed a significantly reduced risk of developing clinical neuropathy in those with enhanced glucose control, an annualized RD of -1.84% (95% confidence interval (CI) -1.11 to -2.56). In a similar analysis of four studies that reported the primary outcome, involving 6669 participants with type 2 diabetes, the annualized RD of developing clinical neuropathy was -0.58% (95% CI 0.01 to - 1.17). Most secondary outcomes were significantly in favor of intensive treatment in both populations.		Both type 1 and type 2 participants had a significant increase in severe adverse events including hypoglycemic events.		Enhanced glucose control significantly prevents the development of clinical neuropathy and reduces nerve conduction and vibration threshold abnormalities in type 1 diabetes mellitus. In type 2 diabetes mellitus, enhanced glucose control reduces the incidence of clinical neuropathy, although this was not formally statistically significant (P = 0.06). However, enhanced glucose control does significantly reduce nerve conduction and vibration threshold abnormalities. Importantly, enhanced glucose control significantly increases the risk of severe hypoglycemic episodes, which needs to be taken into account when evaluating its risk/benefit ratio.	Systematic Review	Neuropathy	4
21346183	Anderson 2011	Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial.	2011	Randomized Controlled Trial	USA, Canada	Clinical	Yes	48 months	48 months	To compare the effect of intensive vs standard glycemic control strategies on health-related quality of life (HRQL) in a substudy of the ACCORD trial.	2053	Type 2 diabetes diagnosis; HbA1c between 7.5 and 11% and either 1) age 40-79 years with cardiovascular disease or 2) age 55-79 years with anatomical evidence of significant atherosclerosis, albuminaria, left ventricular hypertrophy, or at least tow additional risk factors for CVD (dyslipidemia, hypertension, current smoker, or obesity).	Type 2 diabetes diagnosis; HbA1c between 7.5 and 11% and either 1) age 40-79 years with cardiovascular disease or 2) age 55-79 years with anatomical evidence of significant atherosclerosis, albuminaria, left ventricular hypertrophy, or at least tow additional risk factors for CVD (dyslipidemia, hypertension, current smoker, or obesity).	Mean age 62 years, 39% women, 65% white, 19% black and 7% hispanic	1024	Pharmacologic	Intensive glycemic control	1029	Standard glycemic control	Changes in Health-related quality of life (HRQL) that included general health status, diabetes symptoms, depression symptoms and treatment satisfaction.	A total of 1956 (95%) completed the self-report HRQL instrument(s) at baseline. The intensive group had a larger decrease in SF-36 physical health component score than the standard group (-1.6 vs. -1.1, P=0.0345). Treatment satisfaction (DTSQ) showed larger improvement in intensive than standard (P=0.0004). There were no differences in mean scores of the Diabetes Symptom Checklist and PHQ-9. Effects of participant transition following discontinuation of the intensive group on HRQL were not significant.				The ACCORD trial strategy of intensive glycemic control did not lead to benefits in HRQL and was associated with modest improvement in diabetes treatment satisfaction. Thus patient acceptability was apparently not compromised with intensive and complex interventions such as those used in ACCORD.	High		4
20594588	Ismail-Beigi 2010	Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial	2010	Randomized Controlled Trial	USA, Canada	Clinical	Yes			To investigate whether reduction of blood glucose concentration decreases the rate of microvascular complications in people with type 2 diabetes.	10251	Type 2 diabetes mellitus, HbA1c>=7.5%, aged 40-79 years with history of cardiovascular disease or 55-79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular disease (dyslipidemia, hypertension, being a smoker, or obesity)	Type 2 diabetes mellitus, HbA1c>=7.5%, aged 40-79 years with history of cardiovascular disease or 55-79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two risk factors for cardiovascular disease (dyslipidemia, hypertension, being a smoker, or obesity)		5128 (5119)	Pharmacologic	Intensive glycemic target group	5123(5115)	Standard glycemic target group	Microvascular complications	Intensive therapy was stopped before study end in intensive therapy group due to higher mortality in that group, and patients were transitioned to standard therapy. At transition, the first composite outcome was recorded in 443 of 5107 patients in the intensive group vs 444 of 5108 in the standard group (HR 1.00, 95% CI 0.88-1.14; p=1.00), and the second composite outcome was noted in 1591 of 5107 vs1659 of 5108 (0.96, 0.89-1.02; p=0.19). Results were similar at study end (first composite outcome 556 of 5119 vs 586 of 5115 (HR 0.95, 95% CI 0.85-1.07, p=0.42); and second 1956 of 5119 vs 2046 of 5115, respectively (0.95, 0.89-1.01, p=0.12)). Intensive therapy did not reduce the risk of advanced measures of microvascular outcomes, but delayed the onset of albuminuria and some measures of eye complication and neuropathy. Six secondary measures at study end favored intensive therapy (p<0.05).				Microvascular benefits of intensive therapy should be weighed against the increase in total and cardiovascular disease-related mortality, increased weight gain, and high risk for severe hypoglycemia.	High		4
18671796	Abraira 2009	Glycaemic separation and risk factor control in the Veterans Affairs Diabetes Trial: an interim report.	2009	Randomized Controlled Trial	USA	Clinical			4 years	Assess the effect of intensive (INT) vs improved standard (STD) glycaemic control on major cardiovascular (CV) events, treating other risk factors equally in both arms.	1791	Veterans with type 2 diabetes		age 60.5 +/- 8.7 years, diagnosed for 11.5 +/- 7.5 years. Their body mass index (BMI) at baseline was 31 +/- 4 kg/m(2) and mean A1C 9.4 +/- 1.5% after maximum dose of oral agents or insulin treatment.					A1c, blood pressure, triglycerides, LDL-C	A1C improved in both arms. INT kept median A1C <7% all years, A1C separation is 1.5-1.7%. From year 1 to 4, mean blood pressure is <129/74 mmHg, similar throughout. Median LDL-C was <97 mg/dl by year 1 and triglycerides 150 or less by 2 years. Triglycerides were lower in INT (12-16 mg/dl; p < 0.01). By 4 years, 88% are on lipid-lowering agents and 93% are on antiplatelet/anticoagulant agents. BMI is higher in INT every year (0.9-1.6 kg/m(2); p < 0.01).				VADT is maintaining the expected A1C in both STD and INT, and LDL-C, triglycerides and blood pressure are at target. The trial is continuing to June 2008. It will be the first long-term completed type 2 diabetes study of the role of glycaemia on CV disease with modern treatments.	High		4

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
19092145	Duckworth 2009	Glucose control and vascular complications in veterans with type 2 diabetes	2009	Randomized Controlled Trial	USA	Clinical	Staff blinded		30 months study enrollment plus 5 years of follow up	The effects of intensive glucose control on cardiovascular events in patients with long-standing type 2 diabetes mellitus	1791	Military veterans	Selection criteria in- cluded an inadequate response to maximal doses of an oral agent or insulin therapy. Exclusion cri- teria included a glycated hemoglobin level of less than 7.5%, the occurrence of a cardiovascular event during the previous 6 months, advanced conges- tive heart failure, severe angina, a life expectancy of less than 7 years, a body-mass index of more than 40, a serum crea- tinine level of more than 1.6 mg per deciliter and an alanine aminotransferase level of more than three times the upper limit of the normal range.	mean age, 60.4 years; 97% male	892 (344)	Pharmacologic	Intensive glucose treatment	899 (329)	Standard glucose treatment	Primary outcome: the time to the first occurrence of any one of a composite of cardio- vascular events. Secondary cardiovascular outcomes included new or worsening angina, new transient ischemic attacks, new intermittent claudication, new criti- cal limb ischemia, and death from any cause. Secondary outcomes also included microvascular complications	Median glycated hemoglobin levels were 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. The primary outcome occurred in 264 patients in the standard-therapy group and 235 patients in the intensive-therapy group (hazard ratio in the intensive-therapy group, 0.88; 95% confidence interval [CI], 0.74 to 1.05; P=0.14). There was no significant difference between the two groups in any component of the primary outcome or in the rate of death from any cause (hazard ratio, 1.07; 95% CI, 0.81 to 1.42; P=0.62). No differences between the two groups were observed for microvascular complications.		The rates of adverse events, predominantly hypoglycemia, were 17.6% in the standard-ther- apy group and 24.1% in the intensive-therapy group.		Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or micro- vascular complications, with the exception of progression of albuminuria (P = 0.01).	High		4
19318384	NICE-SUGAR Study Investigators, The 2009	Intensive versus conventional glucose control in critically ill patients	2009	Randomized Controlled Trial	Australia, New Zealand, Canada	Clinical	Yes, clinical staff were aware of treatment assignments.			To determine the optimal target range for blood glucose in critically ill patients.	6104	Adult acutely ill patients in ICUs		Mean age 60.4+/- 17.2 years in intensive control group and 59.9+/- 17.1 years in conventional control group	3054(3016)	Pharmacologic	Intensive glucose control	3050(3014)	Conventional glucose control	Primary end point: death from any cause within 90 days after randomization	A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (odds ratio for intensive control, 1.14; 95% CI 1.02-1.28; p=0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratio for death in the intensive control group, 1.31. and 1.07, respectively; p=0.10). Severe hypoglycemia was reported in 206 of 3016 patients (6.8%) in the intensive control group and 15 of 3014 (0.5%) in the conventional control group (p<0.001). There was no significant difference between the two treatment groups in the median number of days in the ICU (p=0.84) or hospital (p=0.86) or the median number of days of mechanical ventilation (p=0.56) or renal-replacement therapy (p=0.39).				In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.	High		4
19465231	Ray 2009	Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials	2009	Meta-Analysis	United Kingdom	Clinical				To determine whether intensive control of glucose reduces macrovascular events and all-cause mortality in individuals with type 2 diabetes mellitus compared to standard treatment.	33040									The five trials provided information on 1497 events of non-fatal myocardial infarction, 2318 of coronary heart disease, 1127 of stroke, and 2892 of all cause mortality during about 163000 person-years of follow up. The mean HbA1c, concentration HbA1c was 0.9% lower for participants given intensive treatment than for those given standard treatment. Intensive glycemic control resulted in a 17% reduction in events of non-fatal myocardial infarction (odds ratio 0.83, 95% CI 0.75-0.93), and a 15% reduction in events of coronary heart disease (0.85, 0.77-0.93). Intensive glycemic control had no significant effect on events of stroke (0.93, 0.81-1.06) for all cause mortality (1.02, 0.87-1.19).				Overall, intensive compared with standard glycemic control significantly reduces coronary events without an increased risk of death. However, the optimum mechanism, speed and extent of HbA1c reduction might be different in differing populations.	Meta-Analysis		4
19655124	Turnbull 2009	Intensive glucose control and macrovascular outcomes in type 2 diabetes	2009	Meta-Analysis	USA, Canada, United Kingdom, France	Clinical				To generate more precise estimates of the effects of more-intensive, compared with less-intensive, glucose control on the risk of major cardiovascular events among patients with type 2 diabetes.	27049	Adults with type 2 diabetes								A total of 27049 participants and 2370 major vascular events contributed to the meta-analysis. Allocated to more-intensive, compared with less-intensive, glucose control reduced the risk of major cardiovascular events by 9% (HR 0·91, 95%CI 0·84-0·99), primarily because of a 15% reduced risk of myocardial infarction (HR 0·85, 95% CI 0·76-0·94). Mortality was not decreased, with non-significant HRs of 1·04 for all cause mortality (95% CI 0·90-1·20) and 1·10 for cardiovascular death (95% CI 0·84-1·42). Intensively treated participants had significantly more major hypoglycemic events (HR 2·48, 95% CI 1·91-3·21). Exploratory subgroup analyses suggested the possibility of a differential effect for major cardiovascular events in participants with and without macrovascular disease (HR 1·00, 95% CI 0·89-1·13 vs HR 0·84, 95% CI 0·74-0·94, respectively; interaction p=0·04).				Targeting more intensive glucose lowering modestly reduced major macrovascular events and increased major hypoglycemia over 4·4 years in persons with type 2 diabetes. The analysis suggest that glucose-lowering regimes should be tailored to the individual.	Meta-Analysis		4
18539917	ACCORD Study Group, The 2008	Effects of intensive glucose lowering in type 2 diabetes	2008	Randomized Controlled Trial	USA, Canada	Clinical	Yes			To determine whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.	10251	Type 2 diabetes patients with established cardiovascular disease or cardiovascular disease risk factors.	Type 2 diabetes patient, age of at least 40 years with established cardiovascular disease or cardiovascular disease risk factors.	Mean age 62.2 years. Median HbA1c of 8.1%. 38% were women and 35% had had a previous cardiovascular event. 64% were white.	Intensive therapy 5128	Pharmacologic	Drug classes: Metformin, Secretagogue, Thiazolidinedione, alpha-glucosidase inhibitors, incretin, any insulin, any bolus insulin. Combination of classes without insulin and combination of classes with insulin.	5123	Standard therapy	The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.	At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval, 0.78 to 1.04; p=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46, p=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).	Yes for mortality in intensive-therapy group and hypoglycemia.	Hypoglycemia and mortality in intensive therapy group. Higher mortality in intensive therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow up.		As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. The findings identify a previously unrecognized harm of intensive glucose lowering in high risk patients with type 2 diabetes.	High		4
18539916	ADVANCE Collaborative Group, The 2008	Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes	2008	Randomized Controlled Trial	Australia	Clinical	Yes	5 years	5 years	To determine the effects of intensive glucose control on vascular outcomes.	11140	Type 2 diabetes patients	Diagnosis of type 2 diabetes mellitus at 30 years of age or older, an age of at least 55 years at the time of study entry, and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease.	Mean 66 years; Mean age when diabetes first diagnosed 58 years and an average duration of diabetes 8 years.	Baseline 5571 (7 were lost to follow up)	Pharmacologic	Gliclazide (modified release) plus other drugs as required to achieve HbA1c value of 6.5% or less.	5569 (10 were lost to follow up)	Standard glucose control	The primary study outcomes were composites of major macrovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy). assessed both jointly and separately.	After a median of 5 years of follow up, the mean HbA1c was lower in the intensive-control group (6.5%) than in the standard control group (7.3%). Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1% vs. 20% with standard control; hazard ratio, 0.90; 95% CI 0.82 to 0.98; p=0.01), as well as that of major microvascular events (9·4% vs. 10·9%; hazard ratio, 0.86; 95% CI, 0.77 to 0·97, p=0·01), primarily because of a reduction in the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0 79; 95% CI, 0.66 to 0 93, p=0.006), with no significant effect on retinopathy (p=0.50). There were no significant effects of the type of glucose control on major macrovascular events (hazard ratio with intensive control, 0.94; 95% CI 0.84 to 1.06; p=0.32), death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI 0.74 to 1.04; p=0.12), or death from any cause (hazard ratio with intensive control 0.93; 95% CI 0.83 to 1.06, p=0.28). Severe hypoglycemia, although uncommon, was more common in the intensive control group (2·7% vs. 1·5% in the standard control group; hazard ratio, 1.86; 95% CI 1.42 to 2.40; P<0.001)	Yes in reduction of incidence of combined major macrovascular and microvascular events and severe hypoglycemia.	Incidence of hypoglycemia in intensive control group.		A strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.	High		4; 7.1
18256393	Gaede 2008	Effect of a multifactorial intervention on mortality in type 2 diabetes	2008	Randomized Controlled Trial	Denmark	Clinical		7.8 years	13.3 years	To determine whether intervention involving tight glucose regulation and the use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents would have an effect on the rates of death from any cause and from cardiovascular causes in patients with type 2 diabetes and microalbuminuria.	160	Adults with type 2 diabetes and persistent microalbuminuria	Adults with type 2 diabetes and persistent microalbuminuria		80 (55)	Pharmacologic	Intensive therapy	80 (38)	Conventional therapy	Primary: Time to death from any cause. Secondary: death from cardiovascular causes and a composite of cardiovascular disease events that included death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, coronary-artery bypass grafting, percutaneous coronary intervention or revascularization for peripheral atherosclerotic arterial disease, and amputation because of ischemia. Tertiary: incident diabetic nephropathy or the development or progression of diabetic retionpathy or neuropathy.	24 patients in the intensive-therapy group died, as compared with 40 in the conventional therapy group (hazard ratio, 0.54; 95% CI 0.32-0.89; p=0.02). Intensive therapy was associated with a lower risk of death from cardiovascular causes (hazard ratio, 0.43; 95% CI, 0.19-0.94; p=0.04) and of cardiovascular events (hazard ratio, 0.41; 95% CI, 0.25-0.67;p<0.0001). One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with sixx patients in the coventional-therapy group (p=0.04). Fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI, 0.23-0.86; p=0.02). Few major side effects were reported.				In at-risk patients with type 2 diabetes, intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes.	High		4
18784091	Holman 2008b	10-year follow-up of intensive glucose control in type 2 diabetes.	2008	Observational	United Kingdom	Clinical			Post-trial monitoring for 5 years		3277	UKPDS patients		For patients with available data in final year of post-trial monitoring: age (62+/-8); male sex 58.5% and 76.1% white	1010 (baseline 2118) completed post-trial monitoring from sulfonylurea or insulin group; 379 (baseline 880) completed post-trial monitoring from primarily diet group and 136 from metformin group (279 baseline).		No attempts were made to maintain previously assigned therapies.			Diabetes related end points (sudden death, death from hyperglycemia or hypoglycemia, fatal or nonfatal myocardial infarction, angina, heart failure, fatal or nonfatal stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction), diabetes-related death (sudden death or death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycemia or hypoglycemia), death from any cause, myocardial infarction (sudden death or fatal or nonfatal infarction), stroke (fatal or nonfatal stroke), peripheral vascular disease (amputation of at least one digit or death from peripheral vascular disease), and microvascular disease (vitreous hemorrhage, retinal photocoagulation, or renal failure)	Between-group differences in glycated hemoglobin levels were lost after the first year. In the sulfonylurea-insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, p=0.04) and microvascular disease (24%, p=0.001), and risk reductions for myocardial infarction (15%, p=0.01) and death from any cause (13%, p=0.007) emerged over time, as more events occurred. In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, p=0.01), myocardial infarction (33%, p=0.005), and death from any cause (27%, P=0.002).				Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow up. A continued benefit after metformin therapy was evident among overweight patients.	Low		4
5.1 Nutrition Therapy																											
23364002	Ajala 2013	Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes	2013	Systematic review	USA			6 months to 4 years		Assess most suitable dietary interventions to induce weight loss, improve glycemic control and the weight profile.	A total of 20 RCTs with n=3703	type 2 diabetes mellitus		None of the included trials reported any significant differences in characteristics of participants in the intervention or treatment group. Four out of 20 studies included patients with and without diabete . All participants were 18 and older, and all but one study included both sexes.		Diets	Low carbohydrate, vegetarian, vegan, low glycemic-index (GI), high fiber, Mediterranean and high protein diets		low fat, high GI, American Diabetes Association, European Association for the study of Diabetes, and low protein diets.	HbA1c (glycemic control), difference in weight lost, and changes in HDL, LDL and triglycerides	The low- carbohydrate, low-GI, Mediterranean, and high-protein diets all led to a greater improvement in glycemic control [glycated hemoglobin reductions of 20.12% (P = 0.04), 20.14% (P = 0.008), 20.47% (P , 0.00001), and 20.28% (P , 0.00001), respectively] compared with their respective control diets, with the largest effect size seen in the Mediterranean diet. Low-carbohydrate and Mediterranean diets led to greater weight loss [20.69 kg (P = 0.21) and 21.84 kg (P , 0.00001), respectively], with an increase in HDL seen in all diets except the high-protein diet.	Significant findings			Low-carbohydrate, low-GI, Mediterranean, and high-protein diets are effective in improving various markers of cardio-vascular risk in people with diabetes.	Systematic Review	Nutrition Therapy/Carb Count	5.1
23432189	Estruch 2013	Primary prevention of cardiovascular disease with a Mediterranean diet	2013	Randomized Controlled Trial	Spain	Clinical		4.8 years	4.8 years	Effects of adherence to the Mediterranean diet and cardiovascular risk.	7447	participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment,	Eligible participants were men (55 to 80 years of age) and women (60 to 80 years of age) with no cardiovascular disease at enrollment, who had either type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated low-density lipoproteincholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature coronary heart dis- ease.	age range, 55 to 80 years; 57% were women.		Diet	Mediterranean Diet with EVOO and Mediterranean Diet with Nuts		control diet (advice to reduce dietary fat)	The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes).	A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.				Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events.	High	MUFA	5.1
21705068	Andrews 2011	Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial	2011	Randomized Controlled Trial	England	Clinical	Yes until patients had to see a dietitician	12 months	4 years	Effects of diet and physical activity on blood pressure and glucose concentrations.	593	Adults aged 30–80 years with type 2 diabetes diagnosis in previous 5–8 months	Eligible patients had been diagnosed within the previous 5–8 months and were older than 30 years at diagnosis.	Usual care (63% male, 97% white, mean age 59.5, married or with long-term partner 72%, smoker 8%); intensive dietary intervention (64% male, 96% white, mean age 60.1, married or with long-term partner 76%, smoker 24%); intensive dietary intervention and activity (66% male, 94% white, mean age 60.0, married or with long-term partner 78%, smoker 16%)	Intensive dietary intervention (n=248 at baseline; n=247 at follow up); intensive dietary intervention and activity (n=246 at baseline; n=243 at follow up)	Diet and physical activity	Intensive dietary intervention(dietary consultation every 3 months with monthly nurse support) and intensive dietary intervention and activity (dietary consultation every 3 months with monthly nurse support+pedmeter-based activity)	n=99 at baseline (n=97 at follow up)	Initial dietary consultation and follow up every 6 months	improvement in glycated haemoglobin A1c (HbA1c) concentration and blood pressure at 6 months	At 6 months, glycaemic control had worsened in the control group (mean baseline HbA1c percentage 6·72, SD 1·02, and at 6 months 6·86, 1·02) but improved in the diet group (baseline-adjusted difference in percentage of HbA1c –0·28%, 95% CI –0·46 to –0·10; p=0·005) and diet plus activity group (–0·33%, –0·51 to –0·14; p<0·001).	Not significant between diet and diet and activity on glycemic control. No significant differences in blood pressure in all 3 groups.			An intensive diet intervention can improve glycemic control. Addition of activity does not confer an additional benefit.	High	Nutritional Therapy	5.1

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
20843978	Azadbakht 2011	Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial	2011	Randomized Controlled Trial	Iran	Clinical	Nonblinded	8 weeks	Run-in period 3 weeks; intervention period 8 weeks; wash out period 4 weeks.	To determine the effects of the Dietary Approaches to Stop Hypertension (DASH) eating pattern on cardiometabolic risks in type 2 diabetic patients.	44	type 2 diabetes mellitus	Type 2 diabetes mellitus with some exclusionary criteria	Ofthe44participants,3 1 type 2 diabetic patients (13 male and 18 female) completed the entire crossover study (one patient was diagnosed with cancer and one with anemia, and eleven patients did not follow the study protocol)	n=44 (n=31)	Diet	DASH diet	n=44 (n=31)	The control diet included a macro-nutrient composition of 50–60% car-bohydrates, 15–20% protein, □30% total fat, and □5% of caloric intake from simple sugars	fasting blood glucose, A1C, weight, waist circumference, and lipid pro- files were the primary outcomes	After following the DASH eating pattern, body weight (P = 0.007) and waist circumference (P = 0.002) reduced significantly. Fasting blood glucose levels and A1C decreased after adoption of the DASH diet (-29.4 ± 6.3 mg/dl; P = 0.04 and -1.7 ± 0.1%, P = 0.04, respectively). After the DASH diet, the mean change for HDL cholesterol levels was higher (4.3 ± 0.9 mg/dl; P = 0.001) and LDL cholesterol was reduced (-17.2 ± 3.5 mg/dl; P = 0.02). Additionally, DASH had beneficial effects on systolic (-13.6 ± 3.5 vs. -3.1 ± 2.7 mmHg; P = 0.02) and diastolic blood pressure (-9.5 ± 2.6 vs. -0.7 ± 3.3 mmHg; P = 0.04).	Significant findings			Among diabetic patients, the DASH diet had beneficial effects on cardiometabolic risks.	High	Nutritional Therapy	5.1
20151996	Elhayany 2010	A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study	2010	Randomized Controlled Trial	Israel	Clinical		1 year	1 year	The effects of a low carbohydrate Mediterranean (LCM), a traditional Mediterranean (TM), and the 2003 American Diabetic Association (ADA) diet were compared, on health parameters during a 12-month period.	259	overweight type 2 diabetes	(i) age 30–65 years; (ii) DM2 diagnosed within 1–10years; (iii) body mass index (BMI) 27–34 kg/m2; (iv) last HbA1c measurement 7–10%; (v) last plasma TG level 1.8–4.5mmol/l; (vi) last serum creatinine <123.2 umol/l; and (vii) no change in diabetes medication for at least 3 months before entering the study. No (i) proliferative diabetic retinopathy; (ii) current insulin treatment; (iii) active oncologic or psychiatric disease; and (iv) uncontrolled hypothyroidism or hyperthyroidism.		ADA 85(55); TM 89(63); LCM 85(61)	Diet	Low carb Med (LCM), traditional Med, ADA diet			fasting plasma glucose, HbA1c and triglyceride (TG) levels.	194 patients out of 259 (74.9%) completed follow-up. After 12 months, the mean weight loss for all patients was 8.3 kg: 7.7 kg for ADA, 7.4 kg for TM and 10.1 kg for LCM diets. The reduction in HbA1c was significantly greater in the LCM diet than in the ADA diet (−2.0 and −1.6%, respectively, p < 0.022). HDL cholesterol increased (0.1 mmol/l ± 0.02) only on the LCM (p < 0.002). The reduction in serum TG was greater in the LCM (−1.3 mmol/l) and TM (−1.5 mmol/l) than in the ADA (−0.7 mmol/l), p = 0.001.				An intensive 12-month dietary intervention in a community-based setting was effective in improving most modifiable cardiovascular risk factors in all the dietary groups. Only the LCM improved HDL levels and was superior to both the ADA and TM in improving glycaemic control.	High	Nutritional Therapy	5.1
18957534	Brehm 2009	One-year comparison of a high–monounsaturated fat diet with a high-carbohydrate diet in type 2 diabetes	2009	Randomized Controlled Trial	USA	Clinical	Nonblinded	52 weeks	study 52 weeks plus extension study 18 months after completion of 1-year intervention	Compare the effects of high–monounsaturated fatty acid (MUFA) and high-carbohydrate (CHO) diets on body weight and glycemic control in men and women with type 2 diabetes.	124	Overweight/obese participants with type 2 diabetes	BMI of 27–40 kg/m2, age 30 –75 years, stable body weight for the preceding 6 months, diagnosis of type 2 diabetes for at least 6 months, A1C of 6.5–9.0%, and treatment by diet or oral agents only (no insulin).	A total of 124 overweight or obese indi- viduals (46 men and 78 women; 92 Cau- casians and 32 African Americans) age = 56.5 +/- 0.8 years, BMI = 35.9 +/- 0.3 kg/m2, and A1C = 7.3 +/- 0.1%	n=52 at follow up for high-CHO diet group and n=43 at follow up for high-MUFA diet group	Diet	High CHO and High MUFA diets			body weight, lean body mass, body fat, blood pressure, total cholesterol, tryglecerides, LDL, HDL, A1c, Glucose, insulin, HOMA-IR	Both groups had similar energy intake but a significant difference in MUFA intake. Both groups had similar weight loss over 1 year (-4.0 +/- 0.8 vs.-3.8 +/- 0.6 kg) and comparable improvement in body fat, waist circumference, diastolic blood pressure, HDL cholesterol, A1C, and fasting glucose and insulin. There were no differences in these parameters between the groups. A follow-up assessment of a subset of participants (n = 36) was conducted 18 months after completion of the 52-week diet. These participants maintained their weight loss and A1C during the follow-up period.				In individuals with type 2 diabetes, high-MUFA diets are an alternative to conventional lower-fat, high-CHO diets with comparable beneficial effects on body weight, body composition, cardiovascular risk factors, and glycemic control.	High	Nutritional Therapy	5.1
19721018	Esposito 2009	Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial	2009	Randomized Controlled Trial	Italy	Clinical	Partial			To compare the effects of a low-carbohydrate Mediterranean-style or a low-fat diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes.	215	Newly diagnosed type 2 diabetes	Inclusion criteria were age 30 to 75 years, body mass index (BMI) greater than 25 kg/m2, and hemoglobin A1c (HbA1c) level less than 11%. Participants also had to be sedentary (<1 hour of physical activity per week) with no evidence of participation in weight-reduction programs and with a stable weight (+/-2 kg) in the past 6 months.	Med diet age 52.4(11.2) and 50% male, low-fat diet age 51.9(10.7) and 48.5% male	Med diet 108(98); low fat diet 107(97)	Diet	Med diet and low fat diet			Start of antihyperglycemic drug therapy, defined by protocol as indicated for follow-up HbA1c level greater than 7% (primary outcome), and changes in weight, glycemic control, and coronary risk factors (secondary outcomes).	After 4 years, 44% of patients in the Mediterranean-style diet group and 70% in the low-fat diet group required treatment (absolute difference, -26.0 percentage points [95% CI, -31.1 to -20.1 percentage points]; hazard ratio, 0.63 [CI, 0.51 to 0.86]; hazard ratio adjusted for weight change, 0.70 [CI, 0.59 to 0.90]; P < 0.001). Participants assigned to the Mediterranean-style diet lost more weight and experienced greater improvements in some glycemic control and coronary risk measures than did those assigned to the low-fat diet.				Compared with a low-fat diet, a low-carbohydrate, Mediterranean-style diet led to more favorable changes in glycemic control and coronary risk factors and delayed the need for anti-hyperglycemic drug therapy in overweight patients with newly diagnosed type 2 diabetes.	Moderate	MUFA	5.1
22283392	Robbins 2008	Nutritionist Visits, Diabetes Classes, and Hospitalization Rates and Charges: the Urban Diabetes Study	2008	Cohort study-observational	USA				8 years 9 months	Association of different types of educational visits for diabetic patients of the 8 Philadelphia Health Care Centers (PHCCs), (public safety-net primary care clinics), with hospital admission rates and charges reported to the Pennsylvania Health Care Cost Containment Council.	18404	Diabetes patients								A total of 31,657 hospitalizations were recorded for 7,839 (42.6%) patients in the cohort. After adjustment for demographic variables, baseline comorbid conditions, hospitalizations prior to the diabetes diagnosis, and number of other primary care visits, having had any type of educational visit was associated with 9.18 fewer hospitalizations per 100 person years (95% confidence interval [CI] 5.02 to 13.33), and $11,571 less (95% CI $6,377 to $16,765) in hospital charges per person. Each nutritionist visit was associated with 4.70 fewer hospitalizations per 100 person years (95% CI 2.23 to 7.16) and a $6,503 reduction (95% CI $3,421 to $9,586) in total hospital charges.				Any type of educational visit was associated with lower hospitalization rates and charges. Nutritionist visits were more strongly associated with reduced hospitalizations than diabetes classes. Each nutritionist visit was associated with a substantial reduction in hospital charges, suggesting that providing these services in the primary care setting may be highly cost-effective for the health care system.	Low		5.1; 5.5
17381504	Brunerova 2007	A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and Type 2 diabetic patients	2007	Randomized Controlled Trial	Czech Republic		Nonblinded	3 months	3 months	Compare the influence of a hypocaloric, high-fat diet enriched with MUFA (M) and conventional diet (C) on weight loss and metabolic parameters in obese non-diabetic and obese Type 2 diabetic subjects over a 3-month period.	27 type 2 diabetes patients and 31 obese non-diabetic participants	Either obese non-diabetic (OB) subjects or Type 2 diabetic patients	Either obese non-diabetic (OB) subjects or Type 2 diabetic patients	Type 2 diabetes patients age 54.5 ± 3.5 years; obese non-diabetic 53.6 ± 3.5 years	baseline n=14 type 2 diabetes MUFA intervention and n=15 obese non-diabetic MUFA	Diet	MUFA diet	n baseline conventiona l diet in type 2 diabetes=13 and n=16 obese non-diabetic conventiona l diet	Conventional diet	body weight, waist–hip ratio, total body fat, levels of C-peptide, triglycerides and homeostasis model assessment (HOMA), fasting blood glucose, HbA1c, and HDL	After 3 months, body weight, waist-hip ratio, total body fat, levels of C-peptide, triglycerides and homeostasis model assessment (HOMA) decreased in all four groups (P < 0.01). However, fasting blood glucose and HbA1c decreased (P < 0.01) and high-density lipoprotein cholesterol increased significantly only in the type diabetes MUFA group (P < 0.05).		None reported		Individualized MUFA and Conventional diets were successful in improving meta-bolic and anthropometric parameters in both the obese non-diabetic and the Type 2 diabetic subjects. Although the superiority of the higher fat diet did not reach statistical significance, the decline in blood glucose and HbA1c in the Type 2 diabetic group on MUFA was encouraging.	Moderate	Nutritional Therapy	5.1
22449317	Nield 2007	Dietary advice for treatment of type 2 diabetes mellitus in adults (Review)	2007	Systematic review	United Kingdom					To assess the effects of type and frequency of different types of dietary advice for adults with type 2 diabetes.	1467	Adults with type 2 diabetes				Diet	Dietary advice			Efficacy of dietary advice on type 2 diabetes treatment	Thirty-six articles reporting a total of eighteen trials following 1467 participants were included. Dietary approaches assessed in this review were low-fat/high-carbohydrate diets, high-fat/low-carbohydrate diets, low-calorie (1000 kcal per day) and very-low-calorie (500 kcal per day) diets and modified fat diets. Two trials compared the American Diabetes Association exchange diet with a standard reduced fat diet and five studies assessed low-fat diets versus moderate fat or low-carbohydrate diets. Two studies assessed the effect of a very-low-calorie diet versus a low-calorie diet. Six studies compared dietary advice with dietary advice plus exercise and three other studies assessed dietary advice versus dietary advice plus behavioural approaches. The studies all measured weight and measures of glycaemic control although not all studies reported these in the articles published. Other outcomes which were measured in these studies included mortality, blood pressure, serum cholesterol (including LDL and HDL cholesterol), serum triglycerides, maximal exercise capacity and compliance. The results suggest that adoption of regular exercise is a good way to promote better glycaemic control in type 2 diabetic patients, however all of these studies were at high risk of bias.				There are no high quality data on the efficacy of the dietary treatment of type 2 diabetes, however the data available indicate that the adoption of exercise appears to improve glycated haemoglobin at six and twelve months in people with type 2 diabetes. There is an urgent need for well-designed studies which examine a range of interventions, at various points during follow-up, although there is a promising study currently underway.	Systematic Review	Nutritional Therapy	5.1
12821964	Ash 2003	Effect of intensive dietetic interventions on weight and glycaemic control in overweight men with Type II diabetes: a randomised trial	2003	Randomized Controlled Trial	Australia	Clinical	Nonblinded	12 weeks	12 weeks intervention period and a follow up visit after 18 months	To investigate the effectiveness of intensive innovative methods for implementing dietary prescriptions on weight management and glycaemic control in overweight men with Type II diabetes.	51	Overweight men with Type II diabetes	Subjects were included in the study if they had Type II diabetes, treated with oral hypoglycaemic agents or by diet alone, were less than 70 y of age and had a body mass index (BMI) between 25 and 40kg/m2.	A total of 51 men with Type II diabetes (mean age 54 y, mean body mass index (BMI) 31.7 kg/m2).	Baseline n=51; N at 12 weeks=51 and N=27 at 18 months	Diet	three isocaloric dietary intervention groups (intermittent energy restriction, pre-portioned meals and self-selected meals) each with weekly dietitian contact			Weight and glycemic control	For all subjects, intensive diet therapy over the 12-week intervention period resulted in a mean reduction in energy intake of 2360+/-2780 kJ/day (564+/-665 kcal/day) and significant reductions in weight (6.4+/-4.6 kg), waist circumference (8.1+/-4.6 cm), percent body fat (1.9+/-1.5%), HbA(1c) (1.0+/-1.4%) and triglyceride levels (0.3+/-0.6 mmol/l) compared to baseline levels. Intervention group did not affect clinical outcomes, with the exception of percent body fat. A total of 27 (52.9%) subjects attended the 18-month follow-up visit. At this visit, none of the improvements in clinical parameters was maintained, with all parameters returning to preintervention levels.	Significant			A dietary prescription of 6000–7000 kJ/day (1400–1700 kcal/day) was effective in achieving a 6% weight loss and improving glycaemic control.	Moderate	Nutritional Therapy/Weight	5.1; 5.3
23633321	He 2013	Effect of longer-term modest salt reduction on blood pressure	2013	Systematic review	United Kingdom, China					To assess 1) the effect of a longer-term modest reduction in salt intake on BP and whether there was a dose-response relationship; 2) the effect of BP by sex and ethnic group; 3) the effect on plasma renin activity, aldosterone, noradrenaline, adrenaline, cholesterol, LDL, HDL and triglycerides	3230													A modest reduction in salt intake for 4 or more weeks causes significant and from a population viewpoint important falls in BP in both hypertensive nad normotensive individuals, irrespective of sex and ethnic group. With salt reduction, there is a small physiological increase in plasma renin activity, aldosterone and noradrenaline. There is no significant change in lipid levels. These results provide further strong support for a reduction in population salt intake. This will likely lower population BP, and thereby reduce cardiovascular disease. Additionally, the analysis demonstrates a significant association between the reduction in 24-hr urinary sodium and the fall in systolic BP, indicating the greater the reduction in salt intake, the greater the fall in systolic BP. The current recommendations to reduce salt intake from 9-12 to 5-6 g/d will have a major effect on BP, but are not ideal. A further reduction to 3 g/d will have a greater effect and should become the long term target for population salt intake.	Systematic Review		5.1
22447019	Suckling 2010	Altered dietary salt intake for preventing and treating diabetic kidney disease	2010	Systematic review	United Kingdom					To evaluate the effect of altered salt intake on BP and markers of cardiovascular disease and DKD.	254	individuals with type 1 and type 2 diabetes									Thirteen studies (254 individuals) met our inclusion criteria. These included 75 individuals with type 1 diabetes and 158 individuals with type 2 diabetes. The median reduction in urinary sodium was 203 mmol/24 h (11.9 g/day) in type 1 diabetes and 125 mmol/ 24 h (7.3 g/day) in type 2 diabetes. The median duration of salt restriction was one week in both type 1 and type 2 diabetes. BP was reduced in both type 1 and type 2 diabetes. In type 1 diabetes (56 individuals), salt restriction reduced BP by -7.11/-3.13 mm Hg (systolic/diastolic); 95% CI: systolic BP (SBP) -9.13 to -5.10; diastolic BP (DBP) -4.28 to -1.98). In type 2 diabetes (56 individuals), salt restriction reduced BP by -6.90/-2.87 mm Hg (95% CI: SBP -9.84 to -3.95; DBP -4.39 to -1.35). There was a greater reduction in BP in normotensive patients, possibly due to a larger decrease in salt intake in this group.				Although the studies are not extensive, this meta-analysis shows a large fall in BP with salt restriction, similar to that of single drug therapy. All diabetics should consider reducing salt intake at least to less than 5-6 g/day in keeping with current recommendations for the general population and may consider lowering salt intake to lower levels, although further studies are needed.	Systematic Review	Nutritional Therapy	5.1
23364002	Ajala 2013	Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes	2013	Systematic review	USA			6 months to 4 years		Assess most suitable dietary interventions to induce weight loss, improve glycemic control and the weight profile.	A total of 20 RCTs with n=3703	type 2 diabetes mellitus		None of the included trials reported any significant differences in characteristics of participants in the intervention or treatment group. Four out of 20 studies included patients with and without diabete. All participants were 18 and older, and all but one study included both sexes.		Diets	Low carbohydrate, vegetarian, vegan, low glycemic-index (GI), high fiber, Mediterranean and high protein diets		low fat, high GI, American Diabetes Association, European Association for the study of Diabetes, and low protein diets.	HbA1c (glycemic control), difference in weight lost, and changes in HDL, LDL and triglycerides	The low- carbohydrate, low-GI, Mediterranean, and high-protein diets all led to a greater improvement in glycemic control [glycated hemoglobin reductions of 20.12% (P = 0.04), 20.14% (P = 0.008), 20.47% (P , 0.00001), and 20.28% (P , 0.00001), respectively] compared with their respective control diets, with the largest effect size seen in the Mediterranean diet. Low-carbohydrate and Mediterranean diets led to greater weight loss [20.69 kg (P = 0.21) and 21.84 kg (P , 0.00001), respectively], with an increase in HDL seen in all diets except the high-protein diet.	Significant findings			Low-carbohydrate, low-GI, Mediterranean, and high-protein diets are effective in improving various markers of cardio-vascular risk in people with diabetes.	Systematic Review	Nutrition Therapy/Carb Count	5.1
23432189	Estruch 2013	Primary prevention of cardiovascular disease with a Mediterranean diet	2013	Randomized Controlled Trial	Spain	Clinical		4.8 years	4.8 years	Effects of adherence to the Mediterranean diet and cardiovascular risk.	7447	participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment,	Eligible participants were men (55 to 80 years of age) and women (60 to 80 years of age) with no cardiovascular disease at enrollment, who had either type 2 diabetes mellitus or at least three of the following major risk factors: smoking, hypertension, elevated low-density lipoproteincholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature coronary heart dis- ease.			Diet	Mediterranean Diet with EVOO and Mediterranean Diet with Nuts		control diet (advice to reduce dietary fat)	The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes).	A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, ver- sus the control group (109 events). No diet-related adverse effects were reported.				Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events.	High	MUFA	5.1

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20843978	Azadbakht 2011	Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial	2011	Randomized Controlled Trial	Iran	Clinical	Nonblinded	8 weeks	Run-in period 3 weeks; intervention period 8 weeks; wash out period 4 weeks.	To determine the effects of the Dietary Approaches to Stop Hypertension (DASH) eating pattern on cardiometabolic risks in type 2 diabetic patients.	44	type 2 diabetes mellitus	Type 2 diabetes mellitus with some exclusionary criteria	Ofthe44participants,3 1 type 2 diabetic patients (13 male and 18 female) completed the entire crossover study (one patient was diagnosed with cancer and one with anemia, and eleven patients did not follow the study protocol)	n=44 (n=31)	Diet	DASH diet	n=44 (n=31)	The control diet included a macro-nutrient composition of 50–60% car-bohydrates, 15–20% protein, □30% total fat, and □5% of caloric intake from simple sugars	fasting blood glucose, A1C, weight, waist circumference, and lipid pro- files were the primary outcomes	After following the DASH eating pattern, body weight (P = 0.007) and waist circumference (P = 0.002) reduced significantly. Fasting blood glucose levels and A1C decreased after adoption of the DASH diet (-29.4 ± 6.3 mg/dl; P = 0.04 and -1.7 ± 0.1%; P = 0.04, respectively). After the DASH diet, the mean change for HDL cholesterol levels was higher (4.3 ± 0.9 mg/dl; P = 0.001) and LDL cholesterol was reduced (-17.2 ± 3.5 mg/dl; P = 0.02). Additionally, DASH had beneficial effects on systolic (-13.6 ± 3.5 vs. -3.1 ± 2.7 mmHg; P = 0.02) and diastolic blood pressure (-9.5 ± 2.6 vs. -0.7 ± 3.3 mmHg; P = 0.04).	Significant findings			Among diabetic patients, the DASH diet had beneficial effects on cardiometabolic risks.	High	Nutritional Therapy	5.1
22093544	Wiebe 2011	A systematic review on the effect of sweeteners on glycemic response and clinically relevant outcomes	2011	Systematic review	Canada					Effects of sweeteners on glycemic response and clinically relevant outcomes	1126	Diabetes patients									Of 3,666 citations, we identified 53 eligible randomized controlled trials with 1,126 participants. In diabetic participants, fructose reduced 2-hour blood glucose concentrations by 4.81 mmol/L (95% CI 3.29, 6.34) compared to glucose. Two-hour blood glucose concentration data comparing hypocaloric sweeteners to sucrose or high fructose corn syrup were inconclusive. Based on two ≥10-week trials, we found that non-caloric sweeteners reduced energy intake compared to the sucrose groups by approximately 250-500 kcal/day (95% CI 153, 806). One trial found that participants in the non-caloric sweetener group had a decrease in body mass index compared to an increase in body mass index in the sucrose group (-0.40 vs 0.50 kg/m2, and -1.00 vs 1.60 kg/m2, respectively). No randomized controlled trials showed that high fructose corn syrup or fructose increased levels of cholesterol relative to other sweeteners.				Considering the public health importance of obesity and its consequences; the clearly relevant role of diet in the pathogenesis and maintenance of obesity; and the billions of dollars spent on non-caloric sweeteners, little high-quality clinical research has been done. Studies are needed to determine the role of hypocaloric sweeteners in a wider population health strategy to prevent, reduce and manage obesity and its consequences.	Systematic Review		5.1
20151996	Elhayany 2010	A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study	2010	Randomized Controlled Trial	Israel	Clinical		1 year	1 year	The effects of a low carbohydrate Mediterranean (LCM), a traditional Mediterranean (TM), and the 2003 American Diabetic Association (ADA) diet were compared, on health parameters during a 12-month period.	259	overweight type 2 diabetes	(i) age 30–65 years; (ii) DM2 diagnosed within 1–10years; (iii) body mass index (BMI) 27–34 kg/m2; (iv) last HbA1c measurement 7–10%; (v) last plasma TG level 1.8–4.5mmol/l; (vi) last serum creatinine <123.2 μmol/l; and (vii) no change in diabetes medication for at least 3 months before entering the study. No (i) proliferative diabetic retinopathy; (ii) current insulin treatment; (iii) active oncologic or psychiatric disease; and (iv) uncontrolled hypothyroidism or hyperthyroidism.		ADA 85(55); TM 89(63); LCM 85(61)	Diet	Low carb Med (LCM), traditional Med, ADA diet			fasting plasma glucose, HbA1c and triglyceride (TG) levels.	194 patients out of 259 (74.9%) completed follow-up. After 12 months, the mean weight loss for all patients was 8.3 kg: 7.7 kg for ADA, 7.4 kg for TM and 10.1 kg for LCM diets. The reduction in HbA1c was significantly greater in the LCM diet than in the ADA diet (−2.0 and −1.6%, respectively, p < 0.022). HDL cholesterol increased (0.1 mmol/l ± 0.02) only on the LCM (p < 0.002). The reduction in serum TG was greater in the LCM (−1.3 mmol/l) and TM (−1.5 mmol/l) than in the ADA (−0.7 mmol/l), p = 0.001.				An intensive 12-month dietary intervention in a community-based setting was effective in improving most modifiable cardiovascular risk factors in all the dietary groups. Only the LCM improved HDL levels and was superior to both the ADA and TM in improving glycaemic control.	High	Nutritional Therapy	5.1
18957534	Brehm 2009	One-year comparison of a high-monosaturated fat diet with a high-carbohydrate diet in type 2 diabetes	2009	Randomized Controlled Trial	USA	Clinical	Nonblinded	52 weeks	study 52 weeks plus extension study 18 months after completion of 1-year intervention	Compare the effects of high–monounsaturated fatty acid (MUFA) and high-carbohydrate (CHO) diets on body weight and glycemic control in men and women with type 2 diabetes.	124	Overweight/obese participants with type 2 diabetes	BMI of 27– 40 kg/m2, age 30 –75 years, stable body weight for the preceding 6 months, diagnosis of type 2 diabetes for at least 6 months, A1C of 6.5–9.0%, and treatment by diet or oral agents only (no insulin).	A total of 124 overweight or obese indi- viduals (46 men and 78 women; 92 Cau- casians and 32 African Americans) age = 56.5 +/- 0.8 years, BMI = 35.9 +/- 0.3 kg/m2, and A1C = 7.3 +/- 0.1%	n=52 at follow up for high-CHO diet group and n=43 at follow up for high-MUFA diet group	Diet	High CHO and High MUFA diets			body weight, lean body mass, body fat, blood pressure, total cholesterol, tryglecerides, LDL, HDL, A1c, Glucose, insulin, HOMA-IR	Both groups had similar energy intake but a significant difference in MUFA intake. Both groups had similar weight loss over 1 year (-4.0 +/- 0.8 vs.-3.8 +/- 0.6 kg) and comparable improvement in body fat, waist circumference, diastolic blood pressure, HDL cholesterol, A1C, and fasting glucose and insulin. There were no differences in these parameters between the groups. A follow-up assessment of a subset of participants (n = 56) was conducted 18 months after completion of the 52-week diet. These participants maintained their weight loss and A1C during the follow-up period.				In individuals with type 2 diabetes, high-MUFA diets are an alternative to conventional lower-fat, high-CHO diets with comparable beneficial effects on body weight, body composition, cardiovascular risk factors, and glycemic control.	High	Nutritional Therapy	5.1
19721018	Esposito 2009	Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial	2009	Randomized Controlled Trial	Italy	Clinical	Partial			To compare the effects of a low-carbohydrate Mediterranean-style or a low-fat diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes.	215	Newly diagnosed type 2 diabetes	Inclusion criteria were age 30 to 75 years, body mass index (BMI) greater than 25 kg/m2, and hemoglobin A1c (HbA1c) level less than 11%. Participants also had to be sedentary (<1 hour of physical activity per week) with no evidence of participation in weight-reduction programs and with a stable weight (+/-2 kg) in the past 6 months.	Med diet age 52.4(11.2) and 50% male, low-fat diet age 51.9(10.7) and 48.5% male	Med diet 108(98); low fat diet 107(97)	Diet	Med diet and low fat diet			Start of antihyperglycemic drug therapy, defined by protocol as indicated for follow-up HbA1c level greater than 7% (primary outcome), and changes in weight, glycemic control, and coronary risk factors (secondary outcomes).	After 4 years, 44% of patients in the Mediterranean-style diet group and 70% in the low-fat diet group required treatment (absolute difference, -26.0 percentage points [95% CI, -31.1 to -20.1 percentage points]; hazard ratio, 0.63 [CI, 0.51 to 0.86]; hazard ratio adjusted for weight change, 0.70 [CI, 0.59 to 0.90]; P < 0.001). Participants assigned to the Mediterranean-style diet lost more weight and experienced greater improvements in some glycemic control and coronary risk measures than did those assigned to the low-fat diet.				Compared with a low-fat diet, a low-carbohydrate, Mediterranean-style diet led to more favorable changes in glycemic control and coronary risk factors and delayed the need for antihyperglycemic drug therapy in overweight patients with newly diagnosed type 2 diabetes.	Moderate	MUFA	5.1
19160276	Thomas 2009	Low glycaemic index, or low glycaemic load, diets for diabetes mellitus	2009	Systematic review	Australia					To assess the effects of low glycaemic index, or low glycaemic load, diets on glycaemic control in people with diabetes.	402	people with either type 1 or 2 diabetes mellitus, whose diabetes was not already optimally controlled.									Eleven relevant randomised controlled trials involving 402 participants were identified. There was a significant decrease in the glycated haemoglobin A1c (HbA1c) parallel group of trials, the weighted mean difference (WMD) was -0.5% with a 95% confidence interval (CI) of - 0.9 to -0.1, P = 0.02; and in the cross-over group of trials the WMD was -0.5% with a 95% CI of -1.0 to -0.1, P = 0.03. Episodes of hypoglycaemia were significantly fewer with low compared to high GI diet in one trial (difference of -0.8 episodes per patient per month, P < 0.01), and proportion of participants reporting more than 15 hyperglycaemic episodes per month was lower for low-GI diet compared to measured carbohydrate exchange diet in another study (35% versus 66%, P = 0.006). No study reported on mortality, morbidity or costs.				A low-GI diet can improve glycaemic control in diabetes without compromising hypoglycaemic events.	Systematic review	Nutritional Therapy	5.1
17381504	Brunerova 2007	A comparison of the influence of a high-fat diet enriched in monounsaturated fatty acids and conventional diet on weight loss and metabolic parameters in obese non-diabetic and Type 2 diabetic patients	2007	Randomized Controlled Trial	Czech Republic		Nonblinded	3 months	3 months	Compare the influence of a hypocaloric, high-fat diet enriched with MUFA (M) and conventional diet (C) on weight loss and metabolic parameters in obese non-diabetic and obese Type 2 diabetic subjects over a 3-month period.	27 type 2 diabetes patients and 31 obese non-diabetic participants	Either obese non-diabetic (OB) subjects or Type 2 diabetic patients	Either obese non-diabetic (OB) subjects or Type 2 diabetic patients	Type 2 diabetes patients age 54.5 ± 3.5 years; obese non-diabetic 53.6 ± 3.5 years	baseline n=14 type 2 diabetes MUFA intervention and n=15 obese non-diabetic MUFA	Diet	MUFA diet	n baseline conventiona l diet in type 2 diabetes=13 and n=16 obese non-diabetic conventiona l diet	Conventional diet	body weight, waist–hip ratio, total body fat, levels of C-peptide, triglycerides and homeostasis model assessment (HOMA), fasting blood glucose, HbA1c, and HDL	After 3 months, body weight, waist–hip ratio, total body fat, levels of C-peptide, triglycerides and homeostasis model assessment (HOMA) decreased in all four groups (P < 0.01). However, fasting blood glucose and HbA1c decreased (P < 0.01) and high-density lipoprotein cholesterol increased significantly only in the type diabetes MUFA group (P < 0.05).		None reported		Individualized MUFA and Conventional diets were successful in improving meta-bolic and anthropometric parameters in both the obese non-diabetic and the Type 2 diabetic subjects. Although the superiority of the higher fat diet did not reach statistical significance, the decline in blood glucose and HbA1c in the Type 2 diabetic group on MUFA was encouraging.	Moderate	Nutritional Therapy	5.1
22449317	Nield 2007	Dietary advice for treatment of type 2 diabetes mellitus in adults	2007	Systematic review	United Kingdom					To assess the effects of type and frequency of different types of dietary advice for adults with type 2 diabetes.	1467	Adults with type 2 diabetes				Diet	Dietary advice			Efficacy of dietary advice on type 2 diabetes treatment	Thirty-six articles reporting a total of eighteen trials following 1467 participants were included. Dietary approaches assessed in this review were low-fat/high-carbohydrate diets, high-fat/low-carbohydrate diets, low-calorie (1000 kcal per day) and very-low-caloric (500 kcal per day) diets and modified fat diets. Two trials compared the American Diabetes Association exchange diet with a standard reduced fat diet and five studies assessed low-fat diets versus moderate fat or low-carbohydrate diets. Two studies assessed the effect of a very-low-calorie diet versus a low-calorie diet. Six studies compared dietary advice with dietary advice plus exercise and three other studies assessed dietary advice versus dietary advice plus behavioural approaches. The studies all measured weight and measures of glycaemic control although not all studies reported these in the articles published. Other outcomes which were measured in these studies included mortality, blood pressure, serum cholesterol (including LDL and HDL cholesterol), serum triglycerides, maximal exercise capacity and compliance. The results suggest that adoption of regular exercise is a good way to promote better glycaemic control in type 2 diabetic patients, however all of these studies were at high risk of bias.				There are no high quality data on the efficacy of the dietary treatment of type 2 diabetes, however the data available indicate that the adoption of exercise appears to improve glycated haemoglobin at six and twelve months in people with type 2 diabetes. There is an urgent need for well-designed studies which examine a range of interventions, at various points during follow-up, although there is a promising study currently underway.	Systematic Review	Nutritional Therapy	5.1
5.2 Physical Activity																												
23012688	Gibbs 2014	Effect of improved fitness beyond weight loss on cardiovascular risk factors in individuals with type 2 diabetes in the Look AHEAD study.	2014	Randomized Controlled Trial				1 year	2 year	Investigate the extent to which increases in fitness explain cardiovascular risk factor improvements independent of weight loss in a lifestyle intervention.	4408	Adults with type 2 diabetes		41% male; 36% non-white; mean age 58.7+-6.8 years		Educational, behavioral	Intensive lifestyle intervention		Diabetes support and education	Glucose, HbA1c, HDL, triglycerides, diastolic blood pressure	Analyses included participants with fitness data and 1-year. Weight change alone improved R(2) for explaining changes in risk factors up to 8.2% in intensive lifestyle intervention group and 1.7% in control group. Fitness change alone improved R(2) up to 3.9% in IL1and 0.8% in DSE. After adjusting for weight change, fitness was independently associated (p<0.05) with improvements in R(2) for glucose (+0.7%), HbA1c (+1.1%), HDL cholesterol (+0.4%), and triglycerides (+0.1%) in DSE. Taken together, weight and fitness changes explained from 0.1-9.3% of the variability in cardiovascular risk factor changes.				Increased fitness explained statistically significant but small improvements in several cardiovascular risk factors beyond weight loss. Further research identifying other factors that explain cardiovascular risk factor change is needed.	High		5.2
23796131	Look AHEAD Research Group, The 2013	Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes	2013	Randomized Controlled Trial	USA					Examine whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among type 2 diabetes patients.	5145	overweight or obese patients with type 2 diabetes	Pa- tients were required to be 45 to 75 years of age and to meet all the following criteria: self-report- ed type 2 diabetes, as verified by the use of glu-cose-lowering medication, a physician's report, or glucose levels; a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25.0 or more (27.0 or greater in pa- tients taking insulin); a glycated hemoglobin level of 11% or less; a systolic blood pressure of less than 160 mm Hg; a diastolic blood pressure of less than 100 mm Hg; a triglyceride level of less than 600 mg per deciliter (6.77 mmol per liter); the ability to complete a valid maximal ex-ercise test, suggesting it was safe to exercise; and an established relationship with a primary care provider. Patients could be using any type of gla- cose-lowering medication, but the percentage of those receiving insulin allowed in the trial was limited to less than 30%.	Control group mean age (sd) 58.9+/-6.9, 59.7% female; intervention group mean age (sd) 58.6+/-6.8, 59.4% female			intensive lifestyle interven- tion that promoted weight loss through decreased caloric intake and increased physical activity		diabetes support and education	The primary outcome was a composite of death from cardiovascu- lar causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years.	The trial was stopped early on the basis of a futility analysis when the median fol- low-up was 9.6 years. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end). The intensive lifestyle intervention also produced greater reductions in gly- cated hemoglobin and greater initial improvements in fitness and all cardiovascu- lar risk factors, except for low-density-lipoprotein cholesterol levels. The primary outcome occurred in 403 patients in the intervention group and in 418 in the con- trol group (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09; P=0.51).				An intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes.	High		5.2; 5.3
21098771	Church 2010	Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial	2010	Randomized Controlled Trial	USA	Research	Staff were blinded to participant randomizatio n assignment	9 months	28 months	To examine the benefits of aerobic training alone, resistance training alone, and a combination of both on hemoglobin A1c (HbA1c) in individuals with type 2 diabetes.	262	Sedentary men and women with type 2 diabetes and HbA1c levels of 6.5% or higher	Sedentary 30- to 75-year-old adults with type 2 diabetes and HbA1c levels of 6.5% to 11.0%. No BMI of 48.0 or higher, blood pressure of 160/100 mm Hg or higher, fasting triglycerides 500 mg/dL or higher, use of an insulin pump, urine protein greater than 100 mg/dL, serum creatinine greater than 1.5 mg/dL, history of stroke, advanced neuropathy or retinopathy, or any serious medical condition that prevented participants from adhering to the protocol or exercising safely.	63.0% women and 47.3% nonwhite, participants who were a mean (SD) age of 55.8 (8.7) years, had a body mass index of 34.9 (5.9), had HbA1c level of 7.7% (1.0%), and duration of diabetes of 7.1 (5.5) years. There were 97.3% taking diabetes medications with 18.3% taking insulin. Many participants had a history of comorbidities. Baseline systolic blood pressure and LDL cholesterol were well controlled.	73 resistance training, 72 to aerobic exercise and 76 to combined aerobic and resistance training	Exercise	Resistance, aerobic and combination of two	41 at baseline (non-exercise group)		Change in HbA1c level. Secondary outcomes included measures of anthropometry and fitness.	Compared with the control group, the absolute mean change in HbA1c in the combination training exercise group was −0.34% (95% confidence interval [CI], −0.64% to −0.03%; P=.03). The mean changes in HbA1c were not statistically significant in either the resistance training (−0.16%; 95% CI, −0.46% to 0.15%; P=.32) or the aerobic (−0.24%; 95% CI, −0.55% to 0.07%; P=.14) groups compared with the control group. Only the combination exercise group improved maximum oxygen consumption (mean, 1.0 mL/kg per min; 95% CI, 0.5-1.5, P<.05) compared with the control group. All exercise groups reduced waist circumference from −1.9 to −2.8 cm compared with the control group. The resistance training group lost a mean of −1.4 kg fat mass (95% CI, −2.0 to −0.7 kg; P<.05) and combination training group lost a mean of −1.7 (−2.3 to −1.1 kg; P<.05) compared with the control group.				Among patients with type 2 diabetes mellitus, a combination of aerobic and resistance training compared with the nonexercise control group improved HbA1c levels. This was not achieved by aerobic or resistance training alone.	High	Exercise	5.2

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
	Li 2010	A population study on the association between leisure time physical activity and self-rated health among diabetics in Taiwan	2010	Observational	Taiwan	Survey				To explore the dose-response association between leisure time physical activity and self-rated health among diabetics in Taiwan.	797	Adult people with diabetes mellitus	A physician confirmed diagnosis of diabetes mellitus and age 18 years and above							Self-rated health status	Odds ratio (OR) for positive health was 2.51 (95% CI: 1.53-4.13), 1.62 (95% CI 0.93-2.84), and 1.35 (95% CI 0.77-2.37), for those with a total weekly energy expenditure of >=1000 kcal, between 500-999 kcal, and between 1 and 499 kcal, respectively, compared to inactive individuals. Those with duration over 10 years (OR 0.53, 95% CI 0.30-0.94), heart disease (OR 0.50, 95% CI 0.30-0.85), and dyslipidemia (OR 0.65, 95% CI 0.43-0.98) were less likely to have positive health than their counterparts. After stratified participants by duration, those with a duration of diabetes<6 years, the adjusted OR for positive health was 1.95 (95% CI 1.02-3.72), 1.22 (95% CI 0.59-2.52) and 1.19 (95% CI 0.58-2.41) for those with a total weekly energy expenditure of >=1000 kcal, between 500-999 kcal, and between 1 and 499 kcal, respectively, compared to inactive individuals. In participants with a duration of diabetes >=6 years, total energy expenditure showed a gradient effect on self-perceived positive health. The adjusted OR for positive health was 3.45 (95% CI 1.53-7.79), 2.77 (95% CI 1.11-6.92) and 1.90 (95% CI 0.73-4.94) for those with a total weekly energy expenditure of >=1000 kcal, between 500-999 kcal, and between 1 and 499 kcal, respectively compared to inactive individuals.				The results highlight that regular leisure activity with an energy expenditure of greater than 500kcal per week is associated with better self-rated health for those with longstanding diabetes.	Moderate		5.2
19878986	Diabetes Prevention Program Research Group 2009	10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study	2009	Randomized Controlled Trial	USA	Clinical	Metformin and placebo were double blinded	2.8 years	2.8 years trial, 1 year bridge period and 6 years followup	Lifestyle and meformin intervention effects on diabetes incidence, weight change, and cardiovascular disease risk factors and their treatment during10 years of follow-up since DPP randomisation.	3234	Diabetes Prevention Program trial participants		Mean age (sd) 55.2 (10.3)	n metformin 1073; n intensive lifestyle 1079 (metformin 746; intensive lifestyle 737)	Lifestyle and medication	intensive lifestyle; metformin	1082 (757)	Placebo	Diabetes incidence	During the 10·0-year (IQR 9·0–10·5) follow-up since randomisation to DPP trial, the original lifestyle group lost, then partly regained weight. The modest weight loss with metformin was maintained. Diabetes incidence rates during the DPP were 4·8 cases per 100 person-years (95% CI 4·1–5·7) in the intensive lifestyle intervention group, 7·8 (6·8–8·8) in the metformin group, and 11·0 (9·8–12·3) in the placebo group. Diabetes incidence rates in this follow-up study were similar between treatment groups: 5·9 per 100 person-years (5·1–6·8) for lifestyle, 4·9 (4·2–5·7) for metformin, and 5·6 (4·8–6·5) for placebo. Diabetes incidence in the 10 years since DPP randomi- sation was reduced by 34% (24–42) in the lifestyle group and 18% (7–28) in the metformin group compared with placebo.				During follow-up after DPP, incidences in the former placebo and metformin groups fell to equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the lifestyle group. Prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.	High	Weight Management	5.2; 5.3
23235674	Orozco 2008	Exercise or exercise and diet for preventing type 2 diabetes mellitus	2008	Systematic review	Spain, Germany					To assess the effects of exercise or exercise and diet for preventing type 2 diabetes mellitus.	2241	persons at risk for type 2 diabetes								diabetes incidence in people at risk for type 2 diabetes	We included eight trials that had an exercise plus diet (2241 participants) and a standard recommendation arm (2509 participants). Two studies had a diet only (167 participants) and exercise only arm (178 participants). Study duration ranged from one to six years. Overall, exercise plus diet interventions reduced the risk of diabetes compared with standard recommendations (RR 0.63, 95% CI 0.49 to 0.79). This had also favourable effects on weight and body mass index reduction, waist-to-hip ratio and waist circumference. However, statistical heterogeneity was very high for these outcomes. Exercise and diet interventions had a very modest effect on blood lipids. However, this intervention improved systolic and diastolic blood pressure levels (weighted mean difference -4 mmHg, 95% CI -5 to - 2 and -2 mmHg, 95% CI -3 to -1, respectively). No statistical significant effects on diabetes incidence were observed when comparing exercise only interventions either with standard recommendations or with diet only interventions. No study reported relevant data on diabetes and cardiovascular related morbidity, mortality and quality of life.				Interventions aimed at increasing exercise combined with diet are able to decrease the incidence of type 2 diabetes mellitus in high risk groups (people with impaired glucose tolerance or the metabolic syndrome). There is a need for studies exploring exercise only interventions and studies exploring the effect of exercise and diet on quality of life, morbidity and mortality, with special focus on cardiovascular outcomes.	Systematic Review	Exercise	5.2
16855995	Thomas 2006	Exercise for type 2 diabetes mellitus	2006	Systematic review	Australia					To assess the effects of exercise in type 2 diabetes mellitus.	377	type 2 diabetes									Fourteen randomised controlled trials comparing exercise against no exercise in type 2 diabetes were identified involving 377 participants. Trials ranged from eight weeks to twelve months duration. Compared with the control, the exercise intervention significantly improved glycaemic control as indicated by a decrease in glycated haemoglobin levels of 0.6% (-0.6 % HbA1c , 95% confidence interval (CI) -0.9 to -0.3; P < 0.05). This result is both statistically and clinically significant. There was no significant difference between groups in whole body mass, probably due to an increase in fat free mass (muscle) with exercise, as reported in one trial (6.3 kg, 95% CI 0.0 to 12.6).There was a reduction in visceral adipose tissue with exercise (-45.5 cm2, 95% CI -63.8 to -27.3), and subcutaneous adipose tissue also decreased. No study reported adverse effects in the exercise group or diabetic complications. The exercise intervention significantly increased insulin response (131 AUC, 95% CI 20 to 242) (one trial), and decreased plasma triglycerides (-0.25 mmol/L, 95% CI -0.48 to -0.02). No significant difference was found between groups in quality of life (one trial), plasma cholesterol or blood pressure.				The meta-analysis shows that exercise significantly improves glycaemic control and reduces visceral adipose tissue and plasma triglycerides, but not plasma cholesterol, in people with type 2 diabetes, even without weight loss.	Systematic review	Exercise	5.2
16084803	Cauza 2005	The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus	2005	Randomized Controlled Trial	Austria	Large public tertiary hospital	Nonblinded	4-months	19 months randomizati on and 4-months intervention	To compare the effects of a 4-month strength training (ST) versus aerobic endurance training (ET) program on metabolic control, muscle strength, and cardiovascular endurance in subjects with type 2 diabetes mellitus (T2D).	43	Type 2 diabetes patients	Patients between the ages of 50 and 70 years with type 2 diabetes	22 men mean age 56.5+/-0.9 years and 21 women mean age 57.4+/-0.9 years	ST baseline 22 and ET baseline 17	Exercise	Strength training (ST) and aerobic endurance training (ET)			Metabolic control, muscle strength, and cardiovascular endurance	A significant decline in HbA1c was only observed in the ST group (8.3%±1.7% to 7.1%±0.2%, P=.001). Blood glucose (204±16mg/dL to 147±8mg/dL, P<.001) and insulin resistance (9.11±1.51 to 7.15±1.15, P=.04) improved significantly in the ST group, whereas no significant changes were observed in the ET group. Baseline levels of total cholesterol (207±8mg/dL to 184±7mg/dL, P<.001), low-density lipoprotein cholesterol (120±8mg/dL to 106±8mg/dL, P=.001), and triglyceride levels (229±25mg/dL to 150±15mg/dL, P=.001) were significantly reduced and high-density lipoprotein cholesterol (43±3mg/dL to 48±2mg/dL, P=.004) was significantly increased in the ST group; in contrast, no such changes were seen in the ET group.				ST was more effective than ET in improving glycemic control.	Low	Exercise	5.2
16625575	Sigal 2004	Physical Activity/Exercise and Type 2 Diabetes	2004	Technical Review	Canada, USA																				Low	Exercise	5.2
12453982	Castaneda 2002	A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes	2002	Randomized Controlled Trial	USA	Research clinical	Nonblinded	16 weeks	16 weeks	To determine the efficacy of high-intensity progressive resistance training (PRT) on glycemic control in older adults with type 2 diabetes.	62	Latino older adults	Diabetes diagnosis,no myocardial infarction (within past 6 months) and any unstable chronic condition, no current participation in resistance training	age about 66 years in both groups; PRT group female to male ratio 21/10 and control group ratio 19/12; BMI 30.9 (1.1) in PRT and 31.0 (1.0) in control group	n=31 (n=29)	Exercise	resistance training plus usual care	n=31(n=31)	Usual care	Glycemic and metabolic control; body composition, physical activity, muscle strength	Sixteen weeks of PRT (three times per week) resulted in reduced plasma glyco-sylated hemoglobin levels (from 8.7 +/- 0.3 to 7.6 +/- 0.2%), increased muscle glycogen stores (from 60.3 +/- 3.9 to 79.1 +/- 5.0 mmol glucose/kg muscle), and reduced the dose of prescribed diabetes medication in 72% of exercisers compared with the control group, P = 0.004 – 0.05. Control subjects showed no change in glycosylated hemoglobin, a reduction in muscle glycogen (from 61.4 +/- 7.7 to 47.2 +/- 6.7 mmol glucose/kg muscle), and a 42% increase in diabetes medications. PRT subjects versus control subjects also increased lean mass (+1.2 +/- 0.2 vs. -0.1 +/- 0.1 kg), reduced systolic blood pressure (-9.7 +/- 1.6 vs. +7.7 +/- 1.9 mmHg), and decreased trunk fat mass (-0.7 +/- 0.1 vs. +0.8 +/-0.1 kg; P = 0.01– 0.05).	Yes			PRT as an adjunct to standard of care is feasible an deffective in improving glycemic control and some of the abnormalities associated with the metabolic syndrome among high-risk older adults with type 2 diabetes.	High	Exercise	5.2
12351469	Dunstan 2002	High-intensity resistance training improves glycemic control in older patients with type 2 diabetes	2002	Randomized Controlled Trial	Australia	Clinical		6-months	6-months	To examine the effect of high-intensity progressive resistance training combined with moderate weight loss on glycemic control and body composition in older patients with type 2 diabetes.	36	Sedentary, overweight men and women with type 2 diabetes, aged 60 – 80 years	Men and women, aged between 60 and 80 years, with treated (diet and/or medication) type 2 diabetes. Subjects were overweight (BMI >27 kg/m2 and <=40 kg/ m2), were sedentary (no strength training and <150 min of brisk walking/moderate exercise per week and <60 min of vigorous exercise per week in the preceding 6 months), had established (>6 months) but not optimally controlled type 2 diabetes (HbA1c range 7–10%), were not taking insulin, and were nonsmokers.	RT&WL group mean (sd) age 67.6(5.2 M/F) ratio 10/6; WL group 66.9(5.3), M/F ratio 6/7	19 (16)	Exercise	high-intensity progressive resistance training plus moderate weight loss (RT & WL group)	17(13)	moderate weight loss plus a control program (WL group)	HbA1c, body weight, fat mass, fasting glucose, insulin, lipid profile, resting blood pressure	HbA1c fell significantly more in RT & WL than WL at 3 months (0.6 +/- 0.7 vs. 0.07 +/- 0.8%, P < 0.05) and 6 months (1.2 +/- 1.0 vs. 0.4 +/- 0.8%, P < 0.05). Similar reductions inbodyweight(RT&WL:2.5+/-2.9vs.WL3.1+/-2.1kg) and fat mass(RT&WL:2.4+/-2.7vs. WL 2.7 +/- 2.5 kg) were observed after 6 months. In contrast, lean body mass (LBM) increased in the RT & WL group (0.5 +/- 1.1 kg) and decreased in the WL group (0.4 +/- 1.0) after 6 months (P < 0.05). There were no between-group differences for fasting glucose, insulin, serum lipids and lipoproteins, or resting blood pressure.				High-intensity progressive resistance training, in combination with moderate weight loss, was effective in improving glycemic control in older patients with type 2 diabetes. Additional benefits of improved muscular strength and LBM identify high-intensity resistance training as a feasible and effective component in the management program for older patients with type 2 diabetes.	High	Exercise	5.2
11559268	Boule 2001	Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials	2001	Meta-Analysis	Canada			>=8weeks	Articles from databases up to and including December 2000	To systematically review and quantify the effect of exercise on HbA1c and body mass in patients with type 2 diabetes.		type 2 diabetes mellitus				Exercise	12 studies with aerobic training intervention, 2 resistance training studies			Effects of exercise trainining on HbA1c and body mass	HbA1c was lower in the exercise groups compared to control groups (7.65% vs. 8.31%, p<0.001); Body mass index difference between exercise groups and control groups (83.02kg vs. 82.48kg, p=0.76)	Significant effect on HbA1c, no significant effect on body mass				Meta-analysis	Exercise	5.2
5.3 Weight Management																											
23796131	Look AHEAD Research Group, The 2013	Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes	2013	Randomized Controlled Trial	USA					Examine whether an intensive lifestyle intervention for weight loss would decrease cardiovascular morbidity and mortality among type 2 diabetes patients.	5145	overweight or obese patients with type 2 diabetes	Pa- tients were required to be 45 to 75 years of age and to meet all the following criteria: self-report- ed type 2 diabetes, as verified by the use of glu-cose-lowering medication, a physician's report, or glucose levels; a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25.0 or more (27.0 or greater in pa- tients taking insulin); a glycated hemoglobin level of 11% or less; a systolic blood pressure of less than 160 mm Hg; a diastolic blood pressure of less than 100 mm Hg; a triglyceride level of less than 600 mg per deciliter (6.77 mmol per liter); the ability to complete a valid maximal ex-ercise test, suggesting it was safe to exercise; and an established relationship with a primary care provider. Patients could be using any type of glu- cose-lowering medication, but the percentage of those receiving insulin allowed in the trial was limited to less than 30%.	C ontrol group mean age (sd) 58.9+/-6.9, 59.7% female; intervention group mean age (sd) 58.6+/-6.8, 59.4% female			intensive lifestyle interven- tion that promoted weight loss through decreased caloric intake and increased physical activity		diabetes support and education	The primary outcome was a composite of death from cardiovascu- lar causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years.	The trial was stopped early on the basis of a futility analysis when the median follow-up was 9.6 years. Weight loss was greater in the intervention group than in the control group throughout the study (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end). The intensive lifestyle intervention also produced greater reductions in gly- cated hemoglobin and greater initial improvements in fitness and all cardiovascu- lar risk factors, except for low-density-lipoprotein cholesterol levels. The primary outcome occurred in 403 patients in the intervention group and in 418 in the control group (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09; P=0.51).				An intensive lifestyle intervention focusing on weight loss did not reduce the rate of cardiovascular events in overweight or obese adults with type 2 diabetes.	High		5.2; 5.3
19272486	Buchwald 2009	Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis	2009	Systematic review	USA					Determine the impact of bariatric surgery on type 2 diabetes in association with the procedure performed and the weight reduction achieved.	621 studies with 888 treatment arms and 135,246 patients	Type 2 diabetes with bariatric surgery		At baseline, the mean age was 40.2 years, body mass index was 47.9 kg/m2, 80% were female, and 10.5% had previous bariatric procedures.		Bariatric surgery	Bariatric surgery			Weight loss and diabetes improvement/resolution	Meta-analysis of weight loss overall was 38.5 kg or 55.9% excess body weight loss. Overall, 78.1% of diabetic patients had complete resolution, and diabetes was improved or resolved in 86.6% of patients. Weight loss and diabetes resolution were greatest for patients undergoing biliopancreatic diversion/duodenal switch, followed by gastric bypass, and least for banding procedures. Insulin levels declined significantly postoperatively, as did hemoglobin A1c and fasting glucose values. Weight and diabetes parameters showed little difference at less than 2 years and at 2 years or more.				The clinical and laboratory manifestations of type 2 diabetes are resolved or improved in the greater majority of patients after bariatric surgery; these responses are more pronounced in procedures associated with a greater percentage of excess body weight loss and is maintained for 2 years or more.	Systematic Review	Weight Management	5.3; 5.4
19878986	Diabetes Prevention Program Research Group 2009	10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study	2009	Randomized Controlled Trial	USA	Clinical	Metformin and placebo were double blinded	2.8 years	2.8 years trial, 1 year bridge period and 6 years followup	Lifestyle and meformin intervention effects on diabetes incidence, weight change, and cardiovascular disease risk factors and their treatment during10 years of follow-up since DPP randomisation.	3234	Diabetes Prevention Program trial participants		Mean age (sd) 55.2 (10.3)	n metformin 1073; n intensive lifestyle 1079 (metformin 746; intensive lifestyle 737)	Lifestyle and medication	intensive lifestyle; metformin	1082 (757)	Placebo	Diabetes incidence	During the 10·0-year (IQR 9·0–10·5) follow-up since randomisation to DPP trial, the original lifestyle group lost, then partly regained weight. The modest weight loss with metformin was maintained. Diabetes incidence rates during the DPP were 4·8 cases per 100 person-years (95% CI 4·1–5·7) in the intensive lifestyle intervention group, 7·8 (6·8–8·8) in the metformin group, and 11·0 (9·8–12·3) in the placebo group. Diabetes incidence rates in this follow-up study were similar between treatment groups: 5·9 per 100 person-years (5·1–6·8) for lifestyle, 4·9 (4·2–5·7) for metformin, and 5·6 (4·8–6·5) for placebo. Diabetes incidence in the 10 years since DPP randomi- sation was reduced by 34% (24–42) in the lifestyle group and 18% (7–28) in the metformin group compared with placebo.				During follow-up after DPP, incidences in the former placebo and metformin groups fell to equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the lifestyle group. Prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.	High	Weight Management	5.2; 5.3

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
15846748	Norris 2005	Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus.	2005	Systematic review	USA					The objective of the review was to assess the effectiveness of lifestyle and behavioral weight loss and weight control interventions for adults with type 2 diabetes.	4659	Adults with type 2 diabetes									The 22 studies of weight loss intervention identified had a 4659 participants and follow up of 1 to 5 years. The pooled weight loss for any intervention in comparison to usual care among 585 subjects was 1.7kg (95% CI 0.3 to 3.2), or 3.1% of baseline body weight among 517 subjects. Other main comparisons demonstrated non significant results: among 126 persons receiving a physical activity and behavioral intervention, those who also received a very low calorie diet lost 3.0kg (95% CI -0.5 to 6.4), or 1.6% of baseline body weight, more than persons receiving a low-calorie diet. Among 53 participants receiving identical dietary and behavioral interventions, those receiving more intense physical activity interventions lost 3.9kg (95% CI -1.9 to 9.7) or 3.6% of baseline body weight, more than those receiving a less intense or no physical activity intervention. Comparison groups often achieved significant weight loss (up to 10.0kg), minimizing between-group differences. Changes in glycated hemoglobin generally corresponded to changes in weight and were not significant when between-group differences were examined. No data identified on quality of life and mortality.				Weight loss strategies using dietary, physical activity, or behavioral interventions produced small between-group improvements in weight. These results were minimized by weight loss in the comparison group, however, and examination of individual study arms revealed that multicomponent interventions including very low calorie diets or low calorie diets may hold promise for achieving weight loss in adults with type 2 diabetes.	Systematic Review		5.3
12821964	Ash 2003	Effect of intensive dietetic interventions on weight and glycaemic control in overweight men with Type II diabetes: a randomised trial	2003	Randomized Controlled Trial	Australia	Clinical	Nonblinded	12 weeks	12 weeks intervention period and a follow up visit after 18 months	To investigate the effectiveness of intensive innovative methods for implementing dietary prescriptions on weight management and glycaemic control in overweight men with Type II diabetes.	51	Overweight men with Type II diabetes	Subjects were included in the study if they had Type II diabetes, treated with oral hypoglycaemic agents or by diet alone, were less than 70 y of age and had a body mass index (BMI) between 25 and 40kg/m2.	A total of 51 men with Type II diabetes (mean age 54 y, mean body mass index (BMI) 31.7 kg/m2).	Baseline n=51; N at 12 weeks=51 and N=27 at 18 months	Diet	three isocaloric dietary intervention groups (intermittent energy restriction, pre-portioned meals and self-selected meals) each with weekly dietitian contact			Weight and glycemic control	For all subjects, intensive diet therapy over the 12-week intervention period resulted in a mean reduction in energy intake of 2360+/-2780 kJ/day (564+/-665 kcal/day) and significant reductions in weight (6.4+/-4.6 kg), waist circumference (8.1+/-4.6 cm), percent body fat (1.9+/-1.5%), HbA1(c) (1.0+/-1.4%) and triglyceride levels (0.3+/-0.6 mmol/l) compared to baseline levels. Intervention group did not affect clinical outcomes, with the exception of percent body fat. A total of 27 (52.9%) subjects attended the 18-month follow-up visit. At this visit, none of the improvements in clinical parameters was maintained, with all parameters returning to preintervention levels.	Significant			A dietary prescription of 6000–7000 kJ/day (1400–1700 kcal/day) was effective in achieving a 6% weight loss and improving glycaemic control.	Moderate	Nutritional Therapy/Weight	5.1; 5.3
5.4 Bariatric Surgery																											
23736733	Ikramuddin 2013	Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial	2013	Randomized Controlled Trial	USA, Taiwan	Hospital	None	12-month	12-month	To compare Roux-en-Y gastric bypass with lifestyle and intensive medical management to achieve control of comorbid risk factors.	120	participants who had a hemoglobin A1c (HbA1c) level of 8.0% or higher, body mass index (BMI) between 30.0 and 39.9, C peptide level of more than 1.0 ng/mL, and type 2 diabetes for at least 6 months	Patients were included if they were aged 30 through 67 years, under a physician's care for type 2 diabetes for at least 6 months before recruitment, had hemo- globin A1c (HbA1c) levels of 8.0% or higher at the time of entry, and had a serum C-peptide level higher than 1.0 ng/mL 90 minutes after a liquid mixed meal. Participants had a BMI of 30.0 to 39.9 and were willing to accept randomization to either treatment group and follow the full treatment protocol. Additional criteria included the absence of conditions that would contraindi- cate surgery, such as serious cardiovas- cular disease, previous gastrointesti- nal surgery, psychological concerns, or history of malignancy.	Lifestyle and Medical Management mean age(SD) 49(8) and 57% women; Roux-en-Y Gastric Bypass 49(9) and 63% women.Par- ticipants had diabetes for an average of 9.0 years (95% CI, 7.9-10.0 years) at en-rollment. Mean (SD) BMI was 34.6 (3.1) with 71 participants (59%) hav- ing a BMI of less than 35. Mean (SD) HbA1c was 9.6%	60(57)	Surgical, diet, exercise	Roux-en-Y Gastric Bypass and lifestyle and intensive medical management	60(57)	lifestyle and intensive medical management only	Composite goal of HbA1c less than 7.0%, low- density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mm Hg.	All 120 patients received the intensive lifestyle-medical management pro- tocol and 60 were randomly assigned to undergo Roux-en-Y gastric bypass. After 12-months, 28 participants (49%; 95% CI, 36%-63%) in the gastric bypass group and 11 (19%, 95% CI, 10%-32%) in the lifestyle-medical management group achieved the primary end points (odds ratio [OR], 4.8; 95% CI, 1.9-11.7). Participants in the gastric bypass group required 3.0 fewer medications (mean, 1.7 vs 4.8; 95% CI for the difference, 2.3-3.6) and lost 26.1% vs 7.9% of their initial body weigh compared with the lifestyle-medical management group (difference, 17.5%; 95% CI, 14.2%- 20.7%). Regression analyses indicated that achieving the composite end point was primarily attributable to weight loss. There were 22 serious adverse events in the gastric bypass group, including 1 cardiovascular event, and 15 in the lifestyle-medical management group. There were 4 perioperative complications and 6 late postoperative complications. The gastric bypass group experienced more nutritional deficiency than the lifestyle-medical management group.		There were 22 serious adverse events in the gas- tric bypass group and 15 in the lifestyle- medical management group. There were 4 perioperative complications and 6 late postoperative complications in the gastric bypass group.		In mild to moderately obese patients with type 2 diabetes, adding gastric bypass surgery to lifestyle and medical management was associated with a greater likelihood of achieving the composite goal. Potential benefits of adding gastric bypass surgery to the best lifestyle and medical management strategies of diabetes must be weighed against the risk of serious adverse events.	High	Bariatric Surgery	5.4
22723580	Cohen 2012	Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity	2012	Cohort study-observational	Brazil	Hospital			6-year follow up	Determine the long-term impact of Roux-en-Y gastric bypass (RYGB) on patients with diabetes and only class I obesity.	66	Type 2 diabetes patients with BMI 30–35 kg/m2 and underwent RYGB	type 2 diabetes and a BMI of 30–34.9 kg/m2, who elected to undergo RYGB. No diabetes as a secondary disease, drug or alcohol addiction, recent vascular event, internal malignancy, portal hypertension, inability to cooperate in long-term follow-up, poor understanding of the operation, or unreal- istic expectations of outcomes or mental impairment	40 men and 26 women, mean age was 47 6 12 years (range 31–63), and all were white.	n=66 (100% follow up)	Prospective follow up-cohort study	Roux-en-Y gastric bypass (RYGB)			Safety and the percentage of patients experiencing diabetes remission (HbA1c ,6.5% without diabetes medication).	For up to 6 years following RYGB, durable diabetes remission occurred in 88% of cases, with glycemic improvement in 11%. Mean HbA1c fell from 9.7 6 1.5 to 5.9 6 0.1% (P , 0.001), despite diabetes medication cessation in the majority. Weight loss failed to correlate with several measures of improved glucose homeostasis, consistent with weight-independent antidiabetes mechanisms of RYGB. C-peptide responses to glucose increased substantially, suggesting im-proved b-cell function. There was no mortality, major surgical morbidity, or excessive weight loss. Hypertension and dyslipidemia also improved, yielding 50–84% reductions in predicted 10-year cardiovascular disease risk of fatal and nonfatal coronary heart disease and stroke.				RYGB safely and effectively ameliorated diabetes and associated comorbidities, reducing cardiovascular risk, in patients with a BMI of only 30–35 kg/m2.	Low	Bariatric Surgery	5.4
21975321	Dorman 2012	Case-matched outcomes in bariatric surgery for treatment of type 2 diabetes in the morbidly obese patient	2012	Case-control study-observational	USA	University of Minnesota Bariatric Surgery Database				To compare the relative efficacy of medical management, the duodenal switch (DS), and the laparoscopic adjustable gastric band (LAGB) to the Roux-en-Y gastric bypass (RYGB) for treatment of type 2 diabetes mellitus (T2DM).	N=29 (non-surgical controls); N=30 (LAGB) and N=27 (DS)	patients with T2DM who had un- dergone bariatric surgery with a body mass index (BMI) greater than 35 kg/m2 between 2001 and 2008.	patients with T2DM who had un-dergone bariatric surgery with a body mass index (BMI) greater than 35 kg/m2 between 2001 and 2008.						Weight loss, HbA1c normalization, and medication score reduction	The Roux-en-Y gastric bypass produced greater weight loss, HbA1C normalization, and medication score reduction compared to both NSC and LAGB-matched cohorts. Duodenal switch produced greater reductions in HbA1C and medication score than RYGB, despite no greater weight loss at 1 year. Surgical complications were rarely life threatening.				After 1 year of follow-up, RYGB is superior to NSC and LAGB with respect to weight loss and improvement in diabetes whereas DS is superior to RYGB in reducing HbA1C and medication score.	Low	Bariatric Surgery	5.4
22258959	Mingrone 2012	Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes	2012	Randomized Controlled Trial	Italy	Clinical	None	2 years	2 years	To assess the effects of bariatric surgery vs conventional therapy for type 2 diabetes.	60	Patients between the ages of 30 and 60 years with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 35 or more, a history of at least 5 years of diabetes, and a glycated hemoglobin level of 7.0% or more	Inclusion criteria were an age of 30 to 60 years, a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 35 or more, a history of type 2 diabetes of at least 5 years, a glycated hemoglobin level of 7.0% or more (as confirmed by at least three analyses), and an ability to understand and comply with the study protocol. Exclusion criteria were a history of type 1 dia- betes, diabetes secondary to a specific disease or glucocorticoid therapy, previous bariatric surgery, pregnancy, other medical conditions requiring short-term hospitalization, severe diabetes com- plications, other severe medical conditions, and geographic inaccessibility.	Medical Therapy mean age 43.45+/-7.27; Biliopancreatic diversion 42.75+/-8.06; Gastric Bypass 43.90+/-7.57	biliopancreatic diversion 20(19); Roux-en-Y gastric bypass 20(19)	Surgical	gastric bypass or biliopancreatic diversion	20(18)	conventional medical therapy	The primary end point was the rate of diabetes remission at 2 years (defined as a fasting glucose level of <100 mg per deciliter [5.6 mmol per liter] and a glycated hemoglobin level of <6.5% in the absence of pharmacologic therapy).Secondary end points were changes from base- line in levels of fasting plasma glucose and gly- cated hemoglobin, the average glycated hemo-globin level, body weight, waist circumference, arterial blood pressure, and levels of plasma cholesterol, HDL cholesterol, and triglycerides at 2 years.	At 2 years, diabetes remission had occurred in no patients in the medical-therapy group versus 75% in the gastric-bypass group and 95% in the biliopancreatic-diversion group (P<0.001 for both comparisons). Age, sex, baseline BMI, duration of diabetes, and weight changes were not significant predictors of diabetes remission at 2 years or of improvement in glycemia at 1 and 3 months. At 2 years, the average baseline glycated hemoglobin level (8.65±1.45%) had decreased in all groups, but patients in the two surgical groups had the greatest degree of improvement (average glycated hemoglobin levels, 7.69±0.57% in the medical-therapy group, 6.35±1.42% in the gastric-bypass group, and 4.95±0.49% in the biliopancreatic-diversion group).				In severely obese patients with type 2 diabetes, bariatric surgery resulted in better glucose control than did medical therapy. Preoperative BMI and weight loss did not predict the improvement in hyperglycemia after these procedures.	Moderate	Bariatric Surgery	5.4
23797426	Schauer 2012	Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes	2012	Randomized Controlled Trial	USA	Clinical	None	12 months	12 months	Evaluate the efficacy of intensive medical therapy alone versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy	150	obese patients with uncontrolled type 2 diabetes	Eligibility criteria were an age of 20 to 60 years, a diagnosis of type 2 diabetes(glycated hemoglobin level, >7.0%), and a BMI of 27 to 43. Patients were excluded if they had undergone previous bar- iatric surgery or other complex abdominal surgery or had poorly controlled medical or psychiatric disorders.	The mean (±SD) age of the patients was 49±8 years, and 66% were women. The average glycated hemoglobin level was 9.2±1.5%.	Of the 150 patients, 93% completed 12 months of follow-up.					The primary end point was the proportion of patients with a glycated hemoglobin level of 6.0% or less 12 months after treatment.	The proportion of patients with the primary end point was 12% (5 of 41 patients) in the medical- therapy group versus 42% (21 of 50 patients) in the gastric-bypass group (P=0.002) and 37% (18 of 49 patients) in the sleeve-gastrectomy group (P=0.008). Glycemic control improved in all three groups, with a mean glycated hemoglobin level of 7.5±1.8% in the medical-therapy group, 6.4±0.9% in the gastric-bypass group (P=0.001), and 6.6±1.0% in the sleeve-gastrectomy group (P=0.003). Weight loss was greater in the gastric-bypass group and sleeve-gastrectomy group (−29.4±9.0 kg and −25.1±8.5 kg, respectively) than in the medical-therapy group (−5.4±8.0 kg) (P<0.001 for both com- parisons). The use of drugs to lower glucose, lipid, and blood-pressure levels decreased significantly after both surgical procedures but increased in patients receiving medical therapy only. The index for homeostasis model assessment of insulin resistance (HOMA-IR) improved significantly after bariatric surgery. Four patients underwent reoperation. There were no deaths or life-threatening complications.				In obese patients with uncontrolled type 2 diabetes, 12 months of medical therapy plus bariatric surgery achieved glycemic control in significantly more patients than medical therapy alone. Further study will be necessary to assess the durability of these results.	High	Bariatric Surgery	5.4
22470429	Maciejewski 2011	Survival Among High-Risk Patients After Bariatric Surgery	2011	Cohort study-observational	USA	Clinical		the mean follow-up was 6.7 years	6years and 11 months	To determine whether bariatric surgery is associated with reduced mortality in a multisite cohort of predominantly older male patients who have a high baseline mortality rate.	850 who had bariatric surgery and 41 244 nonsurgical con- trols	Patients with bariatric surgeries		850 veterans who had bariatric surgery in January 2000 to December 2006 (mean age 49.5 years; SD 8.3; mean body mass index [BMI] 47.4; SD 7.8); 41 244 nonsurgical con- trols (mean age 54.7 years, SD 10.2; mean BMI 42.0, SD 5.0)					All-causemortalitythrough December2008.	Among patients who had bariatric surgery, the 1-, 2-, and 6-year crude mor-tality rates were, respectively, 1.5%, 2.2%, and 6.8% compared with 2.2%, 4.6%, and 15.2% for nonsurgical controls. In unadjusted Cox regression, bariatric surgery was associated with reduced mortality (hazard ratio [HR], 0.64; 95% confidence in- terval [CI], 0.51-0.80). After covariate adjustment, bariatric surgery remained associ- ated with reduced mortality (HR, 0.80; 95% CI, 0.63-0.995). In analysis of 1694 pro- pensity-matched patients, bariatric surgery was no longer significantly associated with reduced mortality in unadjusted (HR, 0.83; 95% CI, 0.61-1.14) and time-adjusted (HR, 0.94; 95% CI, 0.64-1.39) Cox regressions.				In propensity score–adjusted analyses of older severely obese patients with high baseline mortality in Veterans Affairs medical centers, the use of bariatric surgery compared with usual care was not associated with decreased mortality during a mean 6.7 years of follow-up.	Low	Bariatric Surgery	5.4
20805271	Hoerger 2010	Cost-effectiveness of bariatric surgery for severely obese adults with diabetes	2010	Cost-effectiveness	USA	NHANES survey				To analyze the cost-effectiveness of bariatric surgery in severely obese (BMI >or=35 kg/m(2)) adults who have diabetes, using a validated diabetes cost-effectiveness model.			The population with BMI>=35 kg/m2 and diabetes.			Surgical	gastric bypass surgery		usual diabetes care		In all analyses, bariatric surgery increased QALYs and increased costs. Bypass surgery had cost-effectiveness ratios of $7,000/QALY and $12,000/QALY for severely obese patients with newly diagnosed and established diabetes, respectively. Banding surgery had cost-effectiveness ratios of $11,000/QALY and $13,000/QALY for the respective groups. In sensitivity analyses, the cost-effectiveness ratios were most affected by assumptions about the direct gain in QoL from BMI loss following surgery.				Our analysis indicates that gastric bypass and gastric banding are cost-effective methods of reducing mortality and diabetes complications in severely obese adults with diabetes.	Low	Bariatric Surgery	5.4
21666276	Makary 2010	Medication Utilization and Annual Health Care Costs in Patients With Type 2 Diabetes Mellitus Before and After Bariatric Surgery	2010	Cross-sectional study-observational	USA				3 years and 11 months	To examine the relationship of bariatric surgery with the use of diabetes medications and with total health care costs in patients with type 2 diabetes mellitus.	2235	adults with type 2 diabetes and commercial health insurance who underwent bariatric sur- gery in the United States during a 4-year period from Janu- ary 1, 2002, through December 31, 2005.							Medication Utilization and Annual Health Care Costs	Surgery was associated with elimination of diabetes medication therapy in 1669 of 2235 patients (74.7%) at 6 months, 1489 of 1847 (80.6%) at 1 year, and 906 of 1072 (84.5%) at 2 years after surgery. Reduction of use was observed in all classes of diabetes medications. The median cost of the surgical procedure and hospitalization was $29 959. In the 3 years following surgery, total annual health care costs per person increased by 9.7% ($616) in year 1 but then decreased by 34.2% ($2179) in year 2 and by 70.5% ($4498) in year 3 compared with a preoperative annual cost of $6376 observed from 1 to 2 years before surgery.				Bariatric surgery is associated with reduc-tions in the use of medication and in overall health care costs in patients with type 2 diabetes. Health insurance should cover bariatric surgery because of its health and cost benefits.	Low	Bariatric Surgery	5.4
19272486	Buchwald 2009	Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis	2009	Systematic review	USA					Determine the impact of bariatric surgery on type 2 diabetes in association with the procedure performed and the weight reduction achieved.	621 studies with 888 treatment arms and 135,246 patients	Type 2 diabetes with bariatric surgery		At baseline, the mean age was 40.2 years, body mass index was 47.9 kg/m2, 80% were female, and 10.5% had previous bariatric procedures.		Bariatric surgery	Bariatric surgery			Weight loss and diabetes improvement/resolution	Meta-analysis of weight loss overall was 38.5 kg or 55.9% excess body weight loss. Overall, 78.1% of diabetic patients had complete resolution, and diabetes was improved or resolved in 86.6% of patients. Weight loss and diabetes resolution were greatest for patients undergoing biliopancreatic diversion/duodenal switch, followed by gastric bypass, and least for banding procedures. Insulin levels declined significantly postoperatively, as did hemoglobin A1c and fasting glucose values. Weight and diabetes parameters showed little difference at less than 2 years and at 2 years or more.				The clinical and laboratory manifestations of type 2 diabetes are resolved or improved in the greater majority of patients after bariatric surgery; these responses are more pronounced in procedures associated with a greater percentage of excess body weight loss and is maintained for 2 years or more.	Systematic Review	Weight Management	5.3; 5.4
5.5 General Diabetes Self-Management and Education																											
	Guicciardi 2014	Type 2 diabetes mellitus, physical activity, exercise self-efficacy, and body satisfaction: an application of the transtheoretical model in older adults	2014	Observational cross-sectional	Italy					To predict levels of physical activity based on exercise self-efficacy and body satisfaction	308	Type 2 diabetes patients		172 males, 136 females, mean age 65.24+/-8.31 years. Diabetes duration 9.47+/-8.21 years					Insulin (n=96), diet (n=31), oral hypoglycaemic agents (n=164), or other combination (n=17).	Exercise self-efficacy was measured with the Exercise self-efficacy scale; Body satisfaction was measured with the Silhouette-Matching Task. Stage of change for physical activity was assessed by asking participants to read a definition of regular physical activity. Physical activity was measured by asking participants to agree with the definition of regular PA of the American College of Sports Medicine/Centers for Disease Control and Prevention and indicating accordingly their weekly duration of physical activity (minutes).	Exercise self-efficacy increases linearly from precontemplation to maintenance stage, while body satisfaction shows an inverted U shape. However, only stages of change, other than exercise self-efficacy, add a significant and noticeable contribution to prediction levels of PA.				This evidence claims a tailored approach to PA in older adults with T2DM and advises behavioral health interventions based on exercise self-efficacy.	Low		5.5
23597082	Lakerveld 2013	Motivational interviewing and problem solving treatment to reduce type 2 diabetes and cardiovascular disease risk in real life: a randomized controlled trial	2013	Randomized Controlled Trial	Netherlands	Clinical	The research assistants, the principal investigator and the general practitioners were blinded to group assignment.	12-months	12-months	Assess the effectiveness of a primary care based lifestyle intervention to reduce the estimated risk of developing T2DM and for CVD mortality, and to motivate changes in lifestyle behaviors.	622	30-50 years old type 2 diabetes	30-50 years old with type 2 diabetes, self- administered waist-circumference (≥101 cm for men and ≥87 cm for women).	Control group mean age (sd) 43.4(5.5), 60.1% female; Intervention group 43.6(5.1), 56.7% female	314 at baseline, 267 at 6 months and 249 at 12 months		Motivational interviewing and problem solving	308 at baseline, 269 at 6 months follow up and 253 at 12 months follow up	Existing health brochures	Primary outcomes was the estimated diabetes risk according to the formula of the Atherosclerosis Risk In Communities (ARIC) Study, and the estimated risk for CVD mortality according to the Systematic COronary Risk Evaluation (SCORE) formula. Secondary outcomes included lifestyle behavior (diet, physical activity and smoking).	536 (86.2%) of the 622 participants (age 43.5 years) completed the 6-month follow-up, and 502 (81.2%) completed the 12-month follow-up. The mean baseline T2DM risk was 18.9% (SD 8.2) and the mean CVD mortality risk was 3.8% (SD 3.0). The intervention group participated in a median of 2 sessions. Intention-to-treat analyses showed no significant differences in outcomes between the two groups at 6 or 12-months follow-up.				The lifestyle intervention was not more effective than health brochures in reducing risk scores for T2DM and CVD or improving lifestyle behavior in an at-risk population.	Moderate	Motivational Interviewing	5.5

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
18646086	Pal 2013	Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus	2013	Systematic review	United Kingdom					To assess the effects on health status and health-related quality of life of computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus.	3578	Adults with type 2 diabetes								health status and health-related quality of life of computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus.				Computer-based diabetes self-management interventions to manage type 2 diabetes appear to have a small beneficial effect on blood glucose control and the effect was larger in the mobile phone subgroup. There is no evidence to show benefits in other biological outcomes or any cognitive, behavioural or emotional outcomes.	Systematic Review	Self Management	5.5
23073967	Thorpe 2013	Facilitating healthy coping in patients with diabetes: a systematic review	2013	Systematic review	USA					The purpose of this study is to summarize recent literature on approaches to supporting healthy coping in diabetes in 2 specific areas: (1) the impact of different approaches to diabetes treatment on healthy coping and (2) the effectiveness of interventions specifically designed to support healthy coping.	129 articles published August 1, 2006 – April 30, 2011										Evidence suggests that treatment choice may significantly influence quality of life, with treatment intensification in response to poor metabolic control often improving quality of life. The recent literature provides support for a variety of healthy coping interventions in diverse populations, including diabetes self-management education, support groups, problem-solving approaches, and coping skills interventions for improving a range of outcomes. Cognitive Behavior Therapy and collaborative care for treating depression, and family therapy for improving coping in youths.				Healthy coping in diabetes has received substantial attention in the past five years. A variety of approaches show positive results. Research is needed to compare effectiveness of different approaches in different populations and determine how to overcome barriers to intervention dissemination and implementation.	Systematic review	DSME	5.5
22824531	Steinsbekk 2012	Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis	2012	Systematic review	Norway					Assess effects of group-based DSME compared to routine treatment on clinical, lifestyle and psychosocial outcomes in type-2 diabetes patients.	2833	type 2 diabetes					Group-based Diabetes self-management education (DSME)									Group-based DSME in people with type 2 diabetes results in improvements in clinical, lifestyle and psychosocial outcomes.	Systematic review	DSME	5.5
22683130	Tricco 2012	Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis	2012	Systematic review	Canada					Assess the effects of QI strategies on glycated haemoglobin (HbA(1c)), vascular risk management, microvascular complication monitoring, and smoking cessation in patients with diabetes.	84865	patients with diabetes									We reviewed 48 cluster randomised controlled trials, including 2538 clusters and 84865 patients, and 94 patient randomised controlled trials, including 38 664 patients. In random effects meta-analysis, the QI strategies reduced HbA1c by a mean difference of 0·37% (95% CI 0·28–0·45; 120 trials), LDL cholesterol by 0·10 mmol/L (0·05–0·14; 47 trials), systolic blood pressure by 3·13 mm Hg (2·19–4·06, 65 trials), and diastolic blood pressure by 1·55 mm Hg (0·95–2·15, 61 trials) versus usual care. We noted larger effects when baseline concentrations were greater than 8·0% for HbA1c, 2·59 mmol/L for LDL cholesterol, and 80 mm Hg for diastolic and 140 mm Hg for systolic blood pressure. The effectiveness of QI strategies varied depending on baseline HbA1c control. QI strategies increased the likelihood that patients received aspirin (11 trials; relative risk [RR] 1·33, 95% CI 1·21–1·45), antihypertensive drugs (ten trials; RR 1·17, 1·01–1·37), and screening for retinopathy (23 trials; RR 1·22, 1·13–1·32), renal function (14 trials; RR 128, 1·13–1·44), and foot abnormalities (22 trials; RR 1·27, 1·16–1·39). However, statin use (ten trials; RR 1·12, 0·99–1·28), hypertension control (18 trials; RR 1·01, 0·96–1·07), and smoking cessation (13 trials; RR 1·13, 0·99–1·29) were not significantly increased.				Many trials of QI strategies showed improvements in diabetes care. Interventions targeting the system of chronic disease management along with patient-mediated QI strategies should be an important component of interventions aimed at improving diabetes management. Interventions solely targeting health-care professionals seem to be beneficial only if baseline HbA1c control is poor.	Systematic review	DSME	5.5
22116473	Tshiananga 2012	The effect of nurse-led diabetes self-management education on glycosylated hemoglobin and cardiovascular risk factors: a meta-analysis	2012	Meta-Analysis	Switzerland, Germany					The purpose of this meta-analysis was to determine the effect of nurse-led diabetes self-management education (DSME) on blood glucose control and cardiovascular risk factors.	5993			Mean patient age was 52.8 years, 47% were male, and mean A1C at baseline was 8.5%.						Mean change in A1C was a reduction by −0.70% for nurse-led DSME versus −0.21% with usual care (UC). This corresponded to an effect size of 0.506, using a random-effects model for nurse-led DSME versus UC. Effect size was significantly associated with patient age older than 65 years and with duration of follow-up. Nurse-led DSME was also associated with improvements in cardiovascular risk factors, particularly among male patients, among those with good glycemic control, and in studies conducted in the United States.				Nurse-led DSME is associated with improved glycemic control, demonstrating that programs are most effective among seniors and with follow-up periods of 1 to 6 months. Future programs tailored to the needs of patients younger than 65 years may improve the impact of DSME on blood glucose.	Meta-analysis	DSME	5.5
16520473	Radhakrishnan 2011	The efficacy of tailored interventions for self-management outcomes of type 2 diabetes, hypertension or heart disease: a systematic review	2011	Systematic review	USA					To evaluate the evidence on the effectiveness of tailored interventions on self-management behaviours in individuals with heart disease, hypertension or type 2 diabetes.		individuals with heart disease, hypertension or type 2 diabetes.					self- management behaviours in individuals with heart disease, hypertension or type 2 diabetes.				Ten studies were included in the review. Tailored interventions had no impact on self-management activities such as medication adherence, self-monitoring, exercise, smoking, or diet control. However, tailored interventions were modestly successful in improving specific self-management behaviours of dietary fat intake, levels of physical activity or screening. Studies included in the review generally suffered from compromised methodological issues of inadequately powered sample size, non-blinding of data collection or intervention delivery and inadequate reporting of the randomization process.				When cost and resource utilization is taken into consideration, tailored interventions may not be more effective than standard interventions in improving self-management behaviours in individuals with long-term conditions. Future research should explore the effect of robust and resource-optimized tailored interventions on self-management outcomes for long-term conditions with high-quality trials.	Systematic Review		5.5
20729270	Gillett 2010	Delivering the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cost effectiveness analysis.	2010	Cost-effectiveness	United Kingdom	Primary care trusts			12 months	To assess the long term clinical and cost effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) intervention compared with usual care in people with newly diagnosed type 2 diabetes.		Patients with newly diagnosed type 2 diabetes.		Mean age 61 years +/- 12. 26% male, 97% white			A six hour structured group education program delivered in the community by two professional health care educators.		Incremental costs and quality adjusted life years (QALYs) gained.	On the basis of the data in the trial, the estimated mean incremental lifetime cost per person receiving the DESMOND intervention is $326 (95% CI -$1098 to $1773); the incremental gain in QALYs per person is 0.0392 (-0.0813 to 0.1786), and the mean incremental cost per QALY is 5387 pounds. Using "real world" intervention costs, the lifetime incremental cost of the DESMOND intervention is 82 pounds (-831 pounds to 1010 pounds) and the mean incremental cost per QALY gained is 2092 pounds. A probabilistic sensitivity analysis indicated that the likelihood that the DESMOND program is cost effective at a threshold of 20000 pounds per QALY is 66% using trial based intervention costs and 70% using "real world" costs. Results from a one way sensitivity analysis suggest that the DESMOND intervention is cost effective even under more modest assumptions that include the effects of the intervention being lost after one year.				The results suggest that the DESMOND intervention is likely to be cost effective compared with usual care, especially with respect to the real world cost of the intervention to primary care trusts, with reductions in weight and smoking being the main benefits delivered.	Cost-Effectiveness Analysis		5.5
19878986	Deakin 2009	Group based training for self-management strategies in people with type 2 diabetes mellitus	2009	Systematic review	United Kingdom					To assess the effects of group-based, patient-centred training on clinical, lifestyle and psychosocial outcomes in people with type 2 diabetes.	14 publications describing 11 studies involving 1532 participants	Type 2 diabetes							HbA1c, fasting glucose, body weight, systolic blood pressure, improved diabetes knowledge	Fourteen publications describing 11 studies were included involving 1532 participants. The results of the meta-analyses in favour of group-based diabetes education programmes were reduced glycated haemoglobin at four to six months (1.4%; 95% confidence interval (CI) 0.8 to 1.9; P < 0.00001), at 12-14 months (0.8%; 95% CI 0.7 to 1.0; P < 0.00001) and two years (1.0%; 95% CI 0.5 to 1.4; P< 0.00001); reduced fasting blood glucose levels at 12 months (1.2 mmol/L; 95% CI 0.7 to 1.6; P < 0.00001); reduced body weight at 12-14 months (1.6 Kg; 95% CI 0.3 to 3.0; P = 0.02); improved diabetes knowledge at 12-14 months (SMD 1.0; 95% CI 0.7 to 1.2; P < 0.00001) and reduced systolic blood pressure at four to six months (5 mmHg: 95% CI 1 to 10; P = 0.01). There was also a reduced need for diabetes medication (odds ratio 11.8, 95% CI 5.2 to 26.9; P < 0.00001; RD = 0.2; NNT = 5). Therefore, for every five patients attending a group-based education programme expect one patient to reduce diabetes medication.				Group-based training for self-management strategies in people with type 2 diabetes is effective by improving fasting blood glucose levels, glycated haemoglobin and diabetes knowledge and reducing systolic blood pressure levels, body weight and the requirement for diabetes medication.	Systematic Review	Self Management	5.5
19160249	Duke 2009	Individual patient education for people with type 2 diabetes mellitus	2009	Systematic review	Australia	Clinical				To evaluate the effectiveness of individual patient education on metabolic control, diabetes knowledge and psychosocial outcomes.	1359	Adults with Type 2 diabetes mellitus				Education	Individual face to face patient education		Usual care, routine treatment or group education	Glycemic control, Blood pressure and BMI	Individua face to face education did not signficantly improve glycemic control (Weight Mean Difference in HbA1c -0.1% (95% CI -0.3-0.1, P=0.33)) over a 12 to 18 month period. For those patients with a higher mean baseline HbA1c>8% (3 studies), there was signficant benefit on glycemic control (WMD -0.3% 95%CI -0.5, -0.1,P=0.007). No signficant difference in glycemic control between individual or group education at 12 to 18 month with a WMD in HbA1c of 0.03% (95% CI -0.02,0.1, P=0.22). There was no signficiant difference in the impact of individual versus usual care or group education on body mass index systolic or diastolic blood pressure.				This systematic review suggests a benefit of individual education on glycemic control when compared with usual care in a subgroup of those with baseline HbA1c >8%. However, overall there did not appear to a significant difference between individual education and usual care. In the small number of studies comparing group and individual education, there was an equal impact on HbA1c at 12 to 18 months.	Systematic Review		5.5
22283392	Robbins 2008	Nutritionist Visits, Diabetes Classes, and Hospitalization Rates and Charges: the Urban Diabetes Study	2008	Cohort study-observational	USA				8 years 9 months	Association of different types of educational visits for diabetic patients of the 8 Philadelphia Health Care Centers (PHCCs), (public safety-net primary care clinics), with hospital admission rates and charges reported to the Pennsylvania Health Care Cost Containment Council.	18404	Diabetes patients									A total of 31,657 hospitalizations were recorded for 7,839 (42.6%) patients in the cohort. After adjustment for demographic variables, baseline comorbid conditions, hospitalizations prior to the diabetes diagnosis, and number of other primary care visits, having had any type of educational visit was associated with 9.18 fewer hospitalizations per 100 person years (95% confidence interval [CI] 5.02 to 13.33), and $11,571 less (95% CI $6,377 to $16,765) in hospital charges per person. Each nutritionist visit was associated with 4.70 fewer hospitalizations per 100 person years (95% CI 2.23 to 7.16) and a $6,503 reduction (95% CI $3,421 to $9,586) in total hospital charges.				Any type of educational visit was associated with lower hospitalization rates and charges. Nutritionist visits were more strongly associated with reduced hospitalizations than diabetes classes. Each nutritionist visit was associated with a substantial reduction in hospital charges, suggesting that providing these services in the primary care setting may be highly cost-effective for the health care system.	Low		5.1; 5.5
16627396	Siminerio 2006a	Implementing Diabetes self-managemet training programs: breaking through the barriers in primary care.	2006	Reference	USA																				Low		5.5
15451933	Siminerio 2006b	Deploying the Chronic Care Model to Implement and Sustain Diabetes Self-management Training Programs	2006	Quality Improvement Study	USA			1 year 6 months	1 year 6 months	Evaluate the utility of using the 6 elements of the chronic care model (CCM; health system, community, decision support, self-management support, clinical information sys- tems, and delivery system design) to implement and financially sustain an effective diabetes self-manage- ment training (DSMT) program.	4190	Diabetes patients					the utility of using the 6 elements of the chronic care model (CCM; health system, community, decision support, self-management support, clinical information sys- tems, and delivery system design)				Using elements of the CCM, the researchers were able to gain administrative support; expand the number of rec- ognized programs from 3 to 21; cover costs through increased reimbursement; reduce hemoglobin A1C levels (P < .0001), and increase the proportion of patients receiving DSMT through delivery in primary care (26.4% suburban; 19.8% urban) versus hospital-based practices (8.3%; P < .0001).				The CCM serves as an effective model for implementing and sustaining DSMT programs.	Low		5.5
16554429	Siminerio 2005	Implementing the Chronic Care Model for Improvements in Diabetes Care and Education in a Rural Primary Care Practice	2005	Quality Improvement Study	USA					Determine the impact of implementing elements of the chronic care model (CCM; decision support, self-management, and delivery system redesign) on providers' diabetes care practices and patient outcomes in a rural practice setting.	104	type 2 diabetes		age 67+/-8.1, 64.7% male							Provider adherence to ADA Standards of Care increased significantly across all process measures. Patients who received DSME at point of service in the primary care practice setting gained improvements in knowledge, empowerment, A1C, and high-density lipoprotein cholesterol levels.				Implementing systems to support decision support, self-management education, and delivery system redesign has a positive influence on practices and patient outcomes in outlying rural communities.	Low		5.5

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
12854339	Gary 2003	Meta-Analysis of Randomized Educational and Behavioral Interventions in Type 2 Diabetes	2003	Meta-analysis of Randomized Controlled Trials	USA			1-19 months		Effect of educational and behavioral interventions on body weight and glycemic control in type 2 diabetes.	2720	Type 2 diabetes patients				Educational, behavioral				body weight, glycemic control	Glycohemoglobin was reduced by a mean of 0.43%. When stratified by quality score, glycohemoglobin was -0.50% and -0.38% for studies with high and low quality scores, respectively. When weighting studies by sample size, fasting blood glucose was reduced by 24 mg/dL and weight by 3 lbs.				Previous educational and behavioral interventions in type 2 diabetes have produced modest improvements in glycemic control.	Meta-analysis		5.5
6. Metformin																												
22870408	Al-Shareef 2012	Clinical effect of metformin in children and adolescents with type 2 diabetes mellitus: a systematic review and meta-analysis	2012	Systematic review and meta-analysis	Saudi Arabia					To assess the clinical value and of metformin as mono-therapy vs other treatments for type 2 diabetes mellitus in children and adolescents.	1825 studies										In the metformin group there were significant reductions of mean change of HbA1c from baseline. It reduced by -0.71% (P=0.0002) and in the other trial the result was reduced by -1.10 (95% CI:-1.19 to -1.01). In addition, more patients (48.1%) in the metformin group achieved good glycaemic control (<7%) at week 24. The mean changes in FPG from baseline were significantly (P<0.05) different in the metformin group (-16.6% for week 18 and week 24 20.6%). In the second trial there was a significant (P<0.001) reduction in the adjusted mean of FPG from baseline in the metformin group, while there was an increase in the placebo group (-42.9 mg/dl vs +21.4 mg/dl) with mean difference of -64.80 in favor of the metformin group. For BMI, significant (P<0.001) differences were seen at week 12 and week 24 (0.07 and 0.55 kg2) for metformin and glimepiride respectively. There was no significant difference between the placebo and metformin in the other trials. For lipid value there was a significant decrease in LDL levels in the metformin group. No significant changes were found in the other lipid parameters after adjusting.		Adverse events in the metformin group, but not statistically significant.		Limited but not convincing evidence to suggest that metformin can improve the glycaemic control in children and adolescents with type 2 diabetes compared with with other interventions.	Systematic Review/Meta Analysis		6
21617112	Lipska 2011	Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency	2011	Reference	USA																					Low		6
20393934	Salpeter 2010	Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus	2010	Systematic review	USA	Clinical		at least one month		To assess the incidence of fatal and nonfatal lactic acidosis, and to evaluate blood lactate levels, for those on metformin treatment compared to placebo or non-metformin therapies.	347 comparative trials and cohort studies.	Type 2 diabetes					Metformin (alone or in combination with other treatments)		Placebo or any other glucose-lowering therapy	Incidence of fatal and non fatal lactic acidosis per patient-years and blood lactate levels	No cases of fatal or nonfatal lactic acidosis in 70490 patient-years of metformin use or in 55451 patient-yearsin the non-metformin group. Using Poisson statistics the upper limit for the true incidence of lactic acidosis per 100000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group. There was no difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared to non-metformin therapies.				There is no no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis.	Systematic Review	Metformin	6
18955635	Selvin 2008	Cardiovascular outcomes in trials of oral diabetes medications: a systematic review	2008	Systematic review	USA					To systematically examine the peer-reviewed literature on the cardiovascular risk associated with oral agents (second-generation sulfonylureas, biguanides, thiazolidinediones, and meglitinides) for treating adults with type 2 diabetes.											Treatment with metformin hydrochloride was associated with a decreased risk of cardiovascular mortality (pooled OR, 0.74; 95% CI 0.62-0.89) compared with any other oral diabetes agent or placebo; the results for cardiovascular morbidity and all cause mortality were similar but not statistically significant. No other significant associations of oral diabetes agents with fatal or nonfatal cardiovascular disease or all cause mortality were observed. When compared with any other agent or placebo, rosiglitazone was the only diabetes agent associated with an increased risk of cardiovascular morbidity or mortality, but this result was not statistically significant (OR 1.68; 95% CI 0.92-3.06)				Meta-analysis suggested that, compared with other oral diabetes agents and placebo, metformin was moderately protective and rosiglitazone possibly harmful, but lack of power prohibited firmer conclusions. Larger, long-term studies taken to hard end points and better reporting of cardiovascular events in short term studies will be required to draw firm conclusions about major clinical benefits and risks related to oral diabetes agents.	Systematic Review		6
16034881	Saenz 2005	Metformin monotherapy for type 2 diabetes mellitus	2005	Systematic review	Spain, Canada	Clinical				To assess the effects of metformin monotherapy on mortality, morbidity, quality of life, glycemic control, body weight, lipid levels, blood pressure, insulinaemia, and albuminuria in patients with 2 diabetes mellitus.	5259	Adults with type 2 diabetes mellitus								Obese patients allocated to intensive blood glucose control with metformin showed a greater benefit than chlorpropmide, glibenclamide, or insulin for any diabetes-related outcomes (p=0.009), and for all-cause mortality (p=0.03). Obese participants assigned to intensive blood glucose control with metformin showed a greater benefit than overweight patients on conventional treatment for any diabetes-related outcomes (p=0.004), diabetes-related death (p=0.03), all cause mortality (p=0.01), and myocardial infarction (p=0.02). Patients assigned to metformin monotherapy showed a significant benefit for glycemia control, weight, dyslipidemia, and diastolic blood pressure. Metformin presents a strong benefit for HbA1c when compared with placebo and diet; and a moderate benefit for glycemia control, LDL cholesterol, and BMI or weight when compared with sulphonylureas.				Systematic Review		6
9742976	UK Prospective Diabetes Study Group 1998a	Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)	1998	Randomized Controlled Trial	United Kingdom	Clinical			10 years	To compare the effects of intensive blood glucose control with either sulphonylurea or insulin and conventional treatment on the risk of microvascular and macrovascular complications in patients with type 2 diabetes.	3867	Adult patients newly diagnosed with type 2 diabetes	Newly diagnosed diabetes aged 25-65 years.	Median age 54 years (IQR 48-60 years)	2729	Pharmacologic	Sulphonylures, insulin	1138	Conventional treatment (diet)	Diabetes-related mortality, morbidity, all cause mortality	Hemoglobin in the intensive group was reduced by 11% compared to the conventional group. Compared with the conventional goup, the risk in the intensive groupwas 12% lower (95% CI 1-21, p=0.029) for any diabetes-related endpoint; 10% lower (-11 to 27, p=0.34) for any diabetes-related death; and 6% lower (-10 to 20, p=0.44) for all cause mortality. Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25% risk reduction (7-40, p=0.0099) in microvascular endpoints, including the need for retinal photocoagulation. Patients in the intensive group had more hypoglycemic episodes than those in the conventional group on both sides (p<0.0001). Weight gain was significantly higher in the intensive group (mean 2.9 kg) than in the conventional group (p<0.001).				Intensive blood glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes. None of the individual drugs had an adverse effect on cardiovascular outcomes. All intensive treatment increased the risk of hypoglycemia.	High		6
7.1 Antihypertensive Therapy																												
24170669	Arguedas 2013	Blood pressure targets for hypertension in people with diabetes mellitus	2013	Systematic review (5 RCTs included)	Costa Rica, Canada					To determine if 'lower' BP targets (any target less than 130/85 mmHg) are associated with reduction in mortality and morbidity compared with 'standard' BP targets (less than 140 - 160/90 - 100 mmHg) in people with diabetes type 2.							'lower' BP targets (any target less than 130/85 mmHg)		'standard' BP targets (less than 140 - 160/90 - 100 mmHg)	Mortality, morbidity			In ACCORD trial, trying to achieve the 'lower' SBP target was associated with a significant increase in the number of other serious adverse events: RR 2.58, 95% CI 1.70 to 3.91, P < 0.00001, absolute risk increase 2.0%.		Evidence from randomized trials does not support blood pressure targets lower than the standard targets in people with elevated blood pressure and diabetes.	Systematic Review	Hypertension	7.1
21632497	Bangalore 2011	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	2011	Meta-analysis of Randomized Controlled Trials	USA	Clinical			Analyzed trials between 1965-October 2010	Determine optimal Blood Pressure targets in patients with Type 2 Diabetes/Impaired fasting glucose/impaired glucose tolerance	N=37736 in 13 included trials	type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance	Eligible trials had to fulfill the following criteria to be included in this analysis: (1) randomized clinical trials of participants with type 2 diabetes mellitus/IFG/IGT (2) reporting >=1-year outcomes (3) and enrolling at least 100 patients (4) who achieved systolic BP <=140 mm Hg in both arms. Additionally, because the objective of the present study was to test outcomes based on BP targets, the following criteria were required: (1) achieved systolic BP in the intensive BP group of <=135 mm Hg, (2) achieved systolic BP in the standard BP group of <=140 mm Hg, and (3) had a systolic BP difference between the intensive and standard BP group of at least 3 mm Hg.								Macrovascular and microvascular events	Intensive BP control was associated with a 10% reduction in all-cause mortality (odds ratio, 0.90; 95% confidence interval, 0.83 to 0.98), a 17% reduction in stroke, and a 20% increase in serious adverse effects, but with similar outcomes for other macrovascular and microvascular (cardiac, renal, and retinal) events compared with standard BP control. Meta-regression analysis showed continued risk reduction for stroke to a systolic BP of <120 mm Hg. However, at levels <130 mm Hg, there was a 40% increase in serious adverse events with no benefit for other outcomes.				The present body of evidence suggests that in patients with type 2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance, a systolic BP treatment goal of 130 to 135 mm Hg is acceptable. With more aggressive goals (<130 mm Hg), the risk of stroke continued to fall, but there was no benefit regarding the risk of other macrovascular or microvascular (cardiac, renal and retinal) events, and the risk of serious adverse events even increased.	Meta-analysis	Hypertension	7.1
17636747	Nilsson 2011	Target blood pressure in diabetes patients with hypertension – What is the accumulated evidence in 2011?	2011	Systematic review	Sweden																				the new recommended goal should be 130-135 mmHg systolic blood pressure for most patients with type 2 diabetes. Other risk factors should also be controlled with a more ambitious strategy applied in the younger patients with shorter diabetes duration, but a more cautious approach in the elderly and frail patients with a number of vascular or non-vascular co-morbidities. In conclusion, the current strategy is to have a more individualized approach to risk factor control in patients with type 2 diabetes, also relevant for blood pressure control.	Systematic Review	Hypertension	7.1
20228401	ACCORD Study Group, The 2010b	Effects of intensive blood-pressure control in type 2 diabetes mellitus	2010	Randomized Controlled Trial	USA, Canada	Clinical	Nonblinded			Determine whether therapy targeting normal systolic pressure (i.e., <120).	4733	High risk type 2 diabetes mellitus	Type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and 40 years of age or older with cardiovascular disease or 55 years of age or older with anatomical evidence of a substantial amount of arteriosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity). Participants with a systolic blood pressure between 130 and 180mm Hg who were taking three or fewer antihypertensive medications and who had the equivalent of a 24-hour protein excretion rates of less than 1.0g were also eligible for the blood pressure trial.	Mean age (SD): 62.2 (6.9); Female: 47.7%; Race/Ethnicity: 60.5% were non-Hispanic white, 24.1% were Black and 7.0% were Hispanic; Education:32.4% with some college and 24.5% had college degree or higher.		Standard treatment strategies for lowering blood pressure including pharmacologic	Intensive therapy targeting a systolic pressure of less than 120 mm Hg		Standard therapy targeting a systolic pressure of less than 140 mmHg.	Primary: the first occurrence of a major cardiovascular event, which was defined as the composite of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death. Secondary: Combination of primary outcome plus revascularization or hospitalization for congestive heart failure; the combination of a fatal coronary event, nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure.	P1: Primary composite outcome: Int rate of death per at 1.87% vs. 2.09% per year in the control group (Hazard ratio with intensive therapy, 0.88, 95% CI (0.73-1.06). S1: rate of death from any cause 1.28% per year in Int vs. 1.19% in the control group (Hazard ratio with Int 1.07, 95% CI 0.85 to 1.35); S2: rate of death from cardiovascular causes at 0.52% per year in Int vs. 0.49% in the control group (hazard ratio 1.06, 95% CI (0.74 to 1.52); S3: rate of total stroke 0.32% per year in Int vs. 0.53% per year in Cont (hazard ratio 0.63, 95% CI (0.41 to 0.96))	P1: not significant; S1 and S2 not significant. No secondary outcomes were significantly different between Int and Cont except stroke outcomes. S3: Significantly different.	Significantly higher rates of adverse events attributed to antihypertensive treatment in Int group vs. cont group and higher rates in Int group of hypokalemia and elevations in serum creatinine level.		In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.	High	Cardiovascular risk management-antihypertensive treatment	7.1

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
18539916	ADVANCE Collaborative Group, The 2008	Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes	2008	Randomized Controlled Trial	Australia	Clinical	Yes	5 years	5 years	To determine the effects of intensive glucose control on vascular outcomes.	11140	Type 2 diabetes patients	Diagnosis of type 2 diabetes mellitus at 30 years of age or older, an age of at least 55 years at the time of study entry, and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease.	Mean 66 years; Mean age when diabetes first diagnosed 58 years and an average duration of diabetes 8 years.	Baseline 5571 (7 were lost to follow up)	Pharmacologic	Gliclazide (modified release) plus other drugs as required to achieve HbA1c value of 6.5% or less.	5569 (10 were lost to follow up)	Standard glucose control	The primary study outcomes were composites of major macrovascular events (death from cardiovascular causes, nonfatal mycordial infarction, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy), assessed both jointly and separately.	After a median of 5 years of follow up, the mean HbA1c was lower in the intensive-control group (6.5%) than in the standard control group (7.3%). Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1% vs. 20% with standard control; hazard ratio, 0.90; 95% CI 0.82 to 0.98; p=0.01), as well as that of major microvascular events (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97. p=0.01), primarily because of a reduction in the incidence of nephropathy (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93, p=0.006), with no significant effect on retinopathy (p=0.50). There were no significant effects of the type of glucose control on major macrovascular events (hazard ratio with intensive control, 0.94; 95% CI 0.84 to 1.06; p=0.32), death from cardiovascular causes (hazard ratio with intensive control, 0.88; 95% CI 0.74 to 1.04; p=0.12), or death from any cause (hazard ratio with intensive control 0.93; 95% CI 0.83 to 1.06, p=0.28). Severe hypoglycemia, although uncommon, was more common in the intensive control group (2.7% vs. 1.5% in the standard control group, hazard ratio, 1.86; 95% CI 1.42 to 2.40; P<0.001)	Yes in reduction of incidence of combined major macrovascular and microvascular events and severe hypoglycemia.	Incidence of hypoglycemia in intensive control group.		A strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy.	High		4; 7.1
18398080	Howard 2008	Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial	2008	Randomized Controlled Trial	USA	Clinical	open-label,blinded-to-endpoint	3-year	3-year	To compare progression of subclinical atherosclerosis in adults with type 2 diabetes treated to reach aggressive targets of low-density lipoprotein cholesterol (LDL-C) of 70 mg/dL or lower and systolic blood pressure (SBP) of 115 mm Hg or lower vs standard targets of LDL-C of 100 mg/dL or lower and SBP of 130 mm Hg or lower.	499	40 year and older type 2 diabetes patients	Eligibility criteria included docu-mented type 2 diabetes,31,32 plus LDL-C of at least 100 mg/dL and SBP greater than 130 mm Hg within the previous 12 months.	Participants were 499 American Indian men and women aged 40 years or older with type 2 diabetes and no prior CVD events.			Aggressive blood pressure and LDL targets		Standard blood pressure and LDL targets	Meantargetl.DL-CandSBPlevelsforbothgroupswerereached andmain- tained. Mean (95% confidence interval) levels for LDL-C in the last 12 months were 72 (69-75) and 104 (101-106) mg/dL and SBP levels were 117 (115 118) and 129 (128- 130) mm Hg in the aggressive vs standard groups, respectively. Compared with base- line, IMT regressed in the aggressive group and progressed in the standard group (−0.012 mm vs 0.038 mm; P<.001); carotid arterial cross-sectional area also regressed (−0.02 mm2 vs 1.05 mm2; P<.001); and there was greater decrease in left ventricular mass in- dex (−2.4 g/m2.7 vs −1.2 g/m2.7; P = .03) in the aggressive group. Rates of adverse events (38.5% and 26.7%; P = .005) and serious adverse events (n = 4 vs 1; P = .18) related to blood pressure medications were higher in the aggressive group. Clinical CVD events (1 6/ 100 and 1 5/100 person-years; P=.87) did not differ significantly between groups.				Reducing LDL-C and SBP to lower targets resulted in regression of carotid IMT and greater decrease in left ventricular mass in individuals with type 2 diabetes. Clinical events were lower than expected and did not differ significantly between groups. Further follow-up is needed to determine whether these improvements will result in lower long-term CVD event rates and costs and favorable risk-benefit outcomes.	High		7.1
17161769	Estacio 2006	Effect of intensive blood pressure control with valsartan on urinary albumin excretion in normotensive patients with type 2 diabetes	2006	Randomized Controlled Trial	USA	Clinical	Partial	5 years	Terminated after 5 years	Assess effects of Intensive Blood Pressure Control With Valsartan on Urinary Albumin Excretion in Normotensive Patients With Type 2 Diabetes	129	type 2 diabetic patients with a BP of □140/80 to 90 mm Hg without overt albuminuria	Type 2 diabetic patients, 40 to 81 years of age, with a systolic BP <140 mm Hg, a diastolic BP between 80 and 90 mm Hg, and without evidence of overt albuminuria (<200)	Intensive BP group age 56.7+/-7.7 (66.7 male); Moderate BP group 55.5+/-7.7 (68.3% male)	66 (61) intensive BP control	63(58)	Pharmacologic	intensive BP control (diastolic BP goal 75 mm Hg) using an angiotensin II receptor blocker, valsartan		moderate BP control (diastolic BP 80 to 90 mm Hg with placebo initially)	The renal outcomes, creatinine clearance, serum creati- nine, and UAE were measured every 6 months.	The mean entrance BP was 126 +/- 8.8/84 +/- 2.4 mm Hg. The mean follow-up period was 1.9 +/- 1.0 years. During the follow-up period, the mean BP was 118 +/- 10.9/75 +/- 5.7 for the intensive v 124 10 9/80 6.5 mm Hg for the moderate BP groups (P < .001). No difference was observed in change in creatinine clearance or serum creatinine from baseline between the two groups. An analysis of covariance model for change in log (UAE + 1), adjusting for age, HBA1(1c), duration of diabetes, baseline log (UAE + 1), sex, and ethnicity resulted in a significant treatment difference at 2 years (P = .007) with intensive BP control reducing log (UAE+1) compared with moderate BP control.				Intensive BP control with valsartan to <120/80 mm Hg in normotensive patients with type 2 diabetes and normo- or microalbuminuria significantly decreased the progression of UAE and in some cases caused regression of UAE.	High		7.1
12584366	Wing 2003	A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly	2003	Randomized Controlled Trial	Australia	Clinical	Yes-an end point committee whose members were unaware of the treatment group assignments adjudicated all potential end points.		4.1 years	To compare the outcomes in older subjects with hypertension who were treated with angiotensin-converting-enzyme (ACE) inhibitors with the outcomes in those treated with diuretic agents.	6083	Patients, 65-84 years of age with hypertension		49% male; 51% female; Mean age 71.9 years	3044 (2978)	Pharmacologic	ACE inhibitor	3039 (2938)	Diuretic agents	The primary end point was all cardiovascular events or death from any cause.	By the end of the study, blood pressure had decreased in both groups. There were 695 cardiovascular events or deaths from any cause in the ACE-inhibitor group (56.1 per 1000 patient-years) and 736 cardiovascular events or deaths from any cause in the diuretic group (59.8 per 1000 patient-years; the hazard ratio for a cardiovascular event or death with ACE-inhibitor treatment was 0.89 (95% CI 0.79 to 1.00; p=0.05). Among male subjects, the hazard ratio was 0.83 (95% CI, 0.71 to 0.97, p=0.02); among females, the hazard ratio was 1.00 (95% CI, 0.83 to 1.21;p=0.98); the p-value for the interaction between between sex and treatment group assignment was 0.15. The rates of nonfatal cardiovascular events and myocardial infarctions decreased with ACE-inhibitor treatment, whereas a similar number of strokes occurred in each group (although there were more fatal strokes in the ACE-inhibitor group).				Initiation of antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure.	Moderate		7.1
12479763	ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The 2002	Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).	2002	Randomized Controlled Trial	USA	Clinical	Double blind	5 years	8 years	To determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs. treatment with a diuretic.	33357	Participants aged 55 years and older with hypertension and at least 1 other CHD risk factor from 623 North American centers.	Participants aged 55 years and older with hypertension and at least 1 other CHD risk factor from 623 North American centers.	The mean age was 67 years; 47% were women, 35% were black, 19% were Hispanic, and 36% were diabetic. There were nearly identical distributions of baseline factors in the 3 treatment groups.	Chlorthalidone Baseline 15255 (5 year follow up 5301); Amlodipine Baseline 9048 (5 year follow up 3195); Lisinopril Baseline 9054 (5 year follow up 2963)	Pharmacologic	Chlorthalidone (12.5 to 25 mg/d); amlodipine (2.5 to 10 mg/d); lisinopril (10 to 40 mg/d)			The primary outcome was combined fatal CHD or non-fatal myocardial infarction, analyzed by intent to treat. Secondary outcomes were all cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease)	Mean follow up was 4.9 years. The primary outcome occurred in 2956 participants, with no difference between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks were 0.98 (95% CI, 0.90-1.07) for amlodipine (6-year rate, 11.3%) and 0.99 (95% CI 0.91-1.08) for lisinopril (6-year rate 11.4%). Likewise, all cause mortality did not differ between groups. Five year systolic blood pressures were significantly higher in the amlodipine (0.8 mmHg, P=0.03) and lisinopril (2mmHg, P<0.001) groups compared with chlorthalidone, and 5-year diastolic blood pressure was significantly lower with amlodipine (0.8mmHg, P<0.001). For amlodipine vs. chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% vs 7.7%; RR 1.38; 95% CI 1.25-1.52). For lisinopril vs. chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs. 30.9%, RR 1.10; 95% CI 1.05-1.16); stroke (6.3% vs 5.6%; RR 1.15; 95% CI 1.02-1.30); and HF (8.7% vs. 7.7%; RR 1.19; 95% CI 1.07-1.31).				Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.	High		7.1
9635947	Hansson 1998	Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial	1998	Randomized Controlled Trial	Sweden	Clinical	Yes	2 years	4 years	To assess the optimum target diastolic blood pressure and the potential benefit of a low dose of acetylsalicylic acid in the treatment of hypertension.	18790	Patients with hypertension and diastolic blood pressure between 100mmHg and 115mmHg	Patients with hypertension and diastolic blood pressure between 100mmHg and 115mmHg and randomly assigned to one of three target pressure groups.	Mean age 61.5 years. Mean diastolic blood pressure 105mmHg.		Pharmacologic	Felodipine as baseline therapy with the addition of other agents. 9399 patients were randomly assigned acetylsalicylic acid		9391 were assigned placebo.	Major cardiovascular events	Diastolic blood pressure was reduced by 20.3 mmHG, 22.3 mmHg and 24.3 mmHg in the <=90 mmHg, <=85 mmHg, and <=80 mmHg target groups, respectively. The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mmHg; the lowest risk of cardiovascular mortality occurred at 86.5 mmHG. Further reduction below these blood pressures was safe. In patients with diabetes mellitus there was a 51% reduction in major cardiovascular events in target group <=80 mmHg compared with target group <=90 mmHg (p=0.005). Acetylsalicylic acid reduced major cardiovascular events by 15% (p=0.03) and all mycardial infarction by 36% (p=0.002), with no effect on stroke. There were seven fatal bleeds in the acetylsalicylic acid group and eight in the placebo group, and 129 versus 70 non-fatal major bleeds in the two group, respectively (p<0.001).				Intensive lowering of blood pressure in patients with hypertension was associated with a low rate of cardiovascular events. The HOT study shows the benefits of lowering the diastolic blood pressure down to 82.6 mmHg. Acetylsalicylic acid significantly reduced major cardiovascular events with the greatest benefit seen in all myocardial infraction. There was no effect on the incidence of stroke or fatal bleeds, but non-fatal major bleeds were twice as common.	Moderate		7.1
	UK Prospective Diabetes Study (UKPDS) Group 1998b	Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.	1998	Randomized Controlled Trial	United Kingdom	Clinical	Yes		8.4 years	To determine whether tight control of blood pressure prevents macrovascular and microvascular complications in patients with type 2 diabetes.	1148	Hypertensive patients with newly diagnosed type 2 diabetes aged 25-65 years	Hypertensive patients with newly diagnosed type 2 diabetes aged 25-65 years	Mean age 56, mean blood pressure at entry 160/94mmHg; Male in tight control 54%, less tight control 58%; Race 87% white	758	Pharmacologic	Tight control of blood pressure (aim<150/85 mmHg)	390	Less tight control of blood pressure (aim<180/105 mmHg)	Predefined clinical end points, fatal and non-fatal, related to diabetes, deaths related to diabetes, and all cause mortality. Surrogate measures of microvascular disease included urinary albumin excretion and retinal photography.	Mean blood pressure during follow up was significantly reduced in the group assigned tight blood pressure control (144/82 mmHg) compared with the group assigned to less tight control (154/87 mmHg) (P<0.0001). Reductions in risk in the group assigned to tight control compared with that assigned to less tight control were 24% in diabetes related end points (95% CI 8% to 38%) (P=0.0046), 32% in deaths related to diabetes (6% to 51%) (P=0.019), 44% in strokes (11% to 65%) (P=0.013), and 37% in microvascular end points (11% to 56%) (P=0.0092), predominantly owing to a reduced risk of retinal photocoagulation. There was a non-significant reduction in all cause mortality. After nine years of follow up the group assigned to tight blood pressure control also had a 34% reduction in risk in the proportion of patients with deterioration of retinopathy by two steps (99% CI 11% to 50%) (P=0.0004) and a 47% reduced risk (7% to 70%) (P=0.004) of deterioration in visual acuity by three lines of the early treatment of diabetic retinopathy study (ETDRS) chart. After nine years of follow up 29% of patients in the group assigned to tight control required three or more treatments to lower blood pressure to achieve target blood pressures.				Tight blood pressure control in patients with hypertension and type 2 diabetes achieves a clinically important reduction in the risk of deaths related to diabetes, complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.	High		7.1
7.2 Statin Therapy (High Risk)																											
23440795	Taylor 2013	Statins for the primary prevention of cardiovascular disease.	2013	Systematic review						To assess the effects, both harms and benefits, of statins in people with no history of CVD.			Randomised controlled trials of statins versus placebo or usual care control with minimum treatment duration of one year and follow-up of six months, in adults with no restrictions on total, low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol levels, and where 10% or less had a history of CVD.								The latest search found four new trials and updated follow-up data on three trials included in the original review. Eighteen randomised control trials (19 trial arms; 56,934 participants) were included. Fourteen trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria). All-cause mortality was reduced by statins (OR 0.86, 95% CI 0.79 to 0.94); as was combined fatal and non-fatal CVD RR 0.75 (95% CI 0.70 to 0.81), combined fatal and non-fatal CHD events RR 0.73 (95% CI 0.67 to 0.80) and combined fatal and non-fatal stroke (RR 0.78, 95% CI 0.68 to 0.89). Reduction of revascularisation rates (RR 0.62, 95% CI 0.54 to 0.72) was also seen. Total cholesterol and LDL cholesterol were reduced in all trials but there was evidence of heterogeneity of effects. There was no evidence of any serious harm caused by statin prescription. Evidence available to date showed that primary prevention with statins is likely to be cost-effective and may improve patient quality of life. Recent findings from the Cholesterol Treatment Trialists study using individual patient data meta-analysis indicate that these benefits are similar in people at lower (< 1% per year) risk of a major cardiovascular event.				Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people without evidence of CVD treated with statins.	Systematic review	Cardiovascular risk management-statin therapy	7.2; 7.3
23440795	Cholesterol Treatment Trialists' (CTT) Collaboration 2010	Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials	2010	Meta-Analysis	United Kingdom					Assess the safety and efficacy of more intensive lowering of LDL cholesterol with statin therapy	170000	Type 2 diabetes								Occlusive vascular events					Further reduction in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularization, and of ischemic stroke, with each 1.0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2-3 mmol/L would reduce risk by about 40-50%.	Meta-analysis		7.2; 7.3
15007110	Cannon 2004	Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes	2004	Randomized Controlled Trial	USA, Canada, United Kingdom	Clinical	Double blind			Examine the clinical benefit of lowering low-density lipoprotein (LDL) cholesterol levels below the target of <100.	4162	Adult patients who had been hospitalized for an acute coronary syndrome	men and women who were at least 18 years old were el- igible for inclusion if they had been hospitalized for an acute coronary syndrome — either acute myocardial infarction (with or without electrocardio- graphic evidence of ST-segment elevation) or high- risk unstable angina — in the preceding 10 days.		2099	Pharmacologic	80 mg of atorvastatin daily	2063	40 mg of pravastatin daily	a com-positeofdeathfromanycause,myocardialinfarction,documentedunstableanginare-quiringrehospitalization,revascularization(performedatleast30dasyafterrandomiza-tion), and stroke.	The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (2.46 mmol per liter) in the standard-dose pravastatin group and 62 mg per deciliter (1.60 mmol per liter) in the high-dose atorvastatin group (P<0.001). Kaplan–Meier estimates of the rates of the primary end point at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduction in the hazard ratio in favor of atorvastatin (P=0.005; 95 percent confidence interval, 5 to 26 percent). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.				Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels.	High	Cardiovascular risk management-statin therapy	7.2; 7.3

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
12814710	Heart Protection Study Collaborative Group 2003	MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial	2003	Randomized Controlled Trial	United Kingdom	Clinical	Yes	5 years	5 years	To determine the effects of cholesterol LDL lowering on vascular events.	5963 adults with diabetes and 14573 with occlusive arterial disease (but no diagnosed diabetes)	Men and women aged about 40-80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L were eligible if they had a medical history of: diabetes mellitus, coronary disease, occlusive disease of non-coronary arteries; or treated hypertension (if also male and aged at least 65 years)	Men and women aged about 40-80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L were eligible if they had a medical history of: diabetes mellitus, coronary disease, occlusive disease of non-coronary arteries; or treated hypertension (if also male and aged at least 65 years)	Diabetes group mean age 62.1 years +/-8.9 70% men and 33% non-smoker. No diabetes group mean age 64.7 years +/-8.1, 78% men and 22% non smoker		Pharmacologic	40 mg simvastatin daily		Matching placebo	Vascular events	Both among the participants who presented with diabetes and among those who did not, there were highly significant reductions of about a quarter in the first event rate for major coronary events, for strokes, and for revascularizations. For the first occurrence of any of these major vascular events among participants with diabetes, there was a definite 22% (95%CI 13-30) reduction in the event rate (601 (20.2%) simvastatin-allocated vs 748 (25.1%) placebo-allocated, p<0.0001), which was similar to that among the other high-risk individuals studied. There were also highly significant reductions of 33% (95% CI 17-46, p=0.0003) among the 2912 diabetic participants who did not have any diagnosed occlusive arterial disease at entry, and of 27% (95% CI 13-40, p=0.0007) among the 2426 diabetic participants whose pretreatment LDL cholesterol concentration was below 3.0 mmol/L. The proportional reduction in risk was also about a quarter among various other subcategories of diabetic patient studied, including: those with different duration, type, or control of diabetes; those aged over 65 years at entry or with hypertension; and those with total cholesterol below 5.0 mmol/L. In addition, among participants who had a first major vascular event following randomization, allocation to simvastatin reduced the rate of subsquent events during the scheduled treatement period.				The study provides direct evidence that cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations. Allocation to 40 mg simvastatin daily reduced the rate of first major vascular events by about a quarter in a wide rate of diabetic patients studied. After making allowance for non-compliance, actual use of this statin regimen would probably reduce these rates by about a third. For example, among the type of diabetic patient studied without occlusive arterial disease, 5 years of treatment would be expected to prevent about 45 people per 1000 from having at least one major vascular event (and, among these 45 people, to prevent about 70 first or subsequent events during this treatment period). Statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations.	High		7.2; 7.3
12114036	Heart Protection Study Collaborative Group 2002	MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial	2002	Randomized Controlled Trial	United Kingdom	Clinical	Yes	5 years	5 years	To determine the effects of reducing LDL cholesterol on the development of vascular disease, irrespective of initial cholesterol concentrations.	20536	Adults aged 40-80 years with coronary disease, other occlusive arterial disease, or diabetes	Men and women aged about 40-80 years withi non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L were eligible if they were considered to be at substantial 5-year risk of death from coronary heart disease because of a past medical history of: 1) coronary disease, 2) occlusive disease of non-coronary arteries, 3) type 1 or type 2 diabetes mellitus or 4) treated hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories)		10269 (10232)	Pharmacologic	40 mg simvastatin daily	10267 (10237)	Matching placebo	Mortality and fatal and non-fatal vascular events with subsidiary assessments of cancer and of other major morbidity.	All-cause mortality was significantly reduced (1328 (12.9%) deaths among 10269 allocated simvastatin vs 1507 (14.7%) among 10267 allocated placebo; p=0.0003), due to a highly significant 18% (SE .5) proportional reduction in the coronary death rate (587 (5.7%) vs 707 (6.9%); p=0.0005), a marginally significant reduction in other vascular deaths (194 (1.9%) vs. 230 (2.2%); p=0.07), and a non-significant reduction in non-vascular deaths (547 (5.3%) vs 570 (5.6%); p=0.4). There were highly significant reductions of about one-quarter in the first event rate for non-fatal myocardial infraction or coronary death (898 (8.7%) vs 1212 (11.8%); p<0.0001), for non-fatal or fatal stroke (444(4.3%) vs 585(5.7%); p<0.0001), and for coronary or non-coronary revascularization (939(9.1%) vs 1205(11.7%); p<0.0001). For the first occurrence of any of these major vascular events, there was a definite 24% (SE 3; 95% CI 19-28) reduction in the event rate (2033(19.8%) vs 2585(25.2%) affected individuals;p<0.0001). During the first year the reduction in major vascular events was not significant, but subsequently it was highly significant during each separate year. The proportional reduction in the event rate was similar (and significant) in each subcategory of participants studied, including those without diagnosed coronary disease who had cerebrovascular disease, or had peripheral artery disease, or had diabtes; men and separately, women; those aged either under or over 70 years at entry; and even those who presented with cholesterol below 3.0 mmol/L, or total cholesterol below 5.0 mmol/L. The benefits of simvastatin were additional to those of other cardioprotective treatments. The annual excess risk of myopathy with this regimen was about 0.01%. There were no si				Adding simvastatin to existing treatments safely produces substantial additional benefits for a wide range of high-risk patients, irrespective of their intial cholesterol concentrations. Allocation to 40mg simvastatin daily reduced the rates of myocardial infarction, of stroke, of revascularization by about one-quarter. After making allowance for non-compliance, actual use of this regimen would probably reduce these rates by about one-third. Hence, among the many types of high-risk individual studied, 5 years of simvastation would prevent about 70-100 people per 1000 from suffering at least one of these major vascular events (and longer treatment should produce further benefit). The size of 5-year benefit depends mainly on such individuals' overall risk of major vascular events, rather than on their blood lipid concentrations alone.	High		7.2
7.3 Statin Therapy (Moderate Risk)																											
23440795	Taylor 2013	Statins for the primary prevention of cardiovascular disease.	2013	Systematic review						To assess the effects, both harms and benefits, of statins in people with no history of CVD.			Randomised controlled trials of statins versus placebo or usual care control with minimum treatment duration of one year and follow-up of six months, in adults with no restrictions on total, low density lipoprotein (LDL) or high density lipoprotein (HDL) cholesterol levels, and where 10% or less had a history of CVD.								The latest search found four new trials and updated follow-up data on three trials included in the original review. Eighteen randomised control trials (19 trial arms; 56,934 participants) were included. Fourteen trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria). All-cause mortality was reduced by statins (OR 0.86, 95% CI 0.79 to 0.94); as was combined fatal and non-fatal CVD RR 0.75 (95% CI 0.70 to 0.81), combined fatal and non-fatal CHD events RR 0.73 (95% CI 0.67 to 0.80) and combined fatal and non-fatal stroke (RR 0.78, 95% CI 0.68 to 0.89). Reduction of revascularisation rates (RR 0.62, 95% CI 0.54 to 0.72) was also seen. Total cholesterol and LDL cholesterol were reduced in all trials but there was evidence of heterogeneity of effects. There was no evidence of any serious harm caused by statin prescription. Evidence available to date showed that primary prevention with statins is likely to be cost-effective and may improve patient quality of life. Recent findings from the Cholesterol Treatment Trialists study using individual patient data meta-analysis indicate that these benefits are similar in people at lower (< 1% per year) risk of a major cardiovascular event.				Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of adverse events among people without evidence of CVD treated with statins.	Systematic review	Cardiovascular risk management-statin therapy	7.2; 7.3
23796131	Macchia 2012	Statins but Not Aspirin Reduce Thrombotic Risk Assessed by Thrombin Generation in Diabetic Patients without Cardiovascular Events: The RATIONAL Trial	2012	Randomized Controlled Trial	Argentina	Hospital	blinded to events evaluation	8 to 10 weeks.	8 to 10 weeks.	Assess the effects of aspirin and statins on the thrombotic risk assessed by thrombin generation (TG) among patients with type II diabetes mellitus and no previous cardiovascular events.	30	Patients were males or females aged 50 years diagnosed with type 2 diabetes	Patients were males or females aged 50 years diagnosed with type 2 diabetes based on standard criteria at least 1 year prior to study entry. Inclusion criteria included treatment for diabetes with either oral agents or insulin therapy for at least the past one year, no previous cardiovascular events, and no treatment with aspirin or statins during the year prior to recruitment. The main exclusion criteria were current treatment with aspirin or any antiplatelet agent including sporadic use of NSAID and the presence of previous vascular events or any known hemorrhagic condition.	Aspirin mean age 56.5, and 42.9% female; control mean age 63.0 and 53.3% female	Between august 26th 2,009 and september 1st 2010, thirty patients were randomized. Of these, 14 were randomly assigned to receive aspirin and 16 to no aspirin. By 262 factorial design, 15 patients were randomized to receive atorvastatin and 15 were assigned to no atorvastatin group. There were no lost during the follow up, but in four patients (one assigned to aspirin, two to atorvastatin and one to no experimental treatment) measurements of TG was not available due to blood samples were not adequate for assays.	Pharmacologic	aspirin, atorvastatin		Placebo	Primary end point was the level of TG at the end of follow up, as measured by the peak of TG with saline as agonist. Other outcomes were peak TG with arachidonic acid, tissue factor, ADP and lag time with arachidonic acid.			None		While waiting for data from ongoing large clinical randomized trials to definitively outline the role of aspirin in primary prevention, our study shows that among diabetic patients without previous vascular events, statins but not aspirin reduce thrombotic risk assessed by TG.	High	Aspirin	7.3; 7.4
22085343	AIM-HIGH Investigators 2011	Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy	2011	Randomized Controlled Trial	USA, Canada	Clinical	Yes, double blinded	36 months	36 months	To determine whether extended-release niacin added to simvastatin to raise low levels of HDL cholesterol is superior to simvastatin alone in reducing residual cardiovascular risk.	3414	Patients 45 years of age or older and established cardiovascular disease, which was defined as documented stable coronary heart disease, cerebrovascular or carotid disease, or peripheral arterial disease	Patients 45 years of age or older and established cardiovascular disease, which was defined as documented stable coronary heart disease, cerebrovascular or carotid disease, or peripheral arterial disease	Mean age 64 years (+/- 9 years); 85.2% were men, 92.2% were white, 33.9% had either type 1 or type 2 diabetes, 71.4% had hypertension, and 81.0% had the metabolic syndrome.	1718	Pharmacologic	Extended-release niacin plus statin	1696	Placebo plus statin	The primary end point was the first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.	At 2 years, niacin therapy had significantly increased the median HDL cholesterol level from 35 mg per deciliter to 42 mg per deciliter, lowered the triglyceride level from 163 mg per deciliter to 122 mg per deciliter, and lowered the LDL cholesterol level from 74 mg per deciliter to 62 mg per deciliter. The primary end point occurred in 282 patients in the niacin group (16.4%) and in 274 patients in the placebo group (16.2%) (hazard ratio, 1.02; 95 CI 0.87 to 1.21; p=0.79)	No signficiant results in primary end points.	The trial was stopped after a mean follow up period of 3 years due to lack of efficacy. Adverse effects were rare and included liver-function abnormalities, muscle symptoms or myopathy and rhabdomyolysis		Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter, there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36-month follow up period, despite significant improvements in HDL cholesterol and triglyceride levels.	Moderate		7.3
20228404	ACCORD Study Group, The 2010a	Effects of combination lipid therapy in type 2 diabetes mellitus	2010	Randomized Controlled Trial	USA	Clinical	Yes, double blinded				5518	Type 2 diabetes who were being treated with open-label simvastatin	Type 2 dia- betes and a glycated hemoglobin level of 7.5% or more. If patients had evidence of clinical cardio-vascular disease, the age range was limited to 40 to 79 years; if they had evidence of subclinical cardiovascular disease or at least two additional cardiovascular risk factors, the age range was com- pressed to 55 to 79 years. Patients were specifi- cally eligible to participate in the lipid trial if they also had the following: an LDL cholesterol level of 60 to 180 mg per deciliter (1.55 to 4.65 mmol per liter), an HDL cholesterol level below 55 mg per deciliter (1.42 mmol per liter) for women and blacks or below 50 mg per deciliter (1.29 mmol per liter) for all other groups, and a triglyceride level below 750 mg per deciliter (8.5 mmol per li- ter) if they were not receiving lipid therapy or be- low 400 mg per deciliter (4.5 mmol per liter) if they were receiving lipid therapy.	The mean age was 62 years, and 31% of the patients were female. Thirty-seven percent had a history of a cardiovascular event, and about 60% were taking a statin before enrollment.	2765	Pharmacologic	fenofibrate plus simvastatin	2753	placebo plus simvastatin	The prespecified primary outcome was the first occurrence of a major cardiovascular event, including nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Secondary outcomes included the combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure.	The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio in the fenofibrate group, 0.92; 95% confidence interval [CI], 0.79 to 1.08; P=0.32). There were also no significant differences between the two study groups with respect to any secondary outcome. Annual rates of death were 1.5% in the fenofibrate group and 1.6% in the placebo group (hazard ratio, 0.91; 95% CI, 0.75 to 1.10; P=0.33). Prespecified subgroup analyses suggested heterogeneity in treatment effect according to sex, with a benefit for men and possible harm for women (P=0.01 for interaction), and a possible interaction according to lipid subgroup, with a possible benefit for patients with both a high baseline triglyceride level and a low baseline level of high-density lipoprotein cholesterol (P=0.057 for interaction).				The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes.	High	Statin therapy	7.3
23440795	Cholesterol Treatment Trialists' (CTT) Collaboration 2010	Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials	2010	Meta-Analysis	United Kingdom					Assess the safety and efficacy of more intensive lowering of LDL cholesterol with statin therapy.	170000	Type 2 diabetes								Occlusive vascular events				Further reduction in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularization, and of ischemic stroke, with each 1.0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2-3 mmol/L would reduce risk by about 40-50%.	Meta-analysis		7.2; 7.3

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
18191683	Cholesterol Treatment Trialists' (CTT) Collaborators 2008	Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis	2008	Meta-Analysis	United Kingdom					Effects of statin therapy on occlusive vascular events and whether such effects depend on the type of diabetes, lipid profile, or other factors.	18686	Type 1 and Type 2 diabetes									Vascular events	During a mean follow up of 4.3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (RR 0.91, 99% CI 0.82-1.01, p=0.02), which was similar to the 13% reduction in those without diabetes (0.87, 0.82-0.92, p<0.0001). This finding reflected a significant reduction in vascular mortality (0.87, 0.76-1.00, p=0.008) and no effect on non-vascular mortality (0.97, 0.82-1.16, p=0.7) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0.79, 0.72-0.86, p<0.0001), which was similar to the effect observed in those without diabetes (0.79, 0.76-0.82, p<0.0001). In diabetic participants there were reductions in myocardial infarction or coronary death (0.78, 0.69-0.87, p<0.0001), coronary revascularization (0.75, 0.64-0.88, p<0.0001), and stroke (0.79, 0.67-0.93, p=0.0002). Among people with diabetes the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics. After 5 years, 42 (95% CI 30-55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy.				Statin therapy should be considered for all diabetic individuals who are at sufficiently high risk of vascular events.	Meta-analysis		7.3
15007110	Cannon 2004	Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes	2004	Randomized Controlled Trial	USA, Canada, United Kingdom	Clinical	Double blind			Examine the clinical benefit of lowering low-density lipoprotein (LDL) cholesterol levels below the target of <100.	4162	Adult patients who had been hospitalized for an acute coronary syndrome	men and women who were at least 18 years old were eli- igible for inclusion if they had been hospitalized for an acute coronary syndrome — either acute my- ocardial infarction (with or without electrocardio- graphic evidence of ST-segment elevation) or high- risk unstable angina — in the preceding 10 days.		2099	Pharmacologic	80 mg of atorvastatin daily	2063	40 mg of pravastatin daily	A composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 days after randomization), and stroke.	The median LDL cholesterol level achieved during treatment was 95 mg per deciliter (2.46 mmol per liter) in the standard-dose pravastatin group and 62 mg per deciliter (1.60 mmol per liter) in the high-dose atorvastatin group (P<0.001). Kaplan-Meier estimates of the rates of the primary end point at two years were 26.3 percent in the pravastatin group and 22.4 percent in the atorvastatin group, reflecting a 16 percent reduc- tion in the hazard ratio in favor of atorvastatin (P=0.005; 95 percent confidence interval, 5 to 26 percent). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.				Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovas- cular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially be- low current target levels.	High	Cardiovascular risk management-statin therapy	7.2; 7.3
12814710	Heart Protection Study Collaborative Group 2003	MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5,963 people with diabetes: a randomised placebo-controlled trial	2003	Randomized Controlled Trial	United Kingdom	Clinical	Yes	5 years	5 years	To determine the effects of cholesterol LDL lowering on vascular events.	5963 adults with diabetes and 14573 with occlusive arterial disease (but no diagnosed diabetes)	Men and women aged about 40-80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L were eligibile if they had a medical history of: diabetes mellitus, coronary disease, occlusive disease of non-coronary arteries; or treated hypertension (if also male and aged at least 65 years)	Men and women aged about 40-80 years with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L were eligibile if they had a medical history of: diabetes mellitus, coronary disease, occlusive disease of non-coronary arteries; or treated hypertension (if also male and aged at least 65 years)	Diabetes group mean age 62.1 years +/-8.9 70% men and 33% non-smoker. No diabetes group mean age 64.7 years +/-8.1, 78% men and 22% non smoker		Pharmacologic	40 mg simvastatin daily		Matching placebo	Vascular events	Both among the participants who presented with diabetes and among those who did not, there were highly significant reductions of about a quarter in the first event rate for major coronary events, for strokes, and for revascularizations. For the first occurrence of any of these major vascular events among participants with diabetes, there was a definite 22% (95%CI 13-30) reduction in the event rate (601 (20.2%) simvastatin-allocated vs 748 (25.1%) placebo-allocated, p<0.0001), which was similar to that among the other high-risk individuals studied. There were also highly significant reductions of 33% (95% CI 17-46, p=0.0003) among the 2912 diabetic participants who did not have any diagnosed occlusive arterial disease at entry, and of 27% (95% CI 13-40, p=0.0007) among the 2426 diabetic participants whose pretreatment LDL cholesterol concentration was below 3.0 mmol/L. The proportional reduction in risk was also about a quarter among various other subcategories of diabetic patient studied, including: those with different duration, type, or control of diabetes; those aged over 65 years at entry or with hypertension; and those with total cholesterol below 5.0 mmol/L. In addition, among participants who had a first major vascular event following randomization, allocation to simvastatin reduced the rate of subsequent events during the scheduled treatement period.				The study provides direct evidence that cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations. Allocation to 40 mg simvastatin daily reduced the rate of first major vascular events by about a quarter in a wide rate of diabetic patients studied. After making allowance for non-compliance, actual use of this statin regimen would probably reduce these rates by about a third. For example, among the type of diabetic patient studied without occlusive arterial disease, 5 years of treatment would be expected to prevent about 45 people per 1000 from having at least one major vascular event (and, among these 45 people, to prevent about 70 first or subsequent events during this treatment period). Statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations.	High		7.2; 7.3
7.4 Aspirin Therapy																											
18184894	Rosiak 2013	The effect of doubling the dose of acetylsalicylic acid (ASA) on platelet function parameters in patients with type 2 diabetes and platelet hyperreactivity during treatment with 75 mg of ASA: a subanalysis of the AVOCADO study	2013	Randomized Controlled Trial	Poland			2 years 8 months		To determine the effect of doubling the dose of ASA on platelet reactivity in patients with type 2 diabetes and HPR despite treatment of with 75 mg of ASA.	304	type 2 diabetes patients treated with 75 mg of ASA	stable patients aged 30–80 years with at least a 6-month history of type 2 diabetes treated with oral hypo-glycaemic drug and/or insulin, taking 75 mg of ASA daily for at least 3 months, were included into the study	65.8% male, mean age 66.1+/-9.7							Complete clinical data and blood samples were ultimately available for 260 of 304 patients initially enrolled to the study. Subsequently, six patients were excluded from the analysis based on suspected ASA non-compliance (sTXB2 level > 7200 pg/mL). Among 254 patients finally included into analysis, HPR was found in 90 (35.4%) patients of whom 38 patients were randomised to Group 1 and 52 patients to Group 2. Doubling the dose of ASA resulted in a significant CEPI-CT prolongation (D 111 s, p < 0.001) and reduction of sTXB2 level (D –101.3 pg/mL, p = 0.001) but did not significantly affect results of other platelet function tests.				Doubling the dose of ASA improved platelet reactivity in patients with type 2 diabetes and HPR.	Moderate	Aspirin	7.4
23796131	Macchia 2012	Statins but Not Aspirin Reduce Thrombotic Risk Assessed by Thrombin Generation in Diabetic Patients without Cardiovascular Events: The RATIONAL Trial	2012	Randomized Controlled Trial	Argentina	Hospital	blinded to events evaluation	8 to 10 weeks.	8 to 10 weeks.	Assess the effects of aspirin and statins on the thrombotic risk assessed by thrombin generation (TG) among patients with type II diabetes mellitus and no previous cardiovascular events.	30	Patients were males or females aged ≤50 years diagnosed with type 2 diabetes	Patients were males or females aged 50 years diagnosed with type 2 diabetes based on standard criteria at least 1 year prior to study entry. Inclusion criteria included treatment for diabetes with either oral agents or insulin therapy for at least the past one year, no previous cardiovascular events, and no treatment with aspirin or statins during the year prior to recruitment. The main exclusion criteria were current treatment with aspirin or any antiplatelet agent including sporadic use of NSAID and the presence of previous vascular events or any known hemorrhagic condition.	Aspirin mean age 56.5, and 42.9% female; control mean age 63.0 and 53.3% female	Between august 26th 2,009 and september 1st 2010, thirty patients were randomized. Of these, 14 were randomly assigned to receive aspirin and 16 to no aspirin. By 262 factorial design, 15 patients were randomized to receive atorvastatin and 15 were assigned to no atorvastatin group. There were no lost during the follow up, but in four patients (one assigned to aspirin, two to atorvastatin and one to no experimental treatment) measurements of TG was not available due to blood samples were not adequate for assays.	Pharmacologic	aspirin, atorvastatin		Placebo	Primary end point was the level of TG at the end of follow up, as measured by the peak of TG with saline as agonist. Other outcomes were peak TG with arachidonic acid, tissue factor, ADP and lag time with arachidonic acid.	At baseline all groups had similar clinical and biochemical profiles, including TG levels. There was no interaction between aspirin and atorvastatin. Atorvastatin significantly reduced TG measured as peak TG with saline (85.09+/-55.34 nmol vs 153.26+/-75.55 nmol for atorvastatin and control groups, respectively; p = 0.018). On the other hand, aspirin had no effect on TG (121.51+/-81.83 nmol vs 116.85+/-67.66 nmol, for aspirin and control groups, respectively; p = 0.716). The effects of treatments on measurements of TG using other agonists were consistent.		None		While waiting for data from ongoing large clinical randomized trials to definitively outline the role of aspirin in primary prevention, our study shows that among diabetic patients without previous vascular events, statins but not aspirin reduce thrombotic risk assessed by TG.	High	Aspirin	7.3; 7.4
23040422	Soejima 2012	Aspirin Reduces Cerebrovascular Events in Type 2 Diabetic Patients With Poorly Controlled Blood Pressure	2012	Randomized Controlled Trial	Japan	Clinical				To clarify the effect of the primary prevention of aspirin therapy in diabetic patients, the relationship between blood pressure (BP) and the incidence of atherosclerotic events was investigated in participants in the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial.	2539	type 2 diabetic patients from JPAD study without a history of atherosclerotic disease			1517							The incidence of the primary atherosclerotic events, especially cerebrovascular events, was higher in the unattained group than in the attained group. The incidence of cerebrovascular events was higher in the unattained group than in the attained group in patients undergoing aspirin therapy. Cox proportional hazards analysis revealed that BP level was an independent predictor for cerebrovascular events in diabetic patients.		In the unattained and attained groups, there were 7 patients and 9 patients, respectively, with gastrointestinal bleeding. In the unattained group, 2 patients had serious adverse events that necessitated transfusions; 2 patients in the attained group also required transfusions. In the unattained and attained groups, there were 3 patients and 10 patients with retinal hemorrhages. In the unattained group, 7 patients had hemorrhagic strokes; 6 patients in the attained group had hemorrhagic strokes. Over- all, there was no significant difference in the rate of hemor- rhagic events between the unattained group and the attained group.		Aspirin therapy may reduce cerebrovascular events in diabetic patients with higher BP. Aspirin therapy could be an additional strategy as primary prevention for diabetic patients with higher BP.	Low	Aspirin	7.4
23152231	Valentine 2012	Adenosine-diphosphate (ADP) receptor antagonists for the prevention of cardiovascular disease in type 2 diabetes mellitus	2012	Systematic review	Australia					To assess the effects of adenosine-diphosphate (ADP) receptor antagonists for the prevention of cardiovascular disease in type 2 diabetes mellitus.	21379	Type 2 diabetes												The available evidence for ADP receptor antagonists in patients with diabetes mellitus is limited and most trials do not report outcomes for patients with diabetes separately. Therefore, recommendations for the use of ADP receptor antagonists for the prevention of CVD in patients with diabetes are based on available evidence from trials including patients with and without diabetes. Trials with diabetes patients and subgroup analyses of patients with diabetes in trials with combined populations are needed to provide a more robust evidence base to guide clinical management in patients with diabetes.	Systematic Review	Aspirin	7.4
19482214	Antithrombotic Trialists' (ATT) Collaboration 2009	Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials	2009	Meta-analysis of Randomized Controlled Trials	United Kingdom					Assess risks and benefits of aspirin use in primary and secondary prevention of vascular disease	N=95000 in 6 primary prevention trials; N=17000 in 16 secondary prevention trials		Primary prevention trials: at least 1000 non-diabetic participants with at least 2 years of scheduled treatment and no history of occlusive disease at entry. Secondary prevention trials: individuals with previous myocardial infarction (six trials) or stroke or transient cerebral ischaemia (ten trials), and had contributed individual participant data to the 2002 Antithrombotic Trialists' (ATT) report							Serious vascular events	In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0·51% aspirin vs 0·57% control per year, p=0·0001), due mainly to a reduction of about a fifth in non-fatal myocardial infarction (0·18% vs 0·23% per year, p<0·0001). The net effect on stroke was not significant (0·20% vs 0·21% per year, p=0·4: haemorrhagic stroke 0·04% vs 0·03%, p=0·05; other stroke 0·16% vs 0·18% per year, p=0·08). Vascular mortality did not differ significantly (0·19% vs 0·19% per year, p=0·7). Aspirin allocation increased major gastrointestinal and extracranial bleeds (0·10% vs 0·07% per year, p<0·0001), and the main risk factors for coronary disease were also risk factors for bleeding. In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6·7% vs 8·2% per year, p<0·0001), with a non-significant increase in haemorrhagic stroke but reductions of about a fifth in total stroke (2·08% vs 2·54% per year, p=0·002) and in coronary events (4·3% vs 5·3% per year, p<0·0001). In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women.				In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds.	Meta-analysis	Aspirin	7.4

PMID	First Author	Title	Year	Study Type	Country	Setting	Blinding	Int Length	Total Study Duration	Main Study Objective	Target N	Target Population	Eligibility Criteria	Patient Characteristics	Int. n at Baseline (n at Follow-up)	Int. Type	Specific Intervention	Control n at Baseline (n at follow-up)	Specific Control	Outcomes Measured	Results/CI	Significance	Safety and Adverse Events	Additional Findings	Summary	Grade	Recommendations Used For	Document Recommendations Table
18927173	Belch 2008	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	2008	Randomized Controlled Trial	United Kingdom	Clinical	Double blinded		8 years	To determine whether aspirin and antioxidant therapy, combined or alone, are more effective than placebo in reducing the development of cardiovascular events in patients with diabetes mellitus and asymptomatic peripheral arterial disease.	1276	Adults aged 40 or more with type 1 or type 2 diabetes and an ankle brachial pressure index of 0.99 or less but no symptomatic cardiovascular disease.	Adults of either sex, aged 40 or more, with type 1 or type 2 diabetes who were determined as having asymptomatic peripheral arterial disease as detected by a lower than normal ankle brachial pressure index (≤0.99)	Aspirin plus antioxidant group (n=320) mean (SD) age (years) 61.0 (10.0) and 53% women; Aspirin plus placebo group (n=318) mean (SD) age (years) 60.0 (10.1) and 58% women; placebo plus antioxidant (n=320) mean (SD) age (years) 60.0 (10.3) 57% women; placebo plus placebo (n=318) mean (SD) age (years) 60.1 (9.7) 57% women.	Aspirin plus antioxidant n=320 (n=260); Aspirin plus placebo n=318 (n=279); placebo plus antioxidant n=320 (n=260); placebo plus placebo n=318(n=275)	Pharmacologic	Aspirin and antioxidant alone or combined	n=318(n=275)	Placebo alone or combined with placebo	Two hierarchical composite primary end points of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischaemia; and death from coronary heart disease or stroke.	Overall, 116 of 638 primary events occurred in the aspirin groups compared with 117 of 638 in the no aspirin groups (18.2% v 18.3%): hazard ratio 0·98 (95% confidence interval 0·76 to 1·26). Forty three deaths from coronary heart disease or stroke occurred in the aspirin groups compared with 35 in the no aspirin groups (6.7% v 5.5%): 1·23 (0·79 to 1·93). Among the antioxidant groups 117 of 640 (18.3%) primary events occurred compared with 116 of 636 (18.2%) in the no antioxidant groups (1.03, 0.79 to 1.33). Forty two (6.6%) deaths from coronary heart disease or stroke occurred in the antioxidant groups compared with 36 (5.7%) in the no antioxidant groups (1.21, 0.78 to 1.89).	Not significant			No evidence to support the use of aspirin or antioxidants in primary prevention of cardiovascular events and mortality in the population with diabetes studied.	High	Aspirin	7.4
18519931	Ogawa 2008	Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes: A Randomized Controlled Trial	2008	Randomized Controlled Trial	Japan	Clinical	Blinded	5 years and 9 months	5 years 9 months	To examine the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes.	2539	type 2 diabetes without a history of atherosclerotic disease				1262(1165)	Pharmacologic	low-doseaspiringroup(81or100mg per day)	1277(1181)	Nonaspirin	Primary end points were atherosclerotic events, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. Secondary end points included each primary end point and combinations of primary end points as well as death from any cause.	A total of 154 atherosclerotic events occurred: 68 in the aspirin group (13.6 per 1000 person-years) and 86 in the nonaspirin group (17.0 per 1000 person-years) (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58-1.10; log-rank test, P = .16). The combined end point of fatal coronary events and fatal cerebrovascular events oc- curred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; P = .0037). A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14; log-rank test, P = .67). The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and nonaspirin groups.				In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.	High	Aspirin	7.4
17488967	Campbell 2007	Aspirin dose for the prevention of cardiovascular disease: a systematic review	2007	Systematic review	USA					To review the mechanism of action of aspirin and the clinical literature for relationships among aspirin dosage, efficacy, and safety.	11 Studies Included in Review (8 RCTs and 3 observational studies)					Pharmacologic	Aspirin dosing			Relationship of aspirin dosage to efficacy and safety.	The available evidence, predominantly from secondary-prevention observational studies, supports that dosages greater than 75 to 81 mg/d do not enhance efficacy, whereas larger dosages are associated with an increased incidence of bleeding events, primarily related to gastrointestinal tract toxicity.		Increased risk of gastrointestinal bleeding at higher dosages of aspirin		Currently available clinical data do not support the routine, long-term use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher dosages, which may be commonly prescribed, do not better prevent events but are associated with increased risks of gastrointestinal bleeding.	Systematic Review	Aspirin	7.4
23543567	Pignone 2006	Aspirin, Statins, or Both Drugs for the Primary Prevention of Coronary Heart Disease Events in Men: A Cost-Utility Analysis	2006	Cost-utility	USA					To perform a cost-utility analysis of the effects of aspirin therapy, statin therapy, combination therapy with both drugs, and no pharmacotherapy for the primary prevention of CHD events in men.		Middle-aged men without a history of cardiovascular disease at 6 levels of 10-year risk for CHD (2.5%, 5%, 7.5%, 10%, 15% and 25%)				Pharmacologic	Low-dose aspirin, a statin, both drugs as combination therapy, or no therapy			Effects of aspirin therapy, statin therapy, combination therapy with both drugs, and no pharmacotherapy for the primary prevention of CHD events in men.	Base-case analysis: For 45 year-old men who do not smoke, are not hypertensive, and have a 10-year risk for CHD of 7.5%, aspirin was more effective and less costly than no treatment. The addition of a statin to aspirin therapy produced an incremental cost-utility ratio of $56200 per quality-adjusted life year gained compared with aspirin alone. Sensitivity analysis: Excess risk for hemorrhagic stroke and gastrointestinal bleeding with aspirin, risk for CHD, the cost of statins, and the disutility of taking medication had important effects on the cost-utility ratios.				Compared with no treatment, aspirin is less costly and more effective for preventing CHD events in middle-aged men whose 10-year risk for CHD is 7.5% or higher. The addition of a statin to aspirin therapy become more cost-effective when the patient's 10-year risk before treatment is higher than 10%.	Low	Aspirin	7.4