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Strategies for improving cardiovascular health in women with diabetes mellitus: a review of the evidence

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Abstract

Knowledge about cardiovascular (CV) disease in women with diabetes mellitus (DM) has changed substantially over the past 20 years. Coronary artery disease, strokes, and peripheral vascular disease affect women with DM at higher rates than the general population of women. Lifestyle therapies, such as dietary changes, physical activity, and smoking cessation, offer substantial benefits to women with DM. Of the pharmacotherapies, statins offer the most significant benefits, but may not be well tolerated in some women. Aspirin may also benefit high-risk women. Other pharmacotherapies, such as fibrates, ezetimibe, niacin, fish oil, and hormone replacement therapy, remain unproven and, in some cases, potentially dangerous to women with DM. To reduce CV events, risks to women with DM must be better publicized and additional research must be done. Finally, advancements in health care delivery must target high-risk women with DM to lower risk factors and effectively improve cardiovascular health.

Keywords

Female; diabetes mellitus; cardiovascular disease; myocardial infarction; stroke; gender

Introduction

Diabetes mellitus (DM) affects 13.4 million adult women in the United States [¹]. While women previously made up small numbers in clinical trials, many investigators over the past 20 years have recognized the importance of including more women in clinical studies. Through their work, much has been learned about risks particular to women with diabetes. Specifically, diabetes confers higher relative risks of cardiovascular (CV) disease in women than in men and remains a significant source of morbidity and mortality in women. This

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review aims to highlight risk factors and therapies specific to the care for women with diabetes.

Incidence and pathophysiology

While CV disease rates are much lower in women than men in the general population, rates of heart disease and stroke among women with DM are nearly equal to men [2]. In 2011, 31.5% of women with DM in the U.S. reported heart disease or stroke, as compared to 35.5% of men [2]. In effect, DM increases the risks of CV events more in women than in men [3,4]. The reasons for this disparity are unclear. One hypothesis is that women with pre-diabetes and diabetes may have greater endothelial dysfunction than men [5–7]. For example, one study demonstrated that women with pre-diabetes had significantly higher biomarker levels of endothelial dysfunction (E-selectin and soluble intracellular adhesion molecule 1) and fibrinolysis (plasminogen activator inhibitor-1) than women without pre-diabetes, while men with and without pre-diabetes had similar biomarker levels [5]. The Nurses Health Study, an observational study of over 117,000 female nurses followed since 1976, also found that cardiovascular risk increased in women at least 15 years before a clinical diagnosis of diabetes [8]. Thus, early diagnosis of pre-diabetes and diabetes may be especially important for reducing cardiovascular disease in women.

Coronary artery disease

Studies have shown that diabetes increases the risk of both fatal and overall coronary artery disease (CAD) more in women than in men. One meta-analysis of 64 cohort studies among 858,507 individuals with DM showed a 44% greater risk of CAD in women compared to men (adjusted relative risk, RR, 1.44, 95% CI 1.27–1.63)[3]. Another meta-analysis examined fatal CAD in 447,064 patients and found that the relative risk of fatal CAD associated with DM was approximately 50% higher in women than men (RR 1.46, 95% CI 1.14–1.88) [9]. Further, women with DM (but without overt CAD) on glucose-lowering medications have similar rates of myocardial infarction (MI), stroke, and cardiovascular death as women with a prior MI [10]. These studies indicate that diabetes in most women confers risk equivalence to CAD and warrants aggressive CV risk factor management as part of their diabetes care.

Stroke

Like CAD, DM increases the risk of stroke in women more so than in men. A meta-analysis of 64 cohort studies among 775,385 individuals found that DM increased the risk of stroke by 27% (RR 1.27, 95% CI 1.10–1.46) in women compared to men [4]. Further, this study found that women with DM have over twice the risk of stroke compared to women without DM (RR, 2.28, 95% CI 1.93–2.69) [4]. The consequences of stroke among survivors are also greater among women than men; women have higher rates of institutionalization and greater disability following stroke as compared to men [11]. While disability after stroke in women with DM is not generally reported, both female gender and DM are individually associated with worse outcomes [12,13]. For example, in 4,390 patients with strokes, female gender

and DM had ORs of 1.22 (95% CI 1.05–1.42) and 1.51 (95% CI 1.27–1.81), respectively, of severe disability requiring help from others with activities of daily living [13].

Congestive Heart Failure

Congestive heart failure (CHF) is common in patients with diabetes and is often due to ischemia, hypertension, or diabetic cardiomyopathy [14]. Studies indicate that DM disproportionately affects outcomes in women with CHF. In one propensity-matched, longitudinal study of patients with CHF, diabetes-associated increases in mortality were more pronounced in women than in men (HR 1.67 versus HR 1.21, p for interaction=0.005) [15]. The same study also showed that diabetes-associated increases in hospitalization rates were greater in women than men (HR 1.49 versus 1.21, p for interaction=0.011) [15]. A population-based study of Scotland showed similar findings, though only in patients less than 74 years of age [16]. Women with DM and co-morbid CHF, therefore, are high risk for morbidity and mortality and require careful optimization and follow-up.

Peripheral vascular disease

Compared to CAD and strokes, less is known about gender-specific risks of and treatments for peripheral vascular disease (PVD) in general [17,18] and among patients with diabetes. One analysis of over 3.5 million patients estimated an adjusted odds ratio (OR) of peripheral arterial disease of 1.38 (95% CI 1.36–1.41) in women with DM compared to those without DM [19]. Similarly, women with DM had an adjusted OR of carotid artery stenosis of 1.53 (95% CI 1.50–1.56) compared to women without DM. There was no significant difference in rates of abdominal aortic aneurysm among women with or without DM. Women may also suffer greater morbidity from PVD than men. For example, one cross-sectional study of 187 women and 273 men demonstrated a higher prevalence of leg pain on exertion and rest and poorer functioning among women compared to men with peripheral arterial disease [20].

Pregnancy

Acute MI during pregnancy is a rare event, with estimated incidences of 1 in 16,129 to 35,700 deliveries [21]. Stroke, while rare, is more prevalent and has been increasing in incidence in the U.S. with the most recent estimate of 4.8 per 10,000 deliveries [22]. This represents an increase of 61.5% from 1994–1995, which may at least partially be due to an increase in hypertensive disorders over this time period [22]. Unsurprisingly, diabetes has been identified as a risk factor for MI and stroke in pregnancy. Women with diabetes had higher rates of both outcomes than the general population with estimated ORs of MI and stroke of 3.6 (95% CI 1.5–8.3) [23] and 2.5 (95% CI 1.3–4.6) [24], respectively, though absolute rates are still low. PVD, while occurring in 2–12% of diabetic women of reproductive age, has not been extensively studied in pregnant patients [25]. Management of CV disease risk factors in pregnant women is similar to non-pregnant women with guidelines emphasizing healthy food intake, physical activity, smoking cessation, and control of blood glucose, blood pressure (BP), and lipids [25]. Of course, pharmacotherapy needs to be adjusted in pregnancy with some commonly used medications in non-pregnant

patients, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), statins, and aspirin, carrying risks of fetal toxicity [21].

Pregnant women with DM are also at risk for developing hypertensive disorders such as gestational hypertension and pre-eclampsia. In a recent observational study, women with pre-existing DM had an adjusted OR 3.88 (95% CI 2.08–7.26) of developing pre-eclampsia [26]. Pre-eclampsia, in turn, can lead to short-term morbidity (e.g. stroke), but also is associated with higher risk of future chronic hypertension, kidney disease, and CAD [27]. Even women who develop gestational DM have been shown to have higher risk of future CV events (HR 1.71, 95% CI 1.08–2.69), though most of this risk is related to the development of overt DM [28]. Therefore, development of these disorders in pregnancy represents a need for intervention, requiring regular follow-up with a physician after pregnancy for optimization of risk factors.

Primary and secondary prevention of CV events

Many interventions, both pharmacologic and non-pharmacologic, have been studied to reduce CV risk in patients with DM. Results from these interventions are not identical in women and men (Table 1). We describe what gender differences are known and what is yet to be determined.

Diet and weight loss

Poor diet alone is a significant contributor to the development of DM in women [29], and dietary modifications have been studied in patients with DM to assess effects on CV risk reduction. One randomized trial of a Mediterranean diet with either nuts or extra virgin olive oil versus placebo showed reduced CV events (RR 0.71, 95% CI 0.56–0.90), including in female and DM subgroups [30]. The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to decrease LDL, increase HDL, and lower BP in patients with DM without gender differences [31]. However, no trial has specifically looked at CV endpoints in patients with DM with the DASH diet.

While dietary changes have shown benefit, weight loss itself has not definitively been shown to improve CV outcomes. The Look AHEAD (Action for Health in Diabetes) trial randomized 5,145 overweight or obese DM patients (3,063 women) to intensive lifestyle intervention versus a control group that received diabetes support and education [32]. After median 9.6 years follow up, despite persistently greater weight loss in the intervention group, there were no significant differences in CV endpoints. No gender differences were seen. It may be that the study was underpowered or that greater weight loss or longer duration of follow-up is necessary.

Physical Activity

Physical activity is a well-known and validated method for reducing CV risk in men and women [33–35] in general. Women may derive greater benefit from physical activity than men—for example, women who exercise have slightly greater reductions in BP [36] and overall CV mortality [35] than men. Large benefits from physical activity are also seen in

women with DM. In 5,125 women with DM in the Nurses' Health Study cohort, women who were physically active 2 to 3.9 and 4 to 6.9 hours per week had adjusted RR of 0.87 (95% CI, 0.64–1.17) and 0.61 (95% CI 0.44–0.86), respectively, of CV events compared to those who were active less than 1 hour per week [37]. Brisk walking was included in this observational study and can serve as an accessible way for many women with DM to include physical activity as part of their weekly routine.

Physical activity, including walking is also a mainstay of treatment for PVD. As noted earlier, trial evidence for PVD treatment in women are lacking. One small study of 16 women with DM showed that exercise rehabilitation led to a 9 times lower likelihood of increasing claudication onset time and peak walking time compared to men without DM [38]. Further trials in women with DM and PVD are necessary.

Smoking Cessation

Cigarette smoking is a significant risk for cardiovascular disease and may be a greater risk factor in women than men. A meta-analysis that included 2.4 million smokers showed an adjusted female-to-male ratio of relative risk of coronary artery disease of 1.25 (95% CI, 1.12–1.39) [39]. In the Nurses' Health Study cohort, among 6,547 women with DM, compared to non-smokers, the RR for CAD were 1.21 (95% CI, 0.97–1.51) for past smokers, 1.66 (95% CI, 1.10–2.52) for current smokers of 1–14 cigarettes per day, and 2.68 (95% CI, 2.07–3.48) for current smokers of 15 or more cigarettes ($p < 0.001$ for trend) [40].

A major patient concern with smoking cessation is weight gain. For example, in one study, women with DM who quit smoking in the previous 3 years had a mean increase of body weight of 3.0 kg; however, they also had a much lower risk of CAD compared to smokers (relative risk, 0.36; 95% CI 0.16–0.77) [41].

It is not clear if women have lower quit rates than men. Some studies have shown lower relative quit rates by 20–30% [42,43], while others have shown no differences [44]. To date, there also is no definitive evidence that any individual smoking cessation products, including the nicotine patch, bupropion, or varenicline, work better or worse in women than men [43,45–47]. On the other hand, one cohort study of 1,079 smokers attempting to quit (490 women) showed quit rates in women were no different than men when any smoking cessation medication was used, though lower quit rates in women were found among those not prescribed any smoking cessation medication [42]. Studies of pharmacotherapies in patients with DM are limited, but behavioral and psychosocial support can be effective in helping patients with DM quit smoking [48,49]. As several options for smoking cessation now exist, it is important for providers to individualize smoking cessation treatments in order to minimize overall CV risk in women with DM.

Statins

Statins are the most studied and proven medications in reducing CV events and are equally effective in women and men [50,51]. A meta-analysis of 18,686 people with diabetes in 14 randomized trials of statins showed a 9% relative reduction in all-cause mortality (rate ratio 0.91, 99% CI 0.82–1.01, $p = 0.02$) and a 21% relative reduction in major vascular events for

every 1 mmol/L reduction (or 39 mg/dL) in LDL (rate ratio 0.79, 99% CI 0.72–0.86, $p<0.001$) without gender differences [52].

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) issued new guidelines for the treatment of hyperlipidemia that dramatically expanded recommendations for the use of statins for primary prevention in patients with DM [53]. These guidelines recommend moderate or high dose statins for patients with DM if they are between the ages of 40–75 and have an LDL 70–189 mg/dL. If patients with DM have a 10-year CV risk of 7.5% or greater using the accompanying risk calculator, high dose statin therapy should be considered; otherwise, a moderate dose statin is recommended. These guidelines are not gender specific and thus are appropriate for women with DM.

While statins should be recommended for most women with diabetes, they may be less tolerant of statins than men [54]. Discontinuation rates in women ranged from 2.4–15.1% in a meta-analysis of 6 statin trials, though in only one trial did women have significantly higher discontinuation rates than men [55]. The meta-analysis also showed that DM was associated with an increased risk of adverse effects in women, but not in men (HR 1.33, 95% CI 1.09–1.63, $p=0.005$, gender-by-factor interaction $p=0.04$). Management strategies for statin intolerance include changing the statin, reducing the dose, or decreasing the frequency of statin therapy. Pravastatin, fluvastatin, or low dose daily or every other day rosuvastatin may have lower risks of adverse effects and may be considerations [56–58]. A new monoclonal antibody based class of drugs called proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have also demonstrated LDL reduction and short-term tolerability in statin-intolerant patients [59] and may be available in the near future. More research is necessary to determine the tolerability and benefits of these regimens to best treat statin-intolerant women.

Statins also have been associated with a higher risk of developing DM [60], and this risk may be even greater in women. In a meta-regression analysis of 13 placebo-controlled statin trials, a significant relationship was found between the percent of women in statin trials and the OR of developing diabetes, suggesting higher risk in women [60]. However, despite these effects, the reduction of CV events in those taking statins likely outweigh the development of DM—an analysis of patients at high risk for developing DM showed 134 vascular events or death were prevented for every 54 cases of DM diagnosed [61]. In patients with pre-existing DM, small trials have shown worse fasting blood sugar and A1c in patients treated with atorvastatin, but not pravastatin, suggesting potency or drug-related effects [62, 63]. Gender differences in patients with pre-existing DM have not been evaluated. Further studies are required, as certain low CV risk patients with DM may suffer greater detriment than benefit from statin initiation.

Other Dyslipidemia Agents

Unfortunately, other dyslipidemia agents have not proved efficacious for reducing CV events. Fibrates, while reducing triglycerides and increasing HDL [64], are not associated with improved CV outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial did not show significant differences in CV events in 5,518 patients with

DM and high risk of, or pre-existing, CV disease randomized to fibrates or placebo [64]. In fact, the ACCORD trial showed higher rates of CV events among women in the fenofibrate group than the placebo group (9.05% versus 6.64%, p-value for gender interaction=0.01). At this time, the role of fibrates is unclear in women and men with DM.

Niacin also decreases LDL and triglycerides and increases HDL; however niacin may lead to worse glycemic control [65] and should be avoided in patients with diabetes. Two large trials, Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) also did not find any reductions in CV events with extended-release niacin or niacin-laropiprant combination, respectively, in subgroups of patients with DM [65,66] or women.

Ezetimibe is a selective inhibitor of cholesterol and sterol absorption in the small intestines. While effective in reducing LDL [67,68], no study has yet evaluated CV outcomes. An ongoing large secondary prevention trial, IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), is assessing the effect of ezetimibe and simvastatin combination therapy. More research in patients with DM but without previous acute coronary syndrome is necessary.

Fish oil and n-fatty acids have been studied as both food intake and as supplements. They have been shown to decrease triglycerides, but also increase LDL [69]. Epidemiological results from 5,103 women with DM in the Nurses' Health Study found lower relative risks of CAD and total mortality in those with greater intake of fish [70]. However, no effect on CV events was noted in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial. This trial randomly allocated 12,536 patients with impaired fasting glucose, impaired glucose tolerance, or DM to n-3 fatty acids and/or insulin glargine versus placebo [71]. Regardless of insulin glargine allocation, patients randomized to n-3 fatty acids showed no differences in CV events compared to placebo. Differences by gender have not been examined. A Study of Cardiovascular Events in Diabetes (ASCEND), an ongoing trial, has randomized over 15,000 patients with DM to aspirin and/or fish oil versus placebo and may help elucidate the role of fish oil and n-fatty acids [72].

Aspirin

Given that patients with DM have increased risks of CV disease, several studies have examined the utility of aspirin for primary prevention. When taking women and men with DM together, several meta-analyses have shown that aspirin as primary prevention is not effective in reducing total CV events [73-75]. One of these analyses [73] showed reduced risk of MI in men, but not women, and reduced risk of stroke in women, but not men—findings similar to studies of patients without DM [76,77]. Why women do not receive the same benefit of aspirin therapy for prevention of MI as men is not clear. The discrepancy may be related to differences in baseline rates of MI in women versus men, but others have also theorized that increased platelet reactivity in women [78] or greater frequency of aspirin resistance in women [73,78] may play a role.

Based on the conflicting evidence, the American Diabetes Association (ADA) guidelines in 2015 [79] state that it is “reasonable” to recommend low dose aspirin therapy (75–162 mg/day) as primary prevention with 10-year risk of CV events of 10% or greater and in patients without increased risk of bleeding. The guidelines note this generally includes most women over the age of 60 who also have one other risk factor, such as smoking, hypertension, hyperlipidemia, family history of premature CVD, or albuminuria. In patients with 10-year risk of CV events of 5–10%, clinical judgment should be used, while aspirin is not recommended in patients with low CVD risk (<5% risk) due to risk of bleeding. Various CV risk calculators can be used to estimate 10-year risk including the ACC/AHA calculator [79]. Individual patient characteristics and patient preferences (risks of bleeding versus the benefits of stroke prevention) should also be incorporated into decisions regarding aspirin.

Antihypertensives

The ADA recommends a BP goal of at least <140/90 for all patients with DM with the caveat that lower goals may be appropriate for some patients, such as those with greater stroke risk [79]. There are very few trials examining gender-based differences in response to antihypertensive medications in patients with DM. Most studies showed no BP differences among sexes [80–82]. Even among women without DM, only small, likely trivial differences have been noted in large analyses [83,84]. Women have been noted to have 1.5–2 times greater rates of cough with ACEI than men [85]. It should also be noted that ACEIs and ARBs, considered first line for hypertension in patients with DM [79], are contraindicated in pregnancy, while thiazides may reduce the risk of hip fracture [86]. Overall, patient-specific factors, such as adverse effects or co-morbidities, should dictate the most appropriate antihypertensive regimen.

Hormone Replacement Therapy

Hormone replacement therapy remains unproven and possibly dangerous in women, including women with DM. Two placebo-controlled randomized trials of standard HRT in the last 15 years showed no CV benefit when used as primary prevention [87,88]. In one of these trials, the Women’s Health Initiative (WHI), increased CV events and risk of breast cancer were noted [88]. Results were similar among the 734 women with DM in the study [88]. Since the results of these two studies, a “timing hypothesis” has received some support in the literature [89–92]. Advocates of this hypothesis believe that women who receive HRT shortly after menopause receive CV benefit while older women do not. However, this has not been tested as the primary hypothesis of a prospective trial and given the overall uncertainty and potential for harm, HRT should not be given to women with DM for primary or secondary prevention of CVD.

Depression screening and treatment

Depression is approximately two-fold more common in women than men [93], and 20% of women will experience depression in their lifetime [94]. Depression in patients with DM has been linked to poor glycemic control, [95–97], treatment non-adherence [98], and higher risk of myocardial infarction [99]. Women with DM and depression have an adjusted relative

risk of CV mortality of 3.89 (95% CI, 3.00–5.05) versus healthy individuals, compared to relative risks of 2.15 (95% CI, 1.76–2.64) with diabetes alone or 1.56 (95% CI, 1.33–1.84) with depression alone [100]. The relationship between DM and depression is thought to be bidirectional [101, 102], meaning the presence of either condition increases the risk of developing or worsening the other condition.

Psychological and pharmacologic interventions for depression in patients with DM improves depression outcomes with both psychological and pharmacological interventions [103, 104]. Short-term glycemic control was also improved in one meta-analysis [104], though other important endpoints, such as CV events or all-cause mortality have not yet been evaluated. While further research is necessary, depression screening should be part of providers' assessment when treating women with DM.

Achieving CV goals in women

Though women with DM experience cardiovascular morbidity and mortality comparable to men, women are still treated by providers less aggressively. Studies in various populations, both in patients with and without DM, have shown that women have worse control of systolic BP, cholesterol, and A1c than men. Studies have also shown that women with DM less frequently receive lipid lowering medications [105, 106] and ACEI inhibitors [107]. In one study of patients with DM and CAD, women were less frequently prescribed aspirin [105], though this is not a consistent finding in all studies [107]. While some of the discrepancies in reaching treatment goals are related to less treatment, two Italian studies (one exclusively in DM patients) showed that women, despite receiving similar treatment types, still failed to reach treatment goals more frequently than men [108, 109]. It may be that women do not respond to treatments the same as men do or that other factors, including co-morbidities or socioeconomic factors, are playing a role. Thus, to reduce differences in care, it is important to increase the inclusion of women in clinical trials and stratify measures of quality of care by gender.

Innovative Care models: the next step?

Given the high burden of CV morbidity and mortality in patients with DM, innovative care models have increased in recent years to improve quality of care. These innovative care models have been implemented in a wide variety of populations with DM. In a meta-analysis of randomized clinical trials, a wide variety of quality improvement (QI) approaches improved glycemic control, antihypertensive use, and routine foot and eye exams [110]. Successful QI interventions include using multidisciplinary teams and non-physician providers, promotion of patient self-management, case management, and patient education. These studies found small but statistically significant, improvements in LDL, systolic blood pressure, and diastolic blood pressure. Importantly, patient education alone can improve DM related measures, especially in patients with A1c greater than 8.0 [110, 111]. There were no gender-specific analyses though women made up 50% of these study populations. Future trials should consider gender-specific analyses because women may benefit from different types of approaches than men, which could lead to changes in the way these care models are utilized.

Conclusion

Women with DM suffer a disproportional burden of CV disease. This disparity does not have a single cause or culprit and requires a multifaceted approach to correct (Figure 1, Table 2). First and most simply, the disparity should be recognized, publicized, and addressed. Providers should assess the quality of diabetes care by gender in order to identify any disparities. Extra clinical effort may be required to treat women with DM as aggressively as men in regards to the most common CV risk factors, such as LDL and high BP. Second, women should be aggressively recruited into all relevant clinical trials and further research into differences in how men and women respond to treatment is necessary. Finally, and most challenging, will be efforts to change the way we deliver healthcare to women with DM. As we have just discussed, many of the most important ways to decrease CV morbidity and mortality in women with DM are related to behavioral changes—increases in physical activity, an improved diet, or smoking cessation. These ends can be achieved through a comprehensive approach to care, such as those found in many innovative care models, and may require programs designed specifically for women. Women may respond to different types of messaging or may become more engaged with self-management when multi-disciplinary teams are involved. They also may be burdened by co-morbid depression or simply challenged by multiple roles at home and/or work. The additional support of a non-physician provider or case manager can alleviate some of this burden and, in turn, allow for improved diabetes management.

While women with DM are a much more important part of CV research than 20 years ago, much is yet to be done. Lower rates of CV disease in women overall continue to lull providers into a false sense of security regarding the high risk for CV disease among women with DM. With dedicated effort, the substantial work of investigators over the past 20 years can translate into better outcomes for women with DM: reduced incidence, morbidity, and mortality from cardiovascular events.

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Figure 1.
Multifaceted approach to reducing CV risks in women with DM

Table 1

Summary of intervention trials

Study Authors or Title	Study Type	Study Location	Participants	Percent women included	Therapy	Follow up [*]	Results	Gender difference
Diet and weight loss								
Estruch et al (2013) ^[30]	RCT	Spain	7,477 with DM or at least 3 CV risk factors (3,614 with DM)	57%	Olive oil or nut-based Med Diet versus control	IQR: 2.8–5.8 years; Median 4.8 years	Lower CV events in Med Diet groups (HR 0.71, 0.56–0.90), including in DM subgroup	None
Look AHEAD (2013) ^[32]	RCT	U.S.	5,145 with DM	59.5%	Lifestyle intervention for weight loss vs. education	IQR: 8.9–10.3 years; Median 9.6 years	Significantly greater weight loss with intervention; no difference in CV events	None
Physical Activity								
Arem et al (2015) ^[35]	Cohort study	U.S. and Europe	661,137 general population with BMI 15–60	55.9%	Physical activity (varying amounts)	0–15.2 years; Median 14.2 years	Increasing activity associated with lower risk of death (range of RR 0.59–0.82 at different activity levels)	Women vs. men: 1–5% greater risk reduction at most levels of activity
Hu – Nurse’s Health Study (2001) ^[37]	Cohort study	U.S.	5,125 female nurses with DM	100%	Physical activity (varying amounts)	14 years	Greater physical activity associated with fewer CV events [2 to 3.9 vs. <1 hr/wk; adjusted RR 0.87 (0.64–1.17)]	N/A
Smoking Cessation								
Luo et al (2013) ^[41]	Cohort study	U.S.	6,338 women with DM	100%	Smoking Cessation	Mean 8.8 ± 2.8 years	Those who quit smoking had HR 0.36 (0.34–0.45) of CAD compared to current smokers	N/A
Smith (2015) ^[42]	Cohort study	U.S., Canada, U.K., Australia	1,079 smokers who attempted to quit	45.4%	Any SCM	30 day follow-up	No gender differences in quit rates for those prescribed any SCM	Women not prescribed SCM had OR 0.59 (0.39–0.90) of quitting vs. men
Dyslipidemia Agents								
Cholesterol treatment Trialists (2008) ^[52]	Meta-analysis of RCTs	Multiple – including the U.S.	18,686 with DM; 71,370 without DM	33.0% with DM; 21.6% without DM	Statins vs. placebo	1.9–5.6 years	9% reduction in all-cause mortality (RR 0.91, 99% CI 0.82–1.01, p=0.02); 21% reduction in major vascular events (RR 0.79, 99% CI 0.72–0.86, p<0.001)	None
ACCORD (2010) ^[64]	RCT	U.S. and Canada	5,518 patients with DM	30.7%	Fenofibrate vs. placebo	Mean 4.7 years	No difference in CV events	Possible harm to women (gender interaction p=0.01)

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Study Authors or Title	Study Type	Study Location	Participants	Percent women included	Therapy	Follow * up	Results	Gender difference
AIM-HIGH (2011) [66]	RCT	U.S. and Canada	3,414 with CV disease (1,158 with DM)	14.8%	Niacin vs. placebo	Mean 3 years	No difference in CV events including DM subgroup	None
HPS2-THRIVE (2014) [65]	RCT	U.K., Scandinavia, China	25,673 with CV disease or DM (8,299 with DM)	17.3%	Niacin-Laropiprant vs. placebo	Median 3.9 years	No differences in CV events including DM subgroup	None
Hu – Nurses’ Health Study (2003) [70]	Prospective cohort	U.S.	5,103 women with DM	100%	Fish intake (varying levels of intake)	16 years	Reduction in CV events ranging from RR 0.70 to 0.36 with increasing fish intake	N/A
ORIGIN (2012) [71]	RCT	Multiple, including the U.S.	12,536 with IFG, IGT, or DM	35.0%	1 g of n-3 fatty acids versus placebo (1 g olive oil)	Median 6.2 years	No differences in CV events.	Not reported
Aspirin								
Zhang et al (2010) [73]	Meta-analysis of RCTs	Multiple, including the U.S.	11,618 with DM	63.6%	Aspirin (varying doses) vs. placebo	3.7 to 10.1 years	No differences in CV events overall	Trials >50% women: CVA RR 0.67 (0.48–0.92), MI RR 1.1 (0.75–1.62), Trials <50% women: CVA RR 1.05 (0.83–1.33), MI RR 0.71 (0.50–1.00)
De Baradis et al (2009) [74]	Meta-analysis of RCTs	U.S, Italy, Scotland, Japan	10,117 with DM	31.4%	Aspirin (varying doses) vs. placebo	3.6–10.1 years	No differences in CV events	Men: RR 0.57 (0.34–0.84) of MI; No differences in differences in stroke
Simpson (2011) [75]	Meta-analysis of RCTs	Multiple, including the U.S.	17,522 with DM	Not reported	Aspirin (varying doses) vs. placebo	1–11.6 years; Median 3.6 years	No differences in CV events	Not reported
Hormone Replacement Therapy								
Herrington et al (2000) [87]	RCT	U.S.	309 women with angiogram confirmed CAD	100%	CE vs. CE plus MPA vs. placebo	Mean 3.2 ± 0.6 years	Reduced LDL and increased HDL; no differences in progression of CAD by angiogram	N/A
Women’s Health Initiative (2002) [88]	RCT	U.S.	16,608 healthy post-menopausal women	100%	CE plus MPA vs. placebo	Mean 5.2 years	HRT increased CAD (HR 1.29, 1.02–1.63) and stroke (HR 1.41, 1.07–1.85)	N/A
Depression therapies								
Baumeister et al (2014) [104]	Meta-analysis of RCTs	Multiple, including the U.S.	5,238 with DM and depression	Included trials 20–100%	Both psychological & pharmacotherapies	3 weeks to 12 months	Pharmacotherapy, but not psychological interventions, led to improvements in short-term glycemic control	Not reported

Study Authors or Title	Study Type	Study Location	Participants	Percent women included	Therapy	Follow * up	Results	Gender difference
Comprehensive Care Models								
Tricco et al (2012) [110]	Meta-analysis of RCTs	Multiple, including the U.S.	123,529 with DM	50.5%	Variety of QI measures (see text)	1–93.6 months; Median 12 months	Small, but significant improvements in LDL and BP	Not reported

* Follow up times for meta-analyses list the range of means of included trials

Listed ranges are 95% CI unless otherwise stated.

Abbreviation: FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD = Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides; Impact on Global Health Outcomes; HPS2-THRIVE = The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events; ORIGIN = Outcome Reduction with an Initial Glargine Intervention; Look AHEAD = Look Action for Health in Diabetes; RCT = randomized control trial; IQR = interquartile range; Med Diet = Mediterranean Diet; CAD = coronary artery disease; SCM = smoking cessation medication; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; DM = diabetes mellitus; CV = cardiovascular; CE = conjugated estrogen; MPA = medroxy-progesterone acetate; QI = quality improvement; LDL = low-density lipoprotein; BP = blood pressure.

Table 2

Strategies to reduce CV risks in women with DM

Strategy	Rationale
Early identification of pre-diabetes and diabetes	Women, but not men, have increased CV risk with pre-diabetes. Women, but not men, show increased risks of CV disease prior to diabetes diagnosis [⁵⁻⁸]
Stratify quality of care measures by gender	Despite their high risk of CV disease, women with DM are not treated as aggressively as men in reaching target LDL, BP, and A1c [¹⁰⁵⁻¹⁰⁷]
Screening and treatment for depression	Women are disproportionately affected by depression, which worsens DM management and increases CV risk [^{96-100, 104}]
Examine gender-based outcomes in trials	Many trials do not examine the effects of treatments in women versus men, potentially missing gender differences
Ensure adequate inclusion of women in trials	When women make up inadequate portions of study populations, gender differences may be missed
Aggressive smoking cessation efforts in women with DM	Women may have lower quit rates than men [^{42, 43}]
Further research into alternative cholesterol-lowering regimens	Women have higher rates of statin-intolerance than men and may be at higher risk for statin-induced hyperglycemia [^{54, 55, 60}]