stratified analysis of these data, using three different systolic BP cutoffs (150, 140, and 130 mm Hg), achieving an additional 10 mm Hg reduction in systolic BP reduced ASCVD risk in all of the outcomes mentioned above. However, in this meta-analysis, many individuals had established hypertension, and in HOPE 3, there was no reduced risk of CV events among those <140/90 mm Hg (218).

In the DREAM trial (223), the primary outcomes were newly diagnosed diabetes or death, and the mean systolic BP at baseline was 136.1 mm Hg. The results showed no difference in the primary endpoints.

In the ALLHAT trial, 31,512 adults, ≥55 years or age, with hypertension and at least one other risk factor for CHD were stratified into IFG (n = 1399) and normoglycemic (n = 17,012) groups. Participants were randomly assigned to double-blind first-step treatment with chlorthalidone, amlodipine besylate, or lisinopril. The primary outcome was the composite of fatal CHD or nonfatal MI, total mortality, and other clinical complications. There was no significant difference in RR for the primary outcome among those with IFG or normoglycemia irrespective of randomized drug.

Use of thiazide diuretics and/or beta-blockers in people with metabolic syndrome can increase insulin resistance, dyslipidemia, and hyperuricemia and worsen glucose intolerance. However, these metabolic changes have not translated into a reduced cardiovascular benefit. Indeed, as shown in the follow-up of ALLHAT, long-term diuretic use was associated with an increase in fasting glucose levels among those with IFG. This increase in glucose into the diabetes range was not associated with increased ASCVD risk after a 12-year follow-up, as long as the diabetes was treated (224). Additionally, *post hoc* analysis of nearly two-thirds of participants in ALLHAT who met the criteria for metabolic syndrome revealed that chlorthalidone was similar to lisinopril or amlodipine in regard to reducing ASCVD risk (225, 226).

Use of traditional beta-blockers may lead to deterioration of glucose tolerance, dyslipidemia, and inability to lose weight. Several large clinical trials documented a 15% to 29% increased risk of developing diabetes as a result of traditional beta-blocker therapy (227, 228).

However, newer vasodilating beta-blockers (*e.g.*, carvedilol and nebivolol) have shown neutral or favorable effects on metabolic profiles compared with traditional beta-blockers and might be a practical option for the treatment of hypertension in the metabolic syndrome (229–231). The novel vasodilator beta-blocker nebivolol has a very good metabolic profile among beta-blockers but has never been tested for cardiovascular outcomes except in older people (231, 232). Nebivolol has been evaluated in older people with heart failure with and without diabetes, but there are no outcome data in people with metabolic syndrome (233). Notably, a diuretic or beta-blocker, when used alone in individuals who are overweight or obese with IFG, will increase the risk for diabetes development (229, 234, 235). In many cases, diabetes is reversible but not always (236).

Reducing progression to type 2 diabetes

3.9 In individuals with prediabetes, we recommend prescribing lifestyle modification before drug therapy to reduce plasma glucose levels. (1|⊕⊕⊕⊕)

3.10 In individuals with prediabetes who have limitations to physical activity or are not responding to lifestyle modifications, we recommend metformin as a first pharmacologic approach to reduce plasma glucose levels. (1|⊕⊕⊕◯)

Evidence

Clinical trial evidence indicates that the risk for diabetes can be markedly reduced by lowering plasma glucose levels in individuals with prediabetes (as defined in recommendation 1.4). Glucose concentrations can be reduced by either lifestyle intervention (as described in "2. Lifestyle and Behavioral Therapy" above) or drug therapy. In the DPP, both metformin and troglitazone were shown to delay the conversion of prediabetes to diabetes (11, 237). Metformin reduced the risk of developing diabetes by 31% over ~4 years (during randomized blinded active phase of DPP trial) and 18% during 10 and 15 years of follow-up (based of DPP Outcomes Study open follow-up) (238). At the 15-year follow-up, both metformin and lifestyle interventions prevented microvascular events in the DPP Outcomes Study participants (238). Moreover, metformin was estimated to be a cost-saving intervention when prescribed for diabetes prevention (238). Two clinical trials have assessed the effect of thiazolidinediones in diabetes prevention, the Troglitazone in the Prevention of Diabetes (TRIPOD) trial using troglitazone (239) and the DREAM trial using rosiglitazone (223). However, evidence of potential harmful effects related to thiazolidinediones has decreased clinical use in recent years, and careful assessment of the potential harms-to-benefits ratio must be undertaken for each individual before considering treatment with this class (240). Insulin is a highly efficacious drug for lowering glucose: in the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, basal insulin treatment with glargine insulin during a period of 6.2 years resulted in a 28% RR