



64 mmol/mol) in such persons and the ESC-EASD 2019 guideline for levels below 8- 9% (<64-75 mmol/L) (15, 18). However, the target chosen will depend on factors such as age, duration of diabetes, complications, co-morbidities and risk of hypoglycaemia. These target HbA1c levels are higher than the level formulated in the Global Vascular Guidelines for CLTI (< 7,0%, 53 mmol/mol), but as discussed above we concluded that the risk of such tight blood glucose control is too high in this specific population.

Blood pressure goals

The ESC-EASD guidelines state that RCTs have demonstrated the benefit (reduction of stroke, coronary events, and kidney disease) of lowering systolic BP to <140 mmHg and diastolic BP to <90 mmHg (15). Usually, multiple drugs are necessary to reach these levels in people with diabetes. In younger people (e.g., younger than 65 years) level below 130/80 mmHg can be considered if there are no contra-indications for such tight blood pressure control and the risk of orthostatic hypotension is low. Both the ADA and ESC-EASD stress the importance of individualised treatment as overly aggressive blood pressure lowering is not without risk in the usually elderly with a DFU and those with multiple diabetes-related complications and co-morbidities. Therefore, we recommend in these people blood pressures < 140/90 mmHg, but in younger individuals (e.g. < 65 years) and with a small risk of adverse effects of the treatment, lower target levels might be considered.

Lipid goals

The ADA and EASD guidelines recommend in persons with diabetes and atherosclerotic cardiovascular disease an LDL target of < 1.8 mmol/L (70 mmol/L) (18). In line with the 'the lower the better' approach, recent trials suggest that lower levels of LDL of < 1.4 mmol/L (55 mg/dL) can be beneficial in persons with a very high cardiovascular risk. Therefore, the recent ESC-EASD and ESC-EAS guidelines recommend that such very low LDL levels should be the target in these individuals (15, 16). In those with recurrent events within 2 years, even LDL levels < 1.0 mmol/L (40 mg/dL) are suggested as target in ESC-EAS guidelines (16). With statin therapy such as rosuvastatin 20-40 mg or atorvastatin 40-80 mg, marked reductions of LDL cholesterol can be achieved if these relatively simple treatments are tolerated. When the target is not reached ezetimibe can be added, which is available in combination tablets with both statins. These treatments have limited side effects in most (but not all) people and are relatively inexpensive. According to the recent ESC-EASD and ESC-EAS guidelines, an LDL-level below 1.0 mmol/L (40 mg/dL) can be the target in people with recurrent cardiovascular events (within 2 years), based on a limited number of RCT's in which relatively few participants with CLTI and diabetes were included. In order to reach the aforementioned very low LDL levels additional treatment with a PCSK9 inhibitor will be necessary in a proportion of people. PCSK9 inhibitors are monoclonal antibodies which have limited side-effects but have the drawback of high costs, parental administration and at present there is very limited evidence of the costs-effectiveness of PCSK9 inhibitors in people with diabetes, PAD and a foot ulcer or gangrene. In addition, the use of these expensive drugs is a problem for many countries in the world, and for these reasons we did not include a recommendation on LDL-level below 1.0 mmol/L (40 mg/dL) for our specific population, but we acknowledge that in several countries PCSK9 inhibitors are used to reach these goals in those with recurrent cardiovascular events.