REVIEW

Diagnosis of diabetes mellitus as a cardiovascular risk equivalent or risk factor and implications in drug therapy management

Brian K Irons†

Practice Points

- Cardiovascular disease plays a significant role in the management and use of healthcare resources in patients with diabetes and should take a priority in diabetes management.
- Clinical practice guidelines or recommendations for the treatment of diabetes rate the disease as either a cardiovascular risk equivalent or risk factor, and suggest specific targets of drug therapy or use of specific medications without taking an individual patient's overall cardiovascular risk into consideration.
- There are few clinical data to support a significant benefit in cardiovascular prevention by obtaining recommended targets or use of aspirin in patients with diabetes.
- Using targets of therapy based on the diagnosis of diabetes places some patients at risk for adverse drug events, increased drug costs and poorer medication adherence, which may not reduce cardiovascular outcomes.
- There are implications to providers and healthcare systems using the diagnosis of diabetes rather than assessing overall individual cardiovascular risk in drug therapy management decisions.
- Guidelines focused on primary cardiovascular risk reduction in patients with diabetes should provide goals of therapy based on sound clinical data and move toward assessing individual risk to guide medication therapy.

SUMMARY Current diabetes guidelines list the disorder as a cardiovascular risk equivalent or risk factor. Goals of therapy for hypertension or lipids or suggested use of aspirin are common though vary and there are insufficient clinical data to support some recommendations. Using specific goals of therapy for most patients with the diagnosis of diabetes, a population-based approach may benefit some but not all patients. Recommended targets of therapy or suggested medication use are not without risk to patients as they can potentially increase the risk for adverse drug reactions and drug–drug interactions. They may also increase drug costs to patients and lower medication adherence. The goals also carry implications to providers and healthcare systems. While population-based guidelines make some clinical decisions more practical, they do not take into consideration an individual's overall cardiovascular risk. Individualized risk assessment to guide therapy decisions may optimize benefit while minimizing risk.

†Department of Pharmacy Practice, Texas Tech University Health Sciences Center School of Pharmacy, 3601 4th St, Lubbock, TX 79430, USA; Tel.: +1 806 743 4200; Fax: +1 806 743 4209; brian.irons@ttuhsc.edu

part of Future Medicine fsg

While the treatment of Type 1 and Type 2 diabetes mellitus often centers around the control of hyperglycemia, the cardiovascular risk associated with having diabetes has profound impacts on diabetes treatment and the development of diabetes-related complications. Both forms of diabetes carry significant cardiovascular risk with a two- to four-fold increase in the risk for cardiovascular mortality, the leading cause of death in diabetes, compared with patients without the disease [1,2]. Cardiovascular disease (CVD) accounts for the largest direct inpatient and outpatient healthcare expenditures in treating diabetes-related complications [3]. With the projections of the ever increasing prevalence of diabetes, often cited as an epidemic, the costs associated with treating diabetes, and in particular cardiovascular complications, will skyrocket and is a wakeup call for healthcare professionals and systems of care to curb the expense the disease will play in the future [4,5].

Landmark prospective studies have not shown a definitive impact in a reduction of cardiovascular outcomes through improved glycemic control [6–8]. However, pooled meta-analysis data suggest there may be a mild reduction in cardiovascular outcomes [9,10]. There may also be some long lasting cardiovascular benefit if hyperglycemia is better controlled early after diagnosis [11,12]. The issue of improvements in glycemic control and who may benefit from a cardiovascular stand point is a matter of debate. Given the unknowns on the benefit of glycemic control in this area, cardiovascular risk reduction often revolves around antiplatelet therapy, blood pressure (BP) control and lipid management **(Figure 1)**. There are a host of professional guidelines and position statements that address the need to control cardiovascular risk in patients with diabetes. Recommended targets or goals of therapy in BP and lipids as well as the use of antiplatelet therapy are common with many of the leading recommendations in this area listed in **Table 1**. Even with various recommendations in place for many years, efforts to adequately control and meet these goals of therapy, while improved, is not optimal [13–15]. The various goals of therapy or medication recommendations stem from a variety of study data ranging from epidemiological in nature to randomized controlled trials. With few exceptions and depending on how one implements the recommendations, the diagnosis of diabetes suggests a specific target BP or lipid concentration or in some cases the use of a specific class of medication (e.g., angiotensin converting enzyme inhibitors for hypertension control). This is a somewhat 'one-size-fits-all', population-based mentality covering a wide variety of patients based on diagnosis alone. Some recommendations, though few, suggest a certain level of cardiovascular risk before initiation of a particular agent such as aspirin therapy. Even these suggestions may not come directly from clinical data. Some guidelines consider diabetes to be a cardiovascular risk equivalent while others treat diabetes as a cardiovascular risk factor. The use of goals based on the diagnosis of diabetes alone, either as a risk factor or equivalent and the therapeutic modalities employed as a result have the potential for both benefit and risk. If everyone is treated to these goals or with aspirin therapy, such as a population-based approach, absolute cardiovascular event rates will decrease. However this broad-based approach has the potential to increase healthcare costs and increase the risk for adverse events. This approach also treats patients with medications who may not obtain any clinical benefit from the proposed therapy. **Box 1** provides two general patient case scenarios based on BP, age, weight status and lipid concentrations. Despite the drastic differences in diabetes control and related cardiovascular risk factor values, most consensus recommendations would suggest very similar treatment goals and medication use for both patients. However, one could argue that a patient has a considerably lower cardiovascular risk and may not need to be treated as aggressively as patient two. This article discusses some of the limitations of using the diagnosis of diabetes for specific goals of therapy or medication use based on the current clinical literature, the potential implications or risks this may have, and the need to consider more individualized therapy and cardiovascular risk assessment to delineate therapy and therapeutic goals for patients with diabetes. It is focused on primary rather than secondary cardiovascular prevention. It also specifically deals with drug therapy management recommendations and does not address changes in lifestyle such as changes in diet or physical activity.

Diabetes as a cardiovascular risk equivalent

To be considered a true cardiovascular risk equivalent the diagnosis of diabetes mellitus itself would carry the same risk of a cardiovascular

event and/or mortality as a patient already with a history of established CVD. Over 12 years ago Haffner and colleagues provide one of the most cited studies in this field and one used as an impetus for altering therapeutic guidelines in treating cardiovascular risk shortly after its publication [16]. Their results suggested the 7-year risk for myocardial infarction (MI) and cardiovascular mortality were similar in subjects with diabetes and no history of CVD compared with patients with a history of CVD but without diabetes **(Figure 2)**. The results also confirmed the known increased risk for CVD with diabetes compared with patients without the disease and the devastating risk of having both diabetes and established heart disease. Subsequently other much larger prospective cohort data have supported this study while other studies in the area provide conflicting results [17–20]. Controlling for other known cardiovascular risk factors (e.g., age, smoking, BP and lipids) in these studies was variable and none controlled for the level of hyperglycemia. More recently a meta-analysis evaluating 13 studies in the area and involving data from more than 45,000 patients suggests that patients with diabetes with no prior MI are at a 43% reduced risk for coronary heart disease events compared with patients without diabetes but with a previous MI [21].

Other trials have focused on ascertaining other factors in addition to diabetes diagnosis that may help predict cardiovascular risk in patients with diabetes. Hyperglycemia itself may increase overall cardiovascular risk but has not been controlled for in trials assessing diabetes as a cardiovascular risk equivalent. A meta-analysis of observational trials focused on the association between hemoglobin and CVD showed chronic hyperglycemia is associated with an increased cardiovascular risk [22]. A subsequent prospective case–cohort study also showed a continually increased cardiovascular risk with increasing hemoglobin [23]. However, neither of these studies compared the risk to patients without diabetes but with established CVD. Other data suggest the duration of diabetes may be a strong predictor for silent MI [24]. Age may also be a factor in creating a cardiovascular risk equivalent. In a very large, retrospective cohort study, younger male patients (<50 years of age) with Type 2 diabetes mellitus (T2DM) and no history of MI had lower cardiovascular event rates than patients of the same age with a prior MI [25]. Women in the same study had a higher risk for a cardiovascular event without diabetes but a history of MI compared with patients with diabetes alone regardless of age. In a prospective cohort study, the 10-year cumulative incidence of coronary heart disease in patients with T2DM was only similar to patients with a history of CVD without diabetes in those subjects with diabetes and multiple CVD risk factors [26]. More recently, in a prospective study involving over 4000 men age 60 years or greater, it was found that an earlier onset of diabetes diagnosis and longer duration of diabetes of nearly 17 years conferred a similar cardiovascular event rate as those without diabetes but with established CVD [27]. Later onset of diabetes diagnosis in this elderly population, mean duration 4.9 years, was associated with approximately 50% lower cardiovascular risk than those with earlier onset diabetes.

Taken together, these data would suggest that the risk for CVD is obviously greater for patients with diabetes than without, but that the diagnosis of diabetes may be more of a cardiovascular risk factor rather than a risk equivalent. The subsequent risk for cardiovascular events after diabetes diagnosis may be more dependent on age, duration of diabetes, the number of other cardiovascular risk factors present and glycemic control. These parameters should be taken into consideration when assessing a patient's cardiovascular risk.

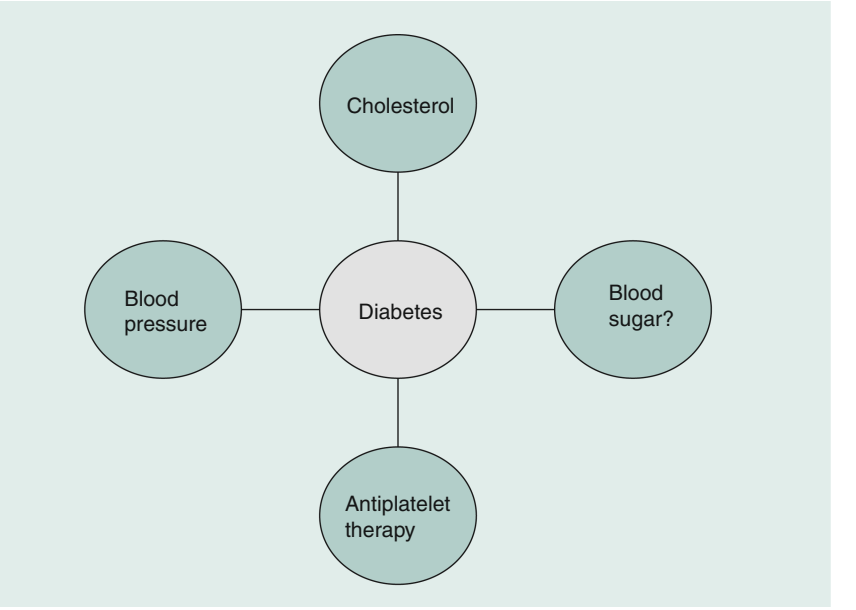

Figure 1. Targets of therapy to reduce cardiovascular risk in patients with diabetes mellitus.

Table 1. Leading professional society guidelines/recommendation goals or targets for primary prevention in patients with diabetes.

Guideline/recommendation	BP goal (mmHg)	LDL-C goal (mg/dl): statin recommendations	Aspirin use criteria	Ref.
American Diabetes Association	SBP <30 in most patients† DBP <80	<100 Statin therapy regardless of baseline LDL-C if >40 years old with one other risk factor	10-year CV Risk >10%	[72]
American Association of Clinical Endocrinologists	<130/80	<100	10-year CV risk >10%	[73]
European Society of Cardiology /European Association for the Study of Diabetes	<130/80	30–40% reduction in LDL-C Statin therapy in T2DM if TC >135 mg/dl and in T1DM if >40 years old	Nothing specific for primary prevention	[78]
Joint National Committee-7	<130/80	NA	NA	[79]
National Cholesterol Education Program	NA	<100	NA	[45]
European Society of Hypertension	2007: <130/80 2009: no specific goal (treat if BP >140/90, pursue sizeable BP reduction)	NA	NA	[55,80]
American Heart Association	<130/80	NA	10-year CV risk >10%	[42,81]
NICE	<140/80 in general <130/80 for those with cerebrovascular, kidney or eye damage	77 mg/dl Statin therapy in those >40 years old	Age 50 years or older if BP is <145/90 mmHg	[71]

†Higher or lower SBP targets may be appropriate depending on response to therapy or patient characteristics.
BP: Blood pressure; CV: Cardiovascular; DBP: Diastolic blood pressure; LDL-C: Low density lipoprotein-cholesterol; NA: Not applicable based on guideline/recommendation focus; SBP: Systolic blood pressure; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; TC: Total cholesterol.

Aspirin therapy

For patients with and without diabetes, the use of aspirin as a means of secondary prevention of cardiovascular events is well founded with the benefits outweighing the potential for bleeding complications [28]. Professional organization recommendations have long advocated for the use of aspirin therapy for primary prevention of CVD in patients with diabetes [29]. Since the mid to late 2000s, who to initiate aspirin therapy in has been based on overall cardiovascular risk and not solely on having the diagnosis of diabetes. For patients with diabetes over 40 years of age or with other risk factors for CVD, the American Diabetes Association (ADA) and the American Heart Association (AHA) have recommended low-dose aspirin treatment (75–162 mg/day) [30–32]. However, these data used as evidence for those recommendations came primarily from large but older studies that included high-risk patients but very few with diabetes [33–35]. Recent studies have cast doubt on the benefit of aspirin as primary prevention in patients with diabetes. In prospective studies specifically designed to assess the benefits and risks of aspirin therapy as primary prevention in patients with T2DM, no clear benefit in cardiovascular morbidity or mortality has been found [36,37]. However, the cardiovascular event rates anticipated in these trials were significantly lower than expected and therefore, the power of the studies to detect a significant difference has been questioned [38]. Subsequent meta-analyses including over 10,000 subjects have suggested very mild (10%) or no relative reduction in cardiovascular events and no effect on mortality [39–40]. However, subgroup analyses reveal a potential risk reduction of MI in men but not in women. Meta-analysis has not suggested a significant increased risk for bleeding complications although the data was highly variable.

More recent statements from the ADA and the AHA have been modified as a result of these recent studies [41,42]. They now recommend the use of aspirin as primary prevention in those with a 10-year cardiovascular risk greater than 10%. However, this recommendation is still not founded upon prospective clinical data. Antiplatelet therapy likely has its risks as data suggests older patients and those with diabetes may be at a higher risk for both hemorrhagic stroke and extracranial bleeding with aspirin use [28]. Likewise, duration of aspirin use and dosage impact on a patient's bleeding risk [43].

Ongoing larger studies may help shed additional light on whether the benefits outweigh the risks from aspirin therapy as primary cardiovascular prevention in patients with diabetes [44].

Lipid management

Therapeutic guidelines lowered low-density lipoprotein cholesterol (LDL-C) goals in the late 1990s and early 2000s to <100 mg/dl for patients with diabetes, a target level consistent with patients with established CVD [45,46]. Most major current guidelines still maintain this LDL-C target (Table 1). Current National Cholesterol Education Program recommendations state the goal is owing to diabetes being a cardiovascular risk equivalent and carries a 10-year risk of a cardiovascular event >20% [45]. There is evidence that statin therapy may reduce the risk for cardiovascular morbidity but these agents have not shown proven reductions in cardiovascular mortality in patients with T2DM [47–50]. However, no trial to date assessing cholesterol lowering medications and their effect on primary prevention of cardiovascular events in patients with diabetes has specifically attempted to obtain a LDL-C <100 mg/dl or studied patients with significantly elevated LDL-C. Rather, subjects were randomized to either placebo or a fixed dose of statin therapy with no dose titration to a target LDL-C. Most included patients with diabetes with at least one other cardiovascular risk factor and were older (mean >60 years of age) but whose baseline LDL-C was only marginally elevated (between 114–130 mg/dl). As such, the overall cardiovascular risk would suggest a high cardiovascular event rate and if diabetes is a cardiovascular risk equivalent then the event rate should be quite high or at least that of patients with established heart disease. However, this has not been the case. The event rates for cardiovascular outcomes was significantly less for placebo treated patients with diabetes and no established heart disease compared with those with heart disease and without diabetes [47,48].

Together the primary prevention trials suggest lowering LDL-C by 28–40% with a fixed dose statin in patients with diabetes and at least one other risk factor for CVD lowers the relative risk for cardiovascular events by 22–37% but has not been shown to reduce cardiovascular or all-cause mortality. The absolute reduction in events is much smaller than in patients with established CVD and therefore the number needed to treat is also much higher. There are no clinical data in younger patients with diabetes or in those with significantly elevated baseline LDL-C. Nor are there data that titrates statin therapy or adds other cholesterol lowering medications in addition to statins purposely to obtain a LDL-C <100 mg/dl. These clinical trial data do not specifically support the arbitrary goal LDL-C <100 mg/dl or that diabetes is a cardiovascular risk equivalent. Using the aggressive LDL target without taking into consideration overall cardiovascular risk can lead to increased use of statin therapy in populations of patients whose benefit is not known and may lead to the addition of other lipid lowering agents whose benefit in reducing cardiovascular outcomes is also unknown.

Box 1. Two diabetes patient case scenarios.

Patient one

- 51 year old Hispanic male with Type 2 diabetes mellitus diagnosed 4 months ago
- Blood pressure = 136/84 mmHg
- BMI = 32 kg/m^2
- A1c = 7.6% (1 month ago)
- LDL-C = 115 mg/dl
- HDL-C = 45 mg/dl
- Triglycerides = 136 mg/dl

Patient two

- 63 year old white female with Type 2 diabetes mellitus diagnosed 15 years ago
- Blood pressure = 144/96 mmHg
- BMI = 33 kg/m^2
- A1c = 8.5% (2 weeks ago)
- LDL-C = 186 mg/dl
- HDL-C = 32 mg/dl
- Triglycerides = 196 mg/dl

HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol.

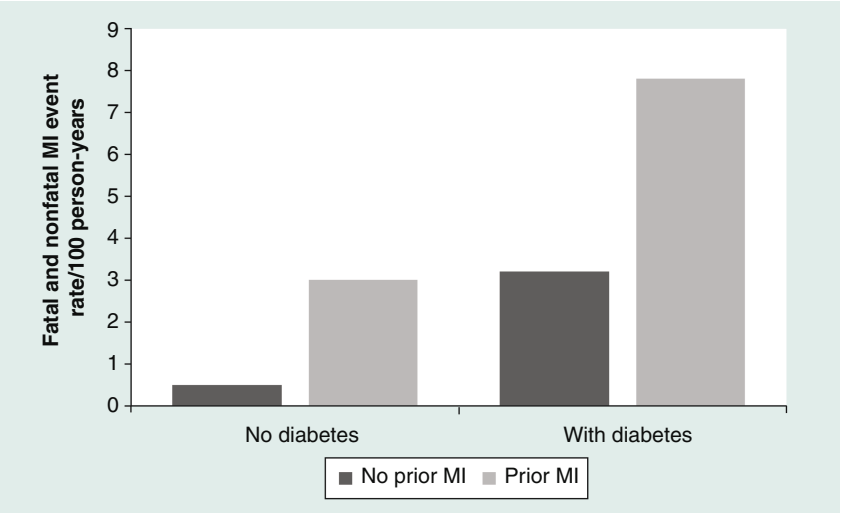

Figure 3. Myocardial infarction risk with and without diabetes.
MI: Myocardial infarction.
Adapted from [16].

Blood pressure management

There is a clear necessity and benefit from prospective clinical and observational studies in treating uncontrolled hypertension in patients with diabetes to reduce cardiovascular outcomes [51,52]. The intensive BP goal of <130/80 mmHg for patients with diabetes, compared with <140/90 mmHg for those without the disease, is common among many professional group recommendations and has been for over a decade (Table 1) [53]. While the diastolic BP (DBP) goal is derived from clinical data, the systolic BP (SBP) target was derived more from epidemiology data than from specific prospective clinical trials. This intensive goal, especially the SBP goal, has come under some scrutiny recently [54–56]. Subgroup analysis of patients with diabetes in the Hypertension Optimal Treatment trial showed a beneficial effect in reducing cardiovascular risk with a DBP <80 mmHg versus <90 mmHg [33]. The mean SBP in the more intensive DBP group was approximately 139 mmHg but SBP was not used to assess cardiovascular outcomes. This study was the momentum for many guidelines in lowering their DBP goal. In addition, a review of older hypertension studies found more intensive DBP lowering was associated with larger reductions in cardiovascular outcomes and total mortality [57]. A small study (n <500) in patients with diabetes with mildly elevated baseline BP (mean 136/84 mmHg) showed an increased risk for stroke (odds ratio: 3.29; 95% CI: 1.06–10.25) but not MI after over a 5 year follow-up when BP was allowed to remain elevated (137/81 mmHg) compared with lower BP (128/75 mmHg) [58]. The same investigators found a nearly 50% reduction in all-cause mortality but no benefit in cardiovascular outcomes in 470 diabetes patients with uncontrolled hypertension (baseline 155/98 mmHg) achieving a BP of 132/78 mmHg compared with 138/86 mmHg [59].

More recent and larger studies on aggressive SBP reductions in patients with diabetes have also shown reductions in stroke risk but not other cardiovascular events. The much talked about Action to Control Cardiovascular Risk in Diabetes BP trial (ACCORD-BP) in 2010 suggested there is no benefit from more intensive BP reduction for patients with diabetes whose BP was already <140/90 mmHg [60]. Patients upon entry had a mean baseline BP of 139/76 mmHg and the investigators targeted a SBP <120 mmHg (average BP achieved 119/64 mmHg) or <140 mmHg (average BP achieved 133/70 mmHg). They found no beneficial effect on cardiovascular outcomes but did observe a reduction in stroke risk. However, this study was underpowered and unable to detect a significant difference in cardiovascular outcomes owing to significantly fewer than anticipated events. Another study suggested there is no further benefit beyond reducing SBP <140 mmHg in patients with both diabetes and CVD [61]. Also, a large observational trial in over 12,000 patients with diabetes followed for 5 years found no significant cardiovascular benefit comparing SBPs in the range of 110–129 mmHg versus 130–139 mmHg but showed a clear risk when SBPs remained above 140 mmHg [62].

There is clear benefit in reducing BP in patients with diabetes to <140/80 mmHg but the literature does not provide convincing evidence that there is additional cardiac benefit of more aggressive hypertension management though there does appear to be some stroke risk reduction. Current target BP goals for patients with diabetes are not patient specific or based on individual cardiovascular risk. Attempting more aggressive BP targets in the ACCORD-BP study was associated with an increased use of hypertensive medications as well as a higher risk for medication-related adverse events [60].

Implications to drug therapy management

Using specific cardiovascular clinical goals or targets of therapy, based primarily on diagnosis alone in the management of diabetes has several

implications to patients. In the two patient case scenarios in **Box 1**, both patients would likely be placed on a similar drug therapy regimen per current recommendations. Both would be considered for aspirin, lipid, BP therapy as well as medications to control for their hyperglycemia. Yet the potential for therapeutic benefit in the form of reduced cardiovascular outcomes is probably very dissimilar. Patient one may only benefit from low-dose statin therapy and not aspirin therapy or antihypertensive therapy to obtain a BP of <130/80 mmHg. The blanket approach using specific targets or particular therapeutic agents on diagnosis alone may provide benefit in many patients but puts other patients on chronic therapy that may or may not help them. Therapeutic regimens are becoming more complex as a result of the use of medications to control cardiovascular risk as well as hyperglycemia and this complexity may have unintentional but real affects on patient adherence with medication treatments [63]. Most patients with diabetes will require more medications over time to control their hyperglycemia. Adherence to medications to control hyperglycemia is often less than optimal and frequently decreases over time [64,65]. Often two or more antihypertensives are required to obtain aggressive goals of therapy. Add to this an array of agents with the intent to minimize cardiovascular risk but provide minimal or no symptomatic benefit to the average patient, the complexity continues to grow and medication adherence may suffer as a result [66].

Out of pocket expenses to the patient from an increased complexity of medications and subsequent therapeutic monitoring may also increase. An increased financial burden could also influence adherence to medications in the diabetic population [67]. In some instances a patient may forgo and become nonadherent to a more costly medication that could be very cardioprotective to them (e.g., owing to markedly elevated BP) in an effort to keep taking another medication that may be cheaper but not provide a real cardiovascular benefit (e.g., a generic oral medication to control mildly elevated hyperglycemia).

In addition, the potential for adverse events increases with the higher utilization of medications. Statin therapy increases the risk, although quite small, for liver toxicity and rhabdomyolysis and can cause less severe but bothersome myopathies. In clinical trials assessing low-dose statin use specifically in patients with diabetes, the risk for elevated alanine transaminase three to four times the upper limit of normal ranged from 0.47–1.0% [48,50]. In at least one study, the occurrence of myalgia was actually higher in patients receiving placebo versus low-dose statin therapy [50]. Depending on the antihypertensive regimen employed, treatment of hypertension increases the risk for electrolyte abnormalities, changes in renal function, peripheral edema or cardiac dysrhythmias. In the ACCORD-BP study, intensive BP control compared with standard therapy was associated with higher rates of hypokalemia (2.1 vs 1.1%, respectively), hyperkalemia (0.4 vs 0.04%, respectively), hypotension (0.7 versus 0.04, respectively) and renal failure (0.2 versus 0.04%, respectively) [60]. Low-dose aspirin therapy in primary prevention also comes with a small risk for gastrointestinal and intracranial bleeding. The risks for adverse events with aspirin therapy may be 55% larger in patients with diabetes compared with those without [28]. The absolute risk for gastrointestinal bleeding with primary prevention use of aspirin is suspected to be three in 10,000 per year [42].

There are also implications to providers or the healthcare system. Increased utilization and complexity of medications to reach specific goals based on a diagnosis rather than individual patient needs can increase the time necessary for a provider to spend with an individual patient or increase the frequency of clinical follow-up. It takes more time to review medication regimens, assess medication adherence, evaluate for medication interactions, perform physical and laboratory assessment for efficacy and adverse events and patient education. These issues may decrease valuable clinical practice resources. This also requires providers to continually update their competency in treating patients with diabetes as the literature continues to expand in the therapeutic management of the disease and as guidelines in the area continue to develop or evolve.

Using population-based approaches to treatment of patients with diabetes may incur increased costs to the healthcare system. One study evaluated a population health primary prevention strategy that would place nearly every adult with diabetes between the ages of 30 and 74 years on statin therapy compared with treating only those whose baseline risk was considered moderate-to-high risk [68]. The investigators found the population approach incurred significantly higher annual expenditures and that using risk along with age cutoffs for initiation

of therapy provided the most cost effective and efficient approach to statin therapy. In addition to costs to the healthcare system, as incentives for improved management through pay for performance or other measures (e.g., goals for Accountable Care Organizations in the USA) increases, providers and healthcare institutions have more incentive to treat patients more aggressively to obtain goals or targets of therapy. Although these goals are often not as difficult to obtain as the more stringent targets found in therapeutic guidelines, these performance incentives continue to change and often are getting more aggressive in their targets based on a population of patients with a diagnosis of diabetes rather than treating individual patients who may specifically benefit from reaching these targets.

Conclusion & future perspective

Preventing cardiovascular outcomes is, and should be, a high priority for clinicians to reduce the impact it plays in patient's lives and on healthcare systems. Treating uncontrolled cardiovascular risk factors through individual or multifactorial interventions has been shown to reduce cardiovascular outcomes [51,52,69]. As a result of improved BP and lipid management over the last decade, the 10-year risk for CVD in patients with diabetes appears to be declining [70]. However, given the use of specific targets based on diagnosis rather than individualized therapeutics or taking into account overall cardiovascular risk is not without potential risk to the patient, provider or healthcare system. More should be done to target patients or patient populations that will benefit the most, from therapeutic management to lower cardiovascular risk. Using arbitrary goals from population-based guidelines or recommendations certainly makes clinical decisions easier and more practical in the management of patients with diabetes.

Current recommendations to providers are not clearly right or wrong. Rather they could be considered somewhere in between and not without risk. A more optimal approach may be to develop a strategy that is the most effective at reducing cardiovascular events yet recommends treatment to the least number of patients. Several diabetes guidelines or recommendations have altered or moved toward being more specific about patient risk for implementation of goals or medication therapy in recent years [71]. This is certainly a step in the right direction. Both the ADA and American College of Clinical Endocrinologists have increased the overall suspected cardiovascular risk for implementation of aspirin therapy as primary prevention [72,73]. The ADA also suggested some patients, although it did not define who, may have less aggressive BP goals. The European Society of Hypertension in 2009 has suggested a more modest approach to hypertension management in patients with diabetes to that of patients with essential hypertension [55]. It is yet to be seen whether leading hypertension guideline updates in the USA will also alter their BP goal for patients with diabetes.

Another way to potentially improve benefit while reducing risk is to shift from population-based guidelines to more individualized guidelines. Models using individualized guidelines and taking into consideration overall cardiovascular risk of an individual patient via risk assessment tools has been shown to lower potential costs or reduce outcomes compared with population-based approaches [68,74]. An increased use of risk evaluation tools may help in identifying patients whose overall cardiovascular risk dictates or warrants more aggressive therapeutic management. Several risk evaluation tools have been applied to patients with diabetes [75,76,101,102]. While useful, there may be limitations to some in their broad applicability to all patients [77]. Risk assessment tools need to take into consideration factors beyond the traditional risk factors commonly assessed including duration of diabetes and overall glycemic control. Providers may then be able to individualize care that optimizes proven treatments to reduce cardiovascular outcomes while minimizing potentially unnecessary medication use and their associated risk in others. Individualizing care does make it more complex for providers and is harder to implement than population-based standards. With changes in technology, information systems, enhancement of risk modeling and availability of patient-specific data, implementation should become less of a barrier to healthcare professionals.

Lastly, more research is needed to validate specific goals or targets of therapy or for the use of specific medications. While epidemiological data may provide useful cutoffs for the potential development of a cardiovascular event, clinical trial data showing a reduction in cardiovascular outcomes from obtaining that goal are necessary. Likewise outcomes data are necessary to validate a reduction in CVD with the use of specific medications or classes of medications and to identify which specific populations benefit the most from these interventions.

From a clinical stand point, healthcare professionals should recognize that guidelines have their limitations and vary in their recommendations in terms of therapeutic goals, treatment options and cardiovascular risk assessment. No one guideline appears better than another, although differences in the degree of clinical evidence in support of their recommendations exists. While it is easier to use specific treatment goals or therapies based on diagnosis, overall cardiovascular risk with or without diabetes is highly variable between patients. Clinicians should attempt to use validated cardiovascular risk tools specific to patients with diabetes to help them make therapeutic decisions in an effort to optimize benefit in their patients while minimizing potential harm to others. Diabetes in and of itself is not sufficient to assess an individual's risk but rather hyperglycemia is likely a continuous variable in risk assessment. Clinicians should strive to inform their patients regarding the significant impact CVD has in diabetes as well as the potential benefits and risks of the various therapies most commonly employed in its treatment. Together, an informed decision on treatment options should hopefully diminish risks while maximizing benefits.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1 Pistrosch F, Natali A, Hanefeld M. Is hyperglycemia a cardiovascular risk factor? *Diabetes Care* 34(Suppl. 2), S128–S131 (2011).

2 Stratmann B, Tschoepe D. Heart in diabetes: not only a macrovascular disease. *Diabetes Care* 34(Suppl. 2), S138–S144 (2011).

3 American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. *Diabetes Care* 31, 1–20 (2008).

4 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27, 1047–1053 (2004).

5 Huang E, Basu A, O'Grady M, Capretta J. Projecting the future diabetes population size and related costs for the U.S. *Diabetes Care* 32, 2225–2229 (2009).

6 UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). *Lancet* 352, 837–853 (1998).

7 The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358, 2545–2559 (2008).

8 Duckworth W, Abraira C, Moritz T *et al.* Glucose control and vascular complications in veterans with Type 2 diabetes. *N. Engl. J. Med.* 360, 129–139 (2009).

9 Ray K, Seshasai S, Wijesuriya S *et al.* Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 373, 1765–1772 (2009).

10 Turnbull F, Abraira C, Anderson R *et al.* Intensive glucose control and macrovascular outcomes in Type 2 diabetes. *Diabetologia* 52, 2288–2298 (2009).

11 The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes. *N. Engl. J. Med.* 353, 2643–2653 (2005).

12 Holman R, Paul S, Bethel M, Matthews D, Neil H. 10-year follow-up of intensive glucose control in Type 2 diabetes. *N. Engl. J. Med.* 359, 1577–1589 (2008).

13 Bertoni A, Clark J, Feeney P *et al.* Suboptimal control of glycemia, blood pressure, and LDL cholesterol in overweight adults with diabetes: the Look AHEAD study. *J. Diabetes Complications* 22, 1–9 (2008).

14 Vouri S, Shaw R, Waterbury N, Egge J, Alexander B. Prevalence of achievement of A1c, blood pressure, and cholesterol (ABC) goal in veterans with diabetes. *J. Manag. Care Pharm.* 17, 304–312 (2011).

■ **Recent retrospective analysis of an older veterans population demonstrating improvements within the same facility for obtaining key diabetes goals but also showing the low frequency of obtaining glycemic, blood pressure and lipid targets.**

15 Ong K, Cheung B, Wong L, Wat N, Tan K, Lam K. Prevalence, treatment, and control of diagnosed diabetes in the U.S. National Health and Nutrition Examination Survey 1999–2004. *Ann. Epidemiol.* 18, 222–229 (2008).

16 Haffner S, Letho S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with Type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N. Engl. J. Med.* 339, 229–234 (1998).

■ **Landmark study exhibiting similar morbidity and mortality for subjects with diabetes and no heart disease compared with those with established heart disease and no diabetes. Also shows the extremely high risk for cardiovascular outcomes with both diabetes and heart disease.**

17 Hu F, Stampfer M, Solomon C *et al.* The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch. Intern. Med.* 161, 1717–1723 (2001).

18 Whiteley L, Padmanabhan S, Hole D, Isles C. Should diabetes be considered a coronary heart disease risk equivalent? Results from 25 years of follow-up in the Renfrew and Paisley Survey. *Diabetes Care* 28, 1588–1593 (2005).

19 Evans J, Wang J, Morris A. Comparison of cardiovascular risk between patients with Type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ* 324, 939–942 (2002).

20 Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J. Sex differences in cardiovascular and total mortality among diabetic and nondiabetic individuals with and without history of myocardial infarction. *Diabetologia* 48, 856–861 (2005).

21 Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabet. Med.* 26, 142–148 (2009).

■■ **Meta-analysis involving over 45,000 subjects that refutes diabetes as a cardiovascular risk equivalent but maintains it as a risk factor. With a mean follow-up of over 13 years the risk for myocardial infarction in patients with diabetes was 43% less compared with those with established heart disease.**

22 Selvin E, Marinopoulos S, Berkenblit G *et al.* Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann. Intern. Med.* 141, 421–431 (2004).

23 Selvin E, Coresh J, Golden S, Brancati F, Folsom A, Steffes M. Glycemic control and coronary heart disease risk in persons with and without diabetes. *Arch. Intern. Med.* 165, 1910–1916 (2005).

24 Wackers F, Young L, Inzucchi S *et al.* Detection of silent myocardial ischemia in asymptomatic diabetic subjects. *Diabetes Care* 27, 1954–1961 (2004).

25 Booth G, Kapral M, Fung K, Tu J. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet* 368, 29–36 (2006).

26 Howard B, Best L, Galloway J *et al.* Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care* 29, 391–397 (2006).

27 Wannamethee S, Shaper G, Whincup P, Lennon L, Sattar. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men. *Arch. Intern. Med.* 171, 404–410 (2011).

■■ **Although this focuses on older men, this study suggests in this population that the duration of diabetes has a profound impact on cardiovascular risk. Diabetes diagnosed earlier and with a longer duration, approximately 17 years, was associated with a higher cardiovascular risk (and more of a cardiovascular risk equivalent) than later onset diabetes and shorter in duration than in men of a similar age.**

28 Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet* 373, 1849–1860 (2009).

29 American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care* 21 (Suppl. 1), S45–S46 (1998).

30 American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care* 27 (Suppl. 1), S72–S73 (2004).

31 American Diabetes Association. Standards of medical care in diabetes-2009. *Diabetes Care* 32(Suppl. 1), S13–S61 (2009).

32 Buse J, Ginsberg H, Bakris G *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 115, 114–126 (2007).

33 Hansson L, Zanchetti A, Carruthers S *et al.* Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principle results of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 351, 1755–1762 (1998).

34 Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N. Engl. J. Med.* 321, 129–135 (1998).

35 Ridker P, Cook N, Lee I *et al.* A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N. Engl. J. Med.* 352, 1293–1304 (2005).

36 Belch J, MacCuish A, Campbell I *et al.* The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 337, A1840 (2008).

37 Ogawa H, Nakayama M, Morimoto T *et al.* Low-dose aspirin for primary prevention of atherosclerotic events in patients with Type 2 diabetes: a randomized controlled trial. *JAMA* 300, 2134–2141 (2008).

38 Farkouh M, Fuster V. Diabetes and aspirin: beware of underpowered negative trials. *Nat. Clin. Pract. Cardiovasc. Med.* 6, 1 (2009).

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

40 De Beradis G, Sacco M, Strippoli G *et al.* Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* 339, b4531 (2009).

41 American Diabetes Association. Standards of medical care in diabetes – 2010. *Diabetes Care* 33(Suppl. 1), S11–S61 (2010).

42 Pignone M, Alberts M, Colwell J *et al.* Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology foundation. *Diabetes Care* 33, 1395–1402 (2010).

43 Huang E, Strate L, Ho W, Lee S, Chan A. Long-term use of aspirin and the risk of gastrointestinal bleeding. *Am. J. Med.* 124, 426–433 (2011).

44 Nicolucci A, Standl E. Antiplatelet therapy for every diabetic person? *Diabetes Care* 34(Suppl. 2), S150–S154 (2011).

45 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285, 2486–2497 (2001).

46 American Diabetes Association. Management of dyslipidemia in adults with diabetes. *Diabetes Care* 21(Suppl. 1), S36–S39 (1998).

47 Knopp R, D'Emden M, Smilde J, Pocock S. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with Type 2 diabetes. *Diabetes Care.* 29, 1478–1485 (2006).

48 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 361, 2005–2016 (2003).

■ **Large subgroup analysis of the largest statin trial to date that showed regardless of baseline low density lipoprotein-cholesterol, moderate simvastatin therapy decreased cardiovascular risk by 25–30%. It also demonstrated a much higher cardiovascular risk for patients with established heart disease and no diabetes compared with patients with diabetes alone.**

49 Sever P, Poulter N, Dahlof B *et al.* Reduction in cardiovascular events with atorvastatin in 2,532 patients with Type 2 diabetes. *Diabetes Care*. 28, 1151–1157 (2005).

50 Colhoun H, Betteridge D, Durrington P *et al.* Primary prevention of cardiovascular disease with atorvastatin in Type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet*. 364, 685–696 (2004).

51 United Kingdom Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complication in Type 2 diabetes: UKPDS 38. *BMJ* 317, 703–713 (1998).

52 ADVANCE Collaborative Group. Effects of fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with Type 2 diabetes mellitus (the ADVANCE trial). *Lancet* 370, 829–840 (2007).

53 American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 24(Suppl. 1), S33–S43 (2001).

54 Grossman E. Blood pressure: the lower, the better: the con side. *Diabetes Care* 34(Suppl. 2), S308–S312 (2011).

55 Mancia G, Laurent S, Agabiti-Rosei *et al.* Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J. Hypertens.* 27, 2121–2158 (2009).

56 Mancia G, Grassi G, Zanchetti A. Antihypertensive treatment and blood pressure in diabetic and nondiabetic patients: the lower, the better? *Diabetes Care* 34(Suppl. 2), S304–S307 (2011).

57 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus. *Arch. Intern. Med.* 165, 1410–1419 (2005).

58 Schrier R, Estacio R, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive Type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int.* 61, 1086–1097 (2002).

59 Estacio R, Jeffers B, Gifford N, Schrier R. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and Type 2 diabetes. *Diabetes Care* 23(Suppl. 2), B54–B64 (2000).

60 The ACCORD Study Group. Effects of intensive blood-pressure control in Type 2 diabetes mellitus. *N. Engl. J. Med.* 362, 1575–1585 (2010).

■■ **A frequently cited and discussed study in the area of aggressive systolic blood pressure obtainment and cardiovascular outcomes in patients with diabetes. The underpowered study suggests little benefit of an aggressive systolic blood pressure goal of less than 120 mmHg compared with less aggressive therapy below 140 mmHg.**

61 Cooper-DeHoff R, Gong Y, Handberg E *et al.* Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 304, 61–68 (2010).

62 Cederholm J, Gudbjornsdottir S, Eliasson B, Zethelius B, Eeg-Olofsson K, Nilsson P. Systolic blood pressure and risk of cardiovascular diseases in Type 2 diabetes: an observational study from the Swedish national diabetes register. *J. Hypertens.* 28, 2026–2035 (2010).

63 Grant R, Pirraglia P, Meigs J, Singer D. Trends in complexity of Diabetes Care in the United States from 1991–2000. *Arch. Intern. Med.* 164, 1134–1139 (2004).

64 Cramer J. A systematic review of adherence with medications for diabetes. *Diabetes Care* 27, 1218–1224 (2004).

65 Poluzzi E, Strahinja P, Vaccherei A *et al.* Adherence to chronic cardiovascular therapies: persistence over the years and dose coverage. *Br. J. Clin. Pharmcol.* 63, 346–355 (2006).

66 Choudhry N, Fisher M, Avorn J *et al.* The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch. Intern. Med.* 171, 814–822 (2011).

■ **A recent study using prescription claims data suggests the greater prescribing and filling complexity compromises patient adherence with medications.**

67 Kurlander J, Kerr E, Krein S, Heisler M, Piette J. Cost-related nonadherence to medications among patients with diabetes and chronic pain. *Diabetes Care* 32, 2143–2148 (2009).

68 Siyambalapitiya S, Bulugahapitiya U, Sithole J, Song S, Fernando D, Idris I. Combining population health and baseline risk strategy by determining an age cutoff for initiating statins in patients with diabetes. *Diabetes Care* 30, 2025–2029 (2007).

69 Gaede P, Lund-Andersen H, Parving H, Pedersen O. Effect of a multifactorial intervention on mortality in Type 2 diabetes. *N. Engl. J. Med.* 358, 580–591 (2008).

70 Ford E. Trends in risk for coronary heart disease among adults with diagnosed diabetes in the US. *Diabetes Care* 34, 1337–1343 (2011).

71 National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). Royal College of Physicians, London, UK (2008).

72 American Diabetes Association. Standards of medical care in diabetes – 2011. *Diabetes Care* 34(Suppl. 1), S11–S61 (2011).

73 Handelsman Y, Mechanick J, Blonde L *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. *Endocr. Pract.* 17, 287–302 (2011).

74 Eddy D, Adler J, Patterson B, Lucas D, Smith K, Morris M. Individualized guidelines: the potential for increasing quality and reducing costs. *Ann. Intern. Med.* 154, 627–634 (2011).

■■ **Recent analysis evaluating differences in potential outcomes between using population-based guidelines in blood pressure management versus more individualized guidelines that take into account additional risk calculation. More individualized guidelines with risk assessment was associated with similar event rate reductions at a lower overall cost or could prevent more events at a similar cost than population-based guidelines.**

75 Stevens R, Kothari V, Adler A, Stratton I. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin. Sci.* 101, 671–679 (2001).

76 Anderson K, Odell P, Wilson P, Kannel W. Cardiovascular disease risk profiles. *Am. Heart J.* 121, 293–298 (1991).

77 Kengne A, Patel A, Colagiuri S *et al.* The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) study. *Diabetologia* 53, 821–831 (2010).

78 Ryden L, Bartnik S, Van den Berghe G *et al.* Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur. Heart J.* 28, 88–136 (2007).

79 Chobanian A, Bakris G, Black H *et al.*; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42, 1206–1252 (2003).

80 Mancia G, De Backer G, Dominiczak A *et al.* 2007 guidelines for the management of arterial hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur. Heart J.* 28, 1462–1536 (2007).

81 Rosendorff C, Black H, Cannon C *et al.* Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation* 115, 2761–2799 (2007).

■ Websites

101 American Diabetes Association Diabetes PHD (Personal Health Decisions): risk assessment tool
www.diabetes.org/phd

102 Atherosclerosis Risk in Communities (ARIC) coronary heart disease risk calculator
http://aricnews.net/riskcalc/html/RC1.html