Appendix 1. Expertise, roles and responsibilities, and conflicts of interest for the guideline development team members and staff

Name	Expertise	Guideline Role and Section Responsibilities	Conflict(s) of Interest
Guideline development team members			
Barbara Farrell	Pharmacist (Geriatric Day Hospital, lead on the Deprescribing guidelines in the elderly project)	• Overall lead • Introduction • Recommendations • Gaps in knowledge • Conclusion	Received research funding for the purposes of developing this guideline; received financial payments from Institute for Healthcare Improvement and Commonwealth Fund for deprescribing guideline summary and from Ontario Pharmacists Association for speaking engagement
Manon Bouchard	Nurse practitioner (Family Health Team)	• Resource implications • Patient values and preferences	None declared
Heather Lochnan	Endocrinologist	• Clinical considerations • Other guidelines	Member of CDA; has received funding and participated in multi-centre diabetes clinical trials with sponsorship from pharmaceutical companies that produce agents for management of diabetes
Lisa McCarthy	Pharmacist (community and primary care settings)	• Review of reviews of harms	Former member of the CDA, Diabetes Educator Section
Carlos Rojas-Fernandez	Pharmacist (geriatrics, primary and long-term care settings)	• Clinical considerations • Other guidelines	None declared
Salima Shamji	Family Physician (Care of the elderly, primary and long-term care settings)	• Review of reviews of harms	None declared
Ross Upshur	Family physician	• Patient values and preferences	None declared
Vivian Welch	Clinical	• Summary of findings	None declared

	epidemiology methodologist	and quality of evidence • GRADE review • Gaps in knowledge	
Support persons			
Cody Black	Staff	• Guideline coordinator • Summary of findings quality of evidence • Resource Implications	None declared
Wade Thompson	Pharmacist (Long-term care), Masters Student, Clinical Epidemiology	• Summary of findings and quality of evidence • GRADE review • Patient values and preferences • Clinical considerations	None declared

Appendix 2. Evidence Reviews and Related References

Summary of Systematic Review Findings

Two controlled before-after studies, were eligible for systematic review [1,2]. Risk of bias for both studies was assessed using the Cochrane ACROBAT tool [3]. We could not meta-analyze these studies due to heterogeneity in study design and intervention.

The first study investigated deprescribing glyburide (discontinuing glyburide and switching to an alternative agent, or discontinuing glyburide and not adding additional medication) in outpatient veterans over 65 years of age (mean age 77 years, 32% with diabetic complications) with renal insufficiency via an educational intervention delivered through pharmacists to prescribers [1]. Pharmacists were provided with a list of patients receiving glyburide to be targeted (n=4368) as the intervention group for discussion with prescribers, while non-targeted patients (n=1886) served as controls. Patients in the intervention group were more likely to stop glyburide (RR: 1.28; 95% CI: 1.22, 1.33) compared with the control group. Baseline to post-intervention A1C was compared in intervention patients who continued glyburide to those discontinuing glyburide who did not start another medication. There was no significant difference in A1C in the group who discontinued glyburide compared with those who continued (A1C increased by 0.04% in those discontinuing glyburide (A1C 7.11 $\pm$ 1.33 before, 7.15 $\pm$ 1.34 after) versus 0.06% in those who continued (A1C 7.16 $\pm$ 1.25 before, 7.22 $\pm$ 1.32 after); mean difference: 0.02% lower; 95% CI: -0.16, 0.12%;). Change in A1C was reported for patients (n=999) switched from glyburide to alternative medications. In patients who were switched to alternative medications, the pre and post-intervention A1C values were 7.29 $\pm$ 1.37 and 7.33 $\pm$ 1.41. Approximately 87% of these patients were switched to glipizide. No significant difference was observed in rates of hypoglycemia post-intervention between the intervention

and control groups (RR: 1.08; 95% CI: 0.78, 1.5). These results suggest that an educational intervention can decrease glyburide use (through discontinuation, or switching to glipizide) without compromising glucose control or reducing hypoglycemic events in community-dwelling older adults. The certainty of evidence for this study was graded as very low due to its observational design and concerns surrounding risk of bias, rated as serious, and imprecision.

The second study [2] investigated withdrawal of all antihyperglycemics (or reducing insulin to 20 units per day for patients on a baseline dose >20 units per day) (n=32) versus continuing antihyperglycemics (n=66) in Swedish nursing home patients (mean age 84 years) with tight glycemic control. The baseline A1C was 5.2% (SD 0.4) in the intervention group and 7.1% (SD 1.6) in the continuation group. The change in A1C was not significantly higher in the intervention group (MD: 1.1%; 95% CI: -0.56, 1.64%). There was no significant difference in mortality between the deprescribing group and continuation group (RR 0.74, 95% CI 0.29 to 1.87). Three patients in the deprescribing group had therapy reintensified following study-related glucose monitoring between 16.6 and 18.3mmol/L. Results of this study suggest that deprescribing antihyperglycemics in elderly nursing home patients with tight glycemic control does not result in clinically significant A1C increases, and with glucose monitoring, is feasible and safe. No data were provided regarding hypoglycemia risk before and after the intervention. The certainty of evidence was graded as very-low due to the study's observational design, and concerns over risk of bias, rated as serious, and imprecision.

Overall, this systematic review suggests that it is not harmful to stop or substitute glyburide in community-dwelling elderly patients [4]. Reducing insulin and/or stopping other antihyperglycemics in nursing home patients with tight glycemic control also appears to be safe.

Neither intervention reduced the risk of hypoglycemia. Summary of findings tables are presented in CFPlus Appendix 3.

Benefits and harms of continued antihyperglycemics use

Benefits

The benefits of Type 2 Diabetes treatment include control of symptomatic hyperglycemia and avoidance of microvascular and macrovascular complications. In older adults, avoidance of sustained hyperglycemia is important to minimize risk of osmotic diuresis, causing polydipsia, polyuria and nocturia, which can result in dehydration, interrupted sleep, falls and associated complications. Wound healing [5] and cognition may also be negatively affected by hyperglycemia [6,7] though improvement in the latter has not been demonstrated with tight vs. standard control [8]. In the absence of large scale intervention studies in older people with Type 2 Diabetes or large scale studies of residents in long-term care facilities, we extrapolate evidence from studies completed with younger adults. Reduction in risk of diabetes-related microvascular complications (e.g. retinopathy progression and albuminuria) and macrovascular complications (e.g. non-fatal myocardial infarction) over 5 to 10+ years of treatment, have been demonstrated [9–12], while there have been reports of glucose-lowering drugs or strategies demonstrating benefit in the reduction of major cardiovascular events [13]. Reductions in the composite endpoint of cardiovascular mortality, non-fatal MI and stroke, and hospitalization for heart failure were recently observed in a clinical trial of empagliflozin versus placebo after 3 years of treatment in patients with established cardiovascular disease[14]. Benefits and risks

associated with pharmacologic management with diabetes are described in detail in the Canadian Diabetes Association's (CDA) Clinical Practice Guidelines [15]. The place of each drug class, including empagliflozin, in the treatment of diabetes, is reviewed in the 2016 update [16].

Recent trials that have included older adults in examining tight glycemic control (targeting A1C <6 or 6.5% vs. 7 to <7.9%) have not found significant differences in macrovascular outcomes; indeed, all-cause mortality was increased in the tight glycemic control group [10,17,18].

Therefore, in older adults, who are otherwise healthy, have good cognitive and physical function, are not at risk of falls and have substantial life expectancy (e.g. >10 years for most treatments), diabetes goals consistent with younger adults (e.g. A1C ≤7%, as per CDA[19], or 7-7.5% as per the International Diabetes Federation[20] and American Geriatrics Society[21]) should be considered to attain the benefit of microvascular risk reduction.

The micro and macrovascular benefits of Type 2 Diabetes treatment and optimal targets in the frail elderly, those with advanced diabetes complications, those with dementia or are nearing end-of-life, are less clear. The mean age of patients in most large randomized controlled trials is between 54 and 66 years [10,17,18,22]. As no randomized controlled trials assessing the effects of tight glycemic control have included frail elderly patients the clinical meaningfulness of microvascular risk reduction remains uncertain [23].

Harms

Harms attributable to antihyperglycemic medications may be categorized as hypoglycemia and its immediate sequelae, and other adverse events associated with continued antihyperglycemic use.

Hypoglycemia: scope and implications

Hypoglycemia manifests in younger adults with adrenergic symptoms such as sweating, tremor and palpitations. In older adults, symptoms are more commonly neuroglycopenic in nature resulting in dizziness, weakness, delirium and confusion[24].

In the context of conventional versus tight glycemic control, older adults, in particular the frail elderly, are at higher risk for hypoglycemia and its consequences[25,26], and such risks are generally considered to outweigh the benefits of tight glycemic control [26–29]. For example, impaired hepatic and renal function can result in reduced gluconeogenesis and renal clearance of antihyperglycemics such as insulin and sulfonylureas; decreased nutrient intake can exaggerate the effects of antihyperglycemics. Autonomic neuropathy and decreased beta-receptor responsiveness can result in absence of typical hypoglycemic symptoms such as diaphoresis, tachycardia and tremor, and patients may thus be unaware of hypoglycemia. As a result of cognitive or physical impairment, patients may be limited in their ability to respond to hypoglycemia by seeking treatment. Comorbid conditions, polypharmacy and history of hypoglycemia have all been shown to increase risk of hypoglycemia. Drug interactions resulting in hypoglycemia are also an important consideration. For example, alcohol [30], monoamine oxidase inhibitors[31] and salicylates[32] can trigger hypoglycemia, while beta-blockers[33,34] can mask common signs and symptoms of hypoglycemia (except sweating) and trimethoprim/sulfamethoxazole can increase serum concentrations of sulfonylureas and repaglinide[36,37]. It is also important to consider the higher propensity of certain antihyperglycemics (e.g.,sulfonylureas, insulin and meglitinides) to cause hypoglycemia [37].

Hypoglycemic episodes in older adults may be severe, leading to impaired cognitive and physical function, falls and fractures, motor vehicle accidents, seizures, emergency room visits, hospitalisations and an increase in mortality risk [38–41]. Recent controlled studies have likewise demonstrated harm, and limited to no benefit associated with tighter (i.e., from <6% or <6.5% vs. 7 to 7.9%) glucose control in people aged 60-66 years [9,16,17]. An increased risk for hypoglycemia was observed in one study when A1C levels were managed according to American Geriatrics Society guidelines (A1C <8%), increasing from 1.1 episodes per 100 patient years to 2.9 episodes per 100 patient years (p=0.03) in a restrospective case-control study [39]. Similar findings were noted by Nelson et al., who observed that compared with patients aged 75 years or older whose A1C were >7%, those with A1C <7% had an increased risk for falls (OR 2.71, 95% CI 1.1,6.7), and the risk was present regardless of the patient's frailty status [42].

Tight glucose control has also been associated with adverse cognitive effects vis a vis hypoglycemia. Studies have documented an increased risk for cognitive impairment and dementia in adults who experience one or more episodes of severe hypoglycemia, and the risk of hospitalization due to hypoglycemia is three times higher in those with dementia.[22,43] In addition, improved functional outcomes were observed in community dwelling older people with diabetes eligible for nursing home care whose A1C levels were between 8-8.9% vs 7-7.9% [44].

The potential population exposed to hypoglycemia related harm from tight control is large. In a cross-sectional study of 1288 older adults (≥65 years of age) with diabetes from the National Health and Nutrition Examination Survey from 2001 to 2010, 61.5% (95% CI, 67.5%-65.3%)

had an A1C of less than 7%. Of those older adults with an A1C less than 7%, 54.9% (50.4%-59.3%) were treated with insulin or suflonylureas [47].

Adverse Effects Associated with Specific Medication Classes

To provide a comprehensive overview of harms associated with antihyperglycemics, we undertook a review of reviews. This approach highlights important harm considerations but does not explore detailed mechanisms or controversies associated with clinical importance. A librarian developed search strategies (available by request) for Ovid Medline and the Cochrane Library for English-language systematic reviews of randomized trials or observational studies presenting associations between antihyperglycemics and harms. Two investigators independently reviewed these results and identified relevant literature. Study design, outcomes and effect sizes were extracted from the relevant studies. CFPlus Appendix 3 summarizes our findings. When weighing the risks and benefits of a particular medication, we encourage readers to consider the effect size for the increased risk in the context of how frequently the medication is used and the patient's baseline risk. In addition when interpreting the evidence for harms, it is important to remember that many of the studies included in systematic reviews were observational studies where residual confounding cannot be completely eliminated.

Metformin

Metformin is associated with vitamin B12 deficiency but not lactic acidosis.[46,47] The risk of lactic acidosis with metformin, even in the presence of renal insufficiency, is estimated to fall between 3 and 10 per 100,000 person-years, which Inzucchi et al report is similar to the rate

with people living with diabetes in general [50]. Wu et al (2015) found metformin use was associated with decreased cancer incidence and cancer-related mortality [51].

Insulin

Zhao et al observed an association between insulin use and diabetic retinopathy,[50] though it is known that glucose control reduces retinopathy in the long-term. Zhang et al. identified a strong association with macular edema and insulin use [53]. In systematic reviews, overall cancer has been linked to insulin,[49,52] but not cancer-related mortality [51]. Singh et al identified an association with hepatocellular cancer.[53] Conflicting findings were reported for studies exploring associations between insulin and colorectal[52,54–56] and pancreatic cancer.[52,57] However, in the ORIGIN trial, which examined use of insulin glargine compared to standard care for a median 6 years, there were no significant differences in overall cancer (HR 1.00; 95% CI, 0.88 to 1.13), cancer-related deaths (HR 0.94, 95% CI, 0.77-1.15) or cancer at specific sites (breast, lung, colon, prostate, melanoma etc.).[58]

Sulfonylureas (e.g. glyburide, chlorpropramide, glibenclamide)

Sulfonylureas are associated with all-cause mortality,[59,60] though conflicting findings have been observed with respect to cardiovascular mortality,[59,61], stroke,[60,61] and cancer [49,53,56,57,62]. Heart failure risk was increased when compared with metformin,[63] while myocardial infarction,[60] and nervous system reactions (dizziness, anxiety, insomnia and vertigo) were not in studies comparing sulfonylureas and placebo.[64] Hypoglycemia risk is greatly increased when sulfonylureas are used with metformin compared with metformin

monotherapy.[64] Glyburide and chlorpropramide are considered potentially inappropriate medications for the elderly in both the Beers[65] and STOPP/START[66] criteria due to increased risk of hypoglycemia compared to other secretagogues and sulfonylureas [67]. Due to these risks, both sets of criteria state that glyburide and chlorpropamide should be avoided in older adults (strong recommendation, very low quality evidence). Chan et al found that gliclazide demonstrated similar HbA1c reductions but carried a lower risk of hypoglycemia compared to other sulfonylureas (i.e., glibenclamide, glimepiride) [70].

Thiazolidinediones (e.g. pioglitazone, rosiglitazone)

Thiazolidinediones have been associated with reduced hip [69], and lumbar spine bone mineral density [69], as well as fractures in women [69,70]. Heart failure [12,63,71,72], edema [71,73], and pneumonia or lower respiratory tract infections are known adverse effects [74]. Myocardial infarction has been noted in two studies [72,75], and one of these studies found no increased risk for cardiovascular death [75]. Loke reported a small increased risk for mortality [72]. Contradictory conclusions exist with respect to bladder cancer [76–80]. Five systematic reviews have examined this risk but all included different original studies. Wu et al. found an increased incidence of all cancer but not in cancer-related mortality [51]. No association with pancreatitis [81], or hypoglycemia (when used in combination with insulin) has been identified [82]. With respect to differences between the agents in the class, Pladevall et al found an increased risk of acute myocardial infarction and stroke for rosiglitazone when compared to pioglitazone [85].

Meglitinides (e.g. repaglinide) and Alpha-glucosidase inhibitors (e.g. acarbose)

Hypoglycemia was not associated with repaglinide both when used in combination with metformin (compared to metformin alone) [84], and compared to sulfonylureas [85]. One retrospective study (not a systematic review) examined an association with cardiovascular mortality but no effect was noted [86]. Acarbose is associated with gastrointestinal adverse effects including flatulence and diarrhea [85,87] and a small increased risk of cancer in one recent study[51].

DPP-4 inhibitors (e.g sitagliptin), GLP-1 agonists (e.g. exenatide), sodium-glucose cotransporter 2 inhibitors (e.g. empaglifozin)

DPP-4 inhibitors, GLP-1 agonists, and sodium-glucose cotransporter 2 inhibitors have been the focus of several systematic reviews. An association between DPP-4 inhibitors and heart failure has been observed [12,88,89]. Conflicting findings are noted for hypoglycemia [92–94], pancreatitis [95,96] and stroke [91,97,98].

Links between GLP-1 agonists and acute pancreatitis [94,97–100], cancer [49,97], fractures [101–103], and nasopharyngitis have been explored but no significant associations have been found [104,105]. Reports of gastrointestinal side effects including diarrhea, nausea and vomiting are noted, particularly with dulaglutide [107,108].

Sodium-glucose cotransporter 2 inhibitors have demonstrated reductions in major cardiovascular events, cardiovascular mortality, and all cause mortality[109]. Associations with genital tract infections have been widely explored and all but one author [110] have found an increased risk [92,107,109–115]. Adverse effects related to osmotic diuresis are reported in some but not all studies(e.g., diarrhea, pollakiuria [i.e., daytime urinary frequency]) [92,110,112]. Conflicting findings are also noted for urinary tract infections

[94,109,110,114,115] and hypoglycemia [92,107–111,113,115]. Concerns about severe dehydration and acidosis requiring hospitalization are supported by some, but not all authors [13,107,116].

Values and patient preferences related to antihyperglycemics

Hypoglycemia is a major concern for people with diabetes. Cross-sectional studies of over 7000 people with type 2 diabetes, with a mean age range of 58-63 years [119–122] suggest that patient-reported quality of life is significantly lower for those experiencing hypoglycemia compared with those who do not. Quality of life may worsen with increasing hypoglycemia severity [119,121] and function may be negatively affected [122]. Patients experiencing hypoglycemia are less satisfied with treatment, and perceive therapy as more burdensome compared with those not experiencing hypoglycemia [117].

The potential burden of diabetes treatment should be considered in the context of patient/caregiver goals and values [123,124]. Survey data suggests patients view insulin and frequent glucose self-monitoring to be burdensome (n=1653, mean age 64 years)[125] and interviews have found intensive therapy may be associated with a decreased quality of life compared with standard treatment in older persons (n=701,mean age 69 years,) [126]. Semi-structured interviews (n=28, mean age 74 years) suggest that older patients with diabetes place greater value on maintaining independence and social function rather than controlling risk or preventing complications [127]. Conversely, a randomized controlled trial in 153 male veterans reported no difference in patient-reported quality of life or perceived health status for patients receiving intensive blood glucose management compared to standard treatment [128]. However, this trial was conducted in younger male patients (40-69 years of age, mean age 60 years); thus, these results may not reflect attitudes of older, more complex, frail patients. In a qualitative

study of 21 caregivers of patients with dementia and diabetes, caregivers reported that caring for these patients was highly burdensome and that they required additional family and health care provider support [131].

There is likely heterogeneity in older patients' preferences in goals with respect to type 2 diabetes management. A survey of 473 patients with diabetes (mean age 74 years of age) found much variation in treatment preferences (tight versus conservative) and patient ratings of the importance of potential complications [130]. There was also variation in the perception of the impact of intensive treatment on quality of life and time trade-offs with respect to intensive treatment and reducing risk of complications [130].

In summary, some older adults may prefer intensive glucose control, while others may prefer less intensive therapy. Some patients feel that pursuing aggressive A1C targets is burdensome and reduces quality of life, and intensive therapy does not appear to improve patient perceived health status. Intensive therapy increases the risk of hypoglycemia, reducing quality of life and adversely impacting function and satisfaction with care. Treatment preferences and goals should be discussed with patients, and treatment should be tailored accordingly.

Resource implications and cost-effectiveness

In a 2011 report from the Public Health Agency of Canada, the prevalence of diabetes was estimated at 6.8% of the population steadily rising with age, affecting >20% of Canadian seniors [131]. Type 2 Diabetes is estimated to account for greater than 90% of all cases in Canada, and the incidence of type 2 diabetes is increasing [131]. A CDA report on the economic burden of estimated expenditures on diabetes totaled $12.2 billion in 2010,

accounting for 3.5% of all healthcare expenditures in Canada, nearly doubling from 2000, with costs expected to rise by $4.7 billion in 2012 [132].

Medications are one of the highest sources of economic burden for diabetes, behind only mortality, long-term disability and hospitalization costs in the general population [132]. Expenditures are different for older adults, with the bulk of costs arising from hospital inpatient stays and medication use [133]. In 2008, $1.7 billion was spent on diabetes medications in Canada, with seniors accounting for $670 million (39.9%) of total drug expenditures in this category [131].

The burden of hypoglycemia is an important consideration when evaluating the economic burden and resource implications of Type 2 Diabetes in older people. Persons with hypoglycemia have been shown to have higher annual all-cause and diabetes-related health care costs than those without hypoglycemia (+$5024 and $3747 USD, respectively) [134]. An analysis by Boulin et al., found incidence rates of drug-induced hypoglyemia were highest for both insulin and sulfonylureas, 8.64 and 4.32 events per person-year respectively in 65-79 year olds, and 12.06 and 6.03 events per person-year for persons aged 80 years or older. These rates of hypoglycemia, along with drug costs, were the main drivers of their cost-effectiveness model. These results suggest that insulin and sulfonylureas may not be cost-effective due to the risks associated with hypoglycemia and associated events [135].

No studies investigating the benefit of antihyperglycemic medications in the frail elderly and those with limited time to benefit, tight glycemic control in elderly populations or the cost-effectiveness of deprescribing antihyperglycemics were identified.

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Appendix 3. Summary of findings tables for systematic review

Deprescribing of glyburide compared to usual care for Type 2 Diabetes

Deprescribing of glyburide compared to usual care for Type 2 Diabetes

Patient or population: Type 2 Diabetes, >65 y.o.
Settings: Community dwelling
Intervention: Deprescribing of Glyburide
Comparison: Control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Deprescribing of Glyburide**				
Change in A1C Follow-up: 3-9 months	Continuation of glyburide	The mean change in A1C in the intervention groups was **0.02 lower** (0.16 lower to 0.12 higher)		3369 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]	
Hypoglycemia ICD-9 Codes in health administrative databases and EMR Follow-up: mean 9 months	**26 per 1000**[4]	**28 per 1000** (20 to 39)	**RR 1.08** (0.78 to 1.5)	6254 (1 study)	⊕⊖⊖⊖ **very low**[1,5,6]	
Discontinuation rate No new prescription for glyburide Follow-up: mean 135 days	**560 per 1000**[4]	**717 per 1000** (684 to 745)	**RR 1.28** (1.22 to 1.33)	6254 (1 study)	⊕⊖⊖⊖ **very low**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very quality: We are very uncertain about the estimate.

[1] Serious risk of bias due to contamination of intervention in control group
[2] 95% CI narrow
[3] Mean difference very small at 0.02%
[4] Usual care
[5] 95% CI around the estimate of effect includes both no effect and appreciable harm
[6] Total number of events <300

Deprescribing versus continuation of antihyperglycemics for type 2 diabetes in the frail elderly

Deprescribing versus continuation of antihyperglycemics for type 2 diabetes in the frail elderly

Patient or population: type 2 diabetes, frail elderly
Settings: Nursing homes in Sweden
Intervention: Deprescribing of antihyperglycemics
Comparison: Continuation of antihyperglycemics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence Comments (GRADE)
	Assumed risk **Continuation of antihyperglycemics**	Corresponding risk **Deprescribing of antihyperglycemics**			
Change in A1C Follow-up: median 6 months		The mean change in A1C in the intervention groups was **1.1% higher** (0.56 to 1.64 higher)		79 (1 study)	⊕⊖⊖⊖ **very low**[1,2]
All-cause mortality	**212 per 1000**	**157 per 1000** (62 to 397)	**RR 0.74** (0.29 to 1.87)	98 (1 study)	⊕⊖⊖⊖ **very low**[1,3]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Very serious risk of bias due to selection bias and potential confounding
[2] 95% CI wide, <400 participants
[3] 95% CI wide, number of events <300

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Appendix 4. Ranges of frequency ratios of harms

Harm	Frequency ratio	Confidence interval	Statistically Significant	Reference	Study design
Biguanides (Metformin)					
Cancer Incidence	RR: 0.86	(0.83-0.90)	Yes	Wu L (2015)	MA of 21 cohort, 22 case-control studies and 23 RCTs
Cancer Mortality	RR 0.70	(0.53-0.94)	Yes	Wu L (2015	MA of 6 cohort, 6 RCTs
Lactic acidosis	WMD: 0.04 mmol/L	(0.00 to 0.13)	No	Salpeter (2010)	MA of 209 prospective comparative trials, 125 prospective cohort studies, 13 retrospective cohort studies
Lactic acidosis in individuals with impaired kidney function	NA	3 and 10 per 100,000 person-years	No	Inzucchi (2014)	SR of 10 metabolic investigations, 20 case series, 31 observational studies, 3 MA, 1 clinical trial
Vitamin B12 deficiency	MD: -53.93	(-81.44 to -26.42)	Yes	Liu (2014)	SR of 6 RCTs
Insulin					
Breast cancer	HR: 1.04 (insulin glargine)	(0.91-1.17)	No	Bronsveld (2015)	MA of 13 epidemiological studies
Colorectal cancer*	RR: 1.69	(1.25-2.27)	Yes	Bu (2014)	MA of 7 case-control, 5 cohort studies

	OR: 1.33	(0.91-1.94)	No	Singh (2013)	MA of 5 case-control, 4 cohort studies
	RR: 1.61	(1.18-1.35)	Yes	Wang (2013)	MA of 1 case-control, 3 cohort studies
	RR: 1.50	(1.08-2.08)	Yes	Janghorbani (2012)	MA of 5 case-control, 10 cohort studies
Cancer-related mortality	RR 1.19	(0.80-1.77)	No	Wu (2015)	MA of 10 cohort, 2 RCTs
Hepatocellular cancer*	OR: 2.61	(1.46-4.65)	Yes	Singh (2013)	MA of 5 case-control, 2 cohort studies
Overall cancer*	RR: 1.21	(1.08-1.36)	Yes	Wu L (2015)	MA of 26 cohort, 34 case-control, 13 RCTs
	RR: 1.39	(1.14-1.70)	Yes	Janghorbani (2012)	MA of 10 cohort, 5 case-control studies
Pancreatic cancer*	OR: 1.59	0.85-2.96	No	Singh (2013)	MA of 5 cohort, 2 case-control studies
	RR: 4.78	(3.12-7.32)	Yes	Janghorbani (2012)	MA of 5 case control, 10 cohort studies
Diabetic retinopathy	RR: 2.30	(1.35-3.93)	Yes	Zhao (2014)	MA of 7 cohort studies
Heart failure	RR: 0.9 (insulin glargine)	(0.77-1.05)	No	Udell (2015)	MA of 14 RCTs

Macular edema	RR: 3.42	(2.42-4.83)	Yes	Zhang (2016)	MA of 3 case-control, 11 cohort studies
Sulfonylureas (SU)					
All cancer	RR: 1.20	(1.13-1.27)	Yes	Wu (2015)	MA of 18 case-control, 16 cohort, 38 RCTs
	RR: 1.55 (cohort)	(1.48-1.63)	Yes	Thakkar (2013)	MA of 2 RCTs, 6 cohort, 10 case-control studies
	RR: 1.17 (RCTs)	(0.95-1.45)	No	Thakkar (2013)	MA of 2 RCTs, 6 cohort, 10 case-control studies
	RR: 1.02 (case control)	(0.93-1.13)	No	Thakkar (2013)	MA of 2 RCTs, 6 cohort, 10 case-control studies
Cancer-related mortality	RR (1.20)	(1.13-1.27)	Yes	Wu (2015)	MA of 18 case-control, 16 cohort, 38 RCTs
All-cause mortality	OR: 1.92	(1.48-2.49)	Yes	Forst (2013)	SR/MA of 17 cohort, 3 case-control studies
	OR: 1.22	(1.01-1.49)	Yes	Monami (2013)	MA of 115 RCTs
Colorectal cancer	OR: OR: 1.11	(0.97-1.26)	No	Singh (2013)	MA of 3 case-control, 4 cohort studies
CV mortality	OR: 2.72	(1.95-3.79)	Yes	Forst (2013)	MA of 17 cohort, 3 case-control studies

	RR: 1.27	(1.18-1.34)	No	Phung (2013)	SR/MA of 12 RCTs, 17 cohort, 4 case-control studies
Hypoglycemia	RR: 0.85 (gliclazide vs. other SUs, DPP-IV inhibitors, glinides)	(0.66-1.09)	No	Chan (2015)	MA of 7 RCTs
	RR: 0.47 (gliclazide vs. other SU)	(0.27-0.79)	Yes	Chan (2015)	MA of 3 RCTs
	RR: 4.09 (SU + metformin compared to metformin alone)	(2.13-7.89)	Yes	Zhang (2013)	MA of 20 RCTs
Heart failure	RR: 1.17 (vs. metformin)	(1.06-1.29)	Yes	Varas-Lorenzo (2014)	MA of 5 cohort studies
Hepatocellular cancer	OR: 1.62	(1.16-2.24)	Yes	Singh (2013)	MA of 4 case-control, 4 cohort studies
Major cardiovascular events (MACE)	RR: 1.10	(1.04-1.16)	No	Phung (2013)	MA of 12 RCTs, 17 cohort, 4 case-control studies
	OR: 1.08	(0.86-1.36)	No	Monami (2013)	MA of 115 RCTs
Myocardial infarction	RR: 1.24 (vs. metformin)	(1.14-1.34)	Yes	Pladevall (2016)	MA of 1 case-control, 16 cohort studies
	OR: 0.88	(0.75-1.04)	No	Monami (2013)	MA of 115 RCTs

Nervous system reactions (dizziness, anxiety, insomnia and vertigo)	RR: 1.27	(1.03-1.57)	No	Zhang (2013)	MA of 20 RCTs
Pancreatic cancer	OR: 1.70	(1.27-2.28)	Yes	Singh (2013)	MA of 5 cohort, 3 case-control studies
Stroke	RR: 1.09	(0.90-1.32)	No	Phung (2013)	MA of 12 RCTs, 17 cohort, 4 case-control studies
	OR: 1.28	(1.03-1.60)	Yes	Monami (2013)	MA of 115 RCTs
Thiazolidinediones (TZDs)					
Cancer Incidence	RR: 0.93	(0.91-0.96)	Yes	Wu (2015)	MA of 12 cohort, 15 case-control studies
Cancer-related mortality	RR 1.40	(0.57-3.40)	No	Wu (2015)	MA of 16 studies
Bladder cancer	RR: 1.20 (pioglitazone)	(1.07-1.34)	No	Bosetti (2013)	MA of 3 case-control, 14 cohort studies
	RR: 1.08 (rosiglitazone)	(0.95-1.23)	No	Bosetti (2013)	MA of 3 case-control, 14 cohort studies
	HR: 1.23 (pioglitazone)	(1.09-1.39)	Yes	Ferwana (2013)	MA of 1 RCT, 4 cohort, 1 nested case-control study
	HR: 1.21 (pioglitazone)	(1.07-1.36)	Yes	He (2013)	MA of 5 cohort, 3 case control, 1 RCT and one case/non-case study

	OR: 2.51 (pioglitazone; from RCTs)	(1.09-5.80)	Yes	Turner (2013)	MA of 5 RCTs, 8 cohort, 4 case-control, and 1 case/non-case study
	OR: 1.21 (pioglitazone; from Observational studies)	(1.09-1.35)	Yes	Turner (2013)	MA of 5 RCTs, 8 cohort, 4 case-control, and 1 case/non-case study
	OR: 0.84 (rosiglitazone; from RCTs)	(0.35-2.04)	No	Turner (2013)	MA of 5 RCTs, 8 cohort, 4 case-control, and 1 case/non-case study
	OR: 1.03 (rosiglitazone; from observational studies)	(0.94-1.12)	No	Turner (2013)	MA of 5 RCTs, 8 cohort, 4 case-control, and 1 case/non-case study
	OR: 1.25 (pioglitazone vs. rosiglitazone)	(0.91-1.72)	No	Turner (2013)	MA of 5 RCTs, 8 cohort, 4 case-control, and 1 case/non-case study
	RR: 1.22 (pioglitazone – cohort)	(1.07-1.39)	Yes	Colmers (2012)	MA of 4 RCTs, 5 cohort, and 1 case-control
	RR: 2.36 (pioglitazone – 1 RCT)	(0.91-6.13)	No	Colmers (2012)	MA of 4 RCTs, 5 cohort, and 1 case-control
	RR: 1.15 (TZDs – cohort)	(1.04-1.26)	Yes	Colmers (2012)	MA of 4 RCTs, 5 cohort, and 1 case-control
	RR: 0.87 (rosiglitazone RCTs)	(0.34-2.23)	No	Colmers (2012)	MA of 4 RCTs, 5 cohort, 1 case-control
Edema	OR: 2.04	(1.85-2.26)	Yes	Hernandez (2011)	MA of 29 RCTs

	OR: 2.26 (TZDs)	(2.02-2.53)	Yes	Berlie (2007)	MA of 26 RCTs
	OR: 2.42 (pioglitazone)	(1.90-3.08)	Yes	Berlie (2007)	MA of 26 RCTs
	OR: 3.75 (rosiglitazone)	(2.70-5.20)	Yes	Berlie (2007)	MA of 26 RCTs
Fractures	OR: 1.94 (women) OR: 1.02 (men)	(1.60-2.35) (0.83-1.27)	Yes No	Zhu (2014)	MA of 22 RCTs
	OR: 1.45 OR: 2.23 (women) OR: 1.0 (men)	(1.18-1.79) (1.65-3.01) (0.73-1.39)	Yes Yes No	Loke (2009)	MA of 10 RCTs, 2 cohort studies
Heart failure	RR : 1.42	(1.15-1.76)	Yes	Udell (2015)	MA of 14 RCTs
	RR: 1.16 (rosiglitazone vs. pioglitazone)	(1.05-1.28)	Yes	Varas-Lorenzo (2014)	MA of 5 cohort studies
	RR: 1.36 (rosiglitazone vs. metformin)	(1.17-1.59)	Yes	Varas-Lorenzo (2014)	MA of 5 cohort studies
	OR: 1.59 (TZDs)	(1.34-1.89)	Yes	Hernandez (2011)	MA of 29 RCTs
	OR: 2.73 (rosiglitazone)	(1.46-5.10)	No	Hernandez (2011)	MA of 29 RCTs

	OR: 1.51 (pioglitazone)	(1.26-1.81)	No	Hernandez (2011)	MA of 29 RCTs
	OR: 1.22 (rosiglitazone compared to pioglitazone)	(1.14-1.31)	Yes	Loke (2011)	MA of 4 case-control, 12 retrospective cohort studies
Hypoglycemia (when used in combination with insulin)	RR: 1.27	(0.99-1.63)	No	Clar (2009)	MA of 8 RCTs
Mortality	OR: 1.14	(1.09-1.20)	Yes	Loke (2011)	MA of 4 case-control, 12 retrospective cohort studies
	OR: 1.03 (CV mortality)	(0.78-1.36)	No	Nissen (2010)	MA of 56 RCTs
Myocardial infarction	RR: 1.13 (rosiglitazone vs. pioglitazone)	(1.04-1.24)	Yes	Pladevall (2016)	MA of 1 case-control, 16 cohort studies
	RR: 1.42 (rosiglitazone vs. metformin)	(1.03-1.98)	Yes	Pladevall (2016)	MA of 1 case-control, 16 cohort studies
	RR: 1.02 (pioglitazone vs. metformin)	(0.75-1.38)	No	Pladevall (2016)	MA of 1 case-control, 16 cohort studies
	RR: 0.99 (rosiglitazone vs. SUs)	(0.78-1.25)	No	Pladevall (2016)	MA of 1 case-control, 16 cohort studies
	OR: 1.16 (rosiglitazone)	(1.07-1.24)	Yes	Loke (2011)	MA of 4 case-control, 12 retrospective cohort studies

	OR: 1.28	(1.02-1.63)	Yes	Nissen (2010)	MA of 56 RCTs
Pancreatitis	OR: 0.786	(0.357-1.734)	No	Monami (2011)	MA of 53 RCTs
Pneumonia or LRTI	RR: 1.40 (any) RR: 1.39 (serious)	(1.08-1.82) (1.05-1.83)	Yes Yes	Singh (2011)	MA of 13 RCTs
Reduced BMD (lumbar spine)	MD: -1.11%	(-2.08 to -0.14)	Yes	Loke (2009)	MA of 10 RCTs, 2 cohort studies
Reduced BMD (hip)	MD: -1.24%	(-2.34 to -0.67)	Yes	Loke (2009)	MA of 10 RCTs, 2 cohort studies
Stroke	RR: 1.18 (rosiglitazone vs. pioglitazone)	(1.02-1.36)	Yes	Pladevall (2016)	MA of 3 cohort studies
Meglitinides					
Cancer incidence	RR: 1.06	(0.83-1.37)	No	Wu (2015)	MA of 3 case-control, 3 cohort, 2 RCTs
CV mortality	RR: 0.81 (compared to other insulin secretagogues)	(0.56-1.19)	N/A	Mogenson (2014)	Retrospective study
Hypoglycemia	RR: 1.24 (Repaglinide +metformin vs metformin alone)	(0.72-2.04)	No	Yin (2014)	MA
	wARD: 0.02 (SU vs repaglinide)	(-0.02-0.05)	N/A	Bolen (2007)	SR of 5 studies

Alpha-Glucosidase inhibitors (acarbose)					
Any adverse effects (mostly GI)	OR: 3.37	(2.60-4.36)	N/A	Laar (2005)	MA
Cancer	RR: 1.1	(1.05-1.15)	Yes	Wu (2014)	MA of 44 cohort, 39 case-control studies, and 182 RCTs
Gastrointestinal effects (flatulence, diarrhea)	15-30% incidence	--	N/A	Bolen (2007)	SR
DPP4 Inhibitors					
Abdominal pain or discomfort	RR: 0.4 (+ metformin)	(0.15-1.01)	No	Kawalec (2014)	MA of 20 RCTs
All-cause mortality	HR: 0.81 (linagliptin)	(0.36-1.81)	No	Rosenstock (2015)	Pooled analysis of 17 RCTs
	OR: 1.00	(0.9-1.13)	No	Agarwal (2014)	MA of 82 RCTs
	RR: 1.064 (short-term)	(0.564-2.005)	No	Savarese (2014)	MA of 94 RCTs
	RR: 1.012 (long-term)	(0.909-1.126)	No	Savarese (2014)	MA of 94 RCTs
Arthralgia	RR: 1.3 (+ metformin)	(0.77-2.19)	No	Kawalec (2014)	MA of 20 RCTs
Back pain	RR: 0.8 (+ metformin)	(0.51-1.18)	No	Kawalec (2014)	MA of 20 RCTs
Bronchitis	RR: 1.1 (+ metformin)	(0.56-2.15)	No	Kawalec (2014)	MA of 20 RCTs
Cancer incidence	RR: 0.92	(0.82-1.04)	No	Wu (2015)	MA of 1 case-control, 2 cohort, 59 RCTs

Constipation	RR: 1.43 (+ metformin)	(0.49-4.14)	No	Kawalec (2014)	MA of 20 RCTs
Cough	RR: 1.02 (vs. SUs; + metformin)	(0.86-1.23)	No	Mishriky (2015)	MA of 16 RCTs
	RR: 1.21 (+ metformin)	(0.68-2.18)	No	Kawalec (2014)	MA of 20 RCTs
CV mortality	HR: 0.88 (linagliptin)	(0.3-2.55)	No	Rosenstock (2015)	Pooled analysis of 17 RCTs
	OR: 0.95	(0.82-1.09)	No	Agarwal (2014)	SR of 82 RCTs
	RR: 1.031 (short-term)	(0.514-2.067)	No	Savarese (2014)	MA of 94 RCTs
	RR: 0.962 (long-term)	(0.843-1.098)	No	Savarese (2014)	MA of 94 RCTs
Diarrhea	RR: 1.01 (vs. SUs; + metformin)	(0.88-1.14)	No	Mishriky (2015)	MA of 16 RCTs
	RR: 0.78 (+ metformin)	(0.59-1.01)	No	Kawalec (2014)	MA of 20 RCTs
Dyspepsia	RR: 1.02 (+ metformin)	(0.43-2.42)	No	Kawalec (2014)	MA of 20 RCTs
Dizziness	RR: 1.49 (+ metformin)	(0.76-2.92)	No	Kawalec (2014)	MA of 20 RCTs
Fatigue	RR: 0.76 (vs. SUs; + metformin)	(0.53-1.08)	No	Mishriky (2015)	MA of 16 RCTs
	RR: 2.03 (+ metformin)	(0.64-6.47)	No	Kawalec (2014)	MA of 20 RCTs
Gastrointestinal AEs	RR: 0.91 (+ metformin)	(0.75-1.09)	No	Kawalec (2014)	MA of 20 RCTs

Genital tract infections	RR: 1.0 (+ metformin)	(0.06-15.65)	No	Kawalec (2014)	MA of 20 RCTs
Headache	RR: 0.98 (+ metformin)	(0.7-1.35)	No	Kawalec (2014)	MA of 20 RCTs
Heart failure*	RR: 1.25	(1.08-1.45)	Yes	Udell (2015)	MA of 14 RCTs
	HR: 1.04 (linagliptin; hospitalization for unstable congestive heart failure)	(0.43-2.47)	No	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo control; 1 active control only)
	OR: 1.19	(1.03-1.37)	Yes	Monami (2014)	MA of 84 RCTs
	RR: 0.668 (short-term; new onset)	(0.318-1.4)	No	Savarese (2014)	MA of 94 RCTs
	RR: 1.158 (long-term; new onset)	(1.011-1.326)	Yes	Savarese (2014)	MA of 94 RCTs
Hypertension	RR: 0.77 (+ metformin)	(0.5-1.18)	No	Kawalec (2014)	MA of 20 RCTs
Hypoglycemia	RR: 0.12 (+ metformin vs. SU + metformin)	(0.1-0.15)	Yes	Foroutan (2016)	MA of 5 RCTs
	RR: 0.14 (+ metformin; vs. SU + metformin)	(0.1-0.2)	Yes	Mishriky (2015)	MA of 16 RCTs
	RR: 0.85 (+ metformin)	(0.53-1.36)	No	Kawalec (2014)	MA of 20 RCTs
Influenza	RR: 0.81 (+ metformin)	(0.57-1.16)	No	Kawalec (2014)	MA of 20 RCTs

MACE	HR: 0.82 (linagliptin)	(0.61-1.09)	No	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo control; 1 active control only)
	HR: 0.78 (linagliptin; composite of 4 MACE)	(0.55-1.12)	No	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo control; 1 active control only)
	HR: 1.09 (linagliptin; composite of 4 MACE vs. placebo only)	(0.68-1.75)	No	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo control; 1 active control only)
	OR: 0.95	(0.86-1.04)	No	Agarwal (2014)	MA of 82 RCTs
Musculoskeletal disorders	RR: 1.02 (vs. SUs; + metformin)	(0.83-1.25)	No	Mishriky (2015)	MA of 16 RCTs
Myocardial infarction	HR: 0.86 (linagliptin; nonfatal)	(0.47-1.56)	No	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo control; 1 active control only)

	OR: 0.98	(0.86-1.10)	No	Agarwal (2014)	SR of 82 RCTs
	RR: 0.584 (short-term)	(0.361-0.943)	Yes	Savarese (2014)	MA of 94 RCTs
	RR: 0.939 (long-term)	(0.835-1.056)	No	Savarese (2014)	MA of 94 RCTs
Nasopharyngitis	RR: 1.05 (vs. SUs; + metformin)	(0.96-1.16)	No	Mishriky (2015)	MA of 16 RCTs
	RR: 0.94 (+ metformin)	(0.75-1.17)	No	Kawalec (2014)	MA of 20 RCTs
Nausea	RR: 0.98 (vs. SUs; + metformin)	(0.75-1.28)	No	Mishriky (2015)	MA of 16 RCTs
	RR: 0.79 (+ metformin)	(0.48-1.3)	No	Kawalec (2014)	MA of 20 RCTs
Pain in extremity	RR: 0.63 (+ metformin)	(0.38-1.02)	No	Kawalec (2014)	MA of 20 RCTs
Pancreatitis	OR: 1.82	(1.17-2.82)	Yes	Roshanov (2015)	MA of 3 RCTs
	OR: 1.03 (incretin-based therapy, analyzed with GLP1RAs)	(0.87-1.2)	No	Wang (2015)	MA of 7 cohort, 2 case-control studies
Pollakiuria (i.e., daytime urinary frequency)	RR: 2.0 (+ metformin)	(0.19-21.52)	No	Kawalec (2014)	MA of 20 RCTs
Stroke	HR: 0.34 (linagliptin; nonfatal)	(0.15-0.75)	Yes	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo

					control; 1 active control only)
	OR: 0.98	(0.77-1.11)	No	Agarwal (2014)	SR of 82 RCTs
	RR: 0.665 (short-term)	(0.365-1.213)	No	Savarese (2014)	MA of 94 RCTs
	RR: 0.953 (long-term)	(0.794-1.144)	No	Savarese (2014)	MA of 94 RCTs
Transient Ischemic Attack	HR: 0.09 (linagliptin)	(0.01-0.75)	Yes	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo control; 1 active control only)
Tremor	RR: 2.07 (+ metformin)	(0.52-8.14)	No	Kawalec (2014)	MA of 20 RCTs
Unstable angina pectoris with hospitalization	HR: 1.08 (linagliptin)	(0.56-2.06)	No	Rosenstock (2015)	Pooled analysis of 19 RCTs (17 placebo-controlled; 1 active agent/placebo control; 1 active control only)
Urinary tract AEs	RR: 0.8 (+ metformin)	(0.22-2.85)	No	Kawalec (2014)	MA of 20 RCTs
	RR: 1.15 (infections; + metformin)	(0.8-1.65)	No	Kawalec (2014)	MA of 20 RCTs
Upper respiratory tract infections	RR: 0.92 (+ metformin)	(0.63-1.34)	No	Kawalec (2014)	MA of 20 RCTs

Vomiting	RR: 1.05 (+ metformin)	(0.35-3.11)	No	Kawalec (2014)	MA of 20 RCTs
GLP1 Agonists					
Acute pancreatitis	OR: 1.03 (incretin-based therapy, analyzed with GLP1RAs)	(0.87-1.2)	No	Wang (2015)	MA of 7 cohort, 2 case-control studies
	RR: 2.1 (liraglutide vs. active agents)	(0.3-16)	No	Jensen (2014)	SR and pooled analysis of 18 RCTs (phase II and III studies)
	RR: 1.7 (liraglutide vs. active agents excluding sitagliptin and exenatide)	(0.2-13.2)	No	Jensen (2014)	SR and pooled analysis of 18 RCTs (phase II and III studies)
	OR: 1.11 (RCT)	(0.57-2.17)	No	Li (2014)	MA of 55 RCTs, 3 retrospective cohort, 2 case-control studies
	OR: 1.01	(0.37-2.76)	No	Monami (2013)	MA of 9 RCTs
	OR: 0.87 (pooled)	(0.64-1.17)	No	Alves (2012)	MA of 3 retrospective cohort, 22 RCTs
Bone fractures	OR: 0.38 (liraglutide)	(0.17-0.87)	No	Su (2015)	MA of 8 RCTs
	OR: 2.09 (exenatide)	(1.03-4.21)	No	Su (2015)	MA of 10 RCTs

	OR: 0.75	(0.28-2.02)	No	Mabilleau (2013)	MA of 7 RCTs
Diarrhea	RR: 2.04 (dulaglutide vs. placebo, sitagliptin, exenatide, liraglutide or glargine)	(1.57-2.65)	Yes	Zhang (2016)	MA of 12 RCTs
	RR: 2.85 (vs. insulin glargine)	(2.01-4.04)	Yes	Fu-peng (2014)	MA of 7 RCTs
Headache	RR: 1.19 (vs. insulin glargine)	(0.92-1.54)	No	Fu-peng (2014)	MA of 7 RCTs
Hypoglycemia	RR: 1.07 (dulaglutide vs. placebo, metformin or liraglutide)	(0.8-1.44)	No	Zhang (2016)	MA of 12 RCTs
	RR: 1.07 (dulaglutide + oral antihyperglycemics vs. placebo, metformin or liraglutide)	(0.89-1.3)	No	Zhang (2016)	MA of 12 RCTs
	RR: 1.12 (severe; vs. insulin glargine	(0.5-2.5)	No	Fu-peng (2014)	MA of 7 RCTs
	RR: 0.56 (minor; vs. insulin glargine)	(0.34-0.95)	Yes	Fu-peng (2014)	MA of 7 RCTs

Nasopharyngitis	RR: 0.95 (vs. insulin glargine)	(0.79-1.14)	No	Fu-peng (2014)	MA of 7 RCTs
	RR: 1.02	(0.64-1.62)	No	Nikfar (2012)	MA of 3 RCTs
Nausea	RR: 2.64 (dulaglutide vs. placebo, sitagliptin, exenatide, liraglutide or glargine)	(1.69-4.12)	Yes	Zhang (2016)	MA of 12 RCTs
	RR: 8.65 (vs. insulin glargine)	(6.03-12.40)	Yes	Fu-peng (2014)	MA of 7 RCTs
Overall cancer	OR: 1.24 (pooled)	(0.68-2.27)	No	Alves (2012)	MA of 3 retrospective cohort, 22 RCTs
Cancer incidence	RR: 1.12	(0.61-2.06)	No	Wu (2015)	MA of 2 cohort, 14 RCTs
Vomiting	RR: 2.58 (dulaglutide vs. placebo, sitagliptin, exenatide, liraglutide or glargine)	(1.53-4.35)	Yes	Zhang (2016)	MA of 12 RCTs
	RR: 4.69 (vs. insulin glargine)	(3.26-6.75)	Yes	Fu-peng (2014)	MA of 7 RCTs
Sodium-Glucose Cotransporter 2 Inhibitors					
Acidosis	RR: 0.57 (from regulatory submissions)	(0.02-14.10)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)

	RR: 1.99 (from scientific reports)	(0.22-17.8)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
AEs related to reported falls	HR: 1.24 (100 mg canagliflozin)	(0.71-2.17)	No	Watts (2016)	Interim analysis of CANVAS‖
	HR 0.84 (100 mg canagliflozin)	(0.46-1.54)	No	Watts 2016	Pooled analysis from 9 RCTs (non-CANVAS studies)
	HR: 2.12 (300 mg canagliflozin)	(1.28-3.51)	Yes	Watts (2016)	Interim analysis of CANVAS‖
	HR 1.13	(0.65-1.96)	No	Watts (2016)	Pooled analysis from 9 RCTS (non-CANVAS studies)
Angina	RR: 0.95	(0.73-1.23)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
All-cause mortality	RR: 0.71	(0.61-0.83)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	Effect estimate: 2.8 (empagliflozin + metformin vs. active agent)#	(0.12-68.22)	No	Zhong (2016)	MA of 7 RCTs

Arthralgia	RR: 0.2 (+ metformin)	(0.02-1.68)	No	Kawalec (2014)	MA of 20 RCTs
Back pain	RR: 0.87 (+ metformin)	(0.37-2.05)	No	Kawalec (2014)	MA of 20 RCTs
Bone fracture	HR: 1.44 (canagliflozin)	(0.87-2.39)	No	Watts (2016)	Analysis of CANVAS
	HR: 0.80 (canagliflozin)	0.49-1.29)	No	Watts 2016	Pooled analysis of 9 RCTs (non-CANVAS)
	RR: 0.99 (from regulatory submissions)	(0.82-1.21)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 0.96 (from scientific reports)	(0.78-1.18)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
Cancer incidence	RR: 0.90 (dapagliflozin)	(0.49-1.65)	No	Wu (2015)	MA 7 studies
Cancer	RR: 1.07 (from regulatory submissions)	(0.85-1.34)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 0.72 (from scientific reports)	(0.34-1.54)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)

Constipation	OR: 0.7 (dapagliflozin)	(0.4-1.22)	No	Musso (2011)	MA of 13 RCTs
Cough	RR: 0.43 (+ metformin)	(0.16-1.13)	No	Kawalec (2014)	MA of 20 RCTs
CV mortality	RR: 0.63	(0.5-0.85)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
Diarrhea	RR: 0.74 (+ metformin)	(0.37-1.48)	No	Kawalec (2014)	MA of 20 RCTs
	OR: 0.94 (dapagliflozin)	(0.65-1.37)	No	Musso (2011)	MA of 13 RCTs
Fatigue	RR: 3.0 (+ metformin)	(0.13-69.09)	No	Kawalec (2014)	MA of 20 RCTs
Gastrointestinal AEs	RR: 1.0 (+ metformin)	(0.23-4.31)	No	Kawalec (2014)	MA of 20 RCTs
Genital tract infections	RR: 4.75 (from regulatory submissions)	(4.0-5.63)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 2.88 (from scientific reports)	(2.48-3.34)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	Effect estimate: 6.67 (empagliflozin + metformin)[#]	(1.15-38.79)	No	Zhong (2016)	MA of 7 RCTs

	Effect estimate: 3.49 (empagliflozin + metformin vs. active agent)[#]	(1.39-8/81)	No	Zhong (2016)	MA of 7 RCTs
	RR: 5.13 (canagliflozin vs. sitagliptin)	(2.92-9.01)	Yes	Kaur (2015)	MA of 5 RCTs
	RR: 11.96 (males; canagliflozin vs. sitagliptin)	(2.84-50.41)	Yes	Kaur (2015)	MA of 5 RCTs
	RR: 3.99 (females; canagliflozin vs. sitagliptin)	(2.15-7.4)	Yes	Kaur (2015)	MA of 5 RCTs
	RR: 2.36 (+ metformin)	(1.17-4.74)	Yes	Kawalec (2014)	MA of 20 RCTs
	OR: 4.39 (10 mg empagliflozin)	(2.1-9.19)	Yes	Liakos (2014)	MA of 10 RCTs
	OR: 3.31 (25 mg empagliflozin)	(1.55-7.09)	Yes	Liakos (2014)	MA of 10 RCTs
	RR: 3.76	(2.23-6.35)	Yes	Yang (2014)	MA of 10 RCTs
	OR: 3.32	(2.40-4.59)	Yes	Monami (2013)	MA of 21 RCTs[+]

	OR: 4.81	(2.97-7.81)	N/A	Vasilakou (2013)	MA of 20 studies[+]
	RR: 3.42 (dapagliflozin)	(2.19-5.33)	Yes	Clar (2012)	SR of 7 RCTs
	OR: 3.57 (dapagliflozin)	(2.59-4.93)	Yes	Musso (2011)	MA of 13 RCTs
Headache	RR: 1.29 (+ metformin)	(0.65-2.56)	No	Kawalec (2014)	MA of 20 RCTs
	OR: 0.69 (dapagliflozin)	(0.48-0.97)	Yes	Musso (2011)	MA of 13 RCTs
Hypoglycemia	RR: 1.0 (from regulatory submissions)	(0.94-1.07)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 0.95 (from scientific reports)	(0.91-1.0)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	Effect estimate: 1.59 (empagliflozin + metformin)[#]	(0.77-3.3)	No	Zhong (2016)	MA of 7 RCTs
	Effect estimate: 3.49 (empagliflozin + metformin vs. active agent)[#]	(0.15-1.53)	No	Zhong (2016)	MA of 7 RCTs

	RR: 1.02 (+ metformin)	(0.44-2.38)	No	Kawalec (2014)	MA of 20 RCTs
	OR: 1.28 (10 mg empagliflozin)	(0.97-1.7)	No	Liakos (2014)	MA of 10 RCTs
	OR: 1.10 (25 mg empagliflozin)	(0.87-1.39)	No	Liakos (2014)	MA of 10 RCTs
	RR: 1.13	(0.40-3.20)	No	Yang (2014)	MA of 10 RCTs
	OR: 1.34	(1.09-1.65)	Yes	Monami (2013)	MA of 22 RCTs
	OR: 1.28	(0.99-1.65)	N/A	Vasilakou (2013)	MA of 21 studies[+]
	OR: 1.27 (dapagliflozin + insulin)	(1.05-1.53)	Yes	Musso (2011)	MA of 13 RCTs
	OR: 1.31 (dapagliflozin – insulin)	(0.93-1.86)	No	Musso (2011)	MA of 13 RCTs
Hypertension	RR: 1.08 (+ metformin)	(0.52-2.22)	No	Kawalec (2014)	MA of 20 RCTs
Influenza	RR: 1.14 (+ metformin)	(0.58-2.24)	No	Kawalec (2014)	MA of 20 RCTs
Kidney disease	RR: 1.21 (from regulatory submissions)	(0.91-1.62)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 0.83 (from scientific reports)	(0.69-1.0)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory

					submissions)
Major CV events	RR: 0.84	(0.75-0.95)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
Nausea	RR: 4.58 (+ metformin)	(0.53-39.36)	No	Kawalec (2014)	MA of 20 RCTs
Nasopharyngitis	RR: 0.79 (+ metformin)	(0.46-1.36)	No	Kawalec (2014)	MA of 20 RCTs
	OR: 0.95 (dapagliflozin)	(0.68-1.33)	No	Musso (2011)	MA of 13 RCTs
Nonfatal myocardial infarction	RR: 0.88	(0.72-1.07)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
Nonfatal stroke	RR: 1.3	(1.0-1.68)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
Osmotic diuresis related AE (diarrhea, pollakiuria)	RR: 3.09 (canagliflozin vs. sitagliptin)	(0.88-10.87)	No	Kaur (2015)	MA of 5 RCTs
	RR: 1.01 (+ metformin; pollakiuria)	(0.2-5.09)	No	Kawalec (2014)	MA of 20 RCTs
	RR: 3.93	(2.25-6.86)	Yes	Yang (2014)	MA of 10 RCTs
Tremor	RR: 3.0 (+ metformin)	(0.13-69.09)	No	Kawalec (2014)	MA of 20 RCTs

Thromboembolism	RR: 1.54 (from regulatory submissions)	(0.63-3.79)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 0.75 (from scientific reports)	(0.42-1.31)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
Urinary infections	RR: 1.15 (from regulatory submissions)	(1.06-1.26)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 1.02 (from scientific reports)	(0.95-1.1)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	Effect estimate: 1.24 (empagliflozin + metformin)[#]	(0.86-1.81)	No	Zhong (2016)	MA of 7 RCTs
	Effect estimate: 0.76 (empagliflozin + metformin vs. active agent)[#]	(0.48-1.22)	No	Zhong (2016)	MA of 7 RCTs
	RR: 0.75 (canagliflozin vs. sitagliptin)	(0.48-1.16)	No	Kaur (2015)	MA of 5 RCTs

	RR: 1.02 (+ metformin)	(0.54-1.91)	No	Kawalec (2014)	MA of 20 RCTs
	RR: 1.11 (+ metformin; reported as urinary AEs)	(0.68-1.83)	No	Kawalec (2014)	MA of 20 RCTs
	OR: 1.2 (10 mg empagliflozin)	(0.92-1.57)	No	Liakos (2014)	MA of 10 RCTs
	OR: 1.03 (25 mg empagliflozin)	(0.81-1.32)	No	Liakos (2014)	MA of 10 RCTs
	RR: 1.19	(0.82-1.73)	No	Yang (2014)	MA of 10 RCTs
	OR: 1.23	(0.99-1.52)	Yes	Monami (2013)	MA of 21 RCTs[+]
	OR: 1.34	(1.03-1.74)	N/A	Vasilakou (2013)	MA of 21 studies
	RR: 1.44 (dapagliflozin)	(1.05-1.98)	Yes	Clar (2012)	SR of 7 RCTs
	OR: 1.34 (dapagliflozin)	(1.05-1.71)	Yes	Musso (2011)	MA of 13 RCTs
Upper respiratory tract infections	RR: 0.4 (+ metformin)	(0.18-0.91)	Yes	Kawalec (2014)	MA of 20 RCTs
Volume depletion related AE	HR: 1.32 (100 mg canagliflozin)	(0.94-1.87)	No	Watts (2016)	Interim analysis of CANVAS[‖]

	HR: 1.76 (300 mg canagliflozin)	(1.27-2.44)	Yes	Watts (2016)	Interim analysis of CANVAS‖
	RR: 1.53 (from regulatory submissions)	(1.27-1.83)	Yes	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 1.16 (from scientific reports)	(0.98-1.38)	No	Wu (2016)	MA of 63 RCTs (57 scientific reports and 6 regulatory submissions)
	RR: 0.76 (canagliflozin vs. sitagliptin)	(0.04-15.41)	No	Kaur (2015)	MA of 5 RCTs
Vomiting	RR: 3.0 (+ metformin)	(0.13-69.09)	No	Kawalec (2014)	MA of 20 RCTs

RR – relative risk
OR – odds ratio
HR – hazard ratio
MD – mean difference
SR – systematic review
MA – Meta-analysis
ARD – Absolute risk difference
* - This is a summary of findings from our review of reviews of harms. Readers are referred to the ORIGIN trial which examined insulin glargine compared to standard care for a median 6 years and showed neutral effects for overall cancer, cancer-related deaths and specific cancers . Readers are referred to the TECOS trial which examined the addition of sitagliptin to usual care for a median of 3 years in patients with type 2 diabetes and cardiovascular disease. Sitagliptin was noninferior to placebo for the primary composite cardiovascular outcome (composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) (hazard ratio, 0.98; 95% CI, 0.88 to 1.09; P<0.001). Rates of hospitalization for heart failure did not differ between the two groups (hazard ratio, 1.00; 95% CI, 0.83 to 1.20; P=0.98).
+ - No breakdown of study type per AE (also high risk of bias)
# Empagliflozin 10 mg (review also presented data for 25 mg dose)
‖ CANVAS – From interim analysis of RCT called CANagliflozin cardioVascular Assessment Study (CANVAS) comparing canagliflozin 100 mg, 300 mg and placebo in addition to standard

care for type 2 diabetes management(50% insulin, 47% sulfonylurea) in patients with high risk for CV disease [52]

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Appendix 5. Targets from the various diabetes guidelines

Guideline	Targets	Comments
Canadian Diabetes Association[1,2]	**Healthy elderly**- same as younger population (A1C ≤ 7%, fasting 4-5 mmol/L, 2 hour post prandial 5-10 mmol/L) **Frail elderly:** while avoiding symptomatic hyperglycemia, A1C ≤ 8.5%, fasting or preprandial 5-12 mmol/L, depending on level of frailty **Elderly with cognitive impairment:** strictly prevent hypoglycemia and less stringent A1C target but not defined	Individualized, higher A1C targets are recommended for those with limited life expectancy, high level of functional dependency, extensive coronary artery disease or high risk of ischemia events, multiple co-morbidities, history of recurrent severe hypoglycemia, hypoglycemia unawareness, longstanding diabetes for whom it is difficult to achieve A1C < 7%, despite effective doses of multiple antihyperglycemic agents, including intensified basal-bolus dose insulin therapy
Diabetes Care Program of Nova Scotia (DCPNS)[3]	**Frail elderly:** • Maintain A1C ≥ 8% • Below 8%- discontinue or decrease diabetes treatment • ≥ 8% to <12%-acceptable if asymptomatic • Above 12%- consider increasing diabetes treatment Random Blood Glucose • <7 mmol/L- decrease diabetes treatment • 7-9.9 mmol/L may be acceptable but consider risk of hypoglycemia; if hypoglycemia occurs decrease treatment • 10-20- acceptable in the absence of reversible symptoms • frequently above 20 - increase treatment	Guidelines were developed for severely frail elderly population specifically (Clinical Frailty Scale >7 and requiring assistance with activities of daily living) State stringent targets should be avoided and specify discontinuation of treatments if A1C < 8% or random glucose < 7 mmol/L

European Diabetes Working Party for Older People (EDWPOP)[4]	**Elderly with single system involvement** (free of other major co-morbidities): A1C 7-7.5% (precise target will depend on existing cardiovascular risk, presence of microvascular complications, and ability to self-manage) Fasting glucose of 6.5-7.7 mmol/l can be regarded as good control **Frail (dependent, multisystem disease, care home residency, including those with dementia)**: A1C of 7.6-8.5% (patients where risk of hypoglycemia is high) Fasting glucose range of 7.6-9.0 mmol/l should minimize risk of hypoglycemia and metabolic decompensation	
American Geriatrics Society[5]	**Older adults**: A1C 7.5-8% A1C < 6.5%- potential harm **Healthy older adults with few comorbidities and good functional status:** A1C 7-7.5% may be appropriate if can be safely achieved **Older adults with multiple comorbidities, poor health, and limited life expectancy:** A1C 8-9% appropriate	

American Diabetes Association[6]	**Healthy** (few coexisting chronic illnesses, intact cognitive and functional status) A1C <7.5% (a lower goal may be set if achievable without recurrent or severe hypoglycemia or undue treatment burden) **Complex/intermediate** (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild to moderate cognitive impairment) A1C <8% **Very complex/poor health** (long-term care or end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ ADL dependence) A1C <8.5% (looser glycemic targets than this may expose patients to acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing)	
International Diabetes Federation[7]	**1. Functionally independent** (living independently, have no important impairments of ADL, and who are receiving none or minimal care support) A1C 7-7.5% 2. **Functionally dependent** (due to loss of function have impairments of ADL): A1C 7-8% A **Frail** (combination of significant fatigue, recent weight loss, severe restriction in mobility and strength, increased propensity to falls, and increased risk of institutionalization): up to 8.5% may be appropriate B **Dementia:** up to 8.5% may be appropriate 3. **End of life care**: avoid symptomatic hyperglycemia	End of life (IDF) target to 9-15 mmol/L (which is ~9.0%)

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Appendix 6. Glycemic targets for varying patient frailty status

	Organization A1C Suggestions				
Patient Status	**CDA**	**PATH**	**ADA**	**AGS**	**IDF**
Healthy aged	≤7%	N/A	N/A	7.5-8.0% (not <7.5 with <6.5 associated with potential harm)	7-7.5% (not <7)
CFS 4-5	7.1-8.5% (depending on level of frailty, however, preventing hypoglycemia should take priority over lowering A1C to less than target.	N/A	N/A	N/A	N/A
CFS 6+		8-12% (if A1C < 8%, decrease or stop diabetes treatment)	<8.5%	8-9%	≤8.5%
CI or dementia	Avoid Symptoms	N/A	NA	N/A	8.5%
End of life	Avoid Symptoms	8-12% & avoid symptoms	N/A	N/A	Avoid Symptoms

CFS= Clinical Frailty Scale; **ADA**=American Diabetes Association; **IDF**= International Diabetes Federation; **AGS**= American Geriatrics Society; **CDA=** Canadian Diabetes Assocation; **PATH=** Palliative and Therapeutic Harmonization Program

Appendix 7. Antihyperglycemics, their A1C lowering effect and likelihood to cause hypolycemia (Adapted from CDA guidelines)

DRUG	A1C LOWERING EFFECT	CAUSES HYPOGLYCEMIA?
Metformin	1.0-1.5%	No
Sulfonylureas	0.8%	Yes (highest risk with glyburide and chlorpropramide; lower risk with short and long-acting gliclazide)
Insulin	0.9-1.1%	Yes (highest risk with regular insulin and NPH insulin)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	0.7%	No
Glucagon-like peptide 1 (GLP-1) agonists	1.0%	No
Thiazolidinediones	0.8%	No
Alpha-glucosidase inhibitor	0.6%	No
Meglitinides	0.7%	Yes (minimal/moderate risk)
Sodium-glucose linked transporter 2 (SGLT2) inhibitors	0.7-1.0%	No

Appendix 8. Drug interactions that may lead to hypoglycemia[139]

Antihyperglycemic	Added Medications that increase risk of hypoglycemia
Repaglinide	Decreased metabolism via CYP 3A4 inhibition – amiodarone, azole antifungals, ciprofloxacin, clarithromycin, erythromycin, cyclosporine, diltiazem, gemfibrozil Decreased metabolism via CYP 2C8 inhibition – clopidogrel, trimethoprim/sulfamethoxazole
Sulfonylureas	Decreased metabolism via 2C9 inhibition – Amiodarone, sulfamethoxazole/trimethroprim, fluvastatin Hypoglycemia with cimetidine, clarithromycin, EtOH, fluconazole, fluoxetine, MAOIs, metronidazole, NSAIDs, quinolones, salicylates & sulfonamides

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Appendix 9. Drugs that may be associated with hypoglycemia in patients with diabetes

Drug/drug class
Angiotensin-converting enzyme (ACE) inhibitors
Beta-blockers
Ethanol or Alcohol
Monoamine Oxidase Inhibitors
Pentamidine
Quinine
Quinolone antibiotics
Salicylates

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Appendix 10. Drugs that may be associated with hyperglycemia in patients with diabetes

Drug/drug class
Atypical antipsychotics (risk may be highest with olanzapine and clozapine)
Beta-blockers (except carvedilol and nebivolol)
Calcineurin inhibitors (cyclosporine, sirolimus, tacrolimus)
Corticosteroids
Protease inhibitors
Quinolone antibiotics (most commonly gatifloxacin)
Thiazide and thiazide-like diuretics

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