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Comparative effectiveness of cardioprotective drugs in elderly individuals with type 2 diabetes

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SUMMARY

Aims: Although many elderly individuals suffer from type 2 diabetes, the effectiveness of cardioprotective drugs in primary prevention of cardiovascular events in clinical practice in this population has rarely been evaluated. We aimed to assess the effectiveness of, (i) angiotensin converting enzyme inhibitors or angiotensin receptor blockers, (ii) statins, (iii) antiplatelet drugs and (iv) the combination of these three drugs, in the prevention of myocardial infarction (MI) and stroke in elderly individuals with type 2 diabetes. **Methods:** Using Quebec administrative databases, we conducted nested case-control analyses among a cohort of 17,384 individuals without a history of cardiovascular disease. Individuals were aged ≥ 66 years, newly treated with oral antidiabetes drugs and had not used any of the three above classes of cardioprotective drugs in the year before cohort entry. For each case (MI/stroke during follow-up), five controls were matched for age, year of cohort entry and sex. Use of each drug and of their combination was defined as current, past or no use. We calculated adjusted odds ratios (AOR) of MI/stroke. **Results:** We observed no reduction in the MI/stroke risk for users of ACEI/ARB nor for users of the three drugs combination. Longer exposure to statins was associated with a lower risk (AOR for every 30 days of therapy: 0.97; 95% CI: 0.96–0.99). By contrast, current use of antiplatelet drugs was associated with an increased risk of MI/stroke (1.40; 1.12–1.75). **Conclusion:** The benefit of cardioprotective drugs in primary prevention was not clear in this cohort of elderly individuals with type 2 diabetes. A short duration of exposure to these drugs might explain the lack of benefit.

What's known

Older people with type 2 diabetes present a high risk of suffering from cardiovascular diseases. Randomized controlled trials have shown that pharmacologic agents are effective in reducing cardiovascular risk in younger population.

What's new

Evidence-based cardioprotective drug regimens had little benefit in terms of prevention of MI or stroke in a large population of elderly individuals with type 2 diabetes. It might however be due to the short duration of exposure to these drugs in this population. There is a need to further evaluate what are the optimal pharmacological treatments for primary prevention of cardiovascular diseases in elderly individuals with type 2 diabetes, and when they should be introduced.

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Background

The elderly people are the age-group most affected by type 2 diabetes (1). Given cardiovascular disease (CVD) is the main complication of diabetes for this age-group (2), proper management of cardiovascular risk factors is paramount. Clinical practice guidelines recommend cardioprotective drugs for individuals with diabetes (3,4) although diabetes *per se* does not necessarily confer a cardiovascular risk equivalent to a previous myocardial infarction (MI) or stroke (5,6). Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), statins and antiplatelet therapy provide vascular protection (3). Yet recommendations to use these drugs are based on results from randomised controlled trials that were mostly conducted in populations of individuals aged less than 65 years. Nonetheless, according to guidelines, older individuals should be treated as aggressively as younger ones although more conservative objectives in terms of blood pressure and cholesterol level targets may be attained for individuals with multiple comorbidities (3).

Because individuals involved in clinical trials may differ from those elderly people treated in clinical practice (in terms of comorbidities, medication adherence and attainment of clinical targets), there is a need to evaluate the effectiveness of cardioprotective drugs in clinical practice. Observational studies suggested a decreased risk of all-cause mortality in individuals with diabetes using ACEIs/ARBs, antihypertensives and statins (7–10). Nevertheless, those studies had limitations. In one study (7), the 51% reduction in mortality risk among ACEI users compared with non-users may have been biased with an artificial survival advantage. Indeed, those who used an ACEI for less than a year were excluded, whereas the others were considered users if they had used an ACEI anytime after cohort entry. In two other studies (8,9), all drugs were considered altogether making

it difficult to disentangle the respective effect of individual drugs or of their combination at reducing mortality. Thus, the comparative effectiveness of cardioprotective drugs in clinical practice is still unclear in primary prevention for elderly people with diabetes, especially for the reduction in cardiovascular events which have not yet been studied to our knowledge. We therefore aimed to assess the effectiveness of, (i) ACEI/ARBs, (ii) statins, (iii) antiplatelet agents and (iv) their combination in the prevention of MI or stroke in a population of ambulatory older individuals newly treated with oral antidiabetes drugs.

Methods

We conducted four nested case-control analyses within a population-based cohort using the Québec health insurance board (*Régie de l'assurance maladie du Québec, RAMQ*) databases and the Québec registry of hospitalisations [*Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* (Med-Écho)]. The public health insurance plan covers all permanent residents ($\approx$ 7.5 million) of the province of Québec, Canada, for both medical services and hospitalisations. Its public drug plan covers almost all non-institutionalised individuals aged $\geq$ 65 years. The drug plan database is known to be accurate (11). From RAMQ, we obtained data on individuals' demographics (age, sex, region of residence), physician services (date and diagnosis), prescription drugs dispensed (drug identification, dispensing date and number of days supply) and death. Med-Écho provided data on hospitalisations (date, primary and secondary diagnoses).

Study population

We identified individuals aged $\geq$ 66 years who had received at least one oral antidiabetes drug between 1 January 1998 and 31 December 2003. We defined the date of cohort entry as being the date of the first claim for any oral antidiabetes drug. We then excluded individuals who, in the year prior to cohort entry: (i) had received an oral antidiabetes drug or insulin; (ii) had not been eligible for the drug plan; (iii) had used any ACEI [Anatomical Therapeutic Chemical (ATC) classification system: C09A, C09B], ARB (ATC: C09C, C09D), statin (ATC: C10AA) or antiplatelet drug (ATC: B01AC). We then excluded individuals with CVD history. CVD was defined as the presence, in the year before cohort entry, of the following International Classification of Diseases, Ninth Revision (ICD-9) codes: 411–414, 420–434, 436–438, 440. A person with a prescription claim for a nitrate was also considered to have CVD. Individuals that were included in the cohort were followed-up until 31 December 2004, ineligibility to the drug plan or death, whichever came first.

Cases and controls

Cases were individuals who had a MI or a stroke during the follow-up period. We used the hospital discharge diagnosis of acute MI (ICD-9 code 410, all diagnostic fields) which has been shown to be valid for elderly individuals (12). To ensure the accuracy of the diagnosis, only individuals whose hospital stay was for $\geq$ 3 days were considered to have had an acute MI, unless individuals were transferred to or from another hospital, had a percutaneous coronary intervention performed or died (13). Stroke was defined by the following ICD-9 codes in Med-Écho database: 430–431, 433.x1, 434.x1 and 435. The index date for cases was defined as the date of occurrence of the first MI or stroke. We randomly selected five controls for each case using incidence density sampling. We matched cases and controls for age at cohort entry, year of entry in the cohort and sex. We assigned to each control their case's index date. The observation period was defined as the interval between cohort entry and the index date.

Exposure assessment

We assessed individuals' use of ACEI/ARBs, statins and antiplatelet drugs during the observation period. Use of each class of drug was classified in three possible categories: current, past or non-use (Figure 1). An individual was deemed as current user if his/her index date was included in the interval between the date of the last drug claim and the date of the end of its days supply, to which a grace period equalled to the number of days supply was added. Otherwise, individuals who used the respective drug in the observation period were considered past users while others were deemed as non-users. Duration of exposure to individual drug treatments was calculated as the number of days of drug use during the observation period. We assessed the use of the combination of all three drugs in a way similar to what we did for each drug individually (Figure 1).

Potentially confounding variables

Potential confounders included (i) individual-, (ii) drug- and (iii) health service-related characteristics. The following individual-related characteristics were considered: residency area, drug plan beneficiary type, the number of different drugs dispensed (14) during the observation period and medical conditions known to increase cardiovascular risk and/or influence use of cardioprotective drugs [Alzheimer's disease (ICD-9:331 or claims for donepezil, galanta-

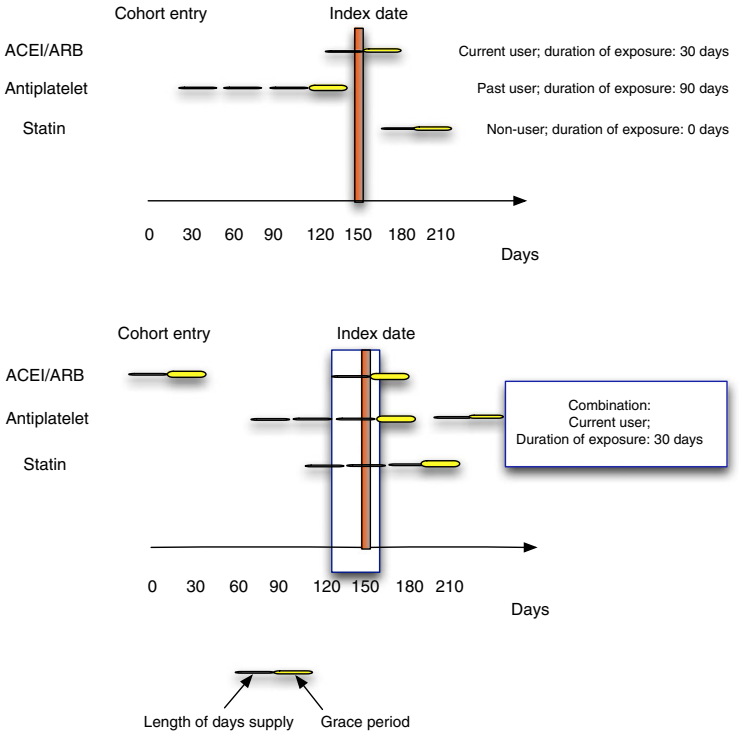

Figure 1 Exposure assessment. Exposure was assessed at index date, the date the case suffered MI or stroke. At the top of the Figure 1, the individual was defined as current user of ACEI/ARB since the date of end of days supply for last claim (plus the grace period) overlapped with the index date. As for antiplatelet drugs, there was at least one claim before the index date, but the length of days supply plus the grace period of the last claim did not overlap with the index date. The individual was thus considered a past user for antiplatelet drugs. Finally, as there was no claim for statin before the index date, the individual was defined as non-user of statin. The number of days the drugs were used was summed to establish duration of exposure for each drug, which resulted in 30 days for ACEI/ARB (one 30-day period), 90 for antiplatelet drugs (three 30-days period) and 0 for statin. At the bottom of figure 1, the individual was defined as a current combination user since at least one drug from each of the three classes of drugs was used in combination at the index date. The number of days the three treatments were used in combination was 30 days.

mine, memantine or rivastigmine); chronic obstructive pulmonary disease (ICD-9:491, 492, 496); cirrhosis (ICD-9:571); depression (ICD-9:296.2, 296.3, 300.4, 309.0, 309.1, 311); renal disease (ICD-9:250.4, 580-9, 791.0) and obesity (ICD-9:278.0)]. Drug-related characteristics considered in the observation period included: the use of insulin; the use of anticoagulant; the number of days of antihypertensive drug (other than an ACEI/ARB) use and the number of days of lipid-lowering drug (other than a statin). Finally, health service-related characteristics included the number of medical visits and hospitalisations during the observation period.

Statistical analysis

Frequency distributions were used to describe matching characteristics and potential confounders of cases and controls. The risk of MI or stroke associated with the use of individual or combined cardioprotective drugs was assessed using multivariate conditional logistic regression. Odds ratios with their 95% confidence intervals calculated from such paired multivariate logistic regression are equivalent to hazard ratios obtained with Cox's proportional hazard models (15,16). Multicollinearity was assessed with the procedure described by Belsley et al. (17). To test the sensitivity of the length of the grace period in defining current users, we repeated the analysis using on the one hand, no grace period, and on the other hand, a grace period equalled to half the number of days supply. Analyses were carried out with SAS, version 9.2.

This research was approved by the *Comité d'éthique du Centre hospitalier affilié universitaire de Québec.*

Results

A total of 17,384 individuals were included in the cohort (Figure 2). During the observation period, there were 1084 (6.2%) cases of MI or stroke. Matching characteristics and potential confounders

Table 1 Distribution of matching and confounding variables of cases and controls

Characteristics	Cases (*N* = 1084)	Controls (*N* = 5369)
Matching variables		
Sex		
Women	516 (48%)	2552 (48%)
Men	568 (52%)	2817 (52%)
Age* (years)†		
66–70	376 (35%)	1880 (35%)
71–75	315 (29%)	1575 (29%)
76–80	224 (21%)	1120 (21%)
81–85	118 (11%)	587 (11%)
86–90	45 (4%)	202 (4%)
91+	6 (0.6%)	5 (0.1%)
Year of cohort entry†		
1998	366 (34%)	1827 (34%)
1999	246 (23%)	1219 (23%)
2000	196 (18%)	968 (18%)
2001	159 (15%)	775 (14%)
2002	73 (7%)	362 (7%)
2003	44 (4%)	218 (4%)
Potential confounding variables		
Residency area†		
Rural	193 (18%)	1046 (20%)
Urban	889 (82%)	4312 (80%)
Undisclosed	2 (0.2%)	11 (0.2%)
Drug plan beneficiary type (income supplement)†		
No guaranteed	527 (49%)	2703 (50%)
Partial	455 (42%)	2250 (42%)
Maximum	102 (9%)	416 (8%)
Anticoagulant used‡		
Yes	66 (6%)	228 (4%)
No	1018 (94%)	5141 (96%)
Insulin used‡		
Yes	33 (3%)	109 (2%)
No	1051 (97%)	5260 (98%)
Number of drugs dispensed‡,§		
First tertile	367 (34%)	2162 (40%)
Second tertile	317 (29%)	1684 (32%)
Third tertile	400 (37%)	1523 (28%)
Number of medical visits‡,¶		
First tertile	285 (26%)	1893 (35%)
Second tertile	358 (33%)	1901 (35%)
Third tertile	441 (41%)	1575 (29%)
Hospitalisation‡		
Yes	500 (46%)	1896 (35%)
No	584 (54%)	3473 (65%)
Alzheimer's disease‡		
Yes	33 (3%)	142 (3%)
No	1051 (97%)	5227 (97%)
Chronic obstructive pulmonary disease‡		
Yes	170 (16%)	557 (10%)
No	914 (84%)	4812 (90%)
Cirrhosis‡		
Yes	30 (3%)	98 (2%)
No	1054 (97%)	5271 (98%)
Depression‡		
Yes	40 (4%)	150 (3%)
No	1044 (96%)	5219 (97%)
Renal disease‡		
Yes	151 (14%)	584 (11%)
No	933 (86%)	4785 (89%)
Obesity‡		
Yes	47 (4%)	155 (3%)
No	1037 (96%)	5214 (97%)

Values represent *n* (%). *Matching was based on the individual's exact age. Grouping was performed for presentation purpose only. †Variables defined at cohort entry. ‡Variables defined during the observation period. §First tertile: 1–7; Second tertile: 8–13; Third tertile: ≥ 14. ¶First tertile: 0–15; Second tertile: 16–48; Third tertile: ≥ 49.

of cases and controls are presented in Table 1. Drug exposure of cases and controls is presented in Table 2.

The risk of MI or stroke was significantly higher for current users of antiplatelet drugs than for non-users [Adjusted odds ratio (AOR):1.40; 95% confidence intervals (CI):1.12–1.75] (Table 3). There was no significant difference in the risk of MI or stroke for other categories of drug use. On the other hand, a longer duration of exposure to a statin was associated with a reduction in risk of MI and stroke (0.97; 0.96–0.99). Results were not sensitive to changes in ways of defining the current use of drugs (data not shown).

Discussion

In this cohort of elderly individuals newly treated with antidiabetes drugs and with no history of CVD, the use of cardioprotective drugs was not associated with a reduced cardiovascular risk. This result contrasts notably with the conclusion of a meta-analysis that indicated that ACEI and ARBs reduced CVD events in individuals with (and without) diabetes with normal blood pressure (18). One possible explanation for the lack of protection may lie on the fact that exposure to ACEI/ARBs in our study may not have been long enough for individuals to benefit from therapy. Nonetheless, our results parallel to the lack of statistically significant benefit of ACEI/ARB observed in the subgroup of patients with diabetes and no CVD in the HOPE trial (19). Longer exposition to statin therapy reduced the risk in our study,

Table 2 Distribution of drug exposure among cases and controls

Drug exposure	Cases (*N* = 1084)	Controls (*N* = 5369)
ACEI/ARB		
Current users	355 (32.8)	1663 (31.0)
Past users	98 (9.0)	400 (7.5)
Non-users	631 (58.2)	3306 (61.6)
Duration of use (by 30 days) [mean (SD)]	7.1 (13.0)	6.9 (13.1)
Other antihypertensive drug		
Duration of use (by 30 days) [mean (SD)]	11.8 (16.3)	10.6 (16.1)
Statins		
Current users	152 (14.0)	976 (18.2)
Past users	43 (4.0)	253 (4.7)
Non-users	889 (82.0)	4140 (77.1)
Duration of use (by 30 days) [mean (SD)]	2.3 (7.1)	3.7 (9.3)
Other lipid-lowering drugs		
Duration of drugs use (by 30 days) [mean (SD)]	1.1 (5.5)	0.9 (4.9)
Antiplatelet		
Current users	278 (25.7)	1158 (21.6)
Past users	88 (8.1)	362 (6.7)
Non-users	718 (66.2)	3849 (71.7)
Duration of use (by 30 days) [mean (SD)]	4.2 (9.0)	3.7 (8.7)
Combination of the three drugs (ACEI/ARB, statins and antiplatelet)		
Current users	49 (4.5)	313 (5.8)
Past users	30 (2.8)	116 (2.2)
Non-users	1005 (92.7)	4940 (92.0)
Duration of use (by 30 days) [mean (SD)]	0.6 (3.4)	0.8 (3.9)

Values represent *n* (%).

which is concordant with the beneficial impact of statins that was observed in clinical trials that included younger populations (20,21). As for antiplatelet drugs, aspirin was the antiplatelet used in 92.4% of all the antiplatelet exposure time in our study. Recent trials have failed to confirm the protective benefits of aspirin in primary prevention of cardiovascular events for individuals with diabetes (22,23); our result is consistent with the fact that clear benefits of aspirin in primary prevention of CVD in people with diabetes remains unproved (24–26). The increased risk of MI or stroke observed for current aspirin users in our study is nonetheless surprising and may result from aspirin being used predominantly by those individuals at very high risk of cardiovascular events. Past users of antiplatelet drugs also showed an increased risk (1.21; 0.92–1.58) although not statistically significant. The lack of statistical significance might be because of the low number of past users of antiplatelet drugs ($n = 88$ for patients and $n = 362$ for controls). Overall, the short duration of exposure to cardioprotective drugs, and notably for the combination of the three drugs, limits the conclusions that can be drawn regarding effectiveness. Indeed, in randomised controlled trials most benefits have been reached with longer duration of exposure to these drugs.

Beyond these possible explanations for the lack of observed benefits, our results have important clinical implications. First, the treatment of individuals in clinical practice may not be adequate enough to gain the benefits identified in clinical trials (suggesting targets in blood pressure or cholesterol levels may not be achieved, for example). In the USA, Casagrande et al. reported significant improvement during the past decade in the attainment of A1C, blood pressure and LDL cholesterol goals for individuals with diabetes (27). Provided that our cohort was followed-up a decade ago, similar improvement could potentially translate in better cardiovascular outcome. The second implication of our results is that individuals that receive cardioprotective drugs might be those at higher risks of cardiovascular events. If true, this latter hypothesis implies that the cardioprotective treatment of elderly individuals with type 2 diabetes could be unduly delayed. Again, the short exposure duration to those drugs and the fact that more than half of the population was not exposed to one or many of these drugs, also suggest cardioprotective treatments might be delayed. Further research is needed to explore the underlying causes.

This study has some limitations inherent in the analysis of administrative databases. First, we assumed that drugs dispensed were actually used. Second, as the databases do not capture clinical data, we could not adjust for some risk factors (e.g. blood pressure, smoking status. . .). Third, although we adjusted our models for several potential confounders, results could be subject to indication bias. This bias arises when a comorbidity, a prognostic factor or the perceived risk of an outcome influences the decision to prescribe a drug (28). Hence, individuals most likely to experience a MI or a stroke in our study may have been more likely to receive cardioprotective drugs. On the other hand, it has been reported that higher risks patients are often denied statins (the so-called: *treatment risk paradox*) (29). If this is the case, part of the beneficial impact we have observed for statin users might be because of the fact they were used by individuals at lower risk for MI or stroke. Finally, since aspirin can be purchased without a prescription, exposure to antiplatelet drugs may have been misclassified. However, as aspirin is

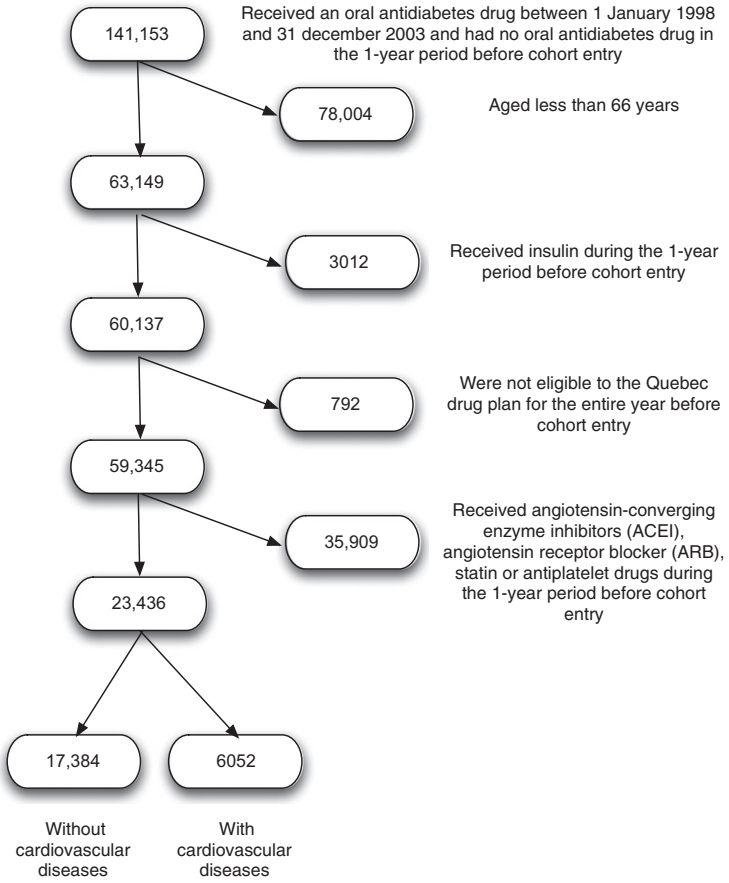

Figure 2 Selection of study subjects

reimbursed under the public drug insurance plan when it is prescribed, the proportion of individuals buying it over the counter has been shown to be low (30).

Other limitations include the fact that we did not evaluate dose–response relationship for the drugs. We also used a composite end-point of ischaemic (myocardial infarction + stroke) and haemorraghic (stroke) events to ensure all cardiovascular outcomes would be represented. The number of haemorrhagic events being low (6%), it was not possible to perform separate analyses for this outcome. Lastly, our results need to be interpreted carefully. As our study was observational, it is not possible to definitely conclude that cardioprotective drugs are not effective.

Table 3 Adjusted odds ratios (AOR) of myocardial infarction or stroke

	Drug exposure							
	ACEI/ARB		Statin		Antiplatelet		Combination*	
	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value
Non-use	1.00		1.00		1.00		1.00	
Current use	1.10 (0.89–1.35)	0.38	0.95 (0.72–1.26)	0.74	1.40 (1.12–1.75)	0.003	0.88 (0.57–1.36)	0.56
Past use	1.17 (0.91–1.51)	0.23	0.85 (0.60–1.21)	0.37	1.21 (0.92–1.58)	0.18	1.12 (0.71–1.76)	0.64
Duration of exposure†	1.00 (0.99–1.00)	0.37	0.97 (0.96–0.99)	0.0002	1.00 (0.98–1.01)	0.34	0.97 (0.95–1.00)	0.09

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers. *Combination is defined as the use, on the same day, of at least one drug from each the three classes (ACEI/ARB, statin, and antiplatelet drug). †30-day periods of exposure.

Conclusion

In conclusion, our results highlight the need for more thorough research among elderly people with diabetes to determine the most appropriate combination of cardioprotective drugs. There is a need to increase the small body of evidence addressing the issue of primary prevention of CVD in elderly people with diabetes (31). For now, clinicians should probably treat according to the individuals' risk (32), ensuring traditional risk factors are well controlled. Outcomes such as side effects and drug–drug interactions should be considered in future research.

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Authors' contributions

CS conceived the design of the study, contributed to the analysis and interpretation of the data and drafted the manuscript. JM contributed to the conception and design of the study, the analysis and interpretation of the data and critically revised the manuscript. PP contributed to the interpretation of the data and critically revised the manuscript. JPG contributed to the conception and design of the study, the analysis of the data and edited and critically revised the manuscript. All authors read and approved the final manuscript.

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