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Cardiovascular Drugs and Metformin Drug Dosage According to Renal Function in Non-Institutionalized Elderly Patients

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RUNNING TITLE: Metformin drug dosage according to GFR

Abstract

Background: Adaptation of drug dosage to kidney function is a common problem in general practice.

Aim: To describe adaptation of cardiovascular drugs and metformin according to renal function and its association with mortality with regard to metformin in a cohort of elderly patients.

Design and Setting : Ancillary study to the S.AGES cohort made up of patients over 65 years old managed by their general practitioner under real-life conditions and followed up prospectively for 3 years.

Methods: The medications studied were digoxin, spironolactone and metformin. Adaptation of their daily dose according to renal function (eGFR according to CKD/EPI) was compared to that recommended in the summaries of product characteristics (SPCs) or international scientific societies (ISS).

Results: 900 patients were included, including 588 on metformin. At baseline, dose adjustment according to renal function was 100% and 87.6% (95%CI:82.6-92.6) for patients on digoxin and spironolactone, respectively.

For metformin, only 71.3% (95%CI:67.6-74.9) or 78.1% (95%CI:74.7-81.4) of patients had their dosage adapted at inclusion according to their renal function depending on whether the SPCs or ISS recommendations were considered. During the 3 year follow-up period, 42/588 patients died (none from lactic acidosis). At inclusion, a metformin dosage not adapted for renal function according to ISS was not associated with an increase in all cause mortality (OR 1.7; 95%CI 0.6-5.0, p=0.32).

Conclusion: Approximately one quarter of elderly patients treated with metformin do not have their dosage adapted for renal function according to ISS although there is no increase in mortality after follow-up for 3 years.

Key words: general practitioner, elderly patients, chronic kidney disease, glomerular filtration rate, drug dosage calculation, antidiabetic drugs, metformin, cardiovascular drugs

Short summary : Whereas adaptation of doses of medications for heart failure according to renal function is excellent, approximately one quarter of patients on metformin receive a dose that is not adapted according to renal function. This is not associated with increased mortality or hospitalization. A change in the SPCs enabling prescribing of metformin at an eGFR of down to 30 ml/min would enable many elderly patients to benefit from metformin therapy

With the ageing of the population in the developed countries, the prevalence of chronic kidney disease (CKD) is increasing significantly, rising to 35% for those over 65 years of age[1]. In parallel with age, the number of chronic diseases is increasing and as a result so is the number of medications prescribed daily.

The dosage of many medications needs to be adapted according to renal function, principally in the elderly as they are often receiving multiple treatments and have reduced renal function.

Many medications commonly prescribed in type 2 diabetes or cardiovascular diseases are excreted by the kidneys, and the dosage of some of these has to be adapted according to renal function. The dosage adaptation recommendations for renal function are included in the wording of the Marketing Authorizations in each country. These are generally superimposable between countries, although for metformin[2], the firstline medication in type 2 diabetes, the recommendations may vary between countries[3] and between the scientific societies and health authorities[2,4,5]. Official recommendations in most countries contraindicate the use of metformin if creatinine is over 150 µmol/l or the glomerular filtration rate (GFR) is under 60 ml/min, whereas the American Diabetes Association, European Association for the Study of Diabetes and National Kidney Foundation Kidney Disease Outcomes Quality Initiative propose that it be used at a GFR of between 30 and 60 ml/min at reduced dosage[2,4]. These recent recommendations from the scientific societies are counter to the official recommendations, based on large real-life condition studies showing that metformin is well tolerated when used at a GFR of between 30 and 60 ml/min[6-9].

The aim of this study was to describe the adjustment of oral cardiovascular and antidiabetic medications according to renal function in patients and the association of these adjustments in terms of metformin in a cohort of elderly non-institutionalized patients (S.AGES cohort) under real-life conditions followed up by their general practitioner.

Patients and Methods

The S.AGES (aged subjects) study is a multicenter prospective cohort study conducted in France[10-12]. The main objective of the S.AGES cohort is specifically to describe the real-life therapeutic management of non-institutionalized elderly subjects. This cohort consists of 3434 non-institutionalized patients aged 65 years and older with either chronic pain (CP) (n=1379), type 2 diabetes mellitus (T2DM) (n=983) or atrial fibrillation (AF) (n=1072). The inclusion criteria were: men or women aged 65 years or older living in France who were able to understand the goal of the study, agreed to participate in the study and signed the informed consent. Patients included in the study also had one of the three following conditions that defined three sub-cohorts:

- CP present for more than three months and requiring care.
- T2DM treated at inclusion by any hypoglycaemic drug.
- AF (defined by ECG or Holter ECG).

Patients could not participate if they were residents of a nursing home at the time of inclusion, could not be followed after inclusion (planned move, homeless), or had a short life expectancy (less than three months).

Patients were recruited by their general practitioners (GP) throughout France. 760 GPs responded favourably and were randomized into one of the three S.AGES sub-cohorts. Inclusion of patients began in June 2009 and ended in September 2011[10]. Patients returned to their GP every 6 months (planned follow-up visits) for a 3-year period.

This ancillary study analysed the data obtained at baseline (inclusion) and during the first three years of follow-up. To be eligible for the present ancillary study, patients had to have a serum creatinine blood sample drawn at inclusion.

Study variables

1) Estimated glomerular filtration rate (eGFR) was derived either from the Cockcroft & Gault[13] formula or from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [14]. As eGFR calculated by Cockcroft & Gault formula is obtained in $ml.min^{-1}$ (as opposed to CKD-EPI formula which is corrected for a $1.73m^{-2}$ body surface area), Cockcroft & Gault formula had to be corrected for a $1.73m^{2}$ body surface area.
2) Study drugs of interest that need to be adapted to eGFR were digoxin, spironolactone, eplerenone, glibenclamide and metformin. For each of these drugs, patients were classified as in contraindication, overdose or well-dosed according to their daily dose and their eGFR (Cockcroft & Gault and CKD-EPI formula) based on the recommendations provided in summarized product characteristics (SPCs) (table 1). For metformin, additional scenario is provided, according to international scientific societies [2,4](table 1).
3) Heart failure was evaluated by the GP according to the NYHA classification[15].
4) Hypertensive patients were defined by use of an antihypertensive treatment or systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg.

The study was approved by the Ethics Committee and by the French Medicines Agency (ANSM). The clinical trial reference of this study is: NCT01065909. All the patients signed the informed consent to participate. Further details about the study have been provided in previously published papers[10-12].

Statistical analysis:

In a first step, a descriptive analysis of the different baseline variables (mean and standard deviation for quantitative variables, frequencies and percentages for qualitative variables) was carried out.

In a second step, patients treated by metformin on baseline (inclusion) were separated in 2 groups: Those whose metformin dose was adapted or not to eGFR (calculated with CKD-EPI formula) and according to International scientific societies (metformin contraindicated if eGFR≤ 30 $ml.min^{-1}.1.73m^{-2}$, or overdosed if metformin doses exceeded 1500mg/d with an eGFR ranging from 30 > eGFR ≤ 60 $ml.min^{-1}.1.73m^{-2}$). Their baseline characteristics were compared using Wilcoxon or Chi^2 tests.

In a third step, the association of metformin over-dosed or contra-indicated at baseline with all-cause mortality during the 3 years of follow-up (dependent variable) was explored using stepwise logistic regression after adjusting for confounding baseline variables (that significantly differed ($p \leq 0.05$) between patients whose metformin dose was adapted or not on eGFR). Odd-ratios and their 95% confidence intervals were determined.

Statistical analyses were conducted using SAS (Statistical Analysis System, version 9.3).

Results

1185 of the 3434 patients included in the initial S.AGES study were receiving one of the cardiovascular treatments selected for the study whose dose should be adapted according to renal function. Of these, 900 who had a calculated eGFR using the CKD-EPI were included in the present ancillary study (fig. 1).

Classification of patients according to whether their dose was or was not adapted according to the eGFR

At inclusion into the study, patients were classified according to whether their daily dose of each of these medications was adapted according to their renal function, overdosed or contraindicated. Results in table 2 show that for the cardiac medications (potassium sparing diuretics and digoxin), doses were relatively well adapted according to the eGFR (between 86.6 and 100% of patients), whereas for the oral diabetics the percentage of patients whose dosage was adapted according to renal function was lower, ranging between 64.6 and 78.6%. Classification of patients using the C&G equation performed consistently more

severe (fewer patients had a dose adapted according to renal function) for all of the medications studied. For metformin, classification of patients according to the SPCs compared to the international scientific societies also penalized the patients.

In addition, in order to predict whether or not the medications of interest were or were not adapted according to renal function, the 2 equations used to calculate eGFR produced relatively similar results, their kappa concordance coefficients being 0.73 (95%CI 0.57-0.89) for digoxin, 0.74 (95%CI 0.50-0.97) for glibenclamide, 0.72 (95%CI 0.65-0.78) for metformin with the scenario according to SPCs and 0.74 (95%CI 0.68-0.81) for metformin with the scenario according to the international scientific societies.

Comparison of patients at inclusion according to adaptation of metformin dosage to renal function

Based on the recent recommendations from the international scientific societies to adapt metformin according to renal function, estimated using the equation which is currently recommended (CKD-EPI), we compared the characteristics of patients treated with metformin at inclusion depending on whether or not their dosage was adapted for renal function (n=459 adapted and n=129, i.e. 22% not adapted), by combining overdoses and contraindications in the same group (table 3).

The non-adapted group was older, contained more women, had a lower smoking history, more were hypertensive and dyslipidaemic and their eGFR was far lower. There were no differences in terms of the duration of the diabetes, use of insulin or average Hb1Ac.

Association of failure to adapt the metformin dosage according to renal function at inclusion on mortality and hospitalizations during the 3-year follow-up:

During the 3-year patient follow-up, there were more deaths (all causes combined) in patients whose daily dose of metformin at inclusion was not adapted according to renal function (19.8% *versus* 6.2%, p<0.0001); none of the deaths were attributed to lactic acidosis. On the other hand, there was no difference in the percentage of patients who were hospitalized between those whose dosage of metformin was adapted or not adapted according to renal function (table 3).

We sought to establish whether having a daily dose of metformin that was not adapted to renal function at inclusion was a predictive factor for subsequent death by adjusting on the differences seen between the 2 groups at inclusion (table 3) particularly age and eGFR. In this multivariate analysis, having a daily dose of metformin which was not adapted according to renal function was no longer associated with death (OR 1.7, 95%CI 0.6-5.0, p=0.32).

Discussion

The aim of this study was to describe how the dosage adaptation guidelines according to renal function were followed and its association with death and hospitalization with respect to metformin in a population of elderly ambulatory patients managed by their general practitioner.

In terms of medications for heart failure, adaptation of the daily dose according to eGFR ranged between perfect (100%) for digoxin and good for the potassium sparing diuretics (87.6%). On the other hand, the corresponding figure was under 80% for the oral antidiabetics, particularly metformin which, depending on whether the official guidelines (according to the SPCs) or the guidelines according to international scientific societies, ranged between 71% and 78%, respectively. In terms of the use of metformin under real-life conditions, many studies have already reported that it is often prescribed when contra-indications to metformin are present[7-9], particularly chronic kidney disease (CKD). This is mostly due, in terms of the unsuitability of dosage for renal function, to differences between the official recommendations (which contra-indicate the use of metformin at an eGFR of <60 ml/min) and those of the international scientific societies (which contra-indicate the use of metformin at a lower eGFR cut off of 30 ml/min). Using the more conservative cut off of 30 ml/min in this study for eGFR supported by the scientific societies, only 1% of patients were deemed to be contra-indicated whereas using the "official" cut off of an eGFR of 60 ml/min, 28.7% were deemed to be contra-indicated.

The major question which arises in choosing between these 2 metformin dosage adaptation scenarios according to renal function is the risk of lactic acidosis[16], a very rare adverse effect of metformin but one which is often fatal. No deaths were reported as being secondary to lactic acidosis in this study. Whereas during the 3-year follow-up period, 6.2% compared to 19.8% (p<0.0001) of patients died in the metformin eGFR adapted and non-adapted groups, this difference was no longer statistically significant when it was adjusted for factors distinguishing between the 2 groups at inclusion, particularly age and the eGFR itself. This

loss of statistical significance in the multivariate analysis is not surprising as eGFR is known to be a major risk factor for all cause mortality[17], even in elderly patients[18]. At inclusion, the patients in the non-adapted group had a far lower eGFR and after adjusting for eGFR, the additional risk of morality in the non-adapted group became insignificant showing that the increased risk was attributable to the reduction in renal function and not to the dose of metformin prescribed.

Our results which showed no additional risk when metformin was not adapted according to the eGFR are similar to those of the two large earlier studies which highlighted that the benefit of metformin in terms of morbidity [19,20] was maintained when the eGFR was under 60 ml/min[6,21]. One possible explanation for this is that although the trough metformin concentrations are moderately higher when the eGFR is between 30 and 60 ml/min, they do not reach the upper therapeutic range of 20 µmoles/l[22] and do not significantly affect circulating lactate levels[23].

In line with the present results, we recently observed that the renal tolerance of cardiovascular drugs among elderly suffering from chronic kidney disease appeared acceptable, supporting their use in such a frail population despite several warnings[24].

Our study does, however, have limitations: firstly, the relatively small number of patients treated with metformin (n=588). Because of this, the lack of association found between non-adaptation of the dose of metformin according to the eGFR and mortality lacks power. In order for the observed OR of 1.70 to be statistically significant, we would have needed to follow up 2086 patients (including 459 overdosed) for 3 years. Secondly, the observational design, risk of residual confounding and especially the limitation of generalizability to the group of patients included in the present study is important to mention. Finally, the fact that the causes of mortality (excluding lactic acidosis) are not known does not enable us to determine whether some causes of death are associated with metformin overdose.

In conclusion, whereas adaptation of doses of medications for heart failure according to renal function is excellent, approximately one quarter of patients on metformin receive a dose that is not adapted according to renal function. This is not associated with increased mortality or hospitalization. Our results support a change in the SPCs enabling prescribing of metformin

at an eGFR of down to 30 ml/min that would enable many elderly patients to benefit from metformin therapy.

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CONFLICT OF INTEREST

Becquemont L: Investigator for Antisens Therapeutics, Alnylam Pharmaceuticals, PregLem SA, ISIS Pharmaceutical, Novartis Pharma, Auris medical, Medday Pharmaceuticals and Gilead. Received consulting fees from Sanofi-Aventis, Pfizer, Servier, Genzyme and lecture fees from Genzyme, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp and Dohme. Close family member working at Sanofi France.

Bauduceau B: Received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Merck Sharp and Dohme, Roche, Novo Nordisk.

Benattar-Zibi L: No conflict of interest.

Berrut G: Received fees from Sanofi, Lundbeck, Eisai, Novartis, Merck Sharp and Dohme, Amgen, Boehringer-Ingelheim, Bayer.

Bertin P: Received consulting fees from Sanofi-Aventis, Pfizer, Ethypharm, Reckitt-Benkiser and speaking fees from Genevrier, Roche, Bristol-Myers Squibb, Merck Sharp and Dohme.

Sophie Bucher: No conflict of interest.

Abdallah Al-Salameh: No conflict of interest.

Corruble E: Received consulting fees from Servier, Lundbeck, Sanofi-Aventis, Bristol-Myers Squibb, Eisai.

Danchin N: Received consulting or speaking fees from AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, MSD-Schering Plough, Novartis, Novo-Nordisk, Pierre Fabre, Pfizer, Roche, Sanofi-Aventis, Servier, Takeda, The Medicines Company.

Derumeaux G: Received consulting or speaking fees from Actelion, Boehringer-Ingelheim, Pfizer, Sanofi-Aventis, and Servier, Research grant from Actelion and AstraZeneca.

Doucet J: Received speaking fees from Novo-Nordisk, consulting fees from Sanofi-Aventis, Novo-Nordisk, Merck-Serono and research partnership with Lilly.

Falissard B: Received consulting fees from Sanofi-Aventis, Servier, Roche, AstraZeneca, Grünenthal, Lilly, HRA, Boeringher-Ingelheim, Bayer, Novartis, Genzyme, Stalergène, Daiichi, Otsuka, Bristol-Myers Squibb.

Forette F: Received speaking and consulting fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Eisaï, Exonhit, Pierre Fabre, Ipsen, Janssen-Cilag, Lilly, Lundbeck, Novartis, Merck Sharp and Dohme, Merz, Pfizer, Roche, Sanofi-Aventis, Servier, Schwarz-Pharma, Specia, Warner-Lambert, Wyeth.

Hanon O: Received speaking and consulting fees from Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer, Eisaï, Exonhit, Janssen-Cilag, Lundbeck, Novartis, Pfizer, Sanofi-Aventis, Servier.

Pasquier F: Investigator for Pfizer, Piramal, Roche, Lilly, Astra Zeneca, Noscira, Pharnext, Forum Phamacteutical and GE Healthcare. Received consulting fees from Lilly, Novartis, Nuticia and Sanofi.

Pinget M: Received speaking and consulting fees from Asdia, AstraZeneca, Bristol-Myers Squibb, Medtronic, Merck Sharp and Dohme, Novo Nordisk, Novartis, Roche Diagnostics, Ypsomed.

Ourabah R: No conflict of interest.

Piedvache C: No conflict of interest.

Figure 1: study flow chart

Among the 900 patients included in the present ancillary study, all of them had a calculated eGFR using the CKD-EPI formula and 876 had a calculated eGFR using the C&G formula (due to weight missing values).

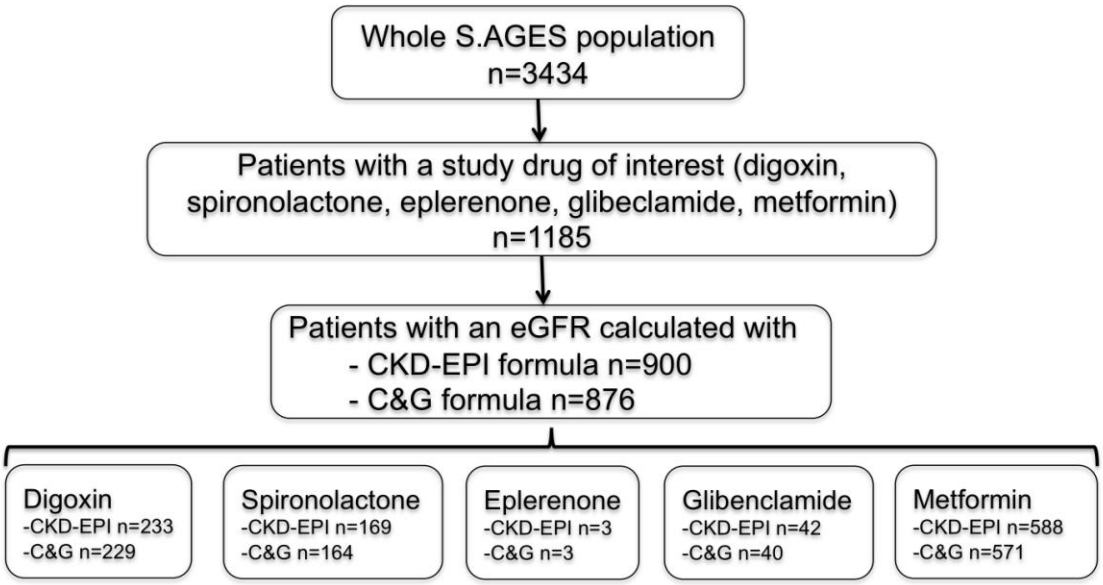

Table 1: Classification of each drug dose according to eGFR

	Overdose In relation to eGFR	**Contra indicated** In relation to eGFR
Digoxin	Dose > 62,5µg/d if eGFR ≤ 10 $ml.min^{-1}.1.73m^{-2}$ or Dose > 250µg/d if 10 > eGFR ≤ 30 $ml.min^{-1}.1.73m^{-2}$	No contra indication in relation to eGFR

Spironolactone	Dose > 12,5mg/d if 10 > eGFR ≤ 30 ml.min^{-1}.1.73m^{-2} or Dose > 25mg/d if 30 > eGFR ≤ 49 ml.min^{-1}.1.73m^{-2}	eGFR ≤ 10 ml.min^{-1}.1.73m^{-2}
Eplerenone	Dose > 25mg/d if 30 ≥ eGFR ≤ 49 ml.min^{-1}.1.73m^{-2}	eGFR < 30 ml.min^{-1}.1.73m^{-2}
Glibenclamide (glyburide)	Dose > 1.25mg/d if 30 ≥ eGFR ≤ 60 ml.min^{-1}.1.73m^{-2}	eGFR < 30 ml.min^{-1}.1.73m^{-2}
Metformin SPC dose adaptation	No overdose in relation to eGFR	eGFR < 60 ml.min^{-1}.1.73m^{-2}
Metformin International scientific societies dose adaptation	Dose > 1500mg/d if 30 > eGFR ≤ 60 ml.min^{-1}.1.73m^{-2}	eGFR ≤ 30 ml.min^{-1}.1.73m^{-2}

SPC: Summary of Product Characteristics

eGFR: estimated Glomerular filtration rate

Table 2: Observed drug dosage according to eGFR

Treatment	Dose-eGFR adapted status according to CKD-EPI	Dose-eGFR adapted status according to G&C
Digoxin	Adapted: 233 (100.0%)	Adapted: 229 (100.0%)
Spironolactone	Adapted: 148 (87.6%; 95% CI : 82.6-92.6) Overdosed: 21 (12.4%; 95% CI : 7.4-17.4)	Adapted: 142 (86.6%;95% CI : 81.4-91.8) Overdosed: 22 (13.4%;95% CI : 8.2-18.6)
Eplerenone	Adapted: 3 (100.0%)	Adapted: 3 (100.0%)
Glibenclamide	Adapted: 33 (78.6%; 95% CI : 66.2-91.0) Overdosed: 7 (16.7%; 95% CI : 5.4-27.9) contraindicated: 2 (4.8%; 95% CI : 0-11.2)	Adapted: 28 (70.0%;95% CI : 55.68-84.2) Overdosed: 10 (25.0%;95% CI : 11.6-38.4) contraindicated: 2 (5.0%;95% CI : 0.0-11.7)
Metformin According to SPCs	Adapted: 419 (71.3%; 95% CI : 67.6-74.9) contraindicated: 169 (28.7%;95% CI :25.1-32.4)	Adapted: 369 (64.6%;95% CI : 60.7-68.5) contraindicated: 202 (35.4%;95% CI : 35.4-39.3)
Metformin According to international scientific societies	Adapted: 459 (78.1%;95% CI : 74.7-81.4) Overdosed: 123 (20.9%;95% CI : 17.6-24.2) contraindicated: 6 (1.0%;95% CI : 0.2-1.8))	Adapted: 420 (73.6%;95% CI : 69.9-77.2) Overdosed: 143 (25.0%;95% CI : 21.5-28.6) contraindicated: 8 (1.4%;95% CI : 0.4-2.4)

SPC: Summary of Product Characteristics

eGFR: estimated Glomerular filtration rate

95%CI: 95th confidence intervals

Table 3: Baseline patients characteristics

	Metformin dose adapted to eGFR* (n=459)	**Metformin overdosed or contra indicated*** (n=129)	P value
Age (years)	75.1 ± 5.6	77.7 ± 5.5	<0.0001
Female gender	206 (45 %)	75 (58%)	0.01
BMI **(kg/m²)**[a]	29.6 ± 5.2	30.0 ± 5.3	0.49
Current smoker [b]	24 (5.2%)	5 (3.9%)	0.53
Smoking (pack-years) [c]	7.9 ± 16.3	4.4 ± 12.4	<0.01
Atherothrombotic disease[d]	90 (19.7%)	24 (18.6%)	0.78
Hypertension [b]	409 (89.3%)	124 (96.1%)	0.02
Atrial fibrillation[d]	89 (19.5%)	33 (25.6%)	0.13
Heart failure (NYHA ≥ 1) [d]	45 (9.8%)	17 (13.2%)	0.28
Dyslipidaemia [d]	278 (60.8%)	92 (71.3%)	0.03
Chronic pain	197 (42.9%)	53 (41.1%)	0.71
Cancer history [b]	60 (13.1%)	22 (17.1%)	0.25
eGFR CKD-EPI calculation ($ml.min^{-1}.1.73m^{-2}$)	75.1 ± 13.0	48.0 ± 9.6	<0.0001
eGFR C&G calculation ($ml.min^{-1}.1.73m^{-2}$)	72.4 ± 16.3	48.0 ± 10.4	<0.0001
Duration of T2DM since diagnosis (years)[e]	10.7 ± 8.5	11.6 ± 7.8	0.08
Concomitant treatment with insulin[f]	63 (13.8%)	19 (14.8%)	0.77
Mean Hb1Ac[g]	6.9 ± 0.9	7.0 ± 1.0	0.57
Metformin daily dose (median, IQR)	1700 mg/d (1000-2000)	2000 mg/d (1700-2550)	

Clinical events during the 3-year follow-up			
Death[h]	22 (6.2%)	20 (19.8%)	<0.0001
Hospitalization[i]	148 (39.6%)	46 (46.0%)	0.25

Calculated with CKD-EPI formula, according to international scientific societies recommendations (i.e. metformin contra indicated if eGFR ≤ 30 ml.min^{-1}.1.73m^{-2} and dose adapted for 30 > eGFR ≤ 60 ml.min^{-1}.1.73m^{-2}).

NA: not applicable. IQR (interquatile range). Missing values in each group: a (11/6); b (1/0); c (33/9); d (2/0); e (6/1); f (3/1); g (118/33); h (103/28); i (85/29).