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Overtreatment and associated risk factors among multimorbid older patients with diabetes

Oliver Baretella MD, PhD[1,2] | **Heba Alwan MD, MSc**[1,3] | **Martin Feller MD, MSc**[1,2] | **Carole E. Aubert MD, MSc**[1,2] | **Cinzia Del Giovane PhD**[1] | **Dimitrios Papazoglou MD**[1,2] | **Antoine Christiaens MD, PhD**[4,5] | **Arend-Jan Meinders MD**[6] | **Stephen Byrne PhD**[7] | **Patricia M. Kearney PhD**[8,9] | **Denis O'Mahony MD**[9,10] | **Wilma Knol MD**[11] | **Benoît Boland MD, PhD**[5,12] | **Baris Gencer MD, MPH**[1,13] | **Drahomir Aujesky MD, MSc**[2] | **Nicolas Rodondi MD, MAS**[1,2]

[1]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[2]Department of General Internal Medicine, Inselspital, Bern University Hospital, Bern, Switzerland

[3]Graduate School for Health Sciences, University of Bern, Bern, Switzerland

[4]Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Université, INSERM, Paris, France

[5]Clinical Pharmacy research group, Louvain Drug Research Institute (LDRI), Université catholique de Louvain, Brussels, Belgium

[6]Department of Internal Medicine, St Antonius Hospital, Nieuwegein, the Netherlands

[7]School of Pharmacy, University College Cork - National University of Ireland, Cork, Republic of Ireland

[8]School of Public Health, University College Cork, Cork, Republic of Ireland

[9]Department of Medicine Cork, University College Cork - National University of Ireland, Cork, Republic of Ireland

[10]Department of Geriatric Medicine Cork, Cork University Hospital Group, Cork, Republic of Ireland

[11]Department of Geriatrics and Expertise Centre Pharmacotherapy in Old Persons (EPHOR), University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

[12]Department of Geriatric Medicine, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium

[13]Service de cardiologie, Hôpitaux Universitaires de Genève (HUG), Geneva, Switzerland

Correspondence
Nicolas Rodondi, Department of General Internal Medicine, Inselspital, Bern University Hospital, Freiburgstrasse 18, CH-3010 Bern, Switzerland.
Email: nicolas.rodondi@insel.ch

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Abstract

Background: In multimorbid older patients with type 2 diabetes mellitus (T2DM), the intensity of glucose-lowering medication (GLM) should be focused on attaining a suitable level of glycated hemoglobin (HbA_{1c}) while avoiding side effects. We aimed at identifying patients with overtreatment of T2DM as well as associated risk factors.

Methods: In a secondary analysis of a multicenter study of multimorbid older patients, we evaluated HbA_{1c} levels among patients with T2DM. Patients were aged ≥70 years, with multimorbidity (≥3 chronic diagnoses) and polypharmacy (≥5 chronic medications), enrolled in four university medical centers across

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Europe (Belgium, Ireland, Netherlands, and Switzerland). We defined overtreatment as HbA_{1c} < 7.5% with ≥1 GLM other than metformin, as suggested by *Choosing Wisely* and used prevalence ratios (PRs) to evaluate risk factors of overtreatment in age- and sex-adjusted analyses.

Results: Among the 564 patients with T2DM (median age 78 years, 39% women), mean ± standard deviation HbA_{1c} was 7.2 ± 1.2%. Metformin (prevalence 51%) was the most frequently prescribed GLM and 199 (35%) patients were overtreated. The presence of severe renal impairment (PR 1.36, 1.21–1.53) and outpatient physician (other than general practitioner [GP], i.e. specialist) or emergency department visits (PR 1.22, 1.03–1.46 for 1–2 visits, and PR 1.35, 1.19–1.54 for ≥3 visits versus no visits) were associated with overtreatment. These factors remained associated with overtreatment in multivariable analyses.

Conclusions: In this multicountry study of multimorbid older patients with T2DM, more than one third were overtreated, highlighting the high prevalence of this problem. Careful balancing of benefits and risks in the choice of GLM may improve patient care, especially in the context of comorbidities such as severe renal impairment, and frequent non-GP healthcare contacts.

KEYWORDS

glucose-lowering medication, HbA_{1c}, multimorbidity, polypharmacy, type 2 diabetes mellitus

INTRODUCTION

In the older person population, the number of patients with type 2 diabetes mellitus (T2DM) is increasing in tandem with population aging. For treatment of T2DM, there are multiple glucose-lowering medications (GLM) available.[1–3] Extended use of GLM increases polypharmacy and the risk of hypoglycemia, especially in multimorbid older patients with T2DM.[2]

The American Geriatrics Society issued recommendations with its *Choosing Wisely* campaign to reduce overtreatment of T2DM in older patients defining metformin as the sole GLM appropriate to achieve hemoglobin A_{1c} (HbA_{1c}) levels <7.5%.[4–6] Overtreatment of patients with T2DM has been evaluated both in North America[7,8] and Europe.[9] However, no study so far has assessed prevalence of T2DM overtreatment in multimorbid older patients by applying the American Geriatrics Society's *Choosing Wisely* definition of T2DM overtreatment, to the best of our knowledge. Only few multicountry studies within different healthcare systems assessed overtreatment of T2DM in multimorbid older patients.[7,9,10] Furthermore, there is a lack of information on potential risk factors associated with overtreatment of T2DM focusing on these most vulnerable older adults, with high levels of comorbidities and polypharmacy.[11] Consequently, we

Key points

- Among multimorbid older patients with T2DM, more than one third are overtreated with HbA_{1c} < 7.5% from using glucose-lowering medication (GLM) other than metformin.
- Severe renal impairment and outpatient visits to specialist physicians or emergency departments were associated with overtreatment.

Why does this paper matter?

We found a high level of overtreatment of T2DM among multimorbid older patients by applying the HbA_{1c} threshold of <7.5% as the indicator of overtreatment endorsed by the American Geriatrics Society's List of Five Things Physicians and Patients Should Question. We also identified severe renal impairment and outpatient visits to specialist physicians or emergency departments as important risk factors for such overtreatment, which may help improve recognition of these at-risk patients.

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TABLE 1 Patient ($n = 564$) characteristics with and without overtreatment.

Sociodemographics		Overtreated ($n = 199$, 35%)**	Not overtreated ($n = 365$, 65%)
Age (years)		77 (73–83)	78 (74–82)
Women		73 (37)	146 (40)
Body mass index (kg/m^2)		29.5 ± 5.9	29.2 ± 6.9
Number of medications		11 (9–14)	10 (8–14)
Education[a]			
Less than high school		56 (29)	117 (32)
High school		83 (43)	166 (46)
University		55 (28)	79 (22)
Healthcare contacts (last 12 months)*			
Hospitalizations, *n*0	0	87 (44)	167 (46)
	1	57 (29)	90 (25)
	≥2	55 (28)	108 (30)
General practitioner visits, *n*[b]	0	10 (5)	21 (6)
	1–2	51 (26)	104 (29)
	3–4	51 (26)	84 (24)
	≥5	86 (43)	148 (41)
Other outpatient/ED visits, *n*[c]	0	48 (24)	115 (32)
	1–2	75 (38)	131 (37)
	≥3	76 (38)	112 (31)
Nursing home residents		11 (6)	32 (9)
Home nursing visits[d]		63 (32)	104 (29)
Informal care receipt[d]		54 (27)	79 (22)
Health indices			
Barthel index[† e]		90 (80–100)	90 (75–100)
EQ-5D descriptive index[‡]		0.87 (0.65–0.97)	0.91 (0.69–1)
Charlson comorbidity index[§]		7 (5–8)	6 (5–8)
Medical conditions[d]			
Cardiovascular disease		110 (55)	222 (61)
Ischemic heart disease		71 (36)	156 (43)
Peripheral artery disease		38 (19)	76 (21)
Cerebrovascular disease & TIA		45 (22.6)	78 (21)
Chronic heart failure		51 (26)	95 (26)
Chronic respiratory disease		44 (22)	93 (26)
Chronic liver disease		19 (10)	23 (6)
Severe renal impairment, eGFR <30		32 (16)	38 (10)
Active Malignancy, except skin		55 (28)	82 (23)
Depression		18 (9)	32 (9)
Dementia		7 (4)	22 (6)
Glucose-lowering medications			
Metformin		89 (45)	201 (55)
Insulin		94 (47)	114 (31)
Sulfonylurea/glinide		75 (38)	47 (13)
Dipeptidyl peptidase 4 inhibitor		61 (31)	34 (9)

(Continues)

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TABLE 1 (Continued)

Sociodemographics		Overtreated ($n = 199$, 35%)**	Not overtreated ($n = 365$, 65%)
Glucagon-like peptide-1 agonist		5 (3)	8 (2)
Sodium-Glucose co-transporter 2 inhibitor		4 (2)	11 (3)
Glucose-lowering medication(s), *n*	1	63 (32)	168 (46)
	2	104 (52)	72 (20)
	3	26 (13)	39 (11)
	4	6 (3)	12 (3)

Note: Numbers are presented as *n* (%), means±SD or medians with interquartile range as appropriate.
Abbreviations: CI, confidence interval; eGFR (in ml/min/1.73 m^2), estimated glomerular filtration rate; ER, emergency room; HbA_{1c}, glycated hemoglobin A_{1c}; TIA, transient ischemic attack.
[a]1–5.
[b]1–7.
[c]0–6.
[d]0–1.
[e]1–8 missing values from patients in each group.
[†]Score to assess activities of daily living; 0 points corresponding to complete dependency, 100 points complete independency in all domains.
[‡]Questionnaire-based health status on a 0 (death) to 1 (perfect health) scale.
[§]The Charlson comorbidity index predicts 10-year survival in multimorbid patients and ranges from 0 to 33 points; higher scores indicate a lower 10-year survival, 7 points correspond to an estimated 0% 10-year survival.
*Healthcare contacts refer to hospitalizations within 12 months prior to enrolment at baseline, or general practitioner visits, ED or outpatient clinic/specialist visits, permanent nursing home residency, home nursing visits, or receipt of informal care (by relatives or other close persons) within 6 months prior to the baseline visit.
**Patients were regarded as overtreated if their HbA_{1c} was <7.5% under GLM other than metformin only, e.g., a patient with HbA_{1c} 7.1% prescribed metformin and sulfonylurea was considered overtreated.

aimed (i) to assess the prevalence of overtreatment of T2DM in a population of hospitalized multimorbid older patients with T2DM, and (ii) to identify risk factors associated with overtreatment of T2DM in these patients.

METHODS

A detailed description of the methods used in this secondary analysis of the OPERAM study[11] can be found in the Supplementary Methods S1. In brief, we applied the definition of overtreatment of T2DM as suggested by the American Geriatrics Society in its *Choosing Wisely* campaign with metformin as the sole GLM appropriate to achieve HbA_{1c} levels <7.5%.[4–6] For associations with risk factors, we performed sensitivity analyses for overtreatment at HbA_{1c} < 7% and <6.5% as well as subgroup analyses for overtreatment in community-dwelling adults after exclusion of nursing home residents. We adjusted all analyses for age and sex in applying generalized linear models and used prevalence ratios (PRs) to evaluate risk factors of overtreatment. PR is calculated in the same way as relative risk, and it is the recommended measure in cross-sectional studies.[12,13] Multimorbidity was defined as at least three chronic conditions defined by the international classification of diseases, 10th revision (ICD-10), codes with an estimated duration of at least six months or based on a clinical decision.[11]

RESULTS

Characteristics of patients

From a total of 2008 OPERAM participants, 564 (28%) had T2DM and were eligible for this substudy. Their mean (± standard deviation) HbA_{1c} was 7.2% (±1.2%), median age was 78 years (interquartile range [IQR] 74–82), 39% were women ($n = 219$), median Charlson comorbidity index (CCI) was 7 (IQR 5–8), and median number of chronic daily medications was 11 (IQR 8 to 14) (Table 1). Forty-three (8%) patients were nursing home residents, and up to one third received home nursing visits ($n = 167$, 30%) or informal care ($n = 133$, 24%), for example, by relatives or other close persons. Estimated 10-year survival ranged from 21% to 0% based on the CCI (score 5–8).[14] Fifty-nine percent of patients with T2DM had cardiovascular ischemic disease ($n = 332$), divided into ischemic heart disease ($n = 227$, 40%), peripheral artery disease ($n = 114$, 20%), and/or cerebrovascular disease and transient ischemic attack ($n = 123$, 22%). Seventy patients (12%) had severe renal impairment (eGFR <30 mL/min). Metformin was the most frequently prescribed GLM (290 patients or 51% were taking metformin). Sulfonylureas/glinides were present more frequently in the overtreated patients ($n = 75$, 13%) compared with patients not overtreated ($n = 47$, 8%), while

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TABLE 2 Age- and sex-adjusted association of medical conditions, health indices, and healthcare contacts with overtreatment of type 2 diabetes mellitus (patients with GLM other than metformin and with $HbA_{1c} < 7.5\%$, $n = 199$).

		Adjusted PR[d]	95% CI	P**	Adjusted PR[d]	95% CI	P**
		Age- and sex-adjusted			analysis multivariable analysis***		
Medical conditions							
Severe renal impairment, eGFR <30		1.36	1.21–1.53	<0.001	1.46	1.33–1.60	<0.001
Chronic liver disease		1.29	1.00–1.68	0.05			
Chronic heart failure		0.99	0.74–1.31	0.94			
Cardiovascular disease		0.85	0.61–1.17	0.31			
Ischemic heart disease		0.80	0.68–0.95	0.01	0.75	0.64–0.89	0.001
Peripheral artery disease		0.92	0.60–1.43	0.72			
Cerebrovascular disease and TIA		1.05	0.74–1.49	0.78			
Chronic respiratory disease		0.88	0.71–1.09	0.23			
Malignancy, except skin		1.18	0.79–1.75	0.42			
Depression		1.02	0.71–1.48	0.90			
Dementia		0.68	0.39–1.19	0.18			
Health indices							
Charlson comorbidity index ≥7[a]		1.30	0.78–2.15	0.31			
EQ-5D < average[b]		1.22	0.99–1.50	0.07			
Healthcare contacts[c]							
Hospitalizations, *n*	0	*Reference*		0.81			
	1	1.12	0.91–1.37				
	≥2	0.98	0.84–1.14				
General practitioner visits, *n*	0	*Reference*		0.52			
	1–2	1.03	0.59–1.77				
	3–4	1.18	0.70–1.99				
	≥5	1.14	0.67–1.95				
Other outpatient physician or ED visits, *n*	0			<0.001			
		Reference					
	1–2	1.22	1.03–1.46		1.24	1.02–1.49	0.03
	≥3	1.35	1.19–1.54		1.40	1.29–1.52	<0.001
Nursing home resident		0.73	0.44–1.21	0.23			
Home nursing visits		1.14	1.00–1.30	0.06			
Receipt of informal care[b]		1.24	0.97–1.59	0.08			

Abbreviations: CI, confidence interval; ED, emergency department; eGFR (in ml/min/1.73 m^2), estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; PR, prevalence ratio; TIA, transient ischemic attack.

[a]The Charlson comorbidity index predicts 10-year survival in multimorbid patients and ranges from 0 to 33 points; higher scores indicate a lower 10-year-survival, 7 points correspond to an estimated 0% 10-year survival.

[b]Questionnaire-based health status on a 1 to 0 scale, a value of 1 corresponds to perfect health and a value of 0 to death.

[c]Healthcare contacts refer to hospitalizations within 12 months prior to enrolment at baseline, or general practitioner visits, ED or outpatient clinic/specialist visits, permanent nursing home residency, home nursing visits, or receipt of informal care (by relatives or other close persons) within 6 months prior to the baseline visit.

[d]Adjusted for age and sex and referring to the individual parameter/risk factor.

**Hospitalizations, general practitioner visits, and other outpatient physician or ED visits, the *P*-value refers to a P for trend.

***Variables: severe renal impairment, ischemic heart disease, other outpatient or ED visits, and adjusted for age and sex.

the frequency of insulin use was similar (overtreated $n = 94$, 17%; not overtreated $n = 114$, 20%; Table 1). DPP-4 inhibitors were prescribed predominantly in the overtreated group ($n = 61$, 11%). Only very few patients were on novel GLM such as GLP-1 agonists ($n = 13$, 2%) or SGLT2 inhibitors ($n = 15$, 3%).

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Factors associated with overtreatment (all analyses adjusted for age and sex)

Among the medical conditions, only severe renal impairment (prevalence ratio [PR] 1.36, 1.21–1.53) was positively associated with overtreatment of T2DM. Ischemic heart disease was negatively associated with overtreatment (PR 0.80, CI 0.68–0.95). More visits to healthcare providers other than the general practitioner (GP) were positively associated with overtreatment (PR 1.22, CI 1.03–1.46 for 1–2 visits, and PR 1.35, CI 1.19–1.54 for ≥3 visits versus no visits; Table 2, Figure 1). In the multivariable analysis, these associations were confirmed for severe renal impairment and other outpatient or emergency department visits as well as the negative association with ischemic heart disease (Table 2).

In sensitivity analyses with an HbA_{1c} cutoff <7% for overtreatment in patients with GLM other than metformin ($n = 140$, 25% of the overall patients with T2DM, 70% of the overtreated), chronic liver disease (PR 1.46, CI 1.16–1.84) and severe renal impairment (PR 1.58, CI 1.17–2.15) were positively associated with overtreatment, while dementia was negatively associated with overtreatment (PR 0.56, CI 0.32–0.99). Furthermore, an association was found between overtreatment at an $HbA_{1c} < 7\%$ threshold and below average quality of life (PR 1.19, CI 1.07–1.32; Table S1) as well as for other outpatient physician or emergency department visits (PR 1.24, CI 1.10–1.39 for ≥3 versus no visits). Home nursing visits (PR 1.30, CI 1.22–1.38) and receipt of informal care (PR 1.57, CI 1.39–1.78) were both associated with overtreatment of T2DM at an $HbA_{1c} < 7\%$.

In sensitivity analyses with an HbA_{1c} cutoff for overtreatment in patients with GLM other than metformin at <6.5% ($n = 83$, 15% of the overall patients with T2DM, 42% of the overtreated), chronic liver disease (PR 2.08, CI 1.12–3.84) was also associated with overtreatment in addition to severe renal impairment (PR 1.84, CI 1.38–2.46). Furthermore, home nursing visits (PR 1.63, CI 1.47–1.81) were associated with overtreatment at an $HbA_{1c} < 6.5\%$ as well as receipt of informal care (PR 1.63, CI 1.07–2.48).

In a subgroup analysis of community-dwelling older adults, after excluding nursing home residents, severe renal impairment (PR 1.20, CI 1.08–1.34) and additionally chronic liver disease (PR 1.40, CI 1.06–1.84) were positively associated with overtreatment in addition to non-GP healthcare contacts (PR 1.27, CI 1.02–1.58 for 1–2 visits, and PR 1.37, CI 1.23–1.52 for ≥3 visits versus no visits), while there was an additional negative association with ischemic heart disease (PR 0.82, CI 0.68–1.00). These results were robust in the multivariable analysis (Table S2). We have found similar results in these community-dwelling older adults than in the main analysis including nursing home residents.

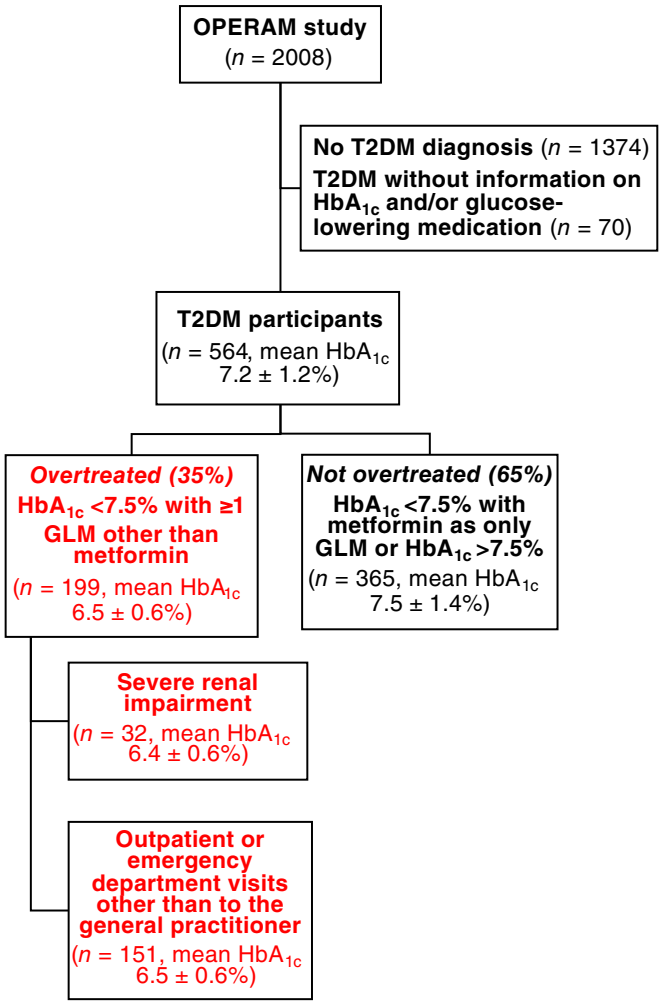

FIGURE 1 Study summary with flow diagram of patients & risk factors associated with overtreatment. GLM, glucose-lowering medication; HbA_{1c}, glycated hemoglobin A_{1c}; T2DM, type 2 diabetes mellitus; factors associated with overtreatment are highlighted in red and the overlap in the bottom two boxes is $n = 23$.

DISCUSSION

In the present study of multimorbid older patients with T2DM, we identified that 35% were overtreated with an $HbA_{1c} < 7.5\%$ on GLM (other than metformin as their only GLM). The presence of severe renal impairment and outpatient or emergency department visits other than to the GP were associated with overtreatment of T2DM (Figure 1). When we changed the threshold of our definition of overtreatment (i.e., $HbA_{1c} < 7\%$ or <6.5%) in sensitivity analyses, the findings remained similar and there were additional associations with

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chronic liver disease, home nursing visits, and the receipt of informal care.

The level of overtreatment of T2DM in our study is comparable to recent studies also having documented a higher proportion of overtreatment than undertreatment.[7,9,10,15,16] A US study using Medicare data found that 11% of patients 65 years and older with T2DM were overtreated, and deintensification of overtreatment by reducing therapy took place only in about 14%.[10,17] The high level of multimorbidity among the patients in our study is illustrated by a CCI of 7 on average, highlighting that the 10-year survival is expected to be 0% (2% with CCI 6, 21% with CCI 5).[18] The patients with T2DM in our study were generally not healthy older adults with a substantial life expectancy and a glycemic target of HbA_{1c} 7.0–7.5% might be associated with more harm than benefit.[5,7]

As compared with other studies,[10,15] older age was not associated with an increased prevalence of T2DM overtreatment, possibly due to our patients all being aged 70 years and older.

Strengths and limitations

A strength of the present study is the focus on multimorbid older patients with polypharmacy, a population commonly excluded from trials, including large studies on T2DM,[2,19] but evaluated in larger observational studies in this context before.[7–9] In addition, the inclusion of OPERAM patients allowed consideration of multiple relevant covariates in the treatment of T2DM, including patient-relevant outcomes.[11,20] The cross-sectional nature of our analyses seems appropriate for our focus on HbA_{1c} as an easily available and generally reliable parameter to assess the treatment of T2DM in reflecting the diabetic control in the preceding months.[21] However, due to the cross-sectional nature of this study, reverse causation cannot be ruled out. In addition, residual confounding influence also cannot be excluded, that is, that increased healthcare contacts are due to more severe illness, which is associated with lower body weight and thus lower HbA_{1c} levels. The relatively lower number of women included in our present substudy is compatible with the overall underrepresentation of women in certain clinical trials also in the older population.[22] Moreover, type 2 diabetes mellitus is more prevalent in men than in women of this age group,[23] which is compatible with our European population in OPERAM having a lower percentage of female participants (45%) in the overall cohort of patients recruited.[11] Another limitation of our study is that OPERAM patients were almost exclusively White individuals, and our results may therefore not be generalizable to other ethnic groups. Our analyses are also limited by the underrepresentation of patients on novel GLMs such as GLP-1 agonists and SGLT2 inhibitors (2%–3%),[3] possibly because our study included multimorbid older patients who are commonly excluded from clinical trials,[19] and in whom these new drugs might have been prescribed less frequently. New GLM regimens might help in further refining current recommendations for T2DM treatment in geriatric patients.[2,4,5] However, life expectancy is often limited in multimorbid older patients and positive effects of careful diabetic control including those on the microvasculature may require about a decade or more of intensive treatment.[2,24] Finally, because this secondary analysis included a subset of OPERAM participants with T2DM originally recruited for the main trial, a risk of selection bias cannot be excluded.

Implications

Treatment deintensification or discontinuation may help to improve quality of care as well as quality of life in multimorbid older patients with polypharmacy and a mortality of almost 20% within the first year of follow-up.[2,11,25] Previous studies indicate that a single GLM is often sufficient to treat T2DM in a proportion of up to 90% of multimorbid older patients with a sole GLM often allowing an appropriate HbA_{1c} level.[2,26] We found that 30% of participants achieved a target HbA_{1c} with a single GLM (Table 1). Additional agents add to the burden of polypharmacy and may not always have significant benefits on clinical outcomes while increasing the risk of hypoglycemia with consecutive morbidity and mortality.[2,7,8,27] In applying the American Geriatrics Society's *Choosing Wisely* definition of overtreatment of type 2 diabetes mellitus, we have identified severe renal impairment as well as outpatient or emergency department visits other than to the GP as important risk factors of overtreatment (Figure 1). This could help clinicians to better recognize these patients and optimize their treatment to prevent possible adverse effects such as hypoglycemia and its detrimental consequences in the future.

Conclusions

In this multicountry study of multimorbid older patients with T2DM, more than one third were overtreated, highlighting the high prevalence of this problem. Careful balancing of benefits and risks in the choice of GLM may improve patient care, especially in the context of

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comorbidities such as severe renal impairment, and frequent non-GP healthcare contacts.

AUTHOR CONTRIBUTIONS

All authors have read and approved the submission of this manuscript. Nicolas Rodondi, Oliver Baretella, Martin Feller, Carole E. Aubert, Dimitrios Papazoglou, and Drahomir Aujesky contributed to the study concept and design. All authors contributed to the acquisition, analysis, and interpretation of data. Oliver Baretella, Heba Alwan, Martin Feller, and Nicolas Rodondi drafted the manuscript. All authors contributed to critical revisions of the manuscript for important intellectual content. Cinzia Del Giovane was responsible for supervision of statistical analyses. Nicolas Rodondi obtained funding and provided overall study supervision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest related to the present study.

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ORCID

Carole E. Aubert https://orcid.org/0000-0001-8325-8784
Antoine Christiaens https://orcid.org/0000-0002-4132-7769

TWITTER

Nicolas Rodondi @nicolasrodondi

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Methods S1. Supporting material.

Table S1. Age and sex-adjusted association of medical conditions, health indices, and health care contacts with overtreatment of type 2 diabetes mellitus at $HbA_{1c} < 7\%$ ($n = 140$) and <6.5% ($n = 83$) in patients with GLM other than metformin.

Table S2. Age and sex-adjusted association of medical conditions, health indices, and health care contacts with overtreatment of type 2 diabetes mellitus (in community-dwelling patients with GLM other than metformin and with $HbA_{1c} < 7.5\%$, $n = 188$; nursing home residents excluded).

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