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Combined use of polypill components in patients with type 2 diabetes mellitus

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Abstract

Objectives: A polypill containing aspirin, a statin and blood pressure (BP)-lowering agents has been proposed for the prevention of cardiovascular disease. To increase adherence and reduce the gaps between indicated and used therapy, a polypill might be of interest for patients with type 2 diabetes (T2DM). Our aim was to assess the prevalence of the combined use of polypill components in patients with T2DM over time.

Methods: The combined use of polypill components was assessed between 1996 and 2015 in patients with T2DM in the prospective SMART cohort ($n = 1828$). The results were dichotomized into patients without ($n = 568$) and with ($n = 1260$) vascular disease. The patient characteristics associated with the use of polypill components were evaluated.

Results: In total, 19% of patients with T2DM without vascular disease received a statin and $\geq$2 BP-lowering agents ('cardiovascular polypill') and 13% received additional oral glucose-lowering therapy ('diabetic polypill'). Of the patients with T2DM with vascular disease, 42% received the combination of an antiplatelet agent, a statin and $\geq$2 BP-lowering agents ('cardiovascular polypill') and 30% received additional glucose-lowering therapy ('diabetic polypill'). The prevalence of the use of the cardiovascular and diabetic polypill combination has substantially increased between 1996 and 2015 to 36 and 32% in patients without vascular disease and to 67 and 57% in patients with vascular disease.

Conclusions: Patients with T2DM frequently use polypill components, often together with oral glucose-lowering agents, and this rate of use has increased steadily between 1996 and 2015. Introducing a cardiovascular or diabetic polypill for patients with T2DM seems to be highly relevant.

Keywords

Fixed-dose combination drugs, cardiovascular disease, diabetic polypills

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Introduction

Type 2 diabetes (T2DM) confers about a two-fold excess risk of vascular disease.[1] With a steadily increasing prevalence, T2DM makes a significant contribution to the high global burden of atherosclerotic vascular morbidity and mortality.[2] Next to adequate glycaemic control in the early stages of T2DM, intensive management of cardiovascular risk factors reduces the risk of vascular disease.[3–5] Current European guidelines recommend the use of statins and blood pressure (BP)-lowering agents with little constraint in patients with T2DM given the high prevalence of hyperlipidaemia and hypertension.[6] Additional antiplatelet therapy is generally indicated in patients with manifest vascular disease.[6]

Despite the importance of optimum risk factor control, only 25–50% of high-risk patients in high-income countries receive cardiovascular preventive medication in accordance with current international guidelines, with even lower rates in low- and middle-income

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countries.[7,8] Non-adherence to indicated medication and physicians' or patients' barriers to treating low-density lipoprotein (LDL) cholesterol and BP may be part of the underlying causes of the residual cardiovascular risk in patients with T2DM. An increasing number of pills and frequency of dosing regimens are among the most important factors for patients' non-adherence.[9] As both T2DM and vascular disease are strongly associated with polypharmacy, suboptimum adherence is common.[10,11]

A cardiovascular fixed-dose combination (FDC) drug containing aspirin, a statin and BP-lowering agents ('the polypill') is marketed for the prevention of cardiovascular disease.[12] FDC drugs have been shown to increase adherence and are preferred by patients over single-component drugs.[13,14] Given the high risk of vascular events in patients with T2DM, a substantial proportion of these patients receives cardiovascular preventive medication. These patients might benefit from substituting individual pharmacological agents by a cardiovascular polypill and could be considered to be the low-hanging fruit of a polypill strategy. Moreover, the concept of the polypill could be extended to a 'diabetic polypill' combining cardiovascular and glucose-lowering therapy in one pill.

Previous studies on a polypill strategy focused exclusively on patients with vascular disease or those at risk of vascular disease, irrespective of comorbid T2DM.[15,16] It is currently unclear whether introducing a polypill is feasible in patients with T2DM because the proportion of patients already using combination therapy is not known, nor do we know the determinants of the 'natural' use of polypill components. The aim of this study was to assess the prevalence of the natural use of polypill components in patients with T2DM, to assess the gaps between indicated and prescribed therapy and to provide insights into the polypill concept in terms of feasibility and applicability.

Methods

Study design and population

The patients originated from the SMART (Second Manifestations of ARTerial disease) study, an ongoing prospective cohort at the University Medical Center Utrecht (UMCU), the Netherlands. Patients aged 18–80 years with clinically manifest atherosclerotic vascular disease or those at high risk of vascular disease (e.g. patients with T2DM) have been included in this cohort since 1996. Most patients are referred for comprehensive vascular screening by the treating medical specialist or by their general practitioner. Individual patients included in the SMART study undergo a standardized vascular screening at enrolment consisting of a physical examination and questionnaires on cardiovascular history, risk factors and current medication use; laboratory tests and ultrasonography are also performed. The prescription of medication is at the discretion of the treating specialist or general practitioner and had already started before referral to the SMART study. Patients with a terminal malignancy, dependency in daily activities or insufficient command of the Dutch language were excluded. All patients gave written informed consent for participation in the study. The study was approved by the Medical Ethical Committee of the UMCU. A detailed description of the SMART study design has been published previously.[17]

Patients included in the SMART study between January 1996 and March 2015 and who were diagnosed with T2DM were selected for the present study. T2DM was defined as a fasting plasma glucose level ≥ 7.0 mmol/L and/or non-fasting serum glucose ≥ 11.1 mmol/L at inclusion, the use of an oral glucose-lowering agent or insulin and/or a self-reported history of T2DM.

According to current guidelines, patients with vascular disease have an indication for the use of additional antiplatelet therapy, in contrast with those without vascular disease.[6] Therefore the study population was dichotomized into patients with T2DM without vascular disease eligible for primary prevention ($n = 568$) and patients with T2DM with vascular disease requiring secondary prevention ($n = 1260$). Vascular disease at baseline includes coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) and aneurysm of the abdominal aorta. The details are presented in the Supplementary Material, available online. If data on the existence of vascular disease were missing ($n = 81$; 4%), then the patients were excluded from further analysis.

Definitions of the cardiovascular and diabetic polypills

As multiple BP-lowering agents are generally required to effectively lower BP in patients with T2DM, the BP-lowering component of the polypill was defined as the use of ≥ 2 different BP-lowering agents.[6]

For patients without vascular disease, two potential polypill combinations were defined: (a) a cardiovascular polypill consisting of a statin and ≥ 2 BP-lowering agents and (b) a diabetic polypill with the addition of an oral glucose-lowering agent. For patients with vascular disease, we defined similar combinations: (a) a cardiovascular polypill consisting of an antiplatelet agent, a statin and ≥ 2 BP-lowering agents and (b) a diabetic polypill with the addition of an oral glucose-lowering agent.

Data collection

Information on the use of medication was obtained through a questionnaire and verified in a conversation with a health care professional. Laboratory tests were carried out after an overnight fast of ≥8 hours. A venous blood sample provided insight in the lipid levels, glucose levels, HbA_{1c} and plasma creatinine. A urine sample was taken to measure excreted creatinine and detect micro-albuminuria. LDL cholesterol was calculated according the Friedewald formula up to a plasma triglyceride level of 9 mmol/L.[18,19] The estimated glomerular filtration rate was assessed using the Modification of Diet in Renal Disease formula.[20] Albuminuria was defined using the KDIGO guideline and metabolic syndrome was defined according to the Revised NCEP criteria.[21,22]

Data analyses

Categorical variables are presented as numbers and percentages of the total number of patients. Continuous variables with a skewed distribution were expressed as median (interquartile range) values and variables with a normal distribution were expressed as mean ± standard deviation values.

The gaps between the indicated and prescribed therapy (treatment gaps) were defined as the difference between indicated and reported medication use at baseline. Indicated medication was based on both the reported use of medication and the treatment targets described in the most recent (2016) European guidelines.[6] Patients were assumed to have an indication for an individual polypill component if the component was prescribed or when the corresponding treatment target was not achieved according to recent guidelines. LDL cholesterol treatment targets differ between patients without vascular disease (LDL cholesterol < 2.5 mmol/L) and patients with vascular disease (LDL cholesterol < 1.8 mmol/L). The BP target is a systolic BP < 140 mmHg in both patients with and without vascular disease. An indication for a polypill was defined as an indication for all separate polypill components. As the guidelines and medication preferences have changed over time, the use of polypill components from 2010 to 2015 was analysed.

Single imputation was used to reduce missing covariate data (Supplementary Material, available online). In patients with an indication for the cardiovascular polypill, the determinants associated with the use of the cardiovascular polypill were identified using a logistic regression analysis to estimate odds ratios with a 95% confidence interval. Potential confounders were identified based on a literature review and were adjusted for in the analyses. Statistical analyses were performed with SPSS 21. A two-sided significance level of 0.05 was used for statistical inferences.

Results

Baseline characteristics

The baseline characteristics are given in Table 1. Of the 1828 patients with T2DM eligible for this study, there were 568 (31%) patients without vascular disease and 1260 (69%) patients with vascular disease. Patients without vascular disease had a mean ± SD age of 55 ± 11 years and 338 (59%) patients were male. On average, patients with vascular disease were older (63 ± 9 years) and predominantly male ($n = 948$, 75%). Of the patients with vascular disease, 842 (67%) had a history of CAD.

Patients with T2DM without vascular disease

Use of polypill components over time. The prevalence of the use of antiplatelet agents, statins, BP-lowering and oral glucose-lowering agents was 15, 34, 64 and 69%, respectively (Supplementary Table S1, available online). In total, 105 (19%) patients were treated with a combination of a statin and ≥2 BP-lowering agents (cardiovascular polypill). In total, 76 (13%) patients received an additional oral glucose-lowering agent (diabetic polypill).

The use of statins markedly increased (from 0 to 64%) between 1996 and 2015, whereas the use of ≥2 BP-lowering agents increased more gradually (from 20 to 60%) (Figure 1a). Over time, the use of the cardiovascular polypill combination increased from 0 to 36% and the use of the diabetic polypill combination increased from 0 to 32%. Analyses of polypill combinations containing ≥1 BP-lowering agent are provided in Supplementary Figure 1A, available online.

Gaps between indicated therapy and reported use. In total, 241 (43%) patients with LDL cholesterol > 2.5 mmol/L did not receive lipid-lowering agents (Supplementary Table S2, available online). Among the patients receiving lipid-lowering agents, 19% did not achieve the current LDL cholesterol treatment target. Of the patients with systolic BP > 140 mmHg, 17% did not receive BP-lowering agents and 41% of patients on BP-lowering agents did not achieve BP target levels. Moreover, 7% of patients did not receive glucose-lowering agents despite HbA_{1c} levels > 53 mmol/mol and 48% had inadequate glycaemic control. Over time, the treatment gaps associated with the cardiovascular and diabetic polypill components decreased, with a remaining gap between indicated and prescribed medication of 24% in 2014–2015 (Figure 2a).

Table 1. Baseline characteristics.

Patient characteristics	Patients with type 2 diabetes without vascular disease ($n = 568$)	Patients with type 2 diabetes with vascular disease ($n = 1260$)
Age (years)	55 ± 11	63 ± 9
Male sex	338 (59)	948 (75)
Current smoker	126 (22)	321 (26)
Body mass index (kg/m^2)	30.2 ± 6.0	28.4 ± 4.3
Metabolic syndrome	453 (80)	944 (75)
Family history of vascular disease	267 (50)	774 (64)
eGFR (ml/min/1.73 m^2)	85.1 ± 22.6	75.9 ± 21.1
Micro-albuminuria	107 (21)	249 (22)
Diabetes		
Duration of diabetes (years)	3 [7]	4 [9]
Glucose (mmol/L)	8.4 [3.7]	8.0 [2.8]
HbA_{1c} (mmol/mol)	58 ± 16	52 ± 12
Antidiabetic therapy		
Oral glucose-lowering agents	388 (68)	822 (65)
Insulin	133 (23)	302 (24)
Lipid fractions		
Total cholesterol (mmol/L)	5.3 ± 1.6	4.6 ± 1.2
Triglycerides (mmol/L)	1.8 [1.5]	1.6 [1.2]
HDL cholesterol (mmol/L)	1.2 ± 0.4	1.1 ± 0.3
LDL cholesterol (mmol/L)	3.0 ± 1.2	2.6 ± 1.0
LDL cholesterol > 1.8 mmol/L	461 (85)	978 (79)
LDL cholesterol > 2.5 mmol/L	342 (63)	597 (48)
Lipid-lowering medication	237 (42)	937 (74)
Blood pressure		
Systolic BP (mmHg)	146 ± 21	145 ± 21
Systolic BP > 140 mmHg	329 (58)	713 (57)
Diastolic BP (mmHg)	86 ± 12	81 ± 11
BP-lowering medication	363 (64)	1050 (83)
History of vascular disease		
Coronary artery disease	–	842 (67)
Cerebrovascular disease	–	364 (29)
Peripheral artery disease	–	269 (21)
Abdominal aortic aneurysm	–	92 (7)
Antithrombotic medication[a]	105 (19)	1086 (86)

Data are presented as *n* (%), mean ± SD or median [IQR] values.
BP: blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A_{1c}; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
[a]Use of antiplatelet agents and/or anticoagulants.

Determinants of the combined use of polypill components. In patients without vascular disease who had an indication for the cardiovascular polypill ($n = 338$), the presence of metabolic syndrome, obesity, increasing body mass index and increasing age were associated with the use of this combination (Supplementary Table S3, available online).

Patients with T2DM with vascular disease

Use of polypill components over time. The prevalence rates of the use of antiplatelet agents, statins, BP-lowering and glucose-lowering agents were 77, 72, 83 and 65%, respectively (Supplementary Table S1, available online). In total, 527 (42%) patients received a

combination of an antiplatelet agent, a statin and ≥2 BP-lowering agents (cardiovascular polypill). In total, 382 (30%) patients used an additional oral glucose-lowering agent (diabetic polypill).

The use of statins increased from 31 to 90% between 1996 and 2015 and the use of ≥2 BP-lowering agents increased from 41 to 78%. The use of the cardiovascular polypill combination substantially increased to 67% in 2014–2015 and the use of the diabetic polypill combination increased to 57% (Figure 1b). Analyses of polypill combinations containing ≥1 BP-lowering agent are provided in Supplementary Figure 1B, available online.

Gaps between indicated therapy and reported use. In total, 14% of patients with vascular disease did not use an antiplatelet or anticoagulant agent (Supplementary Table S2, available online) and 24% of patients with LDL cholesterol levels >1.8 mmol/L did not receive lipid-lowering agents according to current guidelines. Of the patients receiving lipid-lowering agents, 55% did not attain the current LDL cholesterol target. Only 9% of patients with a systolic BP > 140 mmHg did not receive BP-lowering agents. Of the patients who were prescribed BP-lowering agents, almost half (48%) did not achieve their target BP. A total of 6% of patients did not receive glucose-lowering therapy despite HbA_{1c} levels > 53 mmol/mol and 34% had inadequate glycaemic control despite treatment. The treatment gaps associated with the cardiovascular and diabetic polypill have decreased over time. In 2014–2015, the remaining treatment gap for the cardiovascular polypill was 15% and the remaining treatment gap for the diabetic polypill was 12% (Figure 2b).

Determinants of the combined use of polypill components. In patients with vascular disease and an indication for the cardiovascular polypill ($n = 928$), increasing body mass index, obesity, a positive family history of vascular disease and the occurrence of CAD were significantly associated with the use of this combination (Supplementary Table S3, available). Smokers or patients diagnosed with CVD or PAD were less likely to receive the cardiovascular polypill combination.

Use of the polypill combination between 2010 and 2015

In the period 2010–2015, 36 (35%) of 102 patients with T2DM without vascular disease received the cardiovascular polypill combination (Supplementary Table S4, available online). The most commonly used polypill components were simvastatin, ACEi/ARBs and a diuretic. Of these patients, 78% received additional oral glucose-lowering therapy (diabetic polypill), most frequently metformin (75%).

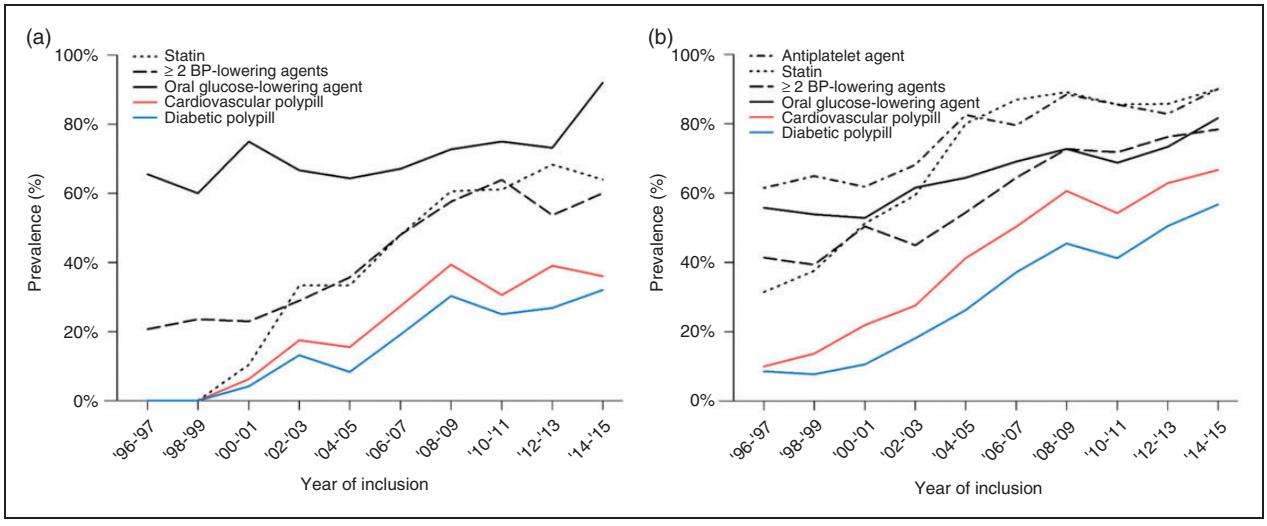

Figure 1. Prevalence of natural use of polypill components.
(a) In patients with T2DM without vascular disease, the cardiovascular polypill consists of a statin and ≥2 BP-lowering agents. The diabetic polypill consists of a statin and ≥2 BP-lowering agents and an oral glucose-lowering agent. (b) In patients with T2DM with vascular disease, the cardiovascular polypill consists of an antiplatelet agent, a statin and ≥2 BP-lowering agents. The diabetic polypill consists of an antiplatelet agent, a statin and ≥2 BP-lowering agents and an oral glucose-lowering agent.
BP: blood pressure; T2DM: type 2 diabetes.

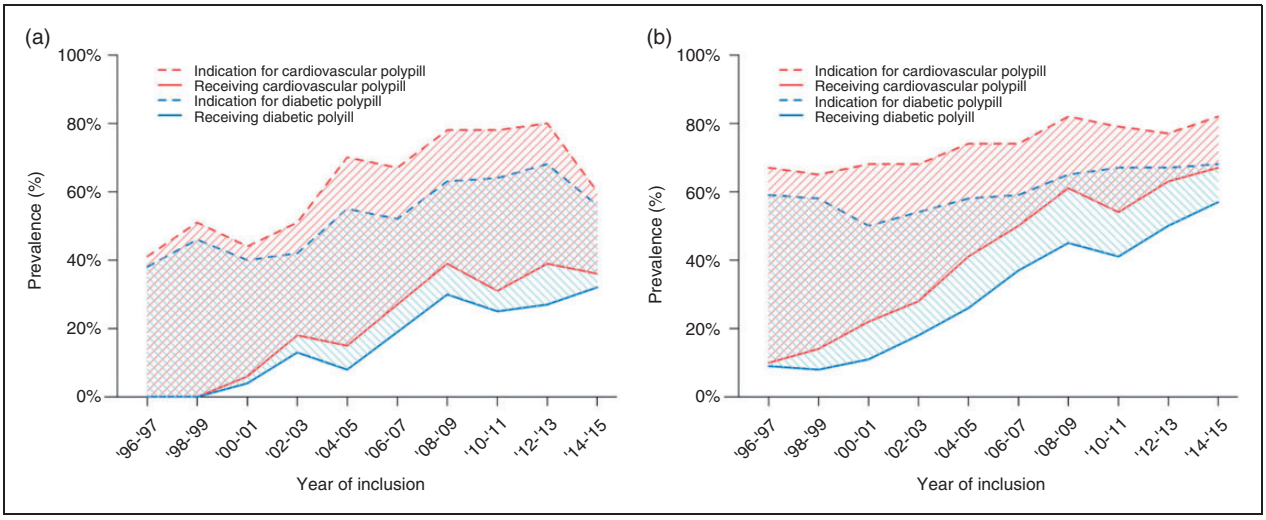

Figure 2. Potential identified treatment gaps.
(a) In patients with T2DM without vascular disease, the cardiovascular polypill consists of a statin and ≥2 BP-lowering agents. The diabetic polypill consists of a statin, ≥2 BP-lowering agents and an oral glucose-lowering agent. (b) In patients with T2DM with vascular disease, the cardiovascular polypill consists of an antiplatelet agent, a statin and ≥2 BP-lowering agents. The diabetic polypill consists of an antiplatelet agent, a statin, ≥2 BP-lowering agents and an oral glucose-lowering agent. An indication for the cardiovascular or diabetic polypill is based on the 2016 European Guidelines on cardiovascular prevention.[8]
BP: blood pressure; T2DM: type 2 diabetes.

Of the 296 patients with T2DM with vascular disease, 177 (60%) received the cardiovascular polypill combination. The polypill components that were most often used were aspirin, simvastatin, ACEi/ARBs and beta-blockers. Of these patients, 80% received additional oral glucose-lowering therapy (diabetic polypill), which was mainly metformin (73%).

Conclusions

This study shows that the use of polypill components by patients with T2DM increased steadily in the period 1996–2015. In patients without vascular disease, the combined use of a statin and ≥2 BP-lowering agents (cardiovascular polypill) increased from 0 to 36%, with a significant treatment gap between indicated and prescribed therapy of 24%. The use of an additional glucose-lowering agent (diabetic polypill) increased from 0 to 32%. In patients with vascular disease, the proportion using a combination of an antiplatelet agent, a statin and ≥2 BP-lowering agents (cardiovascular polypill) was substantially larger and increased from 10 to 67% over the years, with a remaining treatment gap of 15%. Use of an additional oral glucose-lowering agent (diabetic polypill) increased from 9 to 57%.

In a previous analysis of the SMART cohort, the combined use of aspirin, a statin and ≥2 BP-lowering agents in patients with manifest vascular disease or T2DM increased steadily over time. The use of this combination was relatively low in a subgroup of patients with T2DM because current guidelines do not advocate aspirin in primary prevention.[23] Another study evaluating primary and secondary cardiovascular prevention among patients with T2DM in Norway found similar rates of medication use.[24] However, the prevalence of the combined use of medication was not reported. No previous study has described the components of a diabetic polypill based on real-world data in such detailed manner.

Patients with T2DM are at high risk of vascular events.[1] Current guidelines advocate optimum treatment of LDL cholesterol and BP in patients with T2DM to reduce the risk of vascular events.[4,5] Nevertheless, the treatment of these risk factors often remains suboptimal and a significant number of patients do not reach treatment targets or are not treated at all.[8,24,25] Limited physicians' compliance to guidelines and a lack of adherence to dosing by patients are both likely to play a significant part. Treatment guidelines have changed significantly in recent years. Prescription according to the shifting guidelines in usual care is clearly seen in the current study, illustrated by an increase in the combined use of a statin and ≥2 BP-lowering agents. However, the proportion of patients in this study who should be treated according to current guidelines is substantially higher, indicating a remaining treatment gap with unmet medical need. Treatment gaps could be caused by various physicians' barriers to adhere to complex guidelines and inadequate attainment of risk factor levels by patients'

barriers to adhere to prescribed medication. However, it should be noted that treatment goals in guidelines have advanced over time, especially regarding LDL cholesterol. Although these treatment gaps suggest unmet medical needs according to current standards, this does not indicate inadequate risk factor control at the time of inclusion.

Patients with T2DM with vascular disease could be recognized as the low-hanging fruit for a polypill strategy given that about 82% of the patients had an indication for the combined use of an antiplatelet agent, a statin and $\geq$2 BP-lowering agents in 2014. For patients who are not already using this combination, but do have an indication for use, an FDC-based strategy may reduce the apparent treatment gap. Those patients using individual pills could benefit from a reduction of pill burden. Replacing the combined use of individual pills by a polypill may increase treatment adherence.[14,26] Previous research has shown that patients prefer a FDC-regimen over individual agents.[13]

Based on the combinations of polypill components most often used between 2010 and 2015, various polypills could be formulated for patients with T2DM. For patients without vascular disease, the cardiovascular polypill could consist of a generic statin, a thiazide diuretic and an ACEi. The diabetic polypill could additionally contain metformin. Similar formulations additionally containing aspirin can be proposed for patients with vascular disease. In patients with CAD, the thiazide diuretic could be replaced by a beta-blocker. If the polypill consists of low-cost generic medication, it has the potential to increase availability and affordability, which is particularly interesting in low- and middle-income countries.[27]

It should be stressed that the implementation of a polypill regimen does not rule out personalized medicine. If needed, additional medication can be added to standard treatment or several polypills with varying doses of components could be formulated to allow some dose adjustment. A particular challenge of the polypill is the potential risk of overtreatment. Regarding BP, there is uncertainty about the effect of very low systolic and diastolic BP on the risk of vascular events and mortality.[28] A polypill could contribute to increased adherence, but is not a panacea for patients with T2DM. Lifestyle interventions play an important part in the treatment of T2DM and should not be neglected, which might be a risk when introducing a polypill.[29] Although a cardiovascular polypill will not be suitable for every patient, a number of patients might benefit from the use of a single pill. The diabetic polypill will be more challenging because metformin is dosed more often and there is considerable inter-individual variation in terms of the required dose. In general, it should be noted that the effectiveness of a cardiovascular or diabetic polypill in patients with T2DM has not yet been examined in trials regarding the effects on risk factor control, compliance and, ideally, vascular endpoints.

The strengths of the current study include the detailed recording of medication use between 1996 and 2015. The use of real-world data gives a representative overview of secondary T2DM care over a wide period in time. The proportion of patients who refused participation in SMART is considered to be small and therefore is not expected to influence our findings.

Self-report might more accurately represent patients' actual medication use compared with pharmacy records. However, this can lead to reporting bias. Another study limitation is that medication use was only registered at inclusion in the cohort and might have changed over time.

Patients with T2DM often use a combination of polypill components, often with oral glucose-lowering agents. The prevalence of the natural combined use of polypill components increased in the period from 1996 to 2015. Introducing a cardiovascular or a diabetic polypill for patients with T2DM might be feasible considering the large proportion of patients already receiving polypill components in recent years. Substituting regular therapy by a polypill may improve adherence, reduce existing treatment gaps and eventually contribute to reducing the risk of vascular events.

Author contribution

V.J. researched the data and wrote the paper. F.V. reviewed/edited the paper. A.B. reviewed/edited the paper. D.G. reviewed/edited the paper. J.W. reviewed/edited the paper. Y.G. reviewed/edited the paper. M.L. contributed to writing the paper and reviewed the paper.

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