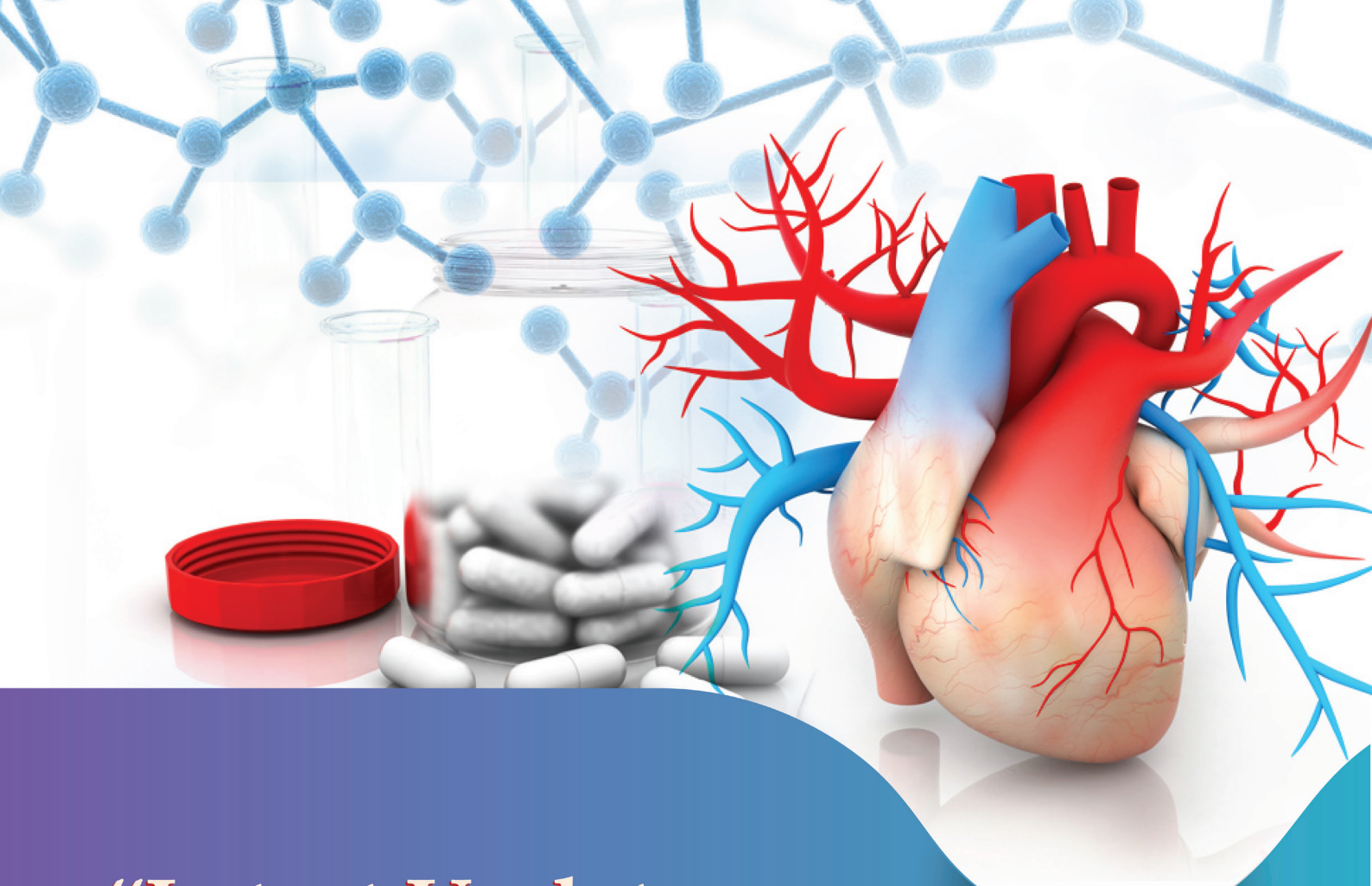

"Latest Update on Statins for Diabetes".

Module 7

Addressing Patient Concerns and Improving Adherence to Statins

CONTENT

Introduction

The efficacy of statin therapy in the prevention of cardiovascular events in adults with dyslipidaemia is well established.1 However, the use of statins in clinical practice is suboptimal.2,3 In a large meta-analysis of international studies assessing long-term adherence to preventive cardiovascular treatments including the use of statins, adherence was found to be as low as 50% in primary prevention and 66% in secondary prevention.4 Although substantial evidence supports the use of statins in secondary prevention of cardiovascular diseases, where adults aged 40–75 years with established cardiovascular disease should be treated with high-intensity statin therapy,1,5 less evidence is available for primary prevention. The latter applies to patients without cardiovascular disease but with increased cardiovascular risk based on individual evaluation using risk scores.1,6 Statin treatment for primary prevention in adults >75 years remains uncertain owing to sparse research evidence.7 Patients who are more likely to have multiple comorbidities and are undergoing polypharmacy treatment were under-represented in randomised controlled trials. Their long-term adherence to statin therapy is reported to decline substantially over time.8 Poor long-term adherence to statin therapy is associated with higher hospitalisation rates and higher total direct healthcare costs compared with good adherence to therapy over the first 2 years of use.9 In addition, statin discontinuation is associated with an increased risk of cardiovascular events that affects overall mortality, particularly in highrisk patients.10,11 Though deemed safe and well tolerated, statins have been associated with side effects, especially at high doses, such as muscle symptoms, new-onset diabetes mellitus, central nervous systemrelated, and hepatic side effects.12 However, side effects are not the only reason for statin discontinuation as inferred from the low rate of long-term adherence; the reported incidence of side effects among statin users is 5–10% in randomised clinical trials and 10–30% in observational studies.13 The latter might be due to symptoms perceived by the patient that are not statin related but still contribute to the higher frequency of side effects observed in clinical practice. In this respect, both treatment and non-treatment-related factors, including patients' characteristics, could contribute to statin discontinuation. Previous studies exploring attitudes towards statin side effects and reasons for statin discontinuation, from the perspectives of both patients14–17 and physicians,18,19 identified several subjective and potentially modifiable factors that could be utilised to improve the long-term adherence to statin therapy. These factors include, but are not limited to, intake of multiple drugs per day (polypharmacy), misunderstanding of treatment benefits, misconception of hypercholesterolaemia as a disease that requires treatment, physician– patient miscommunication, and concerns about side effects. Accordingly, these factors need to be addressed to improve the longterm adherence to statin therapy. GPs represent the healthcare professionals likely to be involved in the initial discussion of statin therapy with patients,20 and in the management of long-term medication. For that reason, a qualitative approach to the proponents of primary care may be useful to identify barriers as well as working strategies for statin therapy. This can contribute to the development and implementation of interventions that enhance therapy adherence and ultimately patient outcomes.

Evaluation of statin prescriptions in type 2 diabetes: India Heart Watch-2

Methods

This research is an independent qualitative study on German GPs' experiences with statin therapy. Sixteen interviews with GPs were conducted between April 2016 and July 2016 by three different researchers with varied academic and clinical backgrounds (general medicine, pharmacology, and pharmacy). Physicians with a specialisation in general medicine, who worked in a primary care sector as an employee or a practice owner, were selected from both the Research Network of the Berlin Institute of General Practice Charité (ANCHOR) and from other independent GP practices in Berlin and Brandenburg. Purposive sampling was employed at this stage to ensure that the sample represented a maximum variation of diverse characteristics such as sex, practice type, size, and grade of urbanisation, including the socioeconomic profile of the patients. In a further step, the sample was carefully selected to make sure there were no personal relationships between the interviewer and the interviewed GP. After contacting the GPs with a sufficient variety in characteristics via an email invitation, 16 GPs agreed to take part. The interviews were based on an interview guide formulated by the authors and based on literature and expert opinions.21 The semistructured interviews were conducted face to face at the GPs' practices and lasted 20–45 minutes; details of the interview questions are available from authors on request. The interviews were recorded and transcribed verbatim. The transcripts were encoded and analysed by the interviewers using qualitative content analysis, according to Mayring,22 who describes an approach of systematic, rule-guided, qualitative text analysis. Two procedures are central: the inductive category development and the deductive category application approach to identify, analyse, and report patterns in the data. Categories were carefully synthesised from both the initial ideas and material, and revised within the process of analysis. First, a preliminary coding scheme was developed and tested by the three researchers coding independently. Points of difference were discussed and revisions were made until a common approach was agreed. Subsequently, all data were coded and used until the final stage, in which some items deemed irrelevant to the research question were not included. This process formed the structure of the results; quotations were used to explicate the subjects. The original German quotations were translated into English.

RESULTS

This study was based on 16 interviews with GPs. The demographics of the participants show variability in sex, additional specialisation, degree of urbanisation, and practice type (Table 1). Generally, there was an overwhelming agreement among GPs that long-term therapy with statins is unsatisfactory. GPs indicated that they encounter several challenges when discussing statin therapy in daily practice. They attributed statin discontinuation mainly to the patients. Nevertheless, they pointed out that attitudes and behaviours on both sides, patients and doctors, could lead to the frequent failure of long-term statin therapy. However, most of the GPs were convinced that confidence in doctors and a stable doctor–patient relationship were strongly associated with patients' adherence to statin treatment. Consequently, they emphasised ways to manage these challenges and motivate patients to therapy through communication skills and person-centred care.

The latter focuses on the dynamics of patient– physician communication and is guided by patients' values and preferences to achieve satisfaction with their care.23 This study aimed to extract issues specific to statins as described below: Patient characteristics GPs perceived that patients' sociodemographic status influenced the long-term therapy with statins. They implied that a low educational level and older age posed a high risk for statin discontinuation. Though these groups of patients prefer to follow the GPs' advice at first, they tend to miss GP appointments to get a new prescription, or fill it at the pharmacy. They also tend to forget the evening intake, according to GPs: 'I guess that people with a lower educational level have difficulties in taking a therapy on a regular basis, to understand at all what might happen to them in the future …' (GP5, male [M]) 'Most of our patients are not highly educated; they do not decline the therapy or have any concerns, they rather forget to take the statins.' (GP15, female [F]) On the other hand, GPs emphasised that patients with a higher educational level could also be particularly challenging. This resulted from scepticism about medications, evidence from clinical trials, as well as the expertise of GPs. A few even conceded that they felt uncomfortable or stressed out around this group of patients. According to GPs, these patients are excessively concerned about developing muscle symptoms that could affect their quality of life or they question the necessity of further therapy after reaching low-density lipoprotein-cholesterol (LDL-C) standard values: 'Many patients, especially those with a higher educational level, are concerned about side effects …"I will not be able to ride the bicycle any more because I will get muscular pain", that is how they react. I get that a lot.' (GP10, F) The nocebo effect The nocebo effect is a detrimental effect on health produced by psychological or psychosomatic factors such as negative expectations of treatment or prognosis.24 Most of the participants suspected that a significant part of perceived symptoms from statins resulted from the nocebo effect. They observed that patients with psychiatric comorbidities such as anxiety and depression were more prone to the nocebo effect: 'Anxious patients with a tendency to hypochondria often develop perceived side effects.' (GP9, F) GPs feared that talking about side effects could lead to poor adherence. As a result, this group of patients were not comprehensively informed about side effects and were less frequently asked about complaints. Some GPs reported that they completely avoid talking about statins with anxious patients: 'To prescribe a statin and point out to pay attention to side effects … is not a good start.' (GP11, M) At the same time, almost all GPs were convinced that less informed patients were more prone to influences from the media and non-expert opinions, which might adversely affect doctor–patient relationships and adherence to statin therapy. They perceived this situation as a dilemma. The impact of media coverage More than half of GPs supposed that recent media coverage of statins had a negative impact on patients and contributed to patient concerns about statins and discontinuation of statin therapy. They stated that media-influenced patients tended to express critical views about side effects and the need for lipidlowering therapies in general: 'When statins are critically discussed in the media, more patients raise doubts about statin therapy and refer to that media source.' (GP16, M) The participants emphasised that media coverage mainly affected patients with lower cardiovascular risk levels or those with no history of cardiovascular disease. Perspectives and attitudes towards primary prevention Most of the GPs considered the relevance of statin therapy to be low, particularly in primary prevention. Some questioned the guidelines and were unconvinced of the evidence for the efficacy of statins in low-risk patients: 'I have second thoughts concerning the primary prevention; I am unconvinced of the data situation. If I recommend statins, it has to make sense for me.' (GP4, F) A few GPs were concerned that statins in primary prevention were used as a substitute for lifestyle change and for that reason were more likely to follow a patient's request to stop primary prevention with statins.

A number of GPs were keen to omit statin therapy first in older patients receiving polypharmacy in order to reduce pill burden, regardless of whether statins were prescribed for primary or secondary prevention. Approaches to improving long-term therapy In addition, the researchers explored approaches and actions undertaken by GPs to improve long-term therapy with statins. The main themes that emerged were patient education, person-centred care, and patient motivation (Figure 1). There was strong agreement among GPs that ongoing patient motivation was needed in statin therapy. They remarked that both the prevention of a discontinuation as well as its management required communication skills and expertise in patient education: 'Usually, you have to motivate patients to statins because hypercholesterolaemia does not cause any discomfort … Yes, you have a great deal to do to motivate patients.' (GP9, F) 'For example, if the patient mentions that he doesn't want the medication, he has concerns, or he is afraid to take it, we discuss jointly his situation and also his individual risk profile. If the patient finally decides against the statin, this is acceptable to me … This is how it works! At the very end, the patients decide …' (GP5, M) The majority of the GPs used computer programs to calculate and visualise the benefits of a cholesterol-lowering therapy. Generally, German GPs prefer two risk profile calculators, the PROCAM risk calculator, based on the results of a large epidemiological study on the German population (Prospective Cardiovascular Münster Study) and the ARRIBA risk calculator, based on the Framingham score. Owing to the different illustrations of risk profiles (charts or smileys), most of the GPs installed both programs and utilised them depending on the patients' educational level. This forms the basis, according to GPs, for a shared decision-making process concerning the therapy regimen: 'I find it easy to work with a computer program, to discuss the risk profile together, that's a good motivation for patients.' (GP14, F) 'It depends on the intellectual abilities of the patients if I use the PROCAM program or show the patients the "risk profile smileys" on the ARRIBA program.' (GP5, M) GPs emphasised the importance of educating patients about the potential interaction of both specific lifestyle changes and statin therapy on cholesterol levels, as well as the limited impact of lifestyle changes alone, for achieving target LDL-C levels. Furthermore, a couple of participants provided patients with printed therapy plans to take with them as well as advice on the evening intake at the time of their first prescription. A few GPs had a good experience with the frequent monitoring of LDL-C levels or checking prescription refill records to assess statin intake and to address patients with adherence problems specifically. Most of the GPs prioritised a stable, longterm therapeutic relationship over the achievement of LDL-C targets or following the guideline recommendations. They suggested a person-centred approach to overcome concerns and resistance or manage perceived side effects: 'It's essential to take patients' concerns and physical complaints seriously, even if you were convinced that they were not caused by statins … It's important to omit the statin first. The patients experience physically that the back pain hasn't gone away and wasn't caused by the statin.' (GP15, F) In addition, most of the GPs switched to another statin after temporary discontinuation instead of returning to their original medication, for psychological reasons: 'Re-exposure is almost never successful, usually causes the same complaints. That's why I always switch the statin, these patients are more likely to continue the medication.' (GP1, F) There was a strong agreement among GPs that long-term adherence to statins can be improved by being aware of barriers and combining the individual approaches, supports (such as technical tools), and guideline recommendations with questions about the patient's personal situation. DISCUSSION Summary The present study offers some insights into GPs' expectations of why long-term adherence to statins is deficient and how they handle this issue in daily routine care. Almost all of the GPs had experiences of challenging patient conversations about statin therapy. They observed different types of resistance in patients, mostly depending on sociodemographic factors.

A low educational level and an older age could be, for different reasons, a predictor for poor long-term adherence to statins, according to GPs. In addition, they considered that the recent media coverage of lipid-lowering therapy had a negative impact on patients' adherence. Attitudes and doubts about the appropriateness of statin use in low-risk patients were perceived to be important barriers affecting both the patients' adherence and the doctors' prescribing behaviour. They suspected that exaggerated concerns about statins, particularly in patients with psychiatric comorbidities, such as anxiety and depression, led to a nocebo effect and ended in statin discontinuation. GPs described various approaches to manage these barriers. They attached great importance to connecting patient education and motivation with person-centred care. For example, individual risk assessment with different computer programs were combined with a shared decision-making process to reach patients of all educational levels. Further approaches to assess and improve adherence such as monitoring of LDL-C levels, checking prescription refill records, printed therapy plans, advice for the evening intake, or switching the statin for psychological reasons were considered helpful. Strengths and limitations The intent of this qualitative study was to understand the range of perspectives and individual views that GPs hold in relation to statins and to add to the knowledge about factors that may affect adherence with statin treatment. Though limited in their generalisability, qualitative research can point to specific patterns and typologies. However, it is not possible to identify causal links to all of the findings in this study and draw a single conclusion or response to the several barriers associated with statin treatment. Though a relatively low total number of 16 interviews were conducted in the present study, the meaningfulness of the results is supported by the saturation of content noticeable in the progression of the interviews. Being interviewed by another physician may have influenced the results and might not always represent a GP's actual behaviour. Another limitation concerns the sampling process: the sampling was restricted to two federal states in Germany and most of the interviewed GPs were working in urban settings. Nevertheless, this study achieved a well-balanced sample concerning characteristics like sex, type of practice, and specialisation. Because GPs had to agree to be interviewed, a sampling bias of very interested and motivated GPs cannot be excluded. In addition, there was no patient involvement so the study only shows the GP's perspective. Comparison with existing literature According to the participating GPs, statin discontinuation was mostly initiated by patients, which concurs with the existing literature.19 Though statins were often discontinued without a prior medical consultation, physicians still play a crucial role in improving adherence and avoiding discontinuation, as highlighted by several studies.25–28 Patient adherence to therapy can be influenced by physicians in several ways; overall, compliance of GPs with cholesterol management guidelines, which recommend regular follow-up of patients, improves patients' adherence to statin therapy.28 In addition, the lack of adequate information about the disease provided by the GPs, as well as the benefits and potential side effects of statins are strong contributors to non-adherence.29,30 The importance of the physician–patient relationship in adherence was repeatedly expressed by GPs in the present study. A previous survey indicated that patients who were taking statins had more confidence in their latest interaction with a GP than those who had stopped or never taken statins.20 The interviewed GPs were more inclined to involve the patients in decision making and to take responsibility for their own treatment choices; however, they emphasised encountering several barriers. For example, they were concerned that the nocebo effect significantly influenced patients' compliance. The nocebo effect is a well-established phenomenon in pharmacotherapy and refers to side effects subjectively perceived from drug therapy due to prior expectation.24 It has been indicated that the nocebo effect is one reason for the high rate of side effects, especially muscle symptoms attributed to statins in observational studies and clinical practice.31

The nocebo effect seemed to affect both the patients and the GPs. Some GPs conceded that they should be more cautious when educating about statin side effects, fearing this could lead to poor adherence. A study conducted in patients discontinuing their statin therapy concluded that being less informed and unconvinced about the treatment were among the most common reasons for statin discontinuation.32 There is much less agreement among physicians about statins in primary prevention than in secondary prevention,20 which was also expressed by the interviewed GPs. A few participants considered the overall relevance of statins in cardiovascular primary prevention. This group tended to stop statins in case of any physical discomforts, polypharmacy, or at a patient's request. Furthermore, GPs observed that negative information about statins promoted by media coverage led to concerns and discontinuation of statin treatment in patients. Various studies have shown that discontinuation of statin therapy was temporarily influenced by negative media coverage.33–36 The present interviews emphasised that barriers to statin therapy depended on demographic characteristics, especially socioeconomic status and educational level. These seemed to be important predictors of adherence to statins according to GPs. Patients with higher socioeconomic status and higher education showed a greater level of long-term statin adherence,25,37 which was also noticed by the majority of GPs. In order to motivate patients to therapy and lifestyle changes, most of the GPs used computer programs with graphic presentations of individual risk profiles and benefits of therapy, for example, the ARRIBA38 and PROCAM tools,39 to actively involve patients in healthcare decision making. Several studies indicate that motivational strategies combining patient education, follow-up and monitoring with computer programs led to a lower rate of discontinuation.27 International guidelines, for example, the guidelines of the National Institute for Health and Care Excellence (NICE), emphasise shared decision making in the prevention of cardiovascular disease and contain recommendations to involve patients in decisions about their medication therapy.40 Implications for research and practice Shared decision making supported by computer-assisted programs seems to be a successful strategy to motivate patients and might serve as a valuable tool in primary care to promote patients' adherence. There is a need for implementing more comprehensible and interactive information about the risk of cardiovascular diseases and risks associated with statin therapy to educate patients. Information leaflets and software applications for lipid-lowering therapy, a healthy lifestyle, evening intake, and clear instructions in case of side effects could be helpful. Switching to statins that could be taken in the morning, for example, newer statins with a longer half-life should be considered if the evening intake is regularly forgotten, and when higher costs do not limit this approach. Practice guidelines with recommendations that are closer to management of patients in daily routine would be supportive for GPs. This can be achieved by incorporating reference case studies in guidelines describing alternative proceedings, such as deviations from LDL-C target values, intermittent dosing therapy, and statins in a polypharmacy situation. Qualitative studies to explore patients' perspectives are needed to reveal further barriers to long-term therapy with statins, particularly the nocebo effect, focusing on the impact of media coverage on patients. Quantitative studies to investigate the efficacy of approaches and strategies employed by GPs for improving adherence to statin therapy are also important areas for future research.

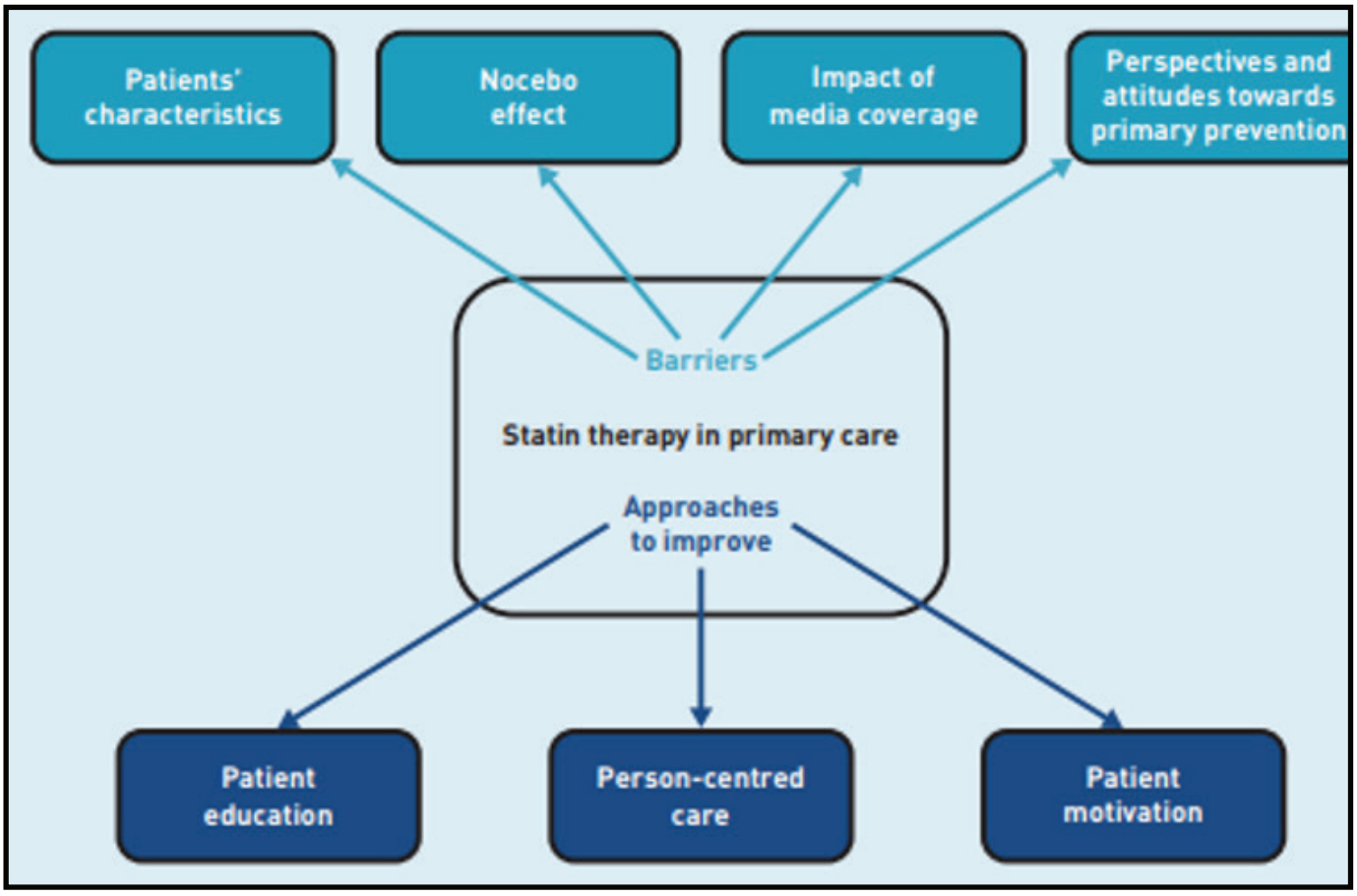

Figure 1. Main barriers in statin therapy and approaches to improve adherence according to GPs

Strategies to Improve Statin Therapy Adherence in Older Adults

Interventions were categorized into five out of the eight possible categories previously mentioned. Simplification of drug regimen: One study attempted to increase patient adherence to statin therapy by using a polypill [32] combining ezetimibe and statins. This approach reports a RR estimating the association of high adherence to treatment (PDC>75%) (Table 2) and single-pill combination of statin and ezetimibe vs. two-pill or separate administration of the two drugs of 2.12 (95% CI: 1.89–2.38) in favor of the single-pill combination for patients aged 65 to 80 years old. Patient education and information: Two studies [31, 33] attempted to increase adherence using education-based strategies. The results of Eussen et al. [33] were inconclusive regarding the effect of in-person counseling visits in a pharmacy setting on the incidence of discontinuation therapy in patients aged>65 years old (HR=0.903 [95% CI: 0.569–1.433]). However, Qvist et al. [31] reported a 10.1% (95% CI: 0.9–19.4) difference in the proportion of adherent (PDC≥80%) males aged 65 to 74 years old in favor of telephone-based counseling at 6 months, but not at 12 or 60 months. Intensified patient care Four trials [25–27, 34] examined, with diverging results, whether intensified patient care could have a positive impact on statin adherence. For example, in the study by Casula et al. [34], an informative educational intervention aimed at general practitioners (which we interpretated as having a downstream intensification of patient care even though this was not specifically identified within the manuscript) succeeded in increasing the MPR of 65–79 years old patients by an absolute increment of 6.3%, and by 8.3% in patients who were aged≥80 years old. The authors declared this increase to be significant, but no confidence interval or p-value was shown in the article. Similarly, Faridi et al. [25] showed that providing a first outpatient visit in the first week after discharge after a hospitalization for ST-elevation myocardial infarction or a non-ST-elevation myocardial infarction had a positive effect on patient adherence in patients when compared to first outpatient visits that took place more than 6 weeks after discharge. On the other hand, results by Guerard et al. [26] and Kooy et al. [27], using a comprehensive wellness assessment program or patient counselling combined with an electronic reminder device respectively, did not show any impact on statin adherence. Of note, although general results were inconclusive, Kooy et al. [27] did report that using only the electronic reminder device had a positive effect on patient adherence in women in a secondary prevention setting (adjusted OR=8.26 [2.20–31.0], p=0.002). Administrative improvements Three studies [28–30] examined whether administrative improvements could increase statin adherence in the target population. Ivers et al. [28] demonstrated an increase in patient adherence measured by the percentage of patients with a high PDC (>80%) if patients were given a higher supply of statins in their initial prescription, with an adjusted OR of 2.0 (1.7– 2.4) for a supply of 31–60 days and of 3.0 (2.6–3.4) for a supply of more than 60 days when compared to a supply of less than 31 days. Lester et al. [29] showed that patients enrolled in an automatic prescription refill program had higher adjusted odds of being adherent (PDC>80%) compared to patients who received usual care (adjusted OR=1.51 [1.26–1.82]). Schmittdiel et al. [30]

studied the impact of increasing mean days supply of statins, higher use of mail-order pharmacies, a lower price of generic drug co-payments and a lower annual out-of-pocket maximum on statin adherence based on observations made in various settings. All these interventions showed a positive association with patient adherence to statin therapy, with adjusted odds ratios ranging from 1.02 to 1.61 in favor of the interventions. Large-scale pharmacy-led automated telephone intervention Two studies [35, 36] examined the impact of largescale pharmacy-led automated telephone interventions on statin adherence. More specifically, Derose et al. [36]] reported that providing educational information and an encouraging prompt to patients who recently received a statin prescription had a positive effect on the proportion of statin dispensation in individuals over 70 years old (OR=2.32 [1.70–3.18]). Similarly, results from Vollmer et al. [35] showed that an interactive voice-recognition calls with or without personalized reminder letters in patients aged 71 years or older that were due or overdue for a statin refill also had a positive effect on patient adherence. More specifically, they showed that combining the call with a personalized letter showed a greater increase in PDC (+3.5% [1.2-5.8%]) than without (+2.9% [0.6-5.1%]) when compared to usual care [35]. Discussion In the present review, we identified five RTCs [27, 31, 33, 35, 36], five cohort studies [25, 26, 28, 30, 32] and two quasi-experimental studies [29, 34] published between 2010 and 2021 reporting on interventions attempting to increase statin adherence in older adults. Overall, our review suggests that simplifying patients' drug regimen, administrative improvements and large-scale pharmacyled automated telephone interventions tend to be effective when trying to improve older patients' adherence to statins. To the best of our knowledge, this review is the first to specifically examine interventions aimed at improving statin adherence amongst older adults. This is particu - larly important as the effectiveness of interventions aiming to improve statin adherence within this patient subset, for multiple reasons (e.g., administrative require - ments, individuals' financial capacity, complex drug regi - mens), could differ from what could be observed within an unrestricted adult population. Prior to conducting our review, two groups conducted two distinct systematic reviews of RCT interventions aimed at improving statin adherence within adult patients (no restriction in regards to patients' age) [16, 37]. Some key differences in terms of results between our and their reviews warrant further discussion. For example, in the review by Schedlbauer et al. [37], interventions focusing on patient re-inforcement and reminders tended to have the best overall effect on adherence (four out of six selected studies showed improvements in patient adherence with average results ranging from 8 to 24%). However, none of the studies included in our review examined an intervention of this type; questions remain as to why this is the case. One potential explanation could be that by offering the inter - vention to an unrestricted adult population, investiga - tors are maximizing its potential to improve adherence within a larger group of individuals. Another potential explanation could be that investigators designing such interventions could have a priori hypotheses (justified or not) that their intervention could be less effective within older patients. Regardless of the reason, considering their positive effect in the general adult population, their effect within older adults should be studied. This reasoning is further strengthened by comparing our results to those highlighted by Rash et al. [16]. Indeed, in their review, simplifying patients' drug regimen had the greatest effect on patients' adherence (with average results of three selected studies showing between 10% and 23% abso - lute increases in patients' adherence). Though less com - mon in the older adult population, we did identify one study that examined the impact of simplifying patients' drug regimen on patients' statin adherence [32]; their results highly supported this treatment strategy within older adults (Table 2). Although we cannot infer that this single study's results can be reproduced within all older adult statin users, alignment of these results with those obtained by Rea et al. [32]

warrant reproducing similar work within other jurisdictions. Beyond these important results, our review also high - lights the risk that, even amongst older adults, interven - tions' effective profile may not be homogeneous. For example, though the intervention examined by Kooy et al. [27] failed to show a statistically significant increase in patient adherence within all patients, they showed a statistically significant increase in adherence among women hinting that individuals' gender could influence Author/year treatment effect. Unfortunately, subgroup analyses were uncommon within the selected studies and no other group highlighted the presence of differential results based on individuals' gender. That being said, just as interventions' effectiveness can differ in function of individuals' age and gender, they could differ in function of other key characteristics as well. Future work in this area needs to better acknowledge that older patients can represent a heterogeneous group and favor prespecified subgroup analyses to examine for presence of differential subgroup effects. The evidence included in this review has limitations. Most studies reporting on interventions aiming to increase statin adherence in patients do not specifically target older adults. Indeed, only six out of 12 included studies [25–30] focused on this population. While some studies stratify analyses by age group, these analyses are based on a lower number of patients, which can lead to a loss of statistical power that might impact the ability to detect intervention effects. Beyond this fact, our assessment of the risk of bias within the selected studies identified also raised several issues (Additional File 4). Though issues differed between studies and study types, patient attrition was a common problem as only three [25, 27, 30] out of the 12 selected studies reported on it. Moreover, most studies that did not report attrition also failed to report on possible reasons for attrition that would help the reviewers make informed decisions about the degree of bias this introduces. Attrition in these cases could be particularly problematic as it could easily be explained by individuals refusing the interventions or requirements of. If that were the case, the true effect of the interventions we reviewed could be poorer than reported. Similarly, our review also highlights that patients' long-term adherence to statin is lacking. Indeed, though all 12 studies included at least some individuals followed up to at least 12 months (proportion of individuals followed up to 12 months differing in function of study design), only three [26, 28, 31] of these allowed the follow-up to extend beyond 12 months. When focusing specifically on these three studies, only one [28] showed a significant positive effect after 12 months (investigators assessing patients' adherence at 18 months). The other two did not show a significant effect and were in intervention categories that yielded mixed results in older adults (intensified patient care) and in both older adults and the general population (patient education and information) [16, 37]. Unfortunately, such results do not allow us to fully define if and how the effectiveness profiles of these interventions vary over time. On one hand, it is possible that adherenceenhancing interventions might have shown a greater benefit if follow-ups had been longer as statin adherence tends to fall substantially over time. On the other, greater follow-up could also have shown that their effectiveness plateaus or even declines beyond that 1-year mark. Lastly, all 12 included studies were performed in highincome countries, which limits the generalisability of the results for low to middle-income countries.The synthesis procedure used in this review has limitations as well. Even if interventions are pragmatically regrouped into categories, substantial differences remain in the nature of interventions within the same category. Because the studies differed in terms of designs, outcome measures (RR/OR/HR/%), study populations (including in terms of indication for statin therapy) and time frames, we could not calculate pooled effects and only reported on the direction and statistical significance of the effect of included interventions. As such, we only conducted a qualitative, narrative synthesis of results. All findings are thus subject to the limitations of this approach.

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Furthermore, though our review identifies some interventions that succeeded and others that fail to improve patient adherence, we were unable to fully explain why this was the case. Unfortunately, out of the 12 studies included in our review, only Qvist et al. [31] specifically examined why participants in their trial did not adhere to their treatment. Another limitation of the used intervention categories is that they do not classify interventions by the reasons for patient nonadherence. Patient adherence is a complex issue and taking patients' reasons for nonadherence into account when devising an intervention or a way to classify them could lead to more comparability and better outcomes. This issue is further complexified by the fact that some interventions (e.g., automated refills) could bias some of our commonly use adherence measures, such as PDC especially if based on administrative data. This was indeed the case in three of our studies [28–30]. Although all three manuscripts recognized that drug possession does not guarantee drug consumption, the retrospective nature of these studies limits the feasibility of directly confirming consumption with those included in their study. Conclusions In conclusion, the evidence suggests that simplifying patients' drug regimen, administrative improvements, and large-scale pharmacy-led automated telephone interventions may have positive effects on patient adherence to statin therapy, while education-based strategies and intensified patient care had mixed results. Although our review was restricted to older patients, we noticed that most studies tended to apply their intervention to the general adult population. As a result, important gaps in knowledge remain regarding interventions to improve statin adherence specifically in older adults. Moreover, patient adherence can be influenced by different factors such as medication side effects or fear of side effects, patient beliefs and memory [38, 39]. Tailoring interventions to address patient's reasons for nonadherence in this vulnerable population and better understanding the mechanisms underlying adherence might lead to strategies that are more effective in improving statin adherence.

Table 1 Characteristics of studies included in the analysis

Author/year	Country	Funding source	Setting	Design	N	Sample
Simplification of drug regimen						
Rea et al. (2021)	Italy	Università degli Studi di Milano – Bicocca, Italian Ministry of Education, University and Research, Italian Ministry of Health	Healthcare utilization databases of Lombardy	Cohort study	65-80 y.o.: 1507	Adults aged 40–80 y.o. and beneficiaries of the NHS
Patient education and information						
Eussen et al. (2010)	Netherlands	National Institute for Public Health and the Environment	Community pharmacy	Randomised controlled trial	314	New ≥ 18 y.o. statin users
Qvist et al. (2020)	Denmark	Central Denmark Region Health Science Research Fund, Family Hede Nielsen Fund, Frimodt-Heineke Fund	Central Denmark Region	Randomised controlled trial	435	Males aged between 65–74 y.o. in the screening arm of the VIVA trial diagnosed with AAA or PAD without prior statin or antithrombotic treatment
Intensified patient care						
Casula et al. (2015)	Italy	Regione Lombardia	General practices	Quasi-experimental study	5323	Pre-intervention: patients with 1st statin prescription between January 1st, 2007 and June 30th, 2007 Post-intervention: patients with 1st statin prescription between July 1st, 2008 and December 31st, 2008
Faridi et al. (2016)	United States	Agency for Healthcare Research and Quality	ACTION Registry-GWTG (US quality improvement registry)	Cohort study	20,219	Patients with at least 90 days of prescription coverage from Medicare Part D prior to discharge
Guerard et al. (2018)	United States	Unclear	Medicare Advantage plan diabetic population (administrative database)	Cohort study	≥ 65 years old: 163,628	Medicare Advantage members who received a new diabetes diagnosis.
Kooy et al. (2013)	Netherlands	Utrecht University	Community pharmacies	Randomised controlled trial	381	Patients who received a statin prescription in the preceding month, with a 50–80% yearly refill adherence over the last 12–18 months
Administrative improvements						
Ivers et al. (2013)	Canada	Cardiac Care Network of Ontario, Canadian Institutes for Health Research	Institute for Clinical Evaluative Sciences (population-based administrative records linked through a unique identifier)	Cohort study	16,134	Patients ≥ 65 y.o. with confirmed CAD
Lester et al. (2016)	United States	NIH National Center for Advancing Translational Sciences	29-store pharmacy chain	Quasi-experimental study	4946	Patients aged ≥ 65 y.o. taking ≥ 1 medication in the therapeutic categories used for calculating the PDC measures

Table 1 (continued)

Author/year	Country	Funding source	Setting	Design	N	Sample
Schmittdiel et al. (2015)	United States	Kaiser Permanente Center for Effectiveness and Safety Research, Agency for Healthcare Research and Quality	Health care delivery systems sites	Cohort study	93,276	Diabetic patients aged ≥ 65 y.o. as of January 1st, 2010
Large-scale pharmacy-led automated telephone intervention						
Derose et al. (2013)	United States	Merck Sharp & Dohme Corp	Health plan pharmacy	Randomised controlled trial	≥ 75years old: 2983	Patients ≥ 24 y.o. with a statin prescription and no record of a statin prescription in the year before the index prescription date enrolled with a health plan pharmacy for ≥ 1 year
Vollmer et al. (2014)	United States	Agency for Healthcare Research and Quality	Kaiser Permanente health plan	Randomised controlled trial	≥ 71 years old: 4357	Patients ≥ 40 y.o. with documented diabetes or CVD and ≥ 1 dispensation of ACEI, ARB, or statin in the preceding 12 months, with suboptimal adherence in the preceding 12 months, and were due or overdue for a refill

Author/year	Intervention	Control	Duration	Retention rate
Simplification of drug regimen				
Rea et al. (2021)	Statin and ezetimibe prescribed in a single-pill formulation	Statin and ezetimibe prescribed separately	12 months	NR for participants over 65
Patient education and information				
Eussen et al. (2010)	Pharmacy visits for 5 individual counseling sessions, each lasting 10–15 min	Usual care	12 months	NR for participants over 65
Qvist et al. (2020)	Telephone-based interview and counselling performed by a study nurse, based on a pragmatically designed semi-structured questionnaire.	Usual care	60 months	NR for participants over 65
Intensified patient care				
Casula et al. (2015)	Informative and educational intervention addressed to general practitioners	Usual care	12 months	NR for participants over 65
Faridi et al. (2016)	Earlier first outpatient visit after discharge for STEMI or NSTEMI	Usual care	3 & 12 months	90 days: 89.8% 1 year: 57.4%
Guerard et al. (2018)	Receiving a CWA in the preceding 12 months of the study	Usual care	60 months	NR for participants over 65
Kooy et al. (2013)	10-minute pharmacist counseling about non-adherence and a compliance card that signals every 24 h	Usual care	12 months	88.22%
Administrative improvements				
Ivers et al. (2013)	Increase in the number of days supplied in the initial prescription fill for each medication class	Usual care	18 months	NR for participants over 65
Lester et al. (2016)	Enrollment in an automatic prescription refill program	Usual care	At least 90 days – 2 months (at least 2 prescription refills)	NR for participants over 65

Table 1 (continued)

Author/year	Intervention	Control	Duration	Retention rate
Schmittdiel et al. (2015)	Mean days supply of drugs in therapeutic category in 2010, Percentage of drugs in therapeutic category refilled through mail order pharmacy in 2010, Generic drug copayment for 30-day supply in 2010, Annual individual out-of-pocket maximum in January 2010	Usual care	12 months	96.51%
Large-scale pharmacy-led automated telephone intervention				
Derose et al. (2013)	Providing patients with educational information and an encouraging prompt to adhere to a recently prescribed statin	Usual care	32–39 days	NR for participants over 65
Vollmer et al. (2014)	IVR calls with or without a personalized reminder letter if patients are due or overdue for a statin refill	Usual care	12 months	NR for participants over 65

AAA = Abdominal Aortic Aneurysm, ACEI = Angiotensin-converting enzyme inhibitors, ARB = Angiotensin II receptor blockers, CAD = Coronary Artery Disease, CVD = cardiovascular disease, CWA = Comprehensive Wellness Assessment, IVR = Interactive voice recognition, IVR + = Interactive voice recognition with a personalized reminder letter MPR = Medication possession ratio, NHS = National Health Service, NR = Not reported, NSTEMI = Non-ST-elevation myocardial infarction, PAD = Peripheral Artery Disease, PDC = Proportion of days covered, STEMI = ST-elevation myocardial infarction, y.o. = years old

Table 2 Outcomes of studies included in the analysis

Author/year	Adherence measure	Outcome measure	Results		Adjustment		
					Sex	Age	Other†
Simplification of drug regimen							
Rea et al. (2021)	Proportion of days covered	RR (95% CI)	Association between PDC > 75% and single-pill combination of statin and ezetimibe vs. two-pill or separate administration: 2.12 (1.89–2.38)		X	X	X
	Treatment discontinuation	RR (95% CI)	Association between single-pill vs. two-pill administration of a statin and ezetimibe and treatment discontinuation: 0.68 (0.63–0.74)				
Patient education and information							
Eussen et al. (2010)	Incidence of discontinuation	HR (95% CI)	> 65 years old: 0.903 (0.569–1.433)				
Qvist et al. (2020)	Proportion of days covered	% (95% CI)	6 months	Continuous: Intervention: 78.3%, Control: 71.4%, ($p = 0.04$) PDC ≥ 80%: Intervention: 63.2 (56.8–69.2) Control: 53.4 (46.5–60.2)			
			12 months	Continuous: Intervention: 75.1%, Control: 69.1%, ($p = 0.12$) PDC ≥ 80%: Intervention: 70.1 (63.9–75.7) Control: 63.2 (56.4–69.6)			
			60 months	Continuous: Intervention: 69.2%, Control: 65.7%, ($p = 0.34$) PDC ≥ 80%: Intervention: 57.6 (51.1–63.8) Control: 53.9 (47.0-60.7)			
		PD (95% CI)	6 months	Crude: 9.8 (0.5–19.0), $p = 0.04$ Adjusted: 10.1 (0.9–19.4), $p = 0.03$			X
			12 months	Crude: 6.9 (-2.0-15.8), $p = 0.13$ Adjusted: 7.1 (-1.7-16.0), $p = 0.11$			
			60 months	Crude: 3.7 (-5.7-13.0), $p = 0.44$ Adjusted: 4.0 (-5.3-13.3), $p = 0.4$			
Intensified patient care							
Casula et al. (2015)	Medication possession ratio	Difference (%)	65–79 years old: +6.3 (NR) post-intervention vs. pre-intervention ≥ 80 years old: +8.3 (NR) post-intervention vs. pre-intervention				

Table 2 (continued)

Author/year	Adherence measure	Outcome measure	Results		Adjustment		
					Sex	Age	Other†
Faridi et al. (2016)	Proportion of days covered	OR (95% CI) of PDC ≥ 80%	90 days	≤ 1 week: Reference 1-2 weeks: 0.95 (0.86-1.04), $p = 0.25$ 2-6 weeks: 0.98 (0.89-1.070), $p = 0.61$ > 6 weeks: 0.78 (0.70-0.87), $p < 0.001$	X	X	X
			1 year	≤ 1 week: Reference 1-2 weeks: 0.93 (0.83-1.05), $p = 0.25$ 2-6 weeks: 0.96 (0.86-1.07), $p = 0.43$ > 6 weeks: 0.78 (0.68-0.89), $p < 0.001$			
Guerard et al. (2018)	Proportion of days covered	IRR	65–80 years old: 1.013 (not significant)		X	X	X
Kooy et al. (2013)	Proportion of days covered	OR (95% CI) of PDC ≥ 80%	Card + Counseling	Crude: 1.22 (0.72–2.06), $p = 0.45$ Adjusted: 1.18 (0.69–2.01), $p = 0.55$			X
			Card only	Crude: 1.33 (0.76–2.32), $p = 0.55$ Adjusted: 1.49 (0.83–2.69), $p = 0.18$			
			Card only, Secondary prevention in women	Adjusted: 8.26 (2.20–31.0), $p = 0.002$			
Administrative improvements							
Ivers et al. (2013)	Proportion of days covered	N (%) of PDC > 80%	< 31 days	8962 (76.1%)	X	X	X
			31–60 days	887 (87.0%)			
			> 60 days	3019 (90.5%)			
		OR (95% CI) of PDC > 80%	< 31 days	1 (Reference)			
			31–60 days	2.0 (1.7–2.4)			
			> 60 days	3.0 (2.6–3.4)			
Lester et al. (2016)	Proportion of days covered	OR (95% CI) of PDC > 80%	1.51 (1.26–1.82)		X*	X	X
Schmittdiel et al. (2015)	Proportion of days covered	RR of PDC ≥ 80%	Mean days supply of drugs in therapeutic category	< 31: Reference 31–60: 1.11, $p < 0.001$ 61–90: 1.47, $p < 0.001$ > 90: 1.61, $p < 0.001$	X	X	X
			Mail order pharmacy	0%: Reference 1-50%: 1.01, $p > 0.05$ 51-100%: 1.07, $p < 0.001$			
			Generic drug copayment for 30-day supply	> 10$: Reference $0-$10: 1.02, $p < 0.01$			
			Annual individual out-of-pocket maximum	>$2000: Reference $0-$2000: 1.02, $p < 0.001$			
Large-scale pharmacy-led automated telephone intervention							

Table 2 (continued)

Author/year	Adherence measure	Outcome measure	Results		Adjustment		
					Sex	Age	Other†
Derose et al. (2013)	Proportion of dispensation	OR (95% CI)	> 70 years old: 2.32 (1.70–3.18)		X	X	X
Vollmer et al. (2014)	Proportion of days covered	PD (95% CI)	IVR + vs. UC	0.035 (0.012–0.058), $p = 0.003$	X	X	X
			IVR vs. UC	0.029 (0.006–0.051), $p = 0.013$			
			IVR + vs. IVR	0.006 (-0.017-0.029), $p = 0.606$			

RR = Risk Ratio, CI = Confidence interval, PDC = Proportion of days covered, HR = Hazard Ratio, PD = Proportion difference, NR = Not reported, OR = Odds Ratio, IRR = Incidence rate ratio, IVR + = Interactive voice recognition with a personalized reminder letter, UC = Usual care, IVR = Interactive voice recognition

*: This manuscript adjusted for gender and not sex

†: Additional covariates were adjusted for within these manuscripts; Examples include high blood pressure, diabetes and total number of medications taken by the patient

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