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## Original article

# Does a cardiovascular event change adherence to statin treatment in patients with type 2 diabetes? A matched cohort design

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Citation: Curr Med Res Opin 2015; 31:595–602**Abstract****Objective:**

To be effective, adherence to statin treatment is essential. We assessed the effect of an apparent first cardiovascular event on statin adherence rates in type 2 diabetes patients.

**Research design and methods:**

A matched cohort study was conducted among type 2 diabetes patients initiating statin treatment for primary prevention in the Groningen University IADB.nl pharmacy database. Patients who had a drug-treated cardiovascular event (index date) after statin initiation were matched to a reference patient without such an event with similar gender, age at statin initiation, initiation date, follow-up period and adherence level before the event. Adherence rates were measured as percentages of days covered (PDC), and shifts in adherence levels (non-adherent/partially adherent/fully adherent) and rates around the event were evaluated.

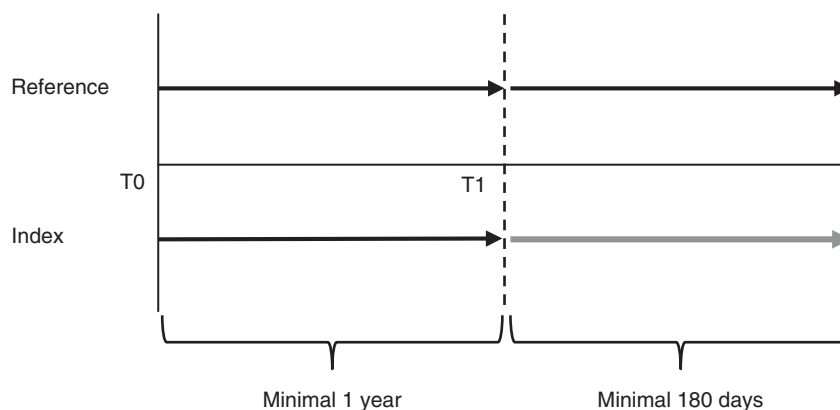
**Results:**We could match 375 of the 855 eligible index patients to a reference patient. Index patients had on average a PDC of 81% after the index date; reference patients had a PDC of 71% ( $p < 0.001$ ) while both had a PDC of 79% before the index date. Index patients were 4.5 times more likely than reference patients to shift from non-adherent to fully adherent (95% CI 1.1–18.8) and 1.8 times more likely to shift from partially adherent to fully adherent (95% CI 1.2–2.6). In the index group, 26% of patients became more adherent after the first cardiovascular event. In contrast, 20% of patients became less adherent.**Limitations:**

Medication proxies were used, which could have caused misclassification. Furthermore, a substantial group of index patients could not be matched to a reference patient due to small ranges in matching criteria.

**Conclusions:**

The occurrence of a drug-treated cardiovascular event appeared to avert the declining statin adherence rate observed in diabetes patients without such an event. On the other hand, one in five patients became less adherent after the event, indicating that there are still important benefits to achieve.

**Introduction**Cardiovascular disease<sup>1</sup> is one of the most common causes of death<sup>1</sup>. Diabetes patients are at increased risk for developing cardiovascular disease<sup>2</sup>. The use of statins is associated with a reduction in the risk of cardiovascular events in diabetes patients with and without previous cardiovascular events<sup>3,4</sup>.



**Figure 1.** Study design. Type 2 diabetes patients initiating statin treatment for a primary objective in both index and reference groups. Index group patients experience a cardiovascular event at T1, time between T0 and T1 should be at least 1 year, and follow up after T1 at least 180 days. Patients in the reference group are followed as long as their matched index patient, reference patients will not experience a cardiovascular event during follow up.

To be effective, however, patients need to adhere to the advised dose regimens. The high adherence rates accomplished in a clinical trial setting may in practice be much lower which reduces the health and economic impact of such preventive medication<sup>5</sup>. Having a cardiovascular history or a high risk for cardiovascular complications is associated with higher adherence rates than having no cardiovascular history or a low risk for cardiovascular complications<sup>6–9</sup>.

Despite this difference between statin adherence rates in primary and secondary prevention, not much is known about adherence patterns of patients who experience a first cardiovascular event while using statins. This occurrence is becoming more common since the population for primary prevention has been extended in most Western countries, but treatment cannot prevent cardiovascular events in all patients<sup>10,11</sup>. Poluzzi *et al.*<sup>12</sup> reported in a sub-analysis of a cohort study that 53% of the patients on statin treatment used more statins after they experienced a cardiovascular event, whereas 26% used the same and 21% used less than before the event. The finding that more patients increased their use might be expected as secondary prevention is associated with higher adherence rates. However, other investigators reported that the occurrence of a cardiovascular event during statin treatment was associated with lower adherence rates<sup>8,9</sup>. The perception that the drug had been ineffective was mentioned as a possible explanation. These three studies did not distinguish between a first or subsequent cardiovascular event, which might explain the disparate findings. None of the studies elucidate the effect of a first event on the adherence rate in primary prevention patients.

We designed a matched cohort study to assess the causal effects of the occurrence of a first drug-treated cardiovascular event on statin adherence rates in type 2 diabetes patients. This design was chosen to reduce the potential for confounding in cohort studies.

## Methods

### Study design

An index-reference matched cohort study was conducted among type 2 diabetes patients initiating statin treatment for primary prevention (Figure 1). Based on their medication, patients in the index group were identified as having experienced a cardiovascular event after initiating statin treatment, whereas the reference group consisted of patients who did not experience such an event after initiating statin treatment. Matching was done on potential confounders for the association between cardiovascular event and adherence rates (see *Study population*).

### Setting

This cohort study was performed with the University of Groningen IADB.nl pharmacy prescription database which contains prescription data from 1994 until 2011 and covers an estimated population of 500,000 persons in the Netherlands. Age, gender, and prescription rates among the database population have been found to be representative for the Netherlands as a whole, and the database is widely researched<sup>13–15</sup>. Each prescription record contains information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician, and the Anatomical Therapeutic Chemical code (ATC code)<sup>16</sup>. Each patient has a unique anonymous identifier; date of birth and gender are known. Due to the high patient-pharmacy commitment in the Netherlands, the medication records of each patient are virtually complete, except for over the counter (OTC) drugs and medication dispensed during hospitalization<sup>17</sup>. Data between January 2001 and December 2011 were used for the analyses.

According to the Code of Conduct for Health Research (Dutch FMWV Code approved by Dutch Data Protection

Authority in 2004), no ethics committee approval is needed for research using anonymous medical records that do not lead to questions from the point of view of privacy.

## Study population

Individuals initiating statin treatment (ATC codes C10AA, C10BA, C10BX) between 2001 and 2011 were selected from the IADB.nl database. Patients were only included in the study when they were present in the database for at least 1 year before initiation of statin treatment. Type 2 diabetes patients were selected by the use of two prescriptions of non-insulin blood-glucose lowering drugs (A10B)<sup>18</sup> within the time interval of 180 days before and 180 days after statin initiation. Patients on insulin monotherapy were not included, as they are mainly type 1 diabetes patients. This implies that around 6% of type 2 diabetes patients that are exclusively treated with insulin were excluded from the study<sup>19</sup>. Identification of primary prevention diabetes patients was done by the use of cardiovascular and cerebrovascular medication proxies (Appendix I)<sup>18</sup>. Diabetes patients who had received at least two prescriptions for vitamin K antagonists (B01AA) or thrombocyte aggregation inhibitors (B01AC) within the interval of 180 days before and 180 days after statin initiation were excluded, as they were considered to be secondary prevention patients. The occurrence of a first cardiovascular event (T1) at the index date was defined by start of medication with a high specificity and sensitivity for indicating such events, i.e. a treatment start for thrombocyte aggregation inhibitors ( $\geq 2$  prescriptions for B01AC within 1 year, see Appendix I). Reference patients did not start thrombocyte aggregation inhibitors but were allowed to use other cardiovascular medication. For calculating adherence rates, complete medication follow-up after the index date (T1) needed to last for at least 180 days. To enable a reliable calculation of adherence rate before the event, patients that shifted to secondary prevention within 1 year after statin initiation were excluded.

All index patients who started thrombocyte aggregation treatment were preliminary matched with potential reference patients on age at statin initiation ( $\pm 1$  year of age), gender, date of statin initiation (between  $-180$  and  $+180$  days), and follow-up period. By requiring a medication follow-up period for reference patients at least as long as their matched index patient we prevented so-called immortal time bias<sup>20</sup>. Next, the adherence level (see Adherence) was measured until the occurrence of the cardiovascular event for index patients, and for each reference patient the same follow-up period as the matched index patient (Figure 1). Subsequently, all index patients were

matched on all five criteria to one reference patient for the analysis.

## Adherence

All statin prescriptions (ATC codes C10AA, C10BA, C10BX) were identified. The expected duration of the prescription was estimated using the number of tablets dispensed and the prescribed number of tablets used per day. Patients were allowed to switch to another statin or another dosage. Adherence rates were measured as the percentages of pill days covered (PDC) which is calculated as the number of days the patient has drugs available divided by the number of days within the specific time period multiplied by 100<sup>21</sup>. Patients were classified into three groups: non-adherent (level 1:  $<20\%$  PDC), partially adherent (level 2:  $20\%$ – $80\%$  PDC), or fully adherent (level 3:  $>80\%$  PDC)<sup>5</sup>.

Adherence rates were calculated for two periods: (1) from initiation of statin treatment until the occurrence of a cardiovascular event for index patients (T0–T1), and for reference patients the same follow-up period as their matched index patient; (2) from the time of the occurrence of a cardiovascular event until the end of follow-up for index patients which is the last date the patient was active within the IADB.nl database. Again we assessed the adherence rates for reference patients over the same follow-up period as their matched index patient.

## Data analysis

Descriptive statistics were used to compare matched with unmatched index patients, and index with reference patients regarding baseline characteristics and duration of follow-up. Furthermore, index and reference patients were compared regarding their use of RAS inhibitors (C09), beta-blockers (C07A), calcium antagonists (C08) and nitrates (C01DA) within the interval of 90 days before and 90 days after the start of statin treatment (T0) and from the occurrence of the first cardiovascular event (T1) until 180 days after T1 using chi-square tests.

Adherence rates before and after the first cardiovascular event (T1) for reference and index patients were compared using Wilcoxon signed rank tests. The mean adherence rate of the index patients after the occurrence of a first cardiovascular event (T1) was compared with that of the reference patients for the same follow-up period as their matched index patient by the use of Mann–Whitney *U* tests. In addition, relative risks (RR) with 95% confidence interval (95% CI) of shifting to another adherence level after the event/index date (T1) were compared between the index and the reference group.

The number of patients who shifted to a higher or lower adherence rate or stayed within the same adherence range were calculated. A shift was defined as having an absolute

Table 1. Baseline characteristics of the index and reference patients.

	Total index group ( <i>n</i> = 855)	Unmatched index ( <i>n</i> = 480)	Matched index ( <i>n</i> = 375)	Reference ( <i>n</i> = 375)
Male, %	51	53	49	49
Age, mean (SD), years	63 (11.0)	63.6 (11.2)	62 (10.7)	62 (10.7)
Follow-up, years	6.7 (2.1)	7.3 (1.7)	5.8 (2.1)	5.8 (2.1)
Time until T1, years	3.4 (1.9)	3.6 (2.0)	3.0 (1.8)	
Time after T1, years	3.3 (2.1)	3.7 (2.2)	2.8 (1.8)	
Year of initiation, <i>n</i>				
2001–2005	629	413	216	225
2006–2010	226	67	159	150
Adherence level before index date				
1: Non-adherent ( $\leq 20\%$ ), % ( <i>n</i> , mean percentage of days covered)	11 (93, 7.1)	14 (68, 7.8)	7 (25, 5.2)	7 (25, 8.3)
2: Partially adherent (20–80%), % ( <i>n</i> , mean percentage of days covered)	25 (213, 53)	25 (120, 54)	25 (93, 52)	25 (93, 52)
3: Fully adherent ( $\geq 80\%$ ), % ( <i>n</i> , mean percentage of days covered)	64 (549, 96)	61 (292, 96)	69 (257, 96)	69 (257, 95)
Mean percentage of days covered (IQR)	75.5 (60.3–99.1)	72.8 (51.8–98.9)	79.0 (68.2–99.3)	79.0 (67.5–99.2)
Co-medication at initiation#:				
RAS inhibitors (C09)	45% (386)	45% (217)	45% (169)	42% (156)
Beta blockers (C07A)	23% (200)	23% (108)	25% (92)	21% (79)
Calcium antagonists (C08)	15% (125)	13% (62)	17% (63)	10% (39)*
Nitrates (C01DA)	2% (21)	2% (8)	3% (13)	1% (3)*
Co-medication at T1:≠				
RAS inhibitors (C09)	68% (581)	67% (322)	69% (259)	57% (212)*
Beta blockers (C07A)	57% (484)	56% (267)	58% (217)	26% (98)*
Calcium antagonists (C08)	27% (231)	27% (128)	27% (103)	15% (56)*
Nitrates (C01DA)	18% (158)	19% (91)	18% (67)	1% (2)*

IQR = interquartile range; T1: the occurrence of the first cardiovascular event of the index patients.

#At least one prescription between 90 days before and 90 days after statin initiation.

≠At least one prescription between T1 and 180 days after T1.

\**p*-Value <0.05; comparing matched index patients with reference patients.

difference of more than 10% PDC before and after the index date. Differences in shifts were compared between index and reference patients by the use of chi-square tests.

## Sensitivity analysis

The adherence rate before the event could have been underestimated when patients are hospitalized for a period of several weeks. In such cases, our proxy for a drug-treated event would lead to a misclassification regarding the date, where the actual event would have occurred earlier in time leading to unreliable adherence rate calculations before the event. Therefore, we performed a sensitivity analysis excluding patients that may have been hospitalized for a long period. Index patients and their matched reference patients that had no prescription in the period of 90 to 30 days before the event date were excluded, as an indicator for patients not active in the database due to a long period of hospitalization.

## Results

### Study population

We identified 855 index patients of whom 375 could be matched to one of the 5829 reference patients. Patient

characteristics of the matched and unmatched index patients and the reference patients are listed in Table 1. There were no substantial differences between the matched index patients and the unmatched index patients concerning age and gender distribution at baseline. Matched index patients were on average 62 years of age when initiating statin treatment and 49% were male. Within the reference group the use of calcium antagonists (chi-square test, *p*-value 0.01) and nitrates (chi-square test, *p*-value 0.01) around initiation of statin treatment was slightly higher compared to the matched index group. As expected, cardiovascular co-medication use was significantly higher in the index group than in the reference group after the occurrence of the first apparent cardiovascular event.

### Adherence rates

The mean PDC before the index date T1 was 79% for both the index group and the reference group (Mann–Whitney *U* test, *p*-value 0.92, Table 1). After the occurrence of an apparent event (T1), the mean PDC for the index group changed to 81% (Wilcoxon signed ranks test, *p*-value 0.032) and a decrease to 71% (Wilcoxon signed ranks test, *p*-value <0.001) was reported in the reference

**Table 2.** Adherence level after the index date for index and reference patients.

Adherence level after event/index date	Total index group ( <i>n</i> = 855)	Unmatched index ( <i>n</i> = 480)	Matched index ( <i>n</i> = 375)	Reference ( <i>n</i> = 375)
1: Non-adherent ( $\leq 20\%$ ) %, ( <i>n</i> , mean percentage of days covered)	11 (96, 3.7)	12 (58, 2.7)	10 (38, 5)	18 (66, 2.6)
2: Partially adherent (20–80%) %, ( <i>n</i> , mean percentage of days covered)	17 (144, 57)	16 (77, 58)	18 (67, 56)	19 (72, 53)
3: Fully adherent ( $\geq 80\%$ ) %, ( <i>n</i> , mean percentage of days covered)	72 (615, 97)	72 (345, 97)	72 (270, 98)	63 (237, 96)
Mean percentage of days covered (IQR)	80 (75.2–100)	79 (75.3–100)	81 (72.0–100)	71 (49–100)

IQR = interquartile range.

**Table 3.** The relative risk (RR) and 95% confidence interval (CI) of shifting from one adherence level to another.

Level before T1	Level after T1	Index ( <i>n</i> )	Reference ( <i>n</i> )	RR	CI (95%)
<b>Non-adherent</b>	<b>Non-adherent</b>	<b>7</b>	<b>16</b>	<b>0.44</b>	<b>0.22–0.88</b>
Non-adherent	Partially adherent	9	7	1.29	0.57–2.90
<b>Non-adherent</b>	<b>Fully adherent</b>	<b>9</b>	<b>2</b>	<b>4.50</b>	<b>1.08–18.77</b>
<b>Partially adherent</b>	<b>Non-adherent</b>	<b>21</b>	<b>39</b>	<b>0.54</b>	<b>0.34–0.84</b>
Partially adherent	Partially adherent	24	27	0.89	0.56–1.42
<b>Partially adherent</b>	<b>Fully adherent</b>	<b>48</b>	<b>27</b>	<b>1.78</b>	<b>1.22–2.58</b>
Fully adherent	Non-adherent	10	11	0.91	0.44–2.27
Fully adherent	Partially adherent	34	38	0.89	0.58–1.37
Fully adherent	Fully adherent	213	208	1.01	0.94–1.09

T1: the occurrence of the first cardiovascular events of the index patients.

group (Table 2). There was a significant difference between reference and index patients after T1 (Mann–Whitney *U* test, *p*-value < 0.001).

## Adherence shifts

Shifts in adherence levels before and after the index date T1 with the relative risks and 95% CIs are shown in Table 3. Index patients were more likely to become fully adherent after the occurrence of a cardiovascular event (T1) compared to their reference patients. The relative risk of shifting from being non-adherent (level 1) to fully adherent (level 3) was 4.5 (95% CI 1.1–18.8), and from partially adherent (level 2) to fully adherent (level 3) was 1.8 (95% CI 1.2–2.6) for the index group. Reference patients were more likely to become non-adherent (level 1) after the index date (T1). The relative risk of remaining non-adherent (level 1) was 0.4 (95% CI 0.2–0.9), and the shift from partially adherent (level 2) to non-adherent (level 1) was 0.5 (95% CI 0.3–0.8) for the index group.

When analyzing the absolute PDC adherence rates, 53% (*n* = 200) of the index patients and 54% (*n* = 203) of the reference patients had a similar adherence rate, i.e. 10% or less PDC difference, before and after the index date. Index patients shifted more often to a higher PDC adherence rate (26%, *n* = 97), whereas reference patients shifted more often to a lower adherence rate (30%, *n* = 111) (chi-square tests; *p*-value < 0.05).

Since the partial adherence level has a wide range in PDC (20–80%), we explored whether the distributions within this partial adherence group differed between the index and reference group before the index date (T1), which showed no significant difference (Mann–Whitney *U* test, *p*-value 0.89).

## Sensitivity analysis

Of the index patients, 34 did not have a prescription in the period 90 to 30 days before the event date. After exclusion of these patients and their matched reference patients, the mean PDC was 80% before the event and 81% after the event for the index patients. For reference patients, the PDC was 79% before the event and 72% after the event. Index patients were more likely to shift from non-adherent to fully adherent (RR 1.4; 95% CI 1.0–2.0) and to shift from partially adherent to fully adherent (RR 1.4; 95% CI 1.1–1.8). Reference patients were more likely to stay non-adherent (RR 0.5; 95% CI 0.3–1.0) and to shift from partially adherent to non-adherent (RR 0.8; 95% CI 0.6–1.0). Twenty percent of the patients decreased their use after the event.

## Discussion

This matched cohort study showed that the mean statin treatment adherence rate of type 2 diabetes patients before

and after a drug-treated cardiovascular event had a small increase in adherence, while among reference patients statin treatment adherence rates declined. Index patients had an average adherence rate of 81% after the occurrence of an apparent cardiovascular event (T1), whereas reference patients had a mean adherence rate of 71% when considering the same follow-up period, while both had mean adherence rates of 79% before the index date (T1). Index patients were more likely to shift from being non-adherent or partially adherent to fully adherent, whereas reference patients were more likely to stay non-adherent or to shift from being partially adherent to non-adherent. Still, 20% of the index patients became less adherent after the occurrence of a first event.

Our results show that a drug-treated cardiovascular event averts the decline in adherence rates for statins seen in patients without such an event. The finding that there were more patients that increased than decreased in their adherence to treatment after an event was in line with previous results from Poluzzi *et al.*<sup>12</sup>. This previous study did not focus on diabetic patients and reported that most patients increased statin adherence after the occurrence of a cardiovascular event, whereas in our study most patients did not change their adherence. This difference could be the result of also including very small changes in the adherence calculation before and after the event as a decrease or increase in adherence in the previous study, whereas our criteria of change were based on an absolute change in PDC of more than 10%. Other investigators<sup>8,9</sup> did not adjust for adherence rates before the event which could lead to confounding by indication. Also, previous studies did not distinguish between first or subsequent cardiovascular events and included both patients in primary and secondary prevention. Thus, it may be that adherence to statin treatment does not decrease after a first event – as shown in our study – but may decrease after subsequent cardiovascular events.

The percentage of patients becoming less adherent after an event in our study was around 20%, similar to that found in a previous study<sup>12</sup>. This amount of patients is lower than for patients who did not experience an event but is still a matter of concern. Our finding that 10% of patients had an adherence rate of less than 20% PDC after an event is especially worrying. This suggests that patients might discontinue treatment after a cardiovascular event, which has been shown to increase mortality rates<sup>22</sup>. To address this problem better in clinical practice, the underlying reasons for this phenomenon need to be studied. Furthermore, it is important to look at whether similar patterns of non-adherence are seen for other medications. What becomes clear from our study is that we should tailor the approach to managing individual patients after a cardiovascular event. We cannot assume that all patients will be motivated to keep using their statin treatment after

such an event. This is important as these patients are at increased risk<sup>23</sup>.

A strength of our study is that we analyzed the effect of the transition from primary to secondary prevention on statin treatment adherence. This transition is important because of the difference between adherence rates in primary and secondary prevention patients. We adjusted for possible bias and confounding by indication, and corrected for immortal time bias by requiring a follow-up period for reference patients to be as long as their matched index patient<sup>20</sup>. Furthermore, adherence rates in our study were not affected by increased medication costs for patients after a cardiovascular event, since drug costs are fully reimbursed in the Netherlands, as is not the case in many other healthcare systems where patients are confronted with co-payments<sup>8</sup>.

The fact that we had to use medication proxies to identify cardiovascular events is a clear limitation to our study. Nevertheless, the use of medication proxies to identify patients with specific diseases or events is common when reliable diagnostic coding is lacking<sup>7,24</sup>. We tested the medication proxies for sensitivity and specificity; however, misclassification could have occurred. Such misclassification would lead to underestimating the impact of the event on the adherence rates and biased the effects towards the null. Further, type 2 diabetes was identified by the use of oral anti-diabetic medication. Patients exclusively treated with insulin were thereby excluded, which might have resulted in excluding some of the more severe cases. Patients using oral anti-diabetic medication for other indications could not be excluded. As the use of medication proxies could have caused some misclassification, we suggest for future research to conduct the analysis linking event data with diagnostic codes to pharmacy dispensing records which would probably result in stronger associations.

Furthermore, we were not able to include data on medication dispensed during hospitalization which could have caused underestimation in our adherence rate calculations in the index group. Excluding patients that appeared not to be active in our database, possibly due to a long period of hospitalization, indeed decreased the point estimate as well as the confidence intervals for the relative risks of shifting to higher adherence levels. However, it did not lead to relevant changes in adherence rates nor in the direction or significance of our findings. Another matter of possible concern is that a substantial group of index patients could not be matched to a reference patient due to the small ranges in our matching criteria. Determining these ranges is balancing between the inclusion of more patients on the one hand and introducing more bias on the other hand. The use of strict matching criteria is preferred to prevent the introduction of bias due to poor matching. Matched and unmatched index patients were relatively similar in terms of age, gender, co-medication use and

adherence levels after the index date. Finally, we did not differentiate between non-adherence and non-persistence, which were both included in the calculation of the adherence level. For the purpose of our study there is no need to distinguish between these two types of non-adherence, since we aim at comparing statin drug-taking behavior over the entire follow-up period.

## Conclusion

In type 2 diabetes patients the occurrence of a drug-treated cardiovascular event during statin treatment is likely to avert the decline in adherence observed in patients without such an event. Since one in five of the patients with an event became less adherent, there are still important health and economic benefits to achieve by tailoring the pharmaceutical management of individual patients.

## Transparency

### Declaration of funding

No sources of funding were used to assist in the preparation of this study.

### Declaration of financial/other relationships

F.M.d.V., P.D., H.J.B. and E.H. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. S.V. has disclosed that he is owner of Vegter Health Economic Research and became an employee of GSK after completion of this study. M.J.P. has disclosed that he received grants, honoraria and travel stipends from various pharmaceutical industries, including those potentially interested in the subject matter of this paper.

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