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ASSESSMENT OF NEW CARDIOVASCULAR DRUGS

Relationships Between Considerations, Professional Characteristics, and Prescribing

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Abstract

Objectives: To study considerations used by professional and academic leaders to assess the position of new cardiovascular drugs in the therapeutic regimen in relationship to professional characteristics and the level of prescribing.
Methods: Interviews with 39 internists, cardiologists, general practitioners, and hospital pharmacists about considerations regarding the therapeutic position and prescribing of a new cardiovascular drug (losartan or atorvastatin) and professional characteristics. Considerations were classified according to Rogers' characteristics of an innovation, i.e., referring to the drug's relative advantage, compatibility, or complexity. Proportions of respondents mentioning advantageous, comparable, and/or disadvantageous characteristics were used to construct patterns to analyze an overall evaluation of the drugs in relation to professional characteristics and level of prescribing.
Results: The majority of considerations referred to the degree of relative advantage, but different subjects were emphasized for both drugs. Overall patterns of evaluation were generally intermediate and negative. The respondents' profession, mentioning commercial sources of information and self-qualification as a (moderately) early adopter of new drugs differentiated the overall evaluation of the drugs, in contrast to expertness and academic affiliation. The level of prescribing differentiated the overall evaluation only in the case of losartan.
Conclusions: These professional and academic leaders critically evaluated the claims when assessing the position of the drugs in the therapeutic regimen but did not show consensus in their considerations. Accepted principles for prescribing were considered when assessing the therapeutic position of the drugs but resulted in varied tendencies for prescribing.

Keywords: Diffusion of innovation, Cardiovascular drugs, Professional practice, Case study, Qualitative evaluation

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Although there are many highly effective drugs nowadays, there is still much room for improvement. New drugs often claim to be such an improvement. A central theme in the adoption of new drugs in medical practice is the assessment of their position in the therapeutic regimen. It can be argued that a truly innovative drug will be recognized and adopted in medical practice just because of its objective benefits. However, numerous reports show inadequate use of these innovations, for instance, of cardiovascular drugs (6;12).

There is large variation in the prescribing of newly marketed drugs (14). In general, the adoption of new drugs depends on characteristics of the prescribers, their professional network, and the drug itself (19). With respect to characteristics of the prescribers, it has been assumed that there are early and late adopters, but this was not fully confirmed by research findings. It seems a more constant doctor characteristic to be a late adopter than being an early adopter (20). Medical leaders learn about new drugs in advance of their colleagues, often well before marketing approval, but there is no evidence that they prescribe new drugs earlier than their colleagues (18). Professional sources of information are considered very important to learn about new drugs, but commercial sources may be important for drugs that are not central to the doctor's specialty (17;18). Theories of diffusion of innovations and behavioral change suggest that opinion leaders could play an important role as a source of information in the professional network to transmit norms and model behavior to their peers (15;19). While the influence of local opinion leaders seems to be limited, the impact of professional or academic leaders has not been sufficiently studied (22).

New drugs can be classified as innovative, semi-innovative, or me-too drugs, the latter class forming the largest group (9). The adoption curves of innovative and me-too drugs in general practice differ, but interestingly, drugs that are not considered to be innovative may still reach high diffusion curves (20). Commercial influence through participation in clinical testing of new drugs was found to lower barriers for the adoption of semi-innovative drugs in hospitals (7). In general, the evaluation of a drug as an advance in treatment was not found to be an essential component of the adoption process (18).

The present study departs from these observations. The characteristics of a drug in itself do not seem to explain why some are widely adopted in practice, but no studies have looked at differences in considerations used by professionals to determine the position of a new drug and which may account for differences in patterns of diffusion. Therefore, we performed a case study to examine which considerations are taken into account by professional or academic opinion leaders when evaluating the position of a new drug (8). Two recently marketed cardiovascular drugs were selected as cases for this study. Qualitative analysis was performed regarding the nature of considerations used to determine the position of the drugs in the therapeutic regimen. Quantitative methods were used to study the relationships between considerations, characteristics of the professional or academic opinion leaders, and the level of adoption of the drug.

METHODS

Data Collection

Selection of Respondents. During the period from November 1998 to June 1999, interviews were held with 32 physicians and 10 hospital pharmacists in the context of a larger research project about the generalizability of premarketing data to medical practice. Selection criteria for the interviewees included involvement in the development of national, regional, or local treatment guidelines or formularies, and/or in clinical research, specifically in the cardiovascular field. Specialists in internal medicine (internists), cardiologists, and general practitioners (GPs) were identified through key informants and publications,

including commentaries on treatment guidelines. The pharmacists were selected from the same hospitals as the specialists, which included six academic teaching hospitals and four regional hospitals throughout the Netherlands.

A total number of 45 persons were asked to participate, of whom an internist, a cardiologist, and a GP refused because of time constraints. Five respondents (one cardiologist, two internists, and two GPs) were not involved in patient care. During the interviews it appeared that one of these GPs as well as two hospital pharmacists were not familiar enough with either one of the selected drugs to reflect on their position in the therapeutic regimen. As a result, these respondents were excluded, and the present paper is based on the outcomes of 39 interviews. Sixteen specialists, four GPs, and four pharmacists worked in academic teaching hospitals, six specialists and four pharmacists in nonteaching hospitals, and five GPs in primary care. One of the physicians and three pharmacists were female. The mean age of the physicians was 51 (range, 37–62) and of the pharmacists, 42 years (range, 32–51).

Selection of Drugs. The cardiovascular drugs selected for the case study were losartan (Cozaar®) and atorvastatin (Lipitor®). Selection criteria included: a) recently marketed drugs; b) innovative properties according to the manufacturer of the drug; and c) drugs likely to be prescribed by different specialists, as well as in primary and secondary care.

The chosen drugs can both be classified as semi-innovative (9), but represent different types of innovations. Losartan was the first representative of a new class of antihypertensives, the angiotensin-II antagonists. It has been claimed that losartan causes fewer side effects than the other antihypertensives acting on the renin-angiotensin system, the angiotensin-converting enzyme (ACE) inhibitors (13;26). Losartan was introduced to the Dutch market in March 1996. At the start of our study in November 1998, another four angiotensin-II antagonists had been marketed. Atorvastatin was marketed in the Netherlands in April 1997 as the fourth cholesterol-lowering drug from the class of HMG-CoA reductase inhibitors. It was claimed to be an improvement over the other products in its class, because of a stronger lipid-lowering effect, in particular on triglycerides (3;11). Atorvastatin was the first product of its class to be registered for hypertriglyceridemia, additionally to hypercholesterolemia. Healthcare insurance companies approved both drugs for reimbursement. Dispensing data from community pharmacies in the Netherlands showed that in 1999, 62% of prescriptions for an angiotensin-II antagonist were losartan, and 23% of prescriptions for HMG-CoA reductase inhibitors were atorvastatin (personal communication with J. L. Tinke, Foundation for Pharmaceutical Studies, The Netherlands, June 2000).

Interview Procedure. All interviews were conducted by the same interviewer (NW) at the offices of the respondents and varied in duration between 45 and 90 minutes. One of either drugs, losartan or atorvastatin, was used in each interview. If the interviewer knew that a respondent was an expert in the field of hypertension or hypercholesterolemia, the matching drug was chosen, i.e., losartan for experts in hypertension and atorvastatin for experts in hypercholesterolemia. Otherwise, the drugs were randomly assigned within the groups of internists, cardiologists, GPs, and hospital pharmacists.

The semi-structured interview schedule started with open questions regarding the frequency of prescribing losartan or atorvastatin, considerations about their position in the therapeutic regimen, and important sources of information to learn about the drugs, continued with questions not relevant for the present paper, and ended with questions regarding the respondents' professional affiliation and characteristics. The interviews were audiotaped and typed verbatim. The recording of two interviews failed, and for these cases notes were taken directly after the interviews.

Methods of Analysis

Qualitative Analysis of Considerations. All verbatim reports and, for two interviews the case notes, were segmented and statements were coded by the principal researcher (NW). To test the validity of this coding system, two experienced researchers in the field of social pharmacy each double-coded two interviews. Regarding the interview segments that were assigned with a code, the interrater agreement with the principal investigator, calculated as Cohen's kappa, varied between 0.6 and 0.8, indicating a moderate to good level of agreement (1). The principal investigator, however, had assigned codes to more segments of the texts. After reaching agreement on the discrepancies and further refinement of the classification scheme, the principal investigator checked all interviews to obtain consequent coding.

Considerations used for the assessment of the position of losartan and atorvastatin in the therapeutic regimen were classified according to Rogers' characteristics of an innovation (19).

Relative advantage:

- Therapeutic considerations indicating that the drug is perceived as advantageous, comparable, or disadvantageous in comparison to other drugs. The following categories were identified: efficacy, side effects, research with the drug, level of experience with the drug, and miscellaneous;
- Economic considerations, i.e., whether the drug is cheaper or more expensive than others;
- Observations referring to the marketing of the drug;
- Convenience, such as the inclusion of the drug into the hospital formulary, so that frequent consultations in order to change prescriptions can be avoided; and
- Patient (dis)satisfaction.

Compatibility:

- Perception of the drug as being (in)consistent with existing values reflecting general principles of prescribing;
- Considerations in view of past experiences, either positive or negative, in prescribing new drugs; and
- Perception of the drug as meeting therapeutic needs or problems.

Complexity:

- Perception of the drug as being complex or difficult to understand and use.

Quantitative Analysis of Considerations, Professional Characteristics, and Level of Adoption. The group of respondents was classified according to the presence or absence of each of six professional characteristics: a) profession; b) involvement in the development of national treatment recommendations, including professional guidelines for primary or secondary care, the Dutch Drug Bulletin, or the Pharmacotherapeutic Compass, an annually published reference book; c) self-reported qualification as expert in hypertension or hypercholesterolemia; d) qualification of the pharmaceutical industry as an important source of information to learn about losartan and atorvastatin; e) self-reported qualification as (moderately) early or late adopter of new drugs; and f) academic or nonacademic affiliation.

The level of adoption of losartan and atorvastatin by the physicians was classified according to the self-reported frequency of prescribing. Prescribing was defined as initiation of new prescriptions, and therefore excluded the continuation of repeat prescriptions initiated by other physicians. Physicians used various descriptions to indicate their frequency of

prescribing. These descriptions were categorized as never prescribing the drug, occasionally (rarely, seldom), or frequently (for example, to 10% or one-third of the patients).

To study the relationship between considerations regarding the drugs, professional characteristics, and the level of adoption, overall patterns were constructed of the advantageous, comparable, and/or disadvantageous therapeutic considerations attributed to the drugs. For each subgroup with a specific professional characteristic and level of adoption, proportions of respondents were calculated, mentioning therapeutic considerations as advantageous, comparable, and/or disadvantageous. Respondents contributed to the calculation of proportions for each different type of considerations they had mentioned. Subsequently, for each professional characteristic and for each level of adoption, a pattern was constructed according to these proportions. Eight basic patterns of proportions could be distinguished (Figure 1). The patterns that were found in the results were classified according to these basic patterns and interpreted as an overall positive, intermediate, or negative evaluation of the drug:

- Three levels of positive evaluation (+++ through + in Figure 1), i.e., the proportion of advantageous considerations is (much) larger than the proportion of disadvantageous considerations, with varying proportions of comparable considerations;
- Intermediate evaluations (both +/− patterns in Figure 1), i.e., the proportions of comparable considerations are much larger than those of the advantageous and disadvantageous considerations, or the proportions of the different types of considerations are equal; and
- Three levels of negative evaluation (− through − − − in Figure 1), i.e., the proportion of disadvantageous considerations is (much) larger than the proportion of advantageous considerations, with varying proportions of comparable considerations.

RESULTS

Considerations Regarding the Drugs

Twenty-one interviews involved losartan and 18 involved atorvastatin. The considerations mentioned by the respondents to assess the position of losartan and atorvastatin in the therapeutic regimen are shown in Table 1. For both drugs, the majority of considerations referred to the perceived relative (dis)advantage.

Losartan was compared with ACE inhibitors, with newer angiotensin-II antagonists, and in general with antihypertensives included in treatment guidelines. Regarding side effects, comparisons were only made with ACE inhibitors. Several respondents mentioned the absence of cough as an advantage of losartan as compared with ACE inhibitors, but others stated that losartan appeared to be comparable to ACE inhibitors in this aspect. Respondents who expressed disadvantages regarding side effects mentioned there was still much uncertainty and that patients had been switched because of side effects of losartan. Advantages regarding experience specifically referred to the fact that losartan was the first product in its class that had been used more frequently in comparison with the newer angiotensin-II antagonists. The majority of miscellaneous considerations referred to whether losartan was perceived as first-choice drug. The other topics indicating a relative advantage referred to the convenience for hospital pharmacists to include losartan in the hospital formulary in order to avoid consultations to change prescriptions, patient satisfaction, and good marketing strategies.

The efficacy of atorvastatin was perceived as advantageous or comparable to other products, in particular to simvastatin. Some respondents mentioned its efficacy in lowering triglycerides as an advantage, but others stated that this effect was not specific for atorvastatin. The majority of respondents who stated that atorvastatin was comparable to other cholesterol-lowering products referred to class effects in efficacy and long-term

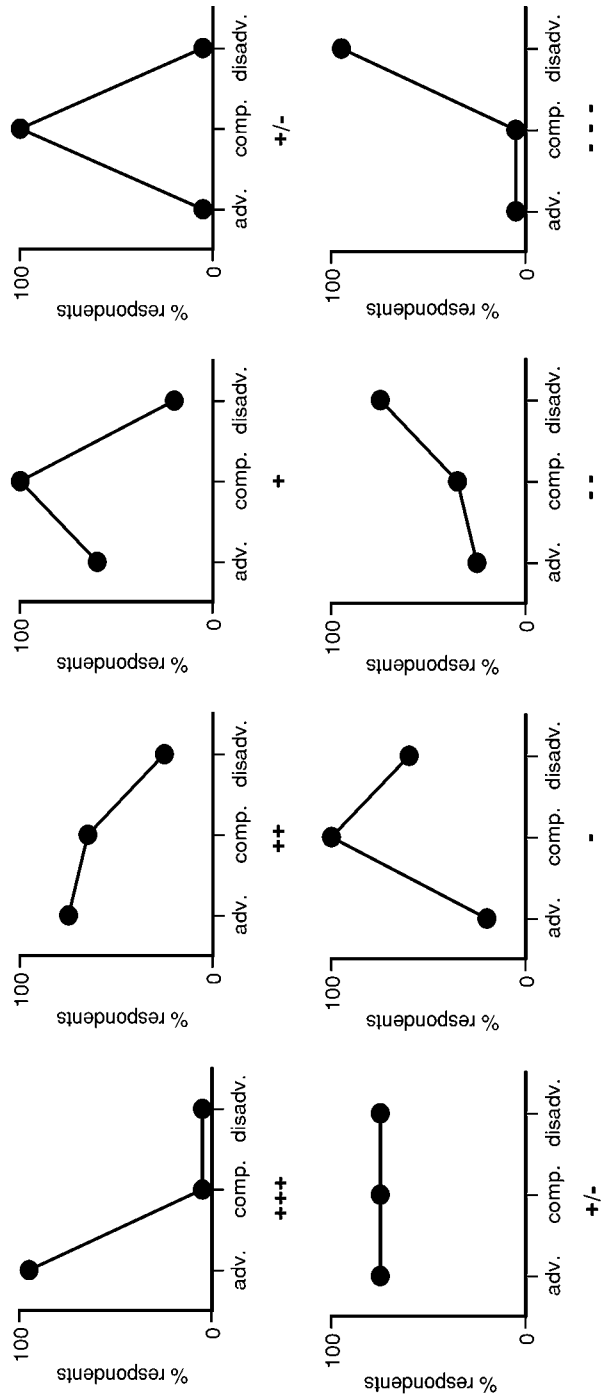

Figure 1. Basic patterns used to interpret the results of the respondents. Patterns were distinguished as an overall positive (+ + + through +), intermediate (both +/− patterns), or negative (− through − − −) evaluation of the drugs. Abbreviations: adv.–advantageous; comp.–comparable; disadv.–disadvantageous.

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Table 1. Considerations Used to Assess the Position of Losartan and Atorvastatin in the Therapeutic Regimen

	Losartan (n = 21)[a]	Atorvastatin (n = 18)[a]
Degree of relative advantage		
Efficacy:		
Advantageous	1	11
Comparable	5	15
Disadvantageous	9	5
Side effects:		
Advantageous	6	3
Comparable	3	4
Disadvantageous	2	2
Research:		
Advantageous	—	2
Comparable	2	—
Disadvantageous	1	6
Experience:		
Advantageous	2	—
Comparable	—	—
Disadvantageous	4	3
Miscellaneous:		
Advantageous	4	1
Comparable	5	2
Disadvantageous	7	3
Convenience	3	5
Satisfaction	2	6
Economic considerations	—	4
Good marketing	2	5
Degree of compatibility		
Existing values	12	19
Previous practice	5	—
Felt needs	—	5
Degree of complexity	5	—
Total	80	101

[a] The total number of respondents who were interviewed about the drugs.

effectiveness. With respect to side effects, atorvastatin was qualified as advantageous to other products by some respondents, whereas others said it was comparable, or doubted that safety issues had been fully resolved. Several respondents mentioned that certain claims of atorvastatin, such as its effect on the endothelial function or its efficacy relative to other drugs, had not been sufficiently studied. The majority of miscellaneous considerations referred to whether atorvastatin was perceived as a first-choice drug. The other topics indicating a relative advantage included the convenience to patients of the once-daily dosing schedule, inclusion of atorvastatin in the hospital formulary, patient satisfaction, lower costs, and the good marketing strategy for atorvastatin.

A relatively large number of respondents, including all professional groups, took into consideration that prescribing losartan or atorvastatin was not compatible with existing values (Table 1). They preferred the use of drugs with proven long-term effectiveness and those included in treatment guidelines. All considerations regarding existing values therefore expressed a negative implication. The other characteristics regarding the degree of compatibility differed in nature between losartan and atorvastatin. Respondents to losartan referred to negative experiences with drugs that were withdrawn from the market because of serious side effects, and felt comfortable with the habit of being a conservative prescriber.

Atorvastatin was considered a drug that meets therapeutic needs in specific situations where other products were inadequate.

Considerations indicating the degree of complexity were only made when talking about losartan. They referred to uncertainty about when to prescribe a new drug such as losartan in terms of unresolved issues in pharmacologic concepts, the complexity of the therapeutic evidence, and the need to critically evaluate the evidence of new drugs such as losartan.

Level of Adoption and Professional Characteristics

Five of the 27 prescribing physicians reported that they did not initiate new prescriptions for losartan or atorvastatin. At the time of data collection, losartan was registered in the Netherlands only for the treatment of hypertension, but some cardiologists reported off-label prescribing to patients with heart failure.

None of the GPs reported prescribing the drugs frequently, in contrast to 11 of 19 specialists. Physicians who said they prescribed losartan or atorvastatin never or occasionally were more likely to be involved in developing national treatment guidelines than those who said they prescribed the drugs frequently. Frequent prescribers more often mentioned the pharmaceutical industry as an important source of information and were more often early or moderately early adopters.

Patterns of Considerations, Professional Characteristics, and Level of Adoption

Figure 2 shows an example of the patterns that were obtained from the proportions of respondents, in this case referring to the self-reported qualification as (moderately) early or late adopter of new drugs, who mentioned advantageous, comparable, and/or disadvantageous considerations about losartan or atorvastatin.

For both drugs, the emphasis was on an intermediate or negative evaluation (Table 2). The internists and pharmacists were more positive than the cardiologists and GPs. In most cases, atorvastatin received a higher evaluation than losartan. Only respondents who were not involved in the development of national treatment guidelines, those who mentioned the industry as an important source of information, and those who qualified themselves as early or moderately early adopters attributed more positive considerations to losartan.

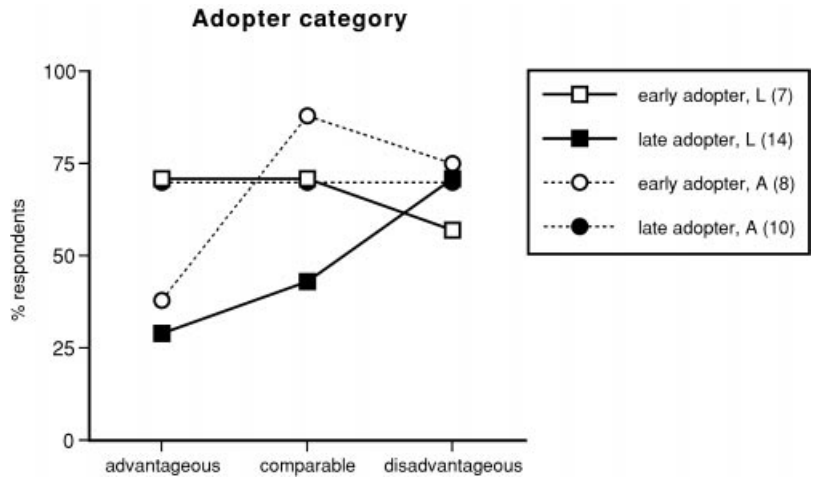

Figure 2. Example of pattern of proportions of respondents who mentioned different types of considerations regarding losartan (L) and atorvastatin (A). Respondents were classified as early (i.e., moderately early + early) or late adopters. Numbers in parentheses are the number of respondents with the specified professional characteristic.

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Table 2. Overall Patterns of Considerations of Losartan (L) and Atorvastatin (A) by Professional Characteristic

		Positive			Intermediate		Negative	
		+++	++	+	+/−	−	−−	−−−
Internists			A (5)				L (7)	
Cardiologists							L (5), A (5)	
GPs							A (4), L (5)	
Pharmacists				A (4)			L (4)	
Involvement in guidelines	Yes					A (8)	L (8)	
	No					L (13)	A (10)	
Expert	Yes						A (8), L (6)	
	No						L (15), A (10)	
Industry for information	Yes			L (6)		A (6)		
	No						A (12), L (15)	
Adopter category	Early		L (7)				A (8)	
	Late					A (10)	L (14)	
Affiliation	Academic						L (12), A (11)	
	Nonacademic						A (7), L (9)	

See the Methods of Analysis section for a description of the professional characteristics.
Numbers in parentheses are the number of respondents in each group.

Table 3. Relationship Between Frequency of Prescribing by 27 Physicians and Patterns of Considerations Regarding Losartan (L) and Atorvastatin (A).

	Positive			Intermediate	Negative		
	+++	++	+	+/−	−	−−	−−−
Frequent prescriber				A (8)	L (3)		
Occasional prescriber				A (2)		L (9)	
Nonprescriber				A (3)			L (2)

Numbers in parentheses are the number of respondents in each group.

Physicians frequently prescribing atorvastatin did not differ from the occasional or nonprescribers with respect to their overall considerations of atorvastatin (Table 3). Regarding losartan, the frequent prescribers were less negative about it than the occasional or nonprescribers.

The nonprescribers differed from the prescribers by mentioning a smaller number of relative advantages of the drugs. Furthermore, they all referred to existing values by preferring to prescribe drugs with proven long-term efficacy and those included in treatment guidelines. The majority of frequent prescribers did not mention these preferences.

DISCUSSION

This case study focuses on an important step in the diffusion process of new drugs, the considerations of professional and academic leaders used for the assessment of a drug's therapeutic value in the regimen.

The professional and academic opinion leaders who were interviewed showed different patterns in their assessment of the therapeutic value of losartan and atorvastatin. The overall evaluation of atorvastatin was more positive than was the case for losartan. The efficacy of atorvastatin was predominantly considered as advantageous or comparable, whereas the efficacy of losartan was considered disadvantageous to competing drugs. Losartan only scored more positively on side effects. Therefore, many considerations used to assess the

position of both drugs in the therapeutic regimen focused on the claims that were made during marketing, i.e., fewer side effects when using losartan, and higher efficacy with atorvastatin. In both cases, however, there were respondents who positively acknowledged these claims, whereas others were not convinced by the claims or disagreed. The professional and academic opinion leaders who were selected for this study therefore did not show a consensus when evaluating the drugs.

A number of professional characteristics differentiated in the overall evaluation of losartan and atorvastatin. Internists and pharmacists were more positive about both drugs, specifically atorvastatin, than the cardiologists and GPs. In contrast, expertness and (non)academic affiliation differentiated minimally in the overall evaluation of the drugs. A number of characteristics differentiated more in the case of losartan than atorvastatin. Respondents who used the pharmaceutical industry as an important source of information and those who qualified themselves as early or moderately early adopters of new drugs were more positive in their evaluation of losartan. These findings suggest that the evaluation of a drug with fewer perceived advantages, such as losartan as compared with atorvastatin, is more likely to be influenced by commercial sources of information.

In terms of prescribing, the adoption of losartan and atorvastatin also differs. A larger number of physicians said they prescribed atorvastatin frequently, as compared with losartan. None of the GPs said they prescribed either of the drugs frequently, which corresponds to other studies showing that GPs generally have stable and conservative prescribing habits (2;21). Physicians who prescrided the drugs frequently were characterized as attaching more importance to commercial sources of information and as early or moderately early adopters, whereas the occasional and nonprescribers are characterized by their involvement in national guideline development.

Prescribing new drugs poses a problem from the viewpoint of practicing evidence-based medicine. There is limited information available from clinical trials, which are performed in selected populations and may have a low applicability to patients in daily practice (10;16;24;25). Specifically, GPs are recommended to limit the prescribing of new drugs until postmarketing data have accumulated and there is evidence of clinical effectiveness from large-scale trials (14). Our data show that the majority of the interviewed professional and academic leaders referred to considerations in favor of evidence-based medicine when assessing the position of losartan and atorvastatin in the therapeutic regimen. However, only a small number of prescribing physicians applied this standard to its full extent in the decision not to prescribe losartan or atorvastatin.

The results of this study should be interpreted in light of its limitations. First, the results should merely be interpreted in terms of a qualitative generalization regarding the nature of relationships, and not in a quantitative manner (8). Second, we questioned specialists and GPs about their prescribing of losartan and atorvastatin and did not check these data with their actual prescribing behavior. During the interviews the respondents were not reluctant to talk about their frequency of prescribing and many elucidated their answers with reasons for this behavior. Therefore, we do not think respondents were wrongfully classified as prescribers or nonprescribers. However, because of the difficulties to accurately estimate one's own behavior in percentages, we limited the analysis to an ordinal classification of prescribing frequency. A third point to consider is that we selected professional and academic opinion leaders in the cardiovascular field who were involved in the assessment of the position of new drugs through activities such as the development of treatment guidelines or clinical research. They are likely to be more aware of the contents of discussions about new drugs in their field of interest than other physicians and therefore may use different considerations in the therapeutic assessment of new drugs. Finally, we used an antihypertensive and a cholesterol-lowering drug as examples in this study, both of which are used in the prevention of cardiovascular events. The diffusion

of such drugs, in terms of their evaluation and prescribing, may differ from that of drugs used in the treatment of symptoms of cardiovascular diseases. Therefore, it is unclear to what extent the conclusions of this study may be generalized to other therapeutic classes.

The diffusion of new drugs is an interesting and important field to study because there is huge pressure for pharmaceutical industries to get their products prescribed in order to earn back the large investments. Consequently, the pressure on those who evaluate new drugs is also large. Specifically, semi-innovative drugs may be prone to an overestimation of the claims for improvement. From this study it is concluded that the professional and academic opinion leaders who were interviewed were well aware of the claims that were made for losartan and atorvastatin. They critically evaluated these claims but did not show consensus in their considerations. Accepted principles for prescribing were considered when assessing the therapeutic position of the drugs but resulted in varied tendencies for prescribing.

POLICY IMPLICATIONS

We found a larger resemblance in professional characteristics between physicians who never prescribe the drugs and those who prescribe them occasionally, than between physicians who prescribe occasionally and those who prescribe frequently. This implies that future studies on the adoption of new drugs should take into account the frequency of prescribing in defining adoption as outcome measure. Merely looking at the first prescription, as was the case in the study by Steffensen et al. (20), may reflect an incidence of trying a new drug (2;4), which will not necessarily lead to inclusion of the drug in the doctor's personal set of preferred medicines.

Professional and academic opinion leaders play an important role as a source of information in the professional network (17). Our findings of the relationship between more positive evaluations and higher levels of prescribing and the importance of the pharmaceutical industry as a source of information add to the existing knowledge about industry and physician interactions (5;23). Policies regarding disclosure of any relationships with the pharmaceutical industry are relevant when contributing to the assessment of the position of new drugs in the therapeutic regimen.

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