A pharmaceutical interview improves clinical outcomes: a randomized controlled study on hypertension, type 2 diabetes and hypercholesterolemia.

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Abstract

Aims: These last years, pharmacists gained more and more importance in the clinical support of patients. However, few studies have explored the clinical outcomes of a pharmaceutical intervention on chronic patients. Methods: A randomized controlled study single blinded, evaluating the impact of a single pharmaceutical interview on hypertension, type 2 diabetes and hypercholesterolemia patients not reaching the therapeutic objectives despite a drug therapy. Patients in the intervention group were interviewed by a pharmacist who provided patient education on pathology management and advice on how to deal with the pathology on a daily basis, and identified any prescription problems. The primary outcome was the proportion of patients reaching the therapeutic objectives for blood pressure, glycated hemoglobin level and low-density lipoprotein cholesterol level at the three-month follow up consultation. Results: Seventy-three patients completed the study. In the control group, 33.3% patients reached the therapeutic objectives with the usual care versus 61.7% in the intervention group (p=0.015). The intervention was significantly more effective on patients with more than five different drugs prescribed (+16.7% vs +60.0%; p=0.005) and with a high education level (+29.4% vs +68.8%; p=0.024). A much lower rate of type 2 diabetes patients reached the therapeutic objectives whatever the group. Interestingly, the efficacy of the intervention did not depend on the number of chronic diseases or age after adjustment for the number of different drugs prescribed. Conclusions: There is a concrete clinical and public health impact of a single pharmaceutic interview, especially on polypharmacy patients with hypertension or hypercholesterolemia.

Statement 1: What is already known about this subject? (up to three bullet points)

- Adherence is a major health issue as an estimated 50% of chronic patients are non-adherent
- A single pharmacist intervention seems to increase chronic patients' satisfaction and adherence to treatments
- There is a need for proof of these interventions' value on direct clinical and public health outcomes

Statement 2: What this study adds: (up to three bullet points)

- Proof of enhanced clinical outcome of patient mentoring by a pharmacist
- A single pharmacist intervention doubles the number of patients reaching the therapeutic objectives in hypertension, type 2 diabetes and hypercholesterolemia
- Polypharmacy patients are a preferential target population

Introduction

In recent years, the roles and the missions entrusted to hospital pharmacists have evolved and pharmacists have gained more and more importance in the support of clinical patients[1,2] particularly through the advent of clinical pharmacy[3]. Clinical pharmacists interventions in clinical services are valued by health care providers[4,5] and result in reducing medication errors[6,7] and drug related hospitalization[8] cost savings[9,10] and even reducing mortality[11]. When addressed to patients, pharmaceutical interventions improved patient satisfaction and decreased non-adherence to medication [12–16].

Non-adherence to medication has become a new public health burden since chronic diseases have supplanted acute diseases in leading death and morbidity causes in modern medicine. The World Health Organization estimates that 50% of patients treated for chronic diseases do not properly take their treatment[17], which has been confirmed by epidemiologic and experimental studies[18–20]. Beside increasing morbidity and mortality[21–24], non-adherence has been estimated to cost annually 100 to 300 billion dollars of avoidable healthcare costs in the USA[25,26].

Then, if pharmaceutical interventions allow to increase the adherence, it should increase clinical outcomes. But is it really the case? All adherence evaluating methods show limitations in determining the real level of adherence[27,28]. Then, an increase in the adherence score does not necessarily mean an improvement in patient clinical condition. Moreover, improving adherence to a treatment is not a final goal but only a way to ultimately improve the pathology control and patient clinical condition. Today, few studies have investigated the direct impact of a pharmaceutical intervention on the patient clinical condition. A recent exhaustive review of randomized controlled studies evaluating general practice-based pharmacist interventions on the pathologies parameters of patients with hypertension, type 2 diabetes or dyslipidemia retrieved only 21 studies, of variable quality[29]. But despite the small number of these studies, there are very encouraging results. Some studies highlighted the usefulness of the pharmacist in decreasing blood pressure (BP)[12,30–33], glycated hemoglobin (HbA1c)[34–37] or low-density lipoprotein cholesterol (LDL-c)[38–40], also suggesting an economically positive effect of this kind of intervention[41–45]. However, the decrease of a pathology parameter does not mean the patient will reach the recommended target of this parameter, and today few studies have focused on the achievement of therapeutic goals set by physicians or recommendations. Moreover, to our knowledge, no such studies have been conducted in France.

In this context, we conducted a randomized controlled physician-blinded clinical study to evaluate the concrete impact in terms of clinical outcomes of a pharmacist interview immediately after a medical consultation, in patients treated for hypertension, hypercholesterolemia or type 2 diabetes but not reaching their therapeutic objectives.

Methods

Screening and recruitment

Patients were recruited in the Hypertension and Cardiovascular Prevention Unit, Diagnosis and Therapeutic Center, Hôtel-Dieu Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), Paris.

Inclusion criteria were to be regularly followed by a physician of the unit, to have at least one chronic pathology among hypertension, hypercholesterolemia and type 2 diabetes, and to not reach the therapeutic objectives despite a drug treatment. Patients under 18 years old, pregnant women and non-French speakers were non-eligible for inclusion.

Study design

This was a single site, single blinded, randomized, controlled, study. Eligible patients were included by the physician at the end of their medical consultation and randomized by the pharmacist with a randomization list kept hidden from the physicians either in the control group or in the intervention group. The intervention group benefited from a pharmaceutical intervention just after the inclusion. Both groups had a follow up consultation three months after the inclusion, as planned in their usual medical care. For ethical reasons, the control group benefited from a pharmaceutical intervention after the follow-up consultation (Figure 1).

Legal aspects

The protocol was approved by an Ethics Committee (Comité de Protection des Personnes d'Île-de-France n°1) in agreement with the European Agency Guidelines for Good Clinical Practice, and declared to the ANSM, the French Medicines Agency (n°2015-A00228-41). Each patient was informed of the purpose of the study, received an information letter and signed a consent form before inclusion.

Data collection and treatments

HbA1c, BP and LDL-c levels were obtained from the physicians at the inclusion and at the follow-up consultation. Information like number of drugs prescribed, other chronic diseases, age and kidney and liver functions were obtained from the patient medical record. The presence of side effects, the adherence score and the information used to estimate the socio-economical level were collected during the inclusion interview. Polypharmacy was defined as a daily intake of five different drugs or more, following previous studies methodology[46,47]. The socio-economical level was estimated based on the education level and the Bachelor's Degree: 1 for an education level below the high school diploma, 2 for an education level equivalent to the high school diploma and 3 for an education level higher than the high school diploma.

Intervention

The same pharmacist (CD) performed all the pharmaceutical interventions. The intervention consisted in providing patient education on pathology management and advice on how to deal with the pathology on a daily basis. The intervention frame for hypertension was set following general literature recommendations[48], the French Society of Hypertension recommendations for the "information and announce consultation" [49] and the "pharmaceutical interviews in case of high blood pressure" elaborated in partnership with the French Society of Clinical Pharmacy[50]. The hypertension frame was adapted for hypercholesterolemia and type 2 diabetes. The following items were discussed with open questions:

- The pathology: definition, origins, consequences, follow-up, non-drug treatment and nutritional-hygienic rules
- Drug mechanisms of action
- Posology and drug intake modalities
- Adherence and behavior in case of missed dose
- Drugs side effects and their handling
- Drug interactions and self-medication
- Medication plan elaboration (if necessary)
- Temporality and chronic aspects
- Patient feelings and perception

The discussion was an open interaction with the patient and all the topics on which he had questions were addressed. The point of this intervention was to determine the patient's knowledge and capabilities regarding his pathology in order to focus on his lack.

Data and statistical analysis

Number of subjects needed

Based on the physician's experience, outcomes were empirically estimated at 25% of patients reaching the therapeutic objectives in the control group *versus* 50% in the intervention group. With a power of 90% and a one-sided error of 5%, the estimated number of patients to be included in the study was 126.

Descriptive analysis

We compared the intervention and the control groups populations based on qualitative and quantitative variables such as: age, body mass index (BMI), sex, social level, kidney function, liver function, number of chronic diseases, number of diseases involved in the study, number of different drugs prescribed, side effects at the inclusion, adherence score at the inclusion, the pathology used for primary outcome and the number of lost of follow up.

Primary outcome

The primary outcome was the proportion of patients reaching the therapeutic objectives decided by the physician at inclusion: HbA1c for type 2 diabetes, LDL-c blood levels for hypercholesterolemia and systolic BP for hypertension. The objectives were set individually for each patient by the physician himself in accordance to French or international recommendations for hypertension[49], type 2 diabetes[51] and hypercholesterolemia[52]. If the patient had more than one pathology, the primary outcome was based upon the pathology specified as the most relevant in terms of cardiovascular prevention by the physician before inclusion.

We proceeded to a *per protocol* analysis on the primary outcomes, in which we excluded all the drop out patients from the analysis. This study was not a drug trial, and we then presumed that loss of follow-up was not due to the study *per se* nor to the intervention but to external reasons. Then, the drop out patients should not necessarily be considered as they did not reach the therapeutic objectives. A *per protocol* analysis seemed acceptable to conclude on our results.

Sensitivity analysis

Intend to treat analysis

To analyze the results for the primary outcomes, we also proceeded to Intent To Treat (ITT) analysis. In the "best case scenario" ITT analysis, we considered all the drop out patients as they reached the therapeutic objectives in the intervention group and as they did not in the control group. In the "worst case scenario", we considered the drop out patients as they reached the therapeutic objectives in the control group and as they did not in the intervention group[53].

Subgroup analysis

We proceeded to subgroup analysis of the number of patients reaching the therapeutic objectives depending on total drugs prescribed, comorbid pathologies, age and socio-economical level.

Statistical tests

To compare the participants and their distribution in the two different groups, we used a Student t test, a chi-square test or a Fischer test. We used a Pearson correlation test to determine the correlation between age and the number of drugs. Statistical tests were performed with GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Values of probability lower than 5% ($p < 0.05$) were considered significant.

RESULTS

Study population

A total of 89 patients were included during a 12 months period. Baseline characteristics were similar across the groups, and did not differ significantly on any criteria (Table 2).

Sixteen (16) patients were lost to follow-up: 11 did not come back to the consultation within the three months as planned and five did not get their therapeutic parameters measured at the follow-up consultation (Figure 2). Five of these patients were in the control group and 11 in the intervention group. Baseline characteristics were similar between the drop out patients and the patients that ended the study (Sup. Data Table 1).

Duration

Interviews lasted between 10 to 90 minutes, with an average of 36.1 minutes (95% confidence interval 31.6 – 40.6 minutes) and a median of 35 minutes (first-last quartile: 25-45 minutes).

Primary outcome

The *per protocol* analysis reported a significantly higher proportion of patients reaching the therapeutic objectives in the intervention group (61.7% *versus* 33.3%; p=0.015) (Table 2).

In the sensitivity analysis, the difference between the two groups was higher in "best case scenario" (71.1% *versus* 29.5%; p<0.0001) and lower in the "worst case scenario" (46.7%*versus* 40.9%; p=0.584) (Table 2).

Subgroup analysis

Number of prescribed drugs

The proportion of patients achieving therapeutic goals was not different between the two groups for patients who took less than five different drugs each day (60.0% *vs.* 64.3%; p=0.812). Conversely, for patients taking five or more different drugs, more patients reached the therapeutic goals in the intervention group compared to the control group (16.7% *vs.* 60.0%; p=0.005) (Table 2).

Age

In patients under 60 years old, no difference appeared in the proportion of patients achieving therapeutic goals between the two groups (50.0%*vs.* 66.7%; p=0.362) (table 2). On the contrary, in patients over 60 years old, patients in the intervention group reached the therapeutic goals more than the patients in the control group (26.1% *vs.*57.9%; p=0.037) (Table 2).

Age and number of drugs prescribed

However, the number of prescribed drugs was correlated to the age in our sample (r=0.42; p<0.00001) (data not shown). After adjusting for number of prescribed drugs, the proportion of patients reaching the therapeutic goals was the same, whatever their age or study group for patients who took less than five different drugs (Table 3). Conversely, for polypharmacy patients, the proportions are higher in the intervention group. The difference between the control and the intervention group is non-significant for patients under 60 (20.0%*vs.* 66.7%; p=0.242) and significant for patients over 60 (15.8%*vs.* 57.1%; p=0.024).

Number of chronic disease

The proportion of patients achieving therapeutic goals decreased with the number of pathologies in both groups (Table 2). This proportion stay higher in the intervention group than in the control group, whether patients had one (50.0% *vs.* 77.7%), two (33.3% *vs.*70.0%) or more (27.3% *vs.* 46.7%) chronic diseases, although no significant differences were retrieved.

Socio-economic level

In the control group, the proportion of patients achieving therapeutic goals decreased as the socio-economic level increased (37.5% to 29.4%) (Table 2). It seemed to be the opposite in the intervention group, in which it increased with the socio-economic level (37.5% to 68.8%) (Table 2). There was no difference between the

two groups for lower education levels (37.5%). The difference appeared for middle education levels (33.3% vs 70.0%; p=0.302) and get significant for higher education levels (29.4% vs 68.8%; p=0.024).

Main pathology involved

The increase of the proportion of patients reaching the therapeutic goals in the intervention group seemed to be the same order of magnitude (+24% and +23%) in hypertension (38.5% *vs.* 62.5% p=0.089) and type 2 diabetes (10.0% *vs.* 33.3%; p=0.303), and more important (+42%) in hypercholesterolemia (37.5% *vs.* 80.0%; p=0.266) (Table 2).

DISCUSSION

Per protocol analysis revealed a positive effect of the pharmaceutical interventions practiced on chronic patients. The proportion of patients reaching the therapeutic goals set by the physician almost doubled at three months (33.3% to 61.7%), consistently to some previous studies[32,37,40]. The lost to follow up population did not differ from the rest of the patients included, confirming the suitability of a *per protocol* analysis. This difference was also retrieved in the sensitivity analysis, logically higher and significant in the "best case scenario". In the "worst case scenario", the difference was no more significant but still suggested a positive effect of the intervention. Thus, if the number of patients included had reached the number statistically estimated as necessary, the difference might also get significant in this more pessimistic analysis. This study therefore demonstrated the direct clinical effect of a single pharmacist intervention on chronic patients with hypertension, type 2 diabetes and hypercholesterolemia.

According to a previous study, the benefit of a pharmacist intervention was greater in polypharmacy patients[54]. The number of patients achieving therapeutic goals decreased conversely to the total number of drugs prescribed in the control group. This result is consistent with the literature, which reports a decrease in compliance with the increase in the number of daily doses[55,56], and an increase in the risk of drugs interaction and side effects in polypharmacy patients[57]. Hence, polypharmacy patients appeared to be a preferential population to benefit from this kind of intervention.

Age and the number of drugs prescribed appeared to have similar effects on the achievement of therapeutic objectives. However, in our population, the number of drugs prescribed was correlated with the age of patients, as previously described[58]. After adjusting for the number of drugs, age did no longer appear as a factor influencing the results of pharmaceutical intervention. Therefore, the age-related effect of pharmaceutical intervention was probably due to the higher number of prescribed drugs in elderly[58], thus revealing age as a confounding factor[59]. Age then appeared as a less important criterion than polypharmacy in selecting a target population for pharmaceutical interventions.

Surprisingly, the intervention was also more effective on patients with a high educational level. It is well established that a low socioeconomic level is related to a bigger morbidity, especially for cardiovascular diseases[60,61] so we could have expected a more important effect on low educational level patients. However, this result should be interpreted with caution, as an inconsistent relationship between the socioeconomic level and the adherence to medication has also been reported[19,62]. Thus, we need further studies to confirm the results related to educational levels and to find a way to reach this population.

Pharmaceutical intervention was effective for all the studied pathologies, which is consistent with the literature and corroborates previous studies concerning hypertension[33,40], hypercholesterolemia[40] and type 2 diabetes[36,37,63]. However, the rate of patients achieving therapeutic objectives, regardless of the group, was lower for type 2 diabetes patients, than for the 2 other diseases. This could be related to the low adherence of type 2 diabetic patients found in the literature[64] and it highlights the need for these interventions in these patients.

Thirty-five minutes were required to discuss all topics with the patient. In France, the average duration of

a consultation with a general practitioner consultation is 10 to 16 minutes[65]. Unfortunately, prescribers cannot afford to spend an additional 20 minutes with all their patients to discuss drug topics in detail in addition to their regular consultations. This implies the necessity to have these interventions performed by a practitioner other than the physician, with a solid knowledge of medicines, whose activity would be at least partially devoted to these interventions. This finding highlighted the difficulty to offer this kind of intervention to all patients. It is therefore necessary to target these pharmaceutical interventions to specific populations of patients who need them most.

Strengths and weaknesses

We faced an important number of lost in follow-up patients. But as these drop out patients presented the same characteristics as the non-drop out patients, it limits the bias they could cause.

We did not reach the estimated number of patients to include. However, despite these small samples, we still found a significant difference in the *per protocol* analysis.

We proceeded to sensitivity analysis that gave us an exhaustive analysis of the results and still showed a difference, even in the "worst case scenario", confirming the positive effect of the interventions.

The same pharmacist performed all the intervention. This gave a better reproducibility of the interviews during the study, but it reduces the reproducibility of potential further studies.

The solid methodology through the physician-blind, the effective randomization and the presence of a control group reinforced the value of these results. However, even if patients of the control did not get a pharmaceutical intervention, it should be noted that they had an inclusion interview with the pharmacist, at the moment of the inclusion. Even if this interview was only intended to collect the necessary data form the patients, the latter often asked questions about their treatments. Thus, the inclusion interview in the control group may have provided information similar to the pharmaceutical intervention, in a lesser extent. Though, if this could represent a bias, it would act as increasing the proportion of patients reacing the therapeutic objectives in the control group which would be defavorable to our hypothesis and reinforces the significance of our findings.

CONCLUSION

This study proved the efficiency of pharmaceutical interviews in hypertension, type 2 diabetes and hypercholesterolemia, by doubling the proportion of patients reaching the therapeutic objectives after three months of a drug therapy. It also made possible to define preferential populations to benefit from these interventions, such as polypharmacy and type 2 diabetic patients.

However, further studies with larger samples are needed to conclude on an effect of the rest of the criteria such as multiple pathologies. Besides, some studies reported a temporary and short-term effect of this type of intervention[12,63]. We have deliberately limited this study to a single intervention and its evaluation after 3 months. Thus, further studies should focus on this effect on the long term, as well as the need for repeated pharmaceutical interventions several times a year, in person or by telephone[54]. In the same way, multicentric studies, will have to be conducted to refine our results. Moreover, we stayed focused on the clinical outcomes of these interventions, and we did not studied the benefits in terms of medicoeconomy and public health outcomes. Thus, further studies assessing the pharmaceutical costs of these interviews as well as the impact in terms of hospitalization, are necessary to evaluate the cost-benefit balance and the public health impact and have a comprehensive view of all the consequences of implementing such practices in routine.

This study confirms the interest of clinical pharmacy and of the evolution of pharmacists' activities, such as medication reconciliation[66] and optimized medication reviews, experimented in community pharmacies since March 2018.

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Conflict of interest:

There are no competing interests to declare.

Data availability statement:

Data available on request due to privacy/ethical restrictions.

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Tables

	Control group (n=44)	Intervention group (n=45)	p-value (t studen
Age (yr)	61,7 ± 4,0	59,4 ± 3,9	0.407[a]
Body mass index (kg/m^2)	28,3 ± 1,7	27,2 ± 1,4	0.323 [a]
Number of men (n)	25 (56.8%)	30 (66.7%)	0.339 [b]
Social level (n)			
1	19 (43.2%)	14 (31.1%)	0.419 [b]
2	7 (15.9%)	11 (24.4%)	
3	18 (40.9%)	20 (44.4%)	
Kidney failure (n)	8 (18.2%)	6 (13.3%)	0.530 [b]
Liver failure (n)	1 (2.3%)	0 (0%)	*NA*
Number of total chronic disease (n)			
1	8 (18.2%)	11 (24.4%)	0.613 [b]
2	12 (27.3%)	14 (31.1%)	
>2	24 (54.5%)	20 (44.4%)	
Number of diseases involved in the study (n)			
1	36 (81.8%)	37 (82.2%)	0.960 [b]
Hypertension	22 (50.0%)	24 (53.3%)	0.613 [b]

	Control group (n=44)	Intervention group (n=45)	p-value (t studen
Type 2 diabetes	7 (15.9%)	5 (11.1%)	
Hypercholesterolemia	7 (15.9%)	8 (17.8%)	
2	8 (18.2%)	7 (15.6%)	0.777 [b]
Hypertension + Type 2 diabetes	6 (13.6%)	6 (13.3%)	1 [b]
Hypertension + Hypercholesterolemia	0 (0.0%)	1 (2.2%)	*NA*
Type 2 diabetes + Hypercholesterolemia	2 (4.5%)	0 (0.0%)	*NA*
3	0 (0.0%)	1 (2.2%)	*NA*
Number of different drugs prescribed	6,2 ± 1,2	5,0 ± 0,8	0.118 [a]
Adjusted number of different drugs prescribed (n)			
<5	18 (40.9%)	18 (40.0%)	0.930 [b]?¿?
5	26 (59.1%)	27 (60.0%)	
Side effects at the inclusion (n)	11 (25.0%)	9 (20%)	0.572 [b]
Adherence score at the inclusion	2,2 ± 0,4	2,0 ± 0,4	0.501 [a]
Patient with hypertension (n)	28 (63.6%)	32 (71.1%)	0.452 [b]
used as primary outcome (n)	28 (63.6%)	27 (60.0%)	0.724 [b]
Patient with type II diabetes (n)	15 (34.1%)	12 (26.7%)	0.446 [b]
used as primary outcome (n)	7 (15.9%)	9 (20.0%)	0.615 [b]
Patient with hypercholesterolemia (n)	9 (20.5%)	10 (22.2%)	0.839 [b]
used as primary outcome (n)	9 (20.5%)	9 (20%)	0.957 [b]
Lost of follow-up (n)	5 (11.4%)	11 (24.4%)	0.108 [b]

Table 1: patients characteristics at baseline. Data are expressed as proportion of patients and in number of patients for qualitative variables, and as mean ± 95% confidence interval for quantitative variables. [a]student t test. [b]chi square test.

	Control group % (No. reaching therapeutic objectives/n)	Intervention group % (No. reaching therapeutic objectives/n)	p value
Primary outcome			
per protocol	33.3% (13/39)	61.7% (21/34)	0.015 [a] *
Intent to treat (ITT)			
"Best case scenario"	29.5% (13/44)	71.1% (32/45)	<0.0001[a]
"Worst case scenario"	40.9% (18/44)	46.7% (21/45)	0.584[a]
Secondary outcomes			
Number of chronic disease			
1	50.0% (4/8)	77.7% (7/9)	0.335[b]
2	33.3% (3/9)	70.0% (7/10)	0.179[b]
>2	27.3% (6/22)	46.7% (7/15)	0.225[a]
Number of prescribed drugs			
< 5	60.0% (9/15)	64.3% (9/14)	0.812[a]
[?]5	16.7% (4/24)	60.0% (12/20)	0.005[b] *
Social level			
1	37.5% (6/16)	37.5% (3/8)	1[b]
2	33.3% (2/6)	70.0% (7/10)	0.302[b]
3	29.4% (5/17)	68.8% (11/16)	0.024[a] *
Age (yr)			
<60	50.0% (7/14)	66.7% (10/15)	0.362[a]

	Control group % (No. reaching therapeutic objectives/n)	Intervention group % (No. reaching therapeutic objectives/n)	p value
[?]60	26.1% (6/23)	57.9% (11/19)	0.037[a] *
Study disease			
Hypertension	38.5% (10/26)	62.5% (15/24)	0.089[a]
Type II diabetes	10.0% (1/10)	33.3% (3/9)	0.303[b]
Hypercholesterolemia	37.5% (3/8)	80.0% (4/5)	0.266[b]

Table 2: primary outcome in ITT and per protocol *analysis, and subgroup analysis at the three-month follow-up consultation. Data are expressed in percentage of patients reaching the therapeutic objectives.* [a]*chi square test.*[b]*Fisher test. *p<0.05.*

	Control group	**Intervention group**	**p value**
<5 drugs prescribed	**<5 drugs prescribed**	**<5 drugs prescribed**	**<5 drugs prescribed**
<60 yr	60.0% (6/10)	66.7% (6/9)	1[a]
[?]60 yr	60.0% (3/5)	60.0% (3/5)	1[a]
[?]5 drugs prescribed	**[?]5 drugs prescribed**	**[?]5 drugs prescribed**	**[?]5 drugs prescribed**
<60 yr	20.0% (1/5)	66.7% (4/6)	0.242[a]
[?]60 yr	15.8% (3/19)	57.1% (8/14)	0.024[a] *

Table 3: proportion and number of patients achieving therapeutic objectives, by age and number of drugs prescribed.[a]*Fisher test. *p<0.05.*

	Drop out patients (n=16)	Patients ending the study (n=73)	p-valu
Age (yr)	62.4 ± 6.8	60.0 ± 3.0	0.532 [a]
Body mass index (kg/m^2)	28.2 ± 1.9	27.6 ± 1.2	0.619 [a]
Number of men (n)	7 (43.8%)	48 (65.7%)	0.100 [b]
Social level (n)			
1	9 (56.3%)	24 (32.9%)	0.211 [b]
2	2 (12.5%)	16 (21.9%)	
3	5 (31.3%)	33 (45.2%)	
Kidney failure (n)	2 (12.5%)	12 (16.4%)	NA
Liver failure (n)	0 (0.0%)	1 (1.4%)	*NA*
Number of total chronic disease (n)			
1	2 (12.5%)	17 (23.3%)	0.324 [b]
2	7 (43.8%)	19 (26.0%)	
>2	7 (43.8%)	37 (50.7%)	
Number of diseases involved in the study (n)			
1	13 (81.3%)	60 (82.2%)	0.929 [b]
Hypertension	6 (37.5%)	40 (54.8%)	0.202 [b]
Type 2 diabetes	5 (31.3%)	10 (13.7%)	
Hypercholesterolemia	2 (12.5%)	10 (13.7%)	
2	3 (18.8%)	12 (16.4%)	0.823 [b]
Hypertension + Type 2 diabetes	3 (18.8%)	9 (12.3%)	0.386 [b]
Hypertension + Hypercholesterolemia	0 (0.0%)	1 (1.4%)	*NA*

	Drop out patients (n=16)	Patients ending the study (n=73)	p-valu
Type 2 diabetes + Hypercholesterolemia	0 (0.0%)	2 (2.8%)	*NA*
3	0 (0.0%)	1 (1.4%)	*NA*
Number of different drugs prescribed	5.6 ± 1.5	5.6 ± 0,8	0.992 [a]
Adjusted number of different drugs prescribed (n)			
<5	7 (43.8%)	29 (39.7%)	0.766 [b]
5	9 (56.3%)	44 (60.3%)	
Side effects at the inclusion (n)	5 (31.3%)	15 (20.5%)	0.352 [b]
Adherence score at the inclusion	1.8 ± 0,6	2,1 ± 0,3	0.348 [a]
Patient with hypertension (n)	9 (56.3%)	51 (69.9%)	0.292 [b]
used as primary outcome	7 (43.8%)	49 (67.1%)	0.080 [b]
Patient with type II diabetes (n)	5 (31.3%)	22 (30.1%)	0.930 [b]
used as primary outcome	5 (31.3%)	11 (15.0%)	0.127 [b]
Patient with hypercholesterolemia (n)	5 (31.3%)	14 (19.2%)	0.286 [b]
used as primary outcome	4 (25%)	13 (17.8%)	0.507 [b]

Supplemental data Table 1: characteristics at baseline of drop out and patients ending the study. Data are expressed as proportion of patients and in number of patients for qualitative variables, and as mean ± 95% confidence interval for quantitative variables. [a] *student t test.* [b] *chi square test.*

Figure legends

Figure 1: Study design. Patients of the intervention group befenited from a pharmaceutical intervention the day of the inclusion (D0; day 0). Both groups had a follow-up consultation three months (M3) after the inclusion, and control group benefited from a pharmaceutical intervention after the follow-up consultation.

Figure 2: Number of inclusion and lost to follow-up