Polypharmacy, defined as taking five or more drugs, is inadequate in the cardiovascular setting

ABSTRACT

Background: By how much polypharmacy (defined by number of drugss) differs from polyactive ingredient use (defined by the number of pharmacologically active ingredients) has not been assessed.

Objectives: to compare the extent of polypharmacy vs. polyactive ingredients among patients taking CV medicines.

Methods: Prospective, 10-year follow-up study conducted among 880 participants of the CoLaus study taking CV drugs at baseline. Polypharmacy was defined as the use of 5 or more CV medicines; polyactive ingredient use was defined as the use of 5 or more pharmacologically active CV ingredients.

Results: The prevalence of polypharmacy increased from 1.4% (0.7 - 2.4) [prevalence rate and (95% confidence interval)] at baseline to 11.9% (9.9 - 14.3) at follow-up, and the prevalence of polyactive ingredients increased from 2.4% (1.5 - 3.6) at baseline to almost 17.6% (15.2 - 20.3) at follow-up. The prevalence of combination drugs increased from 15.7% (13.3 - 18.3) at baseline to 25.9% (23 - 28.9) at follow-up, and the prevalence of 3-component combination use increased from 0.1% (0.0 - 0.6) at baseline to 2.3% (1.4 - 3.5)at follow-up. At baseline, 9/21 participants on polyactive ingredients were not considered as being on polypharmacy; at follow-up, the rate was 50/155 participants.

Conclusion: Among individuals taking CV drugs, polypharmacy as defined by the number of drugs underestimates the prevalence of individuals taking five or more pharmacologically active drugs. Polypharmacy should no longer be based on the number of drugs but on the number of pharmacologically active drugs.

Keywords: polypharmacy; epidemiology; prevalence; prospective study; pharmacoepidemiology

INTRODUCTION

Population aging is associated with an increased frequency of multimorbidity and evidence-based guidelines recommend using several drugs in the treatment of a single condition. Both phenomena have made medication therapy particularly challenging as a growing number of patients take several drugs, which is referred to as polypharmacy (1-3).

Although the term polypharmacy has been used for decades, a precise definition is lacking. The cut off points, methods and settings for exploring polypharmacy vary widely (4, 5). Most studies used a cut-off point of five or more drugs to define polypharmacy (6, 7). A definition based on the number of units or of pharmacologically active ingredients remains an open debate. Indeed, the emergence of drugs combining two or more pharmacologically active ingredients (e.g. polypill for cardiovascular diseases (CVDs) prevention) might change the concept of polypharmacy. By how much polypharmacy (defined by number of drugs) differs from polyactive ingredients (defined by the number of pharmacologically active ingredients) has not been assessed.

Thus, this study aimed to compare the prevalence and 10-year trends of polypharmacy vs. polyactive ingredients among community-dwelling subjects taking CV medicines.

METHODS

Study population and design

The Colaus study is an ongoing prospective survey investigating the biological and genetic determinants of cardiovascular risk factors and CVD in the population of Lausanne, Switzerland. Detailed descriptions of the study design have been reported elsewhere (8). A simple, non-stratified random sample of the Lausanne population aged 35-75 years was drawn. Recruitment began in June 2003 and ended in May 2006 and included 6733 participants, with a participation rate of 41%. The follow-up was conducted 10.7 years on average after the collection of baseline data (May 2014-July 2016).

Polypharmacy and polyactive ingredients

Participants indicated which medicines, prescribed or obtained over-the-counter (OTC) they were currently taking. Medicines were coded according to the Anatomical Therapeutics Chemical (ATC) Classification System of the World Health Organization. For this study, only CV drugs were considered, i.e. all drugs belonging to ATC category "C" (cardiovascular system).

The number of medicines was computed as the number of different drugs taken by the participant. Polypharmacy was defined as taking 5 or more CV drugs, including OTC drugs. The number of pharmacologically active ingredients was computed considering ATC codes corresponding to combinations (**supplementary table 1**). "Polyactive ingredient" was defined similarly to polypharmacy, i.e. 5 or more pharmacologically active CV ingredients. "CV drug combinations are defined as CV medicines combining at least two different active substances in the same product."

Exclusion criteria

Participants were excluded if (i) they did not participate in the follow-up; (ii) they lacked information regarding CV medicines at baseline.

Statistical analysis

Statistical analysis was performed using Stata software version 14.2 (Stata Corp, College Station, TX, USA). Descriptive results were expressed as number of participants (percentage) for categorical variables and as average ± standard deviation or as median [interquartile range] for continuous variables. Between-group comparisons were performed using chi-square for categorical variables and student's t-test or Kruskal-Wallis for continuous variables. Prevalences were expressed as percentage and [95% confidence interval]. Between-survey comparisons were performed using Cochran test for categorical data and Wilcoxon matched-pairs signed-ranks test for continuous data. Statistical significance was considered for a two-side test with $p<0.05$.

RESULTS

Participants

Of the 1332 participants eligible for the study (taking CV drugs), 880 (66.0%, 441 men) were included (**figure 1)**. Included participants were younger, more frequently born in Switzerland and had a higher prevalence of former smokers, while no differences were found regarding gender or alcohol consumption **Supplemental table 2**.

Trends in prevalence of polypharmacy, polyactive ingredient and cardiovascular drug combinations

The trends in the number of drugs, pharmacologically active ingredients, and prevalence of polypharmacy, polyactive ingredient use and CV drug combinations at baseline and after 10 years follow-up are summarized in **table 1**. The prevalence of polypharmacy increased from 1.4% at baseline to almost 12% at follow-up; the prevalence of polyactive ingredients increased from 2.4% at baseline to almost 18% at follow-up, and the prevalence of combination drugs increased from 15.7% at baseline to almost 26% at follow-up. Finally, the prevalence of 3-component combination increased from 0.1% at baseline to 2.3% at follow-up. At baseline, the 95% confidence intervals for polypharmacy and for polyactive ingredient use overlapped, while at follow-up it was no longer the case. While the median of drug use doubled at follow up, the median of active ingredients tripled during the same period (**table 1**).

At baseline, of the 21 participants on polyactive ingredients, 9 (43%) were considered as not being on polypharmacy, while at follow-up, of the 155 participants on polyactive ingredients, 50 (32%) were considered as not being on polypharmacy.

DISCUSSION

In ten years, the prevalence of both polypharmacy and polyactive ingredient increased among community-dwelling CV patients. If at baseline the prevalences of polypharmacy and polyactive ingredient were rather close, ten years afterwards the prevalence of polyactive ingredient was

significantly higher than the prevalence of polypharmacy. Further, at follow-up, a significant number of participants taking 5 or more pharmacologically active drugs was not considered as being on polypharmacy.

"The issue of multidrug medications in cardiovascular treatment is complex. On one side, by reducing the number of drugs to be taken by the patients, cost could be reduced (9). Also, non-compliance is higher in patients taking multiple antihypertensive drugs (10); hence, multidrug medications could be a simple and efficient method to reduce non-compliance and improve treatment efficiency (11, 12). On the other side, the fixed dose combinations reduce personalization of treatment and might complicate medication reviews if the name of the product is not provided."

By counting only the unit of CV drugs, those taking the combination of CV drugs are ignored. A study assessing polypharmacy in the US also mentioned that defining polypharmacy by drug ingredient may be the most biologically plausible approach (13). This issue is particularly important with regard to CVDs due to the emergence of the combinations which are becoming more prevalent. Furthermore, not only the number of combinations increased during the study period, but also the combinations including more than two active ingredients increased; i.e. even if the number of the unit of drugs stays steady, which it also increased here, still the number of active ingredients have been growing. Thus, polypharmacy as defined by the number of drugs may underestimate numbers of patients taking more than five active ingredients and cannot reflect the extent of the issue of polymedication.

Limitations

This study has several limitations worth acknowledging. First, all medicines were collected using self-reported data, which might be prone to information bias. However, a previous study showed that self-reported medication use closely relates with pharmacy records (14).

Conclusion

Among individuals taking CV drugs, polypharmacy as defined by the number of drugs underestimates the prevalence of individuals taking five or more pharmacologically active ingredients. Polypharmacy should be counted as the number of pharmacologically active ingredient.

AUTHORS' CONTRIBUTION

NA suggested the topic and wrote most of the manuscript; PMV collected data, made the statistical analysis and reviewed the manuscript for important intellectual content. PMV had full access to the data and is the guarantor of the study. Both authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors report no conflict of interest.

ETHICAL STATEMENT AND CONSENT

The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud approved the baseline CoLaus study (reference 16/03, decisions of 13th January and 10th February 2003); the approval was renewed for the second (reference 26/14, decision of 11th March 2014) follow-up. The study was performed in agreement with the Helsinki declaration and in accordance with the applicable Swiss legislation. All participants gave their signed informed consent before entering the study.

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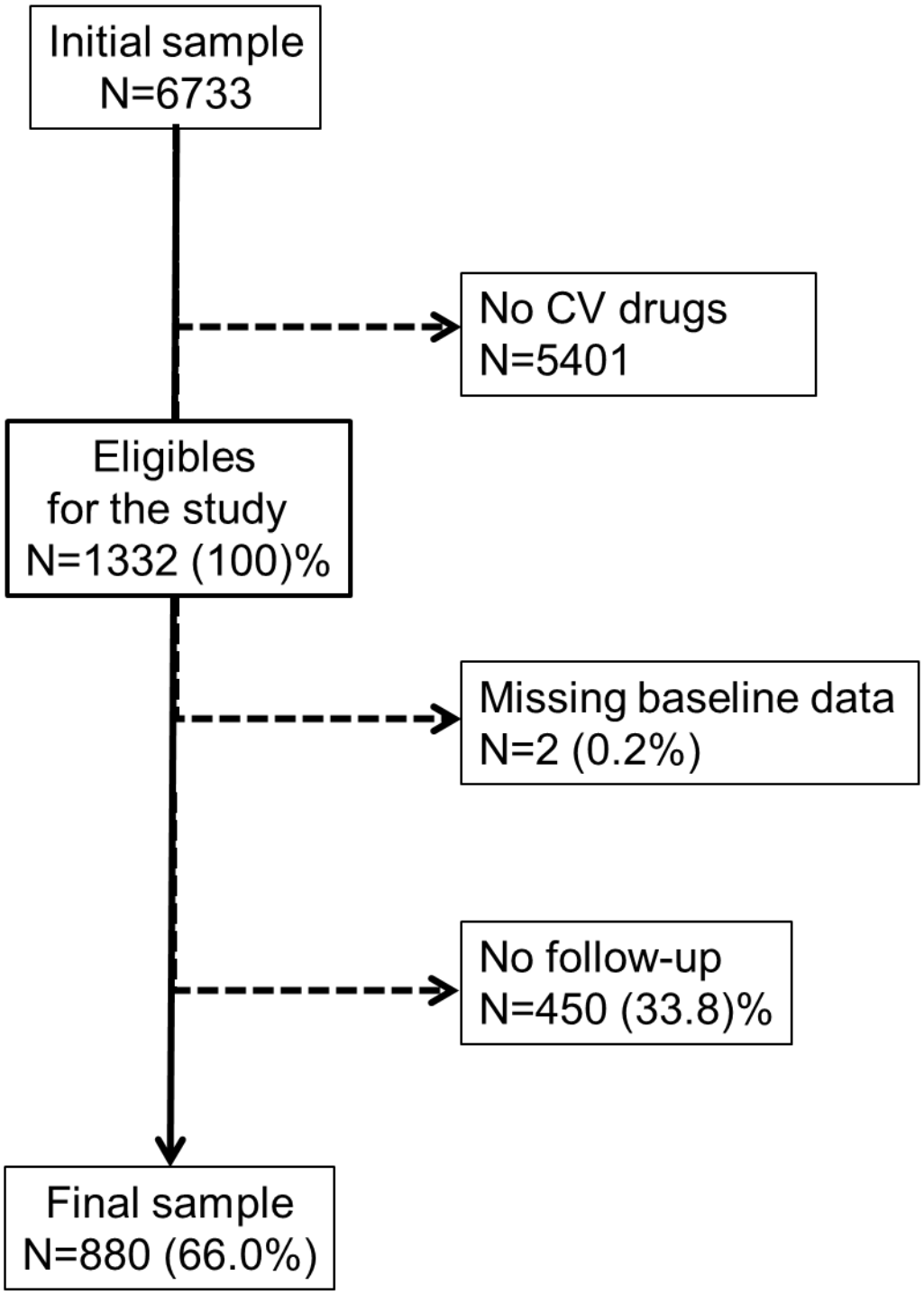
FIGURE LEGENDS

Figure 1: selection procedure of the participants, CoLaus study, Lausanne, Switzerland.



TABLES

Table 1: Trends in the prevalence of polypharmacy, polyactive ingredients and cardiovascular drug combination, CoLaus study, Lausanne, Switzerland

	Baseline	**Follow-up**
Polypharmacy (%)	1.4 (0.7 - 2.4)	11.9 (9.9 - 14.3)
Polyactive ingredient use (%)	2.4 (1.5 - 3.6)	17.6 (15.2 - 20.3)
CV drug combination (%)	15.7 (13.3 - 18.3)	25.9 (23 - 28.9)
Taking 3-component combinations (%)	0.1 (0.0 - 0.6)	2.3 (1.4 - 3.5)
Number of cardiovascular		
Drugs	1 [1 - 2]	2 [1 - 3]
Active ingredients	1 [1 - 2]	3 [1 - 4]

CV, cardiovascular. Polypharmacy : 5 or more CV medicines; polyactive ingredient: 5 or more pharmacologically active CV ingredients. Results are expressed as percentage (95% confidence interval) or as median [interquartile range]. Between-survey comparisons were performed using Cochran test for categorical data and Wilcoxon matched-pairs signed-ranks test for continuous data. All comparisons are significant at $p<0.001$. “CV drug combinations are defined as CV medicines combining at least two different active substances in the same product.”