Effect of a single pill concept on clinical and pharacoeconomic outcomes in cardiovascular diseases

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Abstract and Key Words

Aims: Our study aimed to assess whether a single pill concept (SPC) is superior to a multi pill concept (MPC) in reducing cardiovascular (CV) events, all-cause death, and costs in CV patients.

Method and Results: Anonymized medical claims data covering 2012-2018, including patients with hypertension, dyslipidemia, and CV diseases who started a drug therapy either as SPC or identical MPC were analyzed after 1:1-Propensity Score Matching (PSM). Hospitalizations with predefined CV events, all-cause mortality, and costs were studied in 25,311 patients with SPC and 25,311 patients with MPC using incidence rate ratios (IRRs) and non-parametric tests for continuous variables. IRRs were significantly lower for SPC: stroke (IRR=0.77; 95% CI 0.67-0.88; p<0.001), transitory ischemic attack (IRR=0.61; 95% CI 0.48-0.78; p<0.001), myocardial infarction (IRR=0.76; 95% CI 0.63-0.90; p=0.0016), coronary artery disease (IRR=0.66; 95% CI 0.57-0.77; p<0.001), heart failure (IRR=0.59; 95% CI 0.54-0.64; p<0.001), acute renal failure (IRR=0.54; 95% CI 0.56-0.64; p<0.001), all cause hospitalization (IRR=0.72; 95% CI 0.71-0.74; p<0.001), CV hospitalization (IRR=0.63; 95% CI 0.57-0.69; p<0.001), and all-cause mortality (IRR=0.62; 95% CI 0.57-0.68; p<0.001). Mean time to first events and time to death were also in favor of SPC. Mean total costs were 4,708 € for SPC vs. 5.669 € for MPC, respectively (MR 0.830, p<0.001).

Conclusion: SPC is associated with lower incidence rates of CV events, time to CV events, and all-cause death, and is superior regarding pharmacoeconomic parameters and should therefore become standard of care to improve outcomes and reduce healthcare costs.

Key words
Arterial hypertension, dyslipidemia, cardiovascular disorders, adherence, single pill concept, cardiovascular outcomes
Introduction

Hypertension, dyslipidemia, and diabetes are the most prevalent risk factors leading to cardiovascular morbidity and mortality [1-6]. The risk of stroke, myocardial infarction, heart failure and chronic kidney disease has been shown to be reduced by control of high blood pressure with antihypertensive medications and lipid-lowering drugs [7, 8]. Patients at high cardiovascular risk usually require a combination of different drugs to reach their treatment targets. [9 - 12]. For each of these drugs, their clinical benefit was demonstrated in clinical trials. However, despite protective effects on cardiovascular outcomes, pharmacological treatment is often suboptimal [1, 2, 4, 5]. One explanation is a lack of adherence as a very common phenomenon in primary care [10-15], which strongly influences blood pressure and lipid control, with a relevant impact on the cardiovascular risk imposing a large financial burden on health care systems [16-18]. Current guidelines for the management of arterial hypertension or secondary cardiovascular (CV) prevention recommend combination drug treatments with single pills (SP) [19, 20]. This concept is expected to improve adherence to treatment and, as a consequence, to reduce the risk of adverse CV outcomes associated with these clinical conditions which was shown for patients suffering from hypertension [21].

Aim of our study was to assess whether a SP concept (SPC) is clinically and pharmacoeconomically superior to a MPC with identical drugs in reducing CV events and all-cause mortality in a large real-world population.

Methods

We analyzed anonymized medical claims data from patients aged 18 years or older with CV disease or high risk insured by AOK PLUS, a German statutory health fund, and treated with a combination as SPC or identical MPC during the time period 01/07/2012-30/06/2018. The dataset provided information on socio-demographic characteristics of patients, inpatient and outpatient care as well as all documented diagnoses, prescriptions of medications, and other data such as prescriptions of outpatient aids and devices.
Patients were included in the analysis if they were continuously insured (07/2012-06/2018, death as only exception from this rule) and had at least one inpatient or two outpatient claims (in two different quarters) of at least one of the following diseases in 01/07/2012-30/06/2017: hypertension, CHD, hyperlipidemia, myocardial infarction (MI), HF, stroke, transient ischemic attack (TIA), coronary heart disease or peripheral artery disease. The International Code of Diseases (ICD) was chosen for disease classification because validity of recording and coding is high in statutory health fund data, especially for inpatient and prescription data, as they are directly relevant for reimbursement of hospitals/pharmacies, and regularly checked by external agencies. We predefined the following combinations which are commonly used to treat the predefined diseases and were available as SPC or identical MPC in this population: bisoprolol/amlodipine, valsartan/amlodipine, candesartan/amlodipine, valsartan/amlodipine/hydrochlorothiazide, ramipril/amlodipine, ezetimibe/atorvastatin, acetylsalicylic acid /atorvastatin/ramipril. Patients who started their combination therapy between 01/07/2013 and 30/06/2017 as MPC or SPC were included in the analysis. Observation of patients started at the date of the first prescription of combination therapy (index date), either as SPC or MPC. Index date for the SPC group was the first prescription of a respective SPC. A MPC was assumed to have been prescribed if there were claims of all agents of the targeted combination therapy within 90 days; index date was the prescription date of the last (second/third) agent in that combination.

A propensity score matching (PSM) was done to account for baseline differences. In the PSM analysis, patients in the SPC cohort were, per subgroup, separately matched to patients in the MPC cohort. Propensity scores were calculated using logistic regression (group affiliation as dependent variable) including age, gender, and Charlson Comorbidity Index (CCI) without age factor as fixed independent variables. Covariates in the PSM regarding medication were number of prescribed medications (counting each agent – ATC code level 5 – with at least two prescriptions), use of antihypertensive agents, oral antidiabetic agents, insulin, antiarrhythmic agents, nonsteroidal anti-inflammatory drugs,
antiplatelets, lipid lowering agents, drugs for peptic ulcer and GORD, cardiac glycosides, oral
corticosteroids, and benzodiazepine derivatives. All were based on information related to
index date or a 12-month baseline period. Furthermore, 28 different variables that are
plausible as predictors of CV outcomes available in the database describing the CV event
risk or the general comorbidity profile of above patients, were included as independent
variables. A backward elimination approach was used to eliminate any variables that did not
reach significance in explaining group exposition (p > 0.1); in such cases these variables were
excluded from the specific PSM models. As each covariate included in the PSM analysis was
expected to affect both treatment assignment and the outcomes of interest, PSM quality was
assessed in two ways: 1) standardized differences between comparison groups were used to
assess the balance of covariates after matching (number of variables with – still – significant
differences between SPC and MPC patients); 2) the incidence of specific events that were
expected to be independent of the drug treatment received, such as later knee/hip
replacement in the follow-up period, were compared.

Patients were followed up from index date until one of the following events, whatever
came first: End of data availability (30/06/2018), all-cause death, therapy discontinuation
defined as gap in drug supply of at least 60 days, based on the defined daily dose (DDD)
per agent, in case of a MPC a gap of 60 days for at least one of the combination agents
led to censoring in that respect, switch from SPC to MPC or vice versa.

The following acute and non-planned clinical outcomes reported as main diagnoses were
captured: hospitalization with stroke, transitory ischemic attack, myocardial infarction,
coronary artery disease, heart failure, acute and/or chronic renal failure, all cause
hospitalization, cardiovascular hospitalization, and all-cause mortality.

Based on a patient-specific follow-up period since index date we counted the number of
events per observed 100 patient years and, based on this, calculated incidence rate ratios
(IRRs) for the exposure of a patient to the SPC versus MPC cohorts. In addition, we calculated unadjusted hazard ratios (HRs) based on unadjusted Cox regression models. Third, the percentage of event-free patients over time with regard to the outcomes of interest as well as with regard to a composite outcome consisting of all cause hospitalizations was depicted in Kaplan Meier (KM) curves using log rank tests for testing statistical significance of differences between the observed cohorts.

To address the issue of confounding, two additional analyses were conducted: an analysis of number of events in a Poisson regression and a multivariable Cox regression analysis both based on the unmatched SPC/MPC samples within above cohorts. Results were reported as coefficients for SPC vs. MPC (Poisson regression) and adjusted HRs (aHRs, Cox regression). All variables included in the PSM procedure were included in these models as independent variables using a backward elimination approach.

All reported p-values were two-sided, and 95% CIs were calculated for IRRs, HRs, Poisson-coefficients and aHRs by applying independent t-tests or Wilcoxon Rank Sum tests, where applicable. For categorical variables, the Chi Squared Test was performed. All descriptive analyses were performed with Microsoft SQL Server 2014 and Microsoft Excel 2016. All other statistical analyses were performed with STATA/MP 13.1 and SPSS 17.0.

**Regulatory aspects**

As the study addressed an anonymized dataset no ethical review and no informed consent of patients were needed. However, the study protocol was reviewed by the scientific steering committee (Institut für Pharmakoökonomie und Arzneimittellogistik (IPAM)/Institute for Pharmacoeconomics and Pharmaceutical Logistics, Wismar; AOK PLUS – die Gesundheitskasse für Sachsen und Thüringen; GB Arzneimittel/Heilmittel, Dresden; Institute of Sports Science, Christian-Albrechts-University of Kiel; Cardiology...
Results

50,622 patients (25,311 patients on SPC versus 25,311 patients on MPC) aged ≥ 18 years treated with SPC or MPC with identical drugs were followed up for at least 1 year or until death (Fig. 1). Inclusion diagnoses of the matched cohorts are provided in supplementary table 1, and baseline characteristics of the matched cohorts are given in supplementary table 2. No significant differences in baseline characteristics were observed after PSM. The proportion of patients persistent to treatment one year after initiation of treatment was 63.4% under SPC and 52.4% under MPC, respectively (p<0.001) and was consistently higher under SPC during the whole observational period (HR [95% - CI] SPC vs. MPC 0.76 [0.74 – 0.78], Log Rank: p<0.001, Fig. 2).

Comparisons were done on nine CV outcomes. In all comparisons, significantly lower incidence rate ratios (IRR) were identified for SPC, confirmed by comparison of Kaplan-Meier estimates: hospitalizations with stroke (IRR=0.77; 95% CI 0.67-0.88; p<0.001), hospitalizations with transitory ischemic attack (IRR=0.61; 95% CI 0.48-0.78; p<0.001), hospitalizations with myocardial infarction (IRR=0.76; 95% CI 0.63-0.90; p=0.0016), hospitalizations with coronary artery disease (IRR=0.66; 95% CI 0.57-0.77; p<0.001), hospitalizations with heart failure (IRR=0.59; 95% CI 0.54-0.64; p<0.001), hospitalizations with acute renal failure (IRR=0.54; 95% CI 0.56-0.64; p<0.001), all cause hospitalization (IRR=0.72; 95% CI 0.71-0.74; p<0.001), cardiovascular hospitalization (IRR=0.63; 95% CI 0.57-0.69; p<0.001), and all-cause mortality (IRR=0.62; 95% CI 0.57-0.68; p<0.001) (Fig. 3). The mean time to first events (Fig. 4) and time to death (Fig. 5) were also in favor of SPC.
(any event: SPC 966.052 days/median 873; MPC 846.936 days/median 647; death: SPC 1,719.424 days; MPC 1,657.248 days; log rank for both comparisons: p<0.001).

Health care utilization for CV causes was lower on SPC as judged by outpatient visits (SP 3.96 vs. MP 4.02, Incidence Rate Ratio [IRR] 0.985, p<0.001), specialists visits (SPC 0.30 vs. MPC 0.36, IRR 0.829, p >0.1), days in hospital (SPC 0.54 vs. 0.82 MPC, IRR 0.659, p<0.001), prescriptions (SPC 2.24 vs. MPC 2.79, IRR 0.804, p<0.001), and days absent from work (SPC 2.8 vs. MPC 3.34, IRR 0.837, p<0.001). Similar results were observed for general medical health care utilization: outpatient visits (SPC 4.42 vs. MPC 4.55, IRR 0.971, p<0.001), specialists visits (SPC 0.45 vs. MPC 0.53, IRR 0.854, p = 0.002), days in hospital (SPC 3.77 vs. MPC 5.19, IRR 0.728, p<0.001), number of prescriptions (SPC 5.79 vs. MPC 6.72, IRR 0.862, p<0.001), and days absent from work (SPC 7.84 vs. MPC 7.78, IRR 1.007, p=0.007). The comparison for the medication costs was divided into costs for the focus medication (according to the cohort definitions) and costs for other cardiovascular-related medication. The mean costs for any outpatient medication ranged between 1,140 € and 2,653 € (SPC) and between 1,138 € and 2,701 € (MPC). The mean costs were slightly higher for the SPC groups (IRR 1.028) but not statistically significant. Mean costs related to focus diagnosis per patient per year were 1,214 € in the SPC vs. 1,225 € in the MPC (Mean Ratio [MR] 0.991, p=0.085), mean total costs were 4,708 € under SPC vs. 5,669 € under MPC, respectively (MR 0.830, p<0.001).

Discussion

The major finding of this study in 50,622 patients was that the concept of a SP combination use in CV disease reduced total mortality and improved incidence rates and time to event of nine clinical outcomes significantly compared to a MPC with identical substances. Patients treated with SPC were more and longer persistent to medication than with MPC, which might explain the better prognosis under SPC. Health care utilization and related costs were also in favor of SPC.
In the past, improvement in adherence to medication has been observed for the use of SPC (1, 6, 7, 15, 16, 17). In a meta-analysis comparing adherence to treatment under a SPC compared with the identical MPC in patients with CV disease, SPC showed higher adherence and persistence to medication after 6 months, 12 months and 18 months (22). However, data on outcomes are sparse.

A previous study in patients with CV diseases comparing SPC with MPC demonstrated a reduction in CV events in favor of SPC (23). An analysis with renin-angiotensin system inhibitor combinations given as single pill or multiple pills confirmed this observation in patients with hypertension (21). In the retrospective, observational NEPTUNO study using data from electronic-health records, patients were distributed into 4 different cohorts: a single pill containing acetylsalicylic acid (ASA)/atorvastatin/ramipril (case cohort), identical mono components taken separately. A total of 6,456 patients (1,614 patients per cohort) were analysed. After 2 years, the risk of recurrent MACE was lower in the single pill cohort compared to all control groups with better blood pressure and LDL-cholesterol control (24). These studies were hampered by the use of differently potent drugs between SPC and MPC.

The recently published SECURE study in patients after myocardial infarction within the previous 6 months randomized to a single pill containing acetylsalicylic acid (ASA)/atorvastatin/ramipril or usual care. A total of 2,499 patients were enrolled and followed for a median of 36 months. In the single pill group, patients had a significantly lower risk of major adverse CV events and CV deaths than patients under usual care (25).

Our study extends those findings of previous studies (26, 27). It shows that risk reduction linked to specific substances is superior when used in a single pill providing a concept in CV disease treatment in general, which should be used when patients need combination therapy.

The observed reduction of health care utilization and costs in favor of SPC compared to MPC further supports this concept. Less CV events require less cost and time intensive
interventions. Borghi et. al. (28) designed a microsimulation to project health outcomes between 2020 and 2030 for populations with hypertension managed according to current treatment practices (CTP), single drug treatment with dosage titration and sequential addition of other agents. In this model, simulated outcomes of mortality, chronic kidney disease (CKD), stroke, ischemic heart disease (IHD), and disability-adjusted life years (DALYs) were estimated for 1,000,000 patients for each of the four treatment pathways (28). SPC improved clinical outcomes over the other treatment regimens (28). Ten-year projections indicated SPC is showing the greatest overall benefits, which is linked to improved adherence to medication (28).

The SP concept will also have an influence on pill burden, which was also identified as risk factor for the development of CV events. Derington and colleagues investigated the association of baseline medication burden and clinical outcomes in a subanalysis of the SPRINT trial. High medication burden was associated with worse intensive systolic blood pressure (SBP) control and higher rates of cardiovascular disease events and serious adverse events (29).

Our study has some limitations. Differences between the compared SPC and MPC groups could be a potential limitation as it could reflect differences in intensity of health care in individual patients. However, we quality-checked our propensity score matching by comparing hip and knee replacement surgery frequencies as a potential independent non-cardiovascular outcome. We could not detect any significant differences between the two groups. Second, a higher number of patients in the initial dataset got a prescription for MPC compared to SPC. The exclusion of many MPC patients from the analyses could lead to a bias. However, we addressed this by two additional sensitivity analyses based on unmatched cohorts, with consistent results. Third, we did not have access to clinical data like blood pressure values so that we used claims-based proxies to identify the outcomes of interest. To address potential weaknesses of the study resulting from this, we observed multiple outcomes attributed to CV complications associated with the underlying diseases. Another
limitation is that due to non-availability of data, we could not explore the pill burden of target
patients outside of the CV medications. So, our analysis shows the relative effect of reducing
a CV-related pill burden, independent on the baseline pill burden of a patient. Further studies
should explore whether this baseline pill burden is an effect modifier regarding SPC. Limiting
is also, that disease severity was not accounted for in the propensity matching of patients
with due to data unavailability. However, we tried to minimize a disease-related bias by
including the additional covariates in the PSM regarding comorbidities which were
CHA2DS2-VASc, top five comorbidities that are not covered by the CCI/CHA2DS2-VASc,
level of care, number of hospitalizations with any cardiovascular diagnosis as main
diagnosis, number of hospitalizations with any non-cardiovascular diagnosis as main
diagnosis, participation in a disease management program (DMP), confirmed diagnosis of
dementia, confirmed diagnosis of affective disorders, confirmed mental and behavioral
disorders due to psychoactive substance/alcohol use.

Finally, as is the case for all retrospective database analyses, diagnoses, or outcome
misclassification, although non-differential, constitutes an additional limitation. To minimize
the risk resulting from this limitation and in line with previous similar studies, we only
captured confirmed events requiring an acute hospital admission and a documentation of the
event itself as main diagnosis.

Conclusion

Compared to a MPC with identical substances, SPC is associated with a lower incidence of
CV events and lower all-cause mortality, time to CV events and death as well as with lower
health care utilization and costs. Therefore, SPC should become standard of care in the
treatment of hypertension, dyslipidemia, and secondary prevention of CV disease whenever
available.
Disclosures

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TW did studies for various pharmaceutical companies and received grants from Cytel Inc., a consultancy working for these companies.
SW is on the speaker and advisory bureau of Amgen, Apontis, AstraZeneca, Bayer, Berlin Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Lilly, Novartis, Pfizer, and Vifor.
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Data availability statement

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Institut für Pharmakoökonomie und Arzneimittellogistik e.V., Alter Holzhafen 19, 23966 Wismar/Germany.
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Figure 1: Patient Flow

Figure 1 highlights the consort flow diagram.
Figure 2: Time to Non-Persistence

Figure 2 shows the proportion of patients persistent to medication over the observational period. Comparisons are done between matched SPC versus MPC cohorts.
Figure 3: Event rates per treatment group

Figure 3 shows the number of all-cause mortality, myocardial infarction, stroke, transitory ischemic attack, coronary artery disease, heart failure, acute/chronic renal failure per observed 100 patient years in the respective cohorts. Comparisons are done between matched SPC versus MPC cohorts.
Figure 4: Time to first Event

Figure 4 shows the proportion of patients that are event free over the observational period. Events that were observed were hospitalizations with diagnosis of myocardial infarction, stroke, transitory ischemic attack, coronary artery disease, heart failure, acute and chronic renal failure, any cardiovascular hospitalization, all cause hospitalization, all-cause mortality, Comparisons are done between matched SPC versus MPC cohorts.
Figure 5: Time to Death

Figure 5 shows the proportion of patients surviving over the observational period. Comparisons are done between matched SPC versus MPC cohorts. Patients were followed up from index date until one of the following events, whatever came first: End of data availability (30/06/2018), all-cause death, therapy discontinuation defined as gap in drug supply of at least 60 days, based on the defined daily dose (DDD) per agent, in case of a MPC a gap of 60 days for at least one of the combination agents led to censoring in that respect, switch from SPC to MPC or vice versa.