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ORIGINAL ARTICLE

# The Attitude towards Polypills Questionnaire (APPQ): a phase I–III development and validation study in patients with cerebrovascular disease

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## Abstract

**Background and purpose:** The polypill approach has been proposed to reduce patients' pill burden, increase medication adherence and lower stroke incidence. However, little is known about patients' attitudes towards polypills for cerebrovascular medication.

**Methods:** Based on the European Organization for Research and Treatment of Cancer Quality of Life Group questionnaire development guidelines, a questionnaire to measure patients' attitudes towards polypills for the secondary prevention of stroke (phase I–III) was developed. In phase I, issues were generated via literature review and interviews with patients and healthcare professionals. The issues were operationalized into items in phase II. In phase III the questionnaire was validated in a large single-centre sample, and test–retest and internal validity were evaluated.

**Results:** In phase I, 34 relevant issues were identified through literature search and interviews. Pre-testing the questionnaire indicated high applicability and comprehensibility. The final Attitudes towards Polypills Questionnaire was tested in $N = 260$ patients and showed a two-factor structure. The factors were labelled 'concerns' and 'benefits'. The scales showed acceptable and good internal validity (concerns, Cronbach's $\alpha = 0.85$; benefits, $\alpha = 0.93$), but the scales' test–retest validity was ambiguous. On a 0 to 3 rating scale, concerns were rated lower than benefits (mean 1.07, SD 0.69 vs. mean 1.87, SD 0.89).

**Conclusions:** The Attitudes towards Polypills Questionnaire showed high comprehensibility and content validity to assess German language patients' attitudes towards a polypill medication. Our data and questionnaire may aid the implementation of polypill

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treatments in clinical practice and can be used in the design of future clinical trials on polypill therapy. Further validation of the questionnaire is advised.

**KEYWORDS**
adherence, attitude, benefits, combined pill, concerns, fixed-dose combination, polypill

## INTRODUCTION

Cerebrovascular diseases are amongst the most common causes of death worldwide and one of the most frequent causes of persistent disability [1,2]. After stroke or transient ischaemic attack (TIA), patients need long-term antithrombotic preparations and frequently one or more antihypertensives, antidiabetics and cholesterol lowering drugs [3,4]. Adherence to those long-term medications is crucial to the prevention of secondary cardiovascular disease. However, patients often do not adhere sufficiently to their medication. According to the World Health Organization, adherence to long-term drug treatment lies around 50% in industrialized countries and is estimated to be lower in developing countries [5].

There are a number of diverse potential approaches which aim at increasing medication adherence and range from changes in dosage to patient education and behavioural interventions [6–8]. However, the intervention most likely to succeed is simplification of the medication regimen [9]. The number of drug dosages per day is one of the main predictors for adherence to the prescribed medication regimes. In a study by Claxton et al. [10], medication adherence dropped from 79% for once-daily drug intake to 51% for patients who had to administer medications four times a day. Similar results were found in several other studies [11,12]. The polypill concept—combining different medications in a single pill—can substantially reduce the number of pills needed per day and thereby facilitate the adherence to therapeutic regimes [13–15]. This presents a promising approach for personalized drug therapy and has been proposed as a means for the primary and secondary prevention of stroke [8,16,17]. First results assessing polypill therapy have shown benefits on adherence [13,18] and for cardiovascular risk factors [19,20], but so far there are only preliminary data regarding the effectiveness in stroke specifically [21].

Whilst dosage reduction is a feasible step for improving medication adherence, not all patients and medication regimes necessarily reap its profits [11,22]. Therefore, it is crucial to investigate patients' beliefs and attitudes towards this new form of medication, as those factors are known to influence their medication intake behaviour and adherence [23,24].

To the best of our knowledge, there are no questionnaires that measure attitudes towards polypill approaches in cerebrovascular diseases (or for any other diseases). Whilst there are questionnaires that measure adherence to medication or general attitudes towards medication, those questionnaires are not specific to new forms of medication and instead measure attitudes to medication in general. The objective of this study was to develop a questionnaire to assess the attitude towards the use of polypills for the secondary prevention of stroke in patients with cerebrovascular diseases to evaluate the potential usage in this population.

## METHODS

The questionnaire was constructed based on the procedure for developing questionnaire modules from the European Organization for Research and Treatment of Cancer Quality of Life Group (EORTC QLG) [25]. The development process consists of four phases: (i) compiling an exhaustive list of relevant issues that cover the domains of interest, (ii) constructing an item list that covers all relevant issues, (iii) testing of the questionnaire, (iv) field-testing and validation. For this study, the results of phase I–III are presented with a modified phase III that also includes preliminary validation results. Figure 1 provides an overview of the questionnaire development process. The study was approved by the local ethics committees of the Medical University of Innsbruck (app. number 1125/2018).

Inclusion criteria for patients in all phases were as follows: (i) cerebrovascular disease, that is, TIA or ischaemic stroke diagnosis; (ii) minimum age of 18 years; (iii) receiving first or consecutive treatment lines for the cerebrovascular disease; (iv) no cognitive impairment; (v) fluent in German; (vi) informed study consent.

### Phase I

The goal of phase I was the creation of an exhaustive issue list on patient attitudes towards polypills. Issues were extracted from three different sources: (a) existing literature and questionnaires, (b) healthcare professionals (HCPs), (c) patients.

#### (a) Literature

A systematic literature search was conducted to identify patient attitudes and quotes regarding a polypill therapy. The abstracts and full papers were screened by an expert committee of three independent reviewers. Supplementary File 1 gives a detailed description of the search criteria and study selection process. In the qualitative analysis, patient quotes regarding a polypill therapy were extracted and the expert committee independently paraphrased and categorized each quote. The resulting categories were compared and discussed until content saturation was reached. To test these issues, a provisional issue list was handed to HCPs and patients.

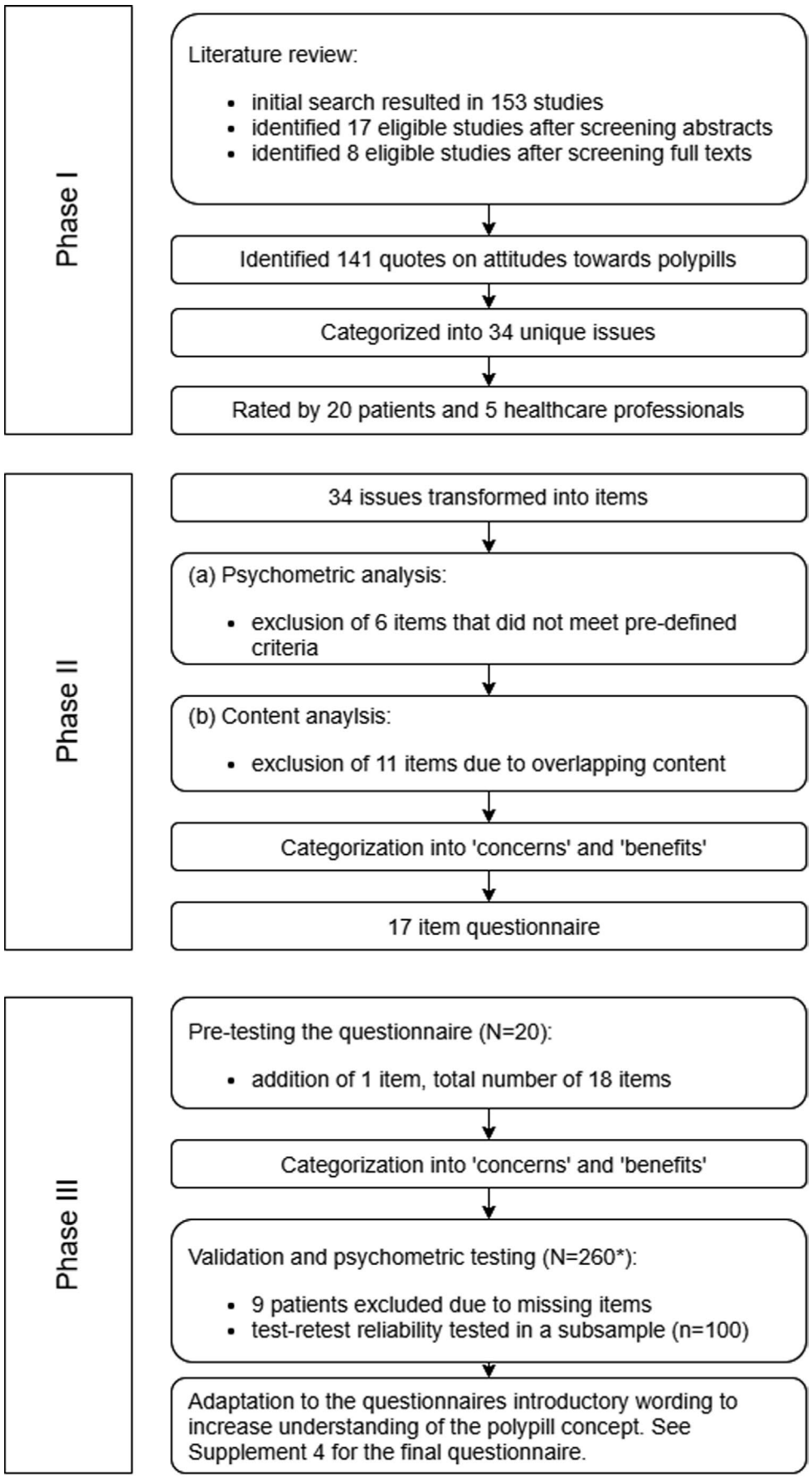


**FIGURE 1** Illustration of the APPQ generation process across all phases. *Part of this sample was also used in a student diploma thesis [26]

### (b) Healthcare professionals

Five HCPs of the Department of Neurology, Medical University of Innsbruck, were handed an issue list and asked to rate the relevance of each issue for their patients on a four-point scale (0, not relevant at all; 3, very relevant). Moreover, HCPs were asked to identify the 25 most important issues. If new issues emerged, they were added to the preliminary issue list.

### (c) Patients

Lastly, the issue list was distributed to 20 patients with TIA or ischaemic stroke. Analogous to HCPs, patients rated the issues on a four-point scale and were asked to choose the 25 most important issues. After rating the issue list, patients were debriefed using a structured interview to identify incomprehensible, unimportant or irritating items, or to suggest new items.

## Phase II

The goal of phase II was to construct an item list based on the results of phase I. A two-step process was employed. First, the psychometric properties of the issues list were analysed (perceived importance, range, skewness, differences between HCPs and patients). Issues were retained if (i) at least 60% of patients or 80% of HCPs considered the issue a priority; (ii) the issue's relevance was rated >1 (i.e., a little, quiet or very relevant) by the patients; (iii) the patients' answer range was ≥3. In the second step, categories based on content were constructed. Similar issues were grouped together and redundant issues were discussed and merged.

## Phase III

In phase III, the questionnaire was pre-tested and validated. A makeshift version of the questionnaire was constructed which, in addition to the questionnaire constructed in phase II, also assessed item comprehensibility (format: yes/no) [...] was given to and completed by a pilot sample of patients. After completing the questionnaire, patients were debriefed using a structured interview to identify incomprehensible, unimportant or irritating items, or to suggest new items. The provisional items from the questionnaire were retained if (i) at least 90% of patients rated an item comprehensible and important; (ii) no concerns of irritation were raised, (iii) at least 95% of patients responded to the item. Items that failed to meet the criteria were considered for rephrasing or dropped from the questionnaire.

The final questionnaire was then tested in a larger sample of patients with cerebrovascular disease. Patients were approached at the neurology ward or outpatient clinic of the Medical University of Innsbruck and asked to participate in the study. A study assistant introduced patients to the study and asked them to complete the Attitudes towards Polypills Questionnaire (APPQ), a basic demographical data assessment sheet. After completion of the questionnaire, patients were debriefed using the structured interview.

To assess test–retest reliability (the degree to which repeated measurements in stable patients return similar results), the APPQ was administered for a second time in a subgroup of patients. Patients were instructed to complete the APPQ a second time 7 to 21 days after the baseline assessment and return it using a prestamped envelope.

## Statistical analysis

Descriptive data (means, standard deviation, percentages) were analysed during all phases. In phase III an explorative principal component analysis with varimax rotation was performed. All factors with an eigenvalue >1 were extracted. The inflection point in the scree plot was used as a secondary measure of factor extraction. Internal reliability was calculated as Cronbach's alpha. The test–retest reliability was judged via the intraclass correlation coefficient (ICC). An ICC >0.70 was regarded as adequate [27].

# RESULTS

## Phase I: Generation of issues

The literature search was conducted in February 2018 and resulted in 153 studies. Eligibility rating of the titles and abstracts by the reviewers resulted in 17 eligible studies (interrater agreement 89%) which were reviewed in full and judged for eligibility once more. Eight studies which contained direct or indirect patient quotes on attitudes towards polypills or combined pills met the inclusion criteria [28–35].

A total of 141 quotes were extracted from the studies. Content analysis of the quotes identified 34 unique issues of patients' attitudes towards polypills. Based on the literature review, the issues were grouped into eight domains: (i) benefits of a polypill; (ii) readiness to take a polypill; (iii) need for information; (iv) concerns about the polypill; (v) individuality and adaptability of the dosage; (vi) concerns about side effects or interactions; (vii) availability concerns; (viii) cost-related aspects.

Twenty patients (seven female, 13 male, mean age 68 years) rated the issue list in phase I (Table 1). Relevance ratings by patients ranged from 0.75 to 2.75. Relevance ratings by the five HCPs who rated the issue list (one female, four male, at least 3 years of experience) ranged from 0.60 to 3.00.

## Phase II: Operationalization of the provisional questionnaire

The issue selection process is shown in Table 1. Two issues (i33, i34) were excluded due to an average relevance rating <1 indicating low

**TABLE 1** Patients' and healthcare professionals' ratings and issue selection process

| Issue | | Mean relevance ratings (0–3) | | Priority rating (%) | | Answer range (patients) |
|---|---|---|---|---|---|---|
| | | Patient-rated | HCP-rated | Patient-rated | HCP-rated | |
| 1 | Eases practical aspects of medical drug intake[d] | 2.75 | 2.00 | 85% | 80% | 3[c] |
| 2 | Easier adherence to treatment due to only taking one pill[d] | 2.60 | 3.00 | 80% | 100% | 3[c] |
| 3 | Reduces medical burden[d] | 2.60 | 2.00 | 75% | 80% | 3[c] |
| 4 | **Expecting easier drug intake** | **2.55** | **3.00** | **90%** | **100%** | **4[c]** |
| 5 | **Securing the right medication** | **2.55** | **2.40** | **90%** | **100%** | **4[c]** |
| 6 | Easier drug management[d] | 2.50 | 2.40 | 75% | 100% | 4[c] |
| 7 | Lessens medication confusion[d] | 2.50 | 2.80 | 85% | 80% | 4[c] |
| 8 | **Considering the polypill for treatment** | **2.50** | **2.60** | **65%** | **80%** | **3[c]** |
| 9 | **Concerns about diffuse causes for possible side effects** | **2.40** | **2.60** | **75%** | **100%** | **4[c]** |
| 10 | **Forgetting to take medications less frequently** | **2.35** | **2.40** | **80%** | **100%** | **4[c]** |
| 11 | **Needing more information about the polypill from the doctors** | **2.35** | **1.80** | **65%** | **100%** | **4[c]** |
| 12 | Needing more scientific proof[d] | 2.35 | 2.40 | 70% | 80% | 4[c] |
| 13 | **Concerns about finding the right dosage** | **2.30** | **1.60** | **80%** | **40%** | **4[c]** |
| 14 | Needing more information about dosage adaptation possibilities[d] | 2.30 | 2.00 | 70% | 40% | 4[c] |
| 15 | **Concerns about side effects** | **2.20** | **2.00** | **80%** | **100%** | **4[c]** |
| 16 | Concerns about unknown side effects[d] | 2.20 | 2.20 | 65% | 80% | 4[c] |
| 17 | **Concerns about being able to adapt the dosage** | **2.20** | **1.80** | **80%** | **80%** | **4[c]** |
| 18 | Trusting HCPs regarding the polypill[b] | 2.10 | 2.00 | 55% | 60% | 4[c] |
| 19 | **Concerns about unwanted pharmacological interactions** | **2.00** | **2.40** | **65%** | **100%** | **4[c]** |
| 20 | Wanting all possible side effects listed in the package insert[d] | 1.85 | 1.80 | 60% | 60% | 4[c] |
| 21 | **Concerns about medications in polypills being less potent** | **1.85** | **1.40** | **80%** | **60%** | **4[c]** |
| 22 | Needing more information about changes in drug intake routine[b] | 1.80 | 1.60 | 50% | 60% | 4[c] |
| 23 | **Concerns about health consequences of missing a pill** | **1.80** | **2.00** | **60%** | **80%** | **4[c]** |
| 24 | Concerns about lack of personalization[d] | 1.80 | 1.00 | 60% | 40% | 4[c] |
| 25 | **Less possibilities to self-adapt the dosage** | **1.75** | **1.60** | **70%** | **40%** | **4[c]** |
| 26 | **Concerns about pill acquisition[e]** | **1.75** | **1.80** | **60%** | **100%** | **4[c]** |
| 27 | Reduced costs for the economy[b] | 1.70 | 1.80 | 50% | 60% | 4[c] |
| 28 | **Reduced costs for patients[f]** | **1.65** | **1.40** | **40%** | **60%** | **4[c]** |
| 29 | **Concerns about the pill being too strong** | **1.55** | **0.60** | **60%** | **20%** | **4[c]** |
| 30 | Concerns about the polypill costing more than traditional medications[b] | 1.55 | 1.40 | 50% | 60% | 4[c] |
| 31 | **Concerns about unwanted changes in routine** | **1.40** | **1.40** | **30%** | **80%** | **4[c]** |
| 32 | Polypill changing the normal drug intake time[d] | 1.20 | 1.00 | 40v | 80% | 4[c] |

(Continues)

**TABLE 1** (Continued)

| Issue | | Mean relevance ratings (0–3) | | Priority rating (%) | | Answer range (patients) |
|---|---|---|---|---|---|---|
| | | Patient-rated | HCP-rated | Patient-rated | HCP-rated | |
| 33 | Polypill being too large to swallow | 0.85[a] | 1.80 | 35% | 80% | 4[c] |
| 34 | Not wanting to change current medication[b] | 0.75[a] | 1.40 | 25% | 40% | 4[c] |

*Note:* Bold items were included.

[a]Excluded due to a mean patient rating <1.

[b]Excluded due to patient importance <60% and HCP importance <80%.

[c]Answer range ≥3.

[d]Excluded due to content redundancy.

[e]Reworded to incorporate qualitative patient remarks.

[f]Rephrased and retained due to content considerations.

relevance. Comparison of the patient and HCP rated importance of issues showed seven issues with a difference in importance of more than 30% between patients and HCPs. An additional four issues (i18, i22, i27, i30) did not meet the required priority rating criterion and were discarded from the list. One issue ('possibility of reduced costs for patients', i28) that did not meet the required priority criteria was retained given that it was the only one to assess cost-related aspects of the polypill, one of the domains identified in phase I.

Eleven issues were discarded or merged with other issues due to overlapping content (i1–i3, i6, i7, i12, i14, i16, i20, i24, i32). The remaining issues were grouped into two main categories: perceived benefits of the polypill (e.g., easier drug intake) and concerns (e.g., insecurity about possible side effects). Two separate aspects concerned the need for additional information (same level of information needed or more information needed than with regular medication) and the willingness to take a polypill for treatment. Due to a patient's remark in phase I, one issue concerning possible acquisition problems was extended to also assess availability problems (i26). The issues were then transformed into questions (i.e., items). The provisional questionnaire comprised 17 items: 11 items measuring aspects provisionally labelled 'concerns', four items measuring aspects provisionally labelled 'benefits', one question on the need for information, one item on the willingness to take a polypill. A four-point item format was chosen with different answer wording for items measuring 'concerns' or 'benefits' (0, 'no concerns/not beneficial at all'; 3, 'strong concerns/very beneficial'). For the items on the need for information and the willingness for a polypill treatment a dichotomous (yes/no) format was chosen.

## Phase III: Pre-testing and validation

### Pre-test

The pre-test sample consisted of 20 patients (12 male; eight female; 10 inpatients, 10 outpatients) with a mean age of 69 years (SD 15.2).

Roughly half (45%) of the patients reported the need for more information on polypills compared to their standard medication. The majority (72%) of patients were willing to try a polypill treatment should it be available to them.

Patients showed good use of the answer range for all non-dichotomous items (range 0–3). Only two items were rated as incomprehensible/hard to understand, each by one single patient (5% incomprehensibility rating). None of the other items were rated as difficult to understand. No item was rated as irritating.

Two patients suggested additional issues that were not covered by the questionnaire. After review of the suggestions, one of those issues (potential problems with medication that needs to be taken at different time points throughout the day) was added to the questionnaire. Subsequently, the APPQ for validation comprised 18 items (Supplementary File 2).

### Validation phase

The validation assessment of the APPQ was carried out between September 2018 and September 2020. A total of 260 patients participated in the validation phase. In line with our predefined criteria, patients were excluded from the respective analysis if they were missing more than four items from the APPQ ($n = 9$ excluded from APPQ baseline analysis).

The sample was 29.1% female and 70.9% male. A greater number of outpatients (77.7% opposed to 22.3% inpatients) were recruited, as long-term cerebrovascular disease medication is more common in the outpatient setting and inpatients had often just started their medication.

Descriptive data are reported in Table 2. Roughly two-thirds (70.1%) of the sample were willing to try a polypill should it be available; three-quarters of the patients (73.2%) reported that they would need more information on the polypill compared to their standard medication.

Sixty-three patients (25.4%) had help filling out the questionnaire. In all cases, the help was provided by a close relative or the study nurse. On average, patients needed 8.4 min (SD 6.2) to complete the APPQ. The compliance rate was high with less than 3.6% of answers missing for the single items. No item was rated difficult

to answer by more than three patients. Four patients considered either single items or the whole questionnaire inappropriate or inept, reporting difficulties because currently there is no such medication as the polypill, or concerns that one question addressed a topic that was not important to medical care (financial aspects of the polypill). Fifteen patients noted additional remarks in the debriefing questionnaire, all of which were either mainly personal comments (e.g., 'I currently do not take medication; therefore, I found the questions hard to answer'), statements of affirmation for a polypill medication, or comments on the concept of polypills. Review of the comments did not lead to the construction of additional items.

## Principal component analysis

The Kaiser–Meyer–Olkin measure confirmed the adequacy of the data (KMO = 0.899). Bartlett's test of sphericity was significant ($\chi^2(120) = 2025.8$, $p < 0.001$). In the principal component analysis, two factors with an eigenvalue >1 were extracted which explained a total of 59.3% (43.5% and 15.8%) of variance. The two factors correspond to the subscales 'benefits' (items 1–12) and 'concerns' (items 13–16) that were suggested in phase II. The two-factor structure was confirmed by visual inspection of the scree plot (Supplementary File 3). Standardized factor loadings ranged between 0.66 and 0.80 for the concerns subscale and between 0.72 and 0.88 for the benefits subscale. Item descriptives and factor loadings are depicted in Table 3. Potential concerns were, on average, rated 1.06 (SD 0.69). Benefits were rated 1.86 (SD 0.84). The possible answer range (0–3) was fully used by the sample.

The scales showed good internal consistency with Cronbach's alpha 0.93 for concerns and 0.85 for benefits. Item–scale correlations ranged between 0.36 and 0.75 for concerns and 0.48 and 0.75 for benefits. The descriptive results of the APPQ are reported in Tables 3 and 4. The highest rated concern item was 'I have concerns that it might be a problem to combine drugs in a single pill that require intake at different points in time'. The highest rated benefit item was 'Benefit that the polypill is less costly for me (e.g., lower prescription fees)'.

## Test–retest reliability

The return rate for test–retest questionnaires was 62% ($n = 62$). The ICC values were 0.58 (95% confidence interval [CI] 0.37–0.73) for the concerns subscale and 0.19 (95% CI −0.08–0.44) for the benefits subscale, indicating low test–retest reliability for both scales. Further analysis of the data showed that the low ICCs were not caused by single items but rather by a small subsample of patients (<10%) with extreme changes in their answer pattern. For concerns, exclusion of one patient (who reported an average concern rating of 0.2 at the hospital and 2.9 at home) resulted in an ICC of 0.72 (95% CI 0.56–0.83). For benefits, exclusion of five patients (average ratings at the hospital of 3, 0, 0, 0, 3 and at home 0, 3, 3, 2.3, 0.8 respectively) resulted in an ICC of 0.56 (95% CI 0.34–0.72).

**TABLE 2** Descriptive data

| Characteristics | *N* (%) |
|---|---|
| Sex | |
| Male | 178 (70.9) |
| Female | 73 (29.1) |
| Age | |
| Mean | 67.3 |
| SD | 12.4 |
| Diagnosis | |
| Stroke | 195 (77.7) |
| Transitory ischaemic attack | 56 (22.3) |
| Recruitment | |
| Outpatient | 55 (21.9) |
| Inpatient | 196 (78.1) |
| Education | |
| Compulsory school graduation or lower | 30 (12.3) |
| Compulsory school graduation (apprenticeship) | 123 (50.4) |
| Final secondary-school examinations | 61 (25.0) |
| University degree | 26 (10.7) |
| Other | 4 (1.6) |
| Missing | 7 |
| Occupation | |
| Homekeeper | 10 (4.0) |
| Unemployed | 1 (0.4) |
| Part-time | 12 (4.9) |
| Full-time | 38 (15.4) |
| Retired | 178 (72.1) |
| Pension submitted | 2 (0.8) |
| On sick leave (>3 months) | 5 (2.0) |
| Other | 1 (0.4) |
| Missing | 4 |
| Relationship status | |
| Married | 168 (67.2) |
| Long-term relationship (>1 year) | 21 (8.4) |
| Divorced | 23 (9.2) |
| Single | 38 (15.2) |
| Missing | 1 |
| Housing situation | |
| Alone | 55 (22.3) |
| With partner/family/kids | 183 (74.1) |
| Living with family of origin | 4 (1.6) |
| Living in an institution | 5 (2.0) |
| Average pill intake per day (mean)[a] | 4.5 |
| For outpatients (mean) | 5.2 |
| For inpatients (mean) | 3.2 |

*Note:* $N = 251$; data are the number of patients, number (%), or mean, or range.

[a]Due to administrative reasons, the pill intake was only assessed in a subsample of $n = 144$ patients (95 outpatients, 49 inpatients).

**TABLE 3** Item descriptive statistics and rotated factor loadings

| | Item [translation] | Mean | SD | Factor loadings ('concerns') | Factor loadings ('benefits') |
|---|---|---|---|---|---|
| 1 | *(Bedenken, dass) … die Kombinationspille andere Nebenwirkungen hat als die Tabletten, die ich bisher eingenommen habe.*<br>[I have concerns that the polypill has other side effects than the pills I have taken so far] | 0.88 | 0.85 | 0.75 | |
| 2 | *(Bedenken, dass)… es nicht klar ist, welcher Inhaltsstoff in der Kombinationspille für mögliche Nebenwirkungen verantwortlich ist.*<br>[I have concerns that it is not clear which substance in the polypill causes potential side effects] | 1.13 | 0.83 | 0.80 | |
| 3 | *(Bedenken, dass)… ich nicht ausreichend darüber informiert bin, welcher Inhaltsstoff welche Nebenwirkungen verursachen kann.*<br>[I have concerns that I am not sufficiently informed which side effects might be caused by which substance] | 1.11 | 0.94 | 0.76 | |
| 4 | *(Bedenken, dass)… die Wirkstoffe der Kombinationspille Wechselwirkungen haben können.*<br>[I have concerns that the substances in the polypill might have drug interactions] | 1.10 | 0.89 | 0.79 | |
| 5 | *(Bedenken, dass)… die unterschiedlichen Wirkstoffe nicht mehr gleich gut wirken, wenn sie in einer Tablette kombiniert sind.*<br>[I have concerns that the combined pills are not as effective as when taken separately] | 0.94 | 0.94 | 0.78 | |
| 6 | *(Bedenken, dass)… es bei der Kombinationspille nicht möglich ist, die richtige Medikamentendosis für mich einzustellen.*<br>[I have concerns that with the polypill it is not possible to achieve the correct drug dosage for me] | 1.12 | 0.93 | 0.78 | |
| 7 | *(Bedenken, dass)… es schwierig sein kann, die Kombinationspille anzupassen, falls sich die benötigte Dosis der Inhaltsstoffe ändert.*<br>[I have concerns that it might be difficult to adapt the polypill if my required drug dosage is changed] | 1.25 | 0.92 | 0.82 | |
| 8 | *(Bedenken, dass)… ich mit der Kombinationspille weniger Möglichkeiten habe die Dosis der Medikamente selbst anzupassen.*<br>[I have concerns that with the polypill I would have less possibilities to adapt the dosage myself] | 1.16 | 0.99 | 0.73 | |
| 9 | *(Bedenken, dass)… die Kombinationspille die vertraute Routine (z.B. Einnahmezeit) der Medikamenteneinnahme zu meinem Nachteil verändern wird.*<br>[I have concerns that the polypill would change my intake schedule to my disadvantage] | 0.66 | 0.82 | 0.66 | |
| 10 | *(Bedenken, dass)… es gesundheitliche Konsequenzen haben kann, wenn ich vergesse die Kombinationspille einzunehmen.*<br>[I have concerns that forgetting to take the polypill may have negative consequences for my health] | 1.18 | 0.97 | 0.65 | |
| 11 | *(Bedenken, dass)… es mit Schwierigkeiten verbunden ist, die Kombinationspille zu bekommen.*<br>[I have concerns that it might be difficult to obtain the polypill] | 0.98 | 0.94 | 0.66 | |
| 12 | *(Bedenken, dass)… es ein Problem ist verschiedene Medikamente in einer Pille zu kombinieren, wenn sie zu unterschiedlichen Zeitpunkten eingenommen werden müssen.*<br>[I have concerns that it might be a problem to combine drugs in a single pill that require intake at different points in time] | 1.35 | 1.01 | 0.69 | |
| 13 | *(Vorteil, dass)… die Kombinationspille die Medikamenteneinnahme erleichtert (z.B. weniger Tabletten; einfachere Routine der Einnahme)*[Benefit that the polypill simplifies the medication intake (e.g., fewer pills; easier intake routine)] | 1.97 | 1.85 | | 0.88 |

(Continues)

**TABLE 3** (Continued)

| | Item [translation] | Mean | SD | Factor loadings ('concerns') | Factor loadings ('benefits') |
|---|---|---|---|---|---|
| 14 | *(Vorteil, dass)… die Kombinationspille sicherstellt, dass ich die für mich richtig Medikation erhalte.* [Benefit that the polypill ensures that I receive the correct medication] | 1.77 | 0.98 | | 0.85 |
| 15 | *(Vorteil, dass)… man seltener vergisst die Kombinationspille einzunehmen, weil man nur eine Tablette einnehmen muss.* [Benefit that one is less likely to forget to take the pill, since it is just one pill to take] | 1.79 | 1.17 | | 0.82 |
| 16 | *(Vorteil, dass)… die Kombinationspille möglicherweise kostengünstiger für mich als Patient/ Patientin ist (bspw. weniger Rezeptgebühren).* [Benefit that the polypill is less costly for me (e.g., lower prescription fees)] | 1.99 | 1.08 | | 0.72 |

*Note:* Factor loadings <0.25 not shown.

**TABLE 4** Descriptive results of the APPQ

| APPQ scale or item | Rating or *N* (%) |
|---|---|
| Concerns (items 1–12) | |
| Mean rating | 1.07 |
| SD | 0.69 |
| Benefits (items 13–16) | |
| Mean rating | 1.88 |
| SD | 0.89 |
| Would need additional information on the polypill therapy (item 17) | |
| Yes | 183 (73.2) |
| No | 67 (26.8) |
| Missing data[a] | 1 |
| Would be interesting in receiving a polypill therapy (item 18) | |
| Yes | 171 (70.1) |
| No | 73 (29.9) |
| Missing data[a] | 7 |

*Note:* $N = 251$, SD standard deviation.

[a]Missing data were not included in the calculation of percentages.

## DISCUSSION

In this study, a questionnaire was developed to assess cerebrovascular patients' attitudes towards polypills. The phase I–III questionnaire development approach by the EORTC QLG was followed which included input by patients and HCPs and ensured content validity. The APPQ was found to be a comprehensible and applicable questionnaire to assess the attitudes of patients with cerebrovascular disease towards a potential polypill medication.

### Patients' attitudes towards the polypill for the secondary prevention of cerebrovascular disease

Patients in our study were generally open towards using the polypill. A polypill therapy, even if only presented hypothetically, was perceived positively and, on average, potential benefits were rated higher than concerns. This finding is in line with previous studies which suggest that patients with cardiovascular disease are open towards this type of medication [33,35,36] and extend qualitative findings for patients with cerebrovascular disease [28]. At the same time, 73% of our sample reported that they would need additional information from their doctor when receiving a polypill therapy, compared to usual medication. This shows that, even if a polypill therapy is generally perceived positively, there are still a number of concerns that need to be addressed by HCPs in order to successfully implement it [30].

### Factor structure of benefits and concerns

During phase II, the APPQ items were operationalized into possible concerns and benefits. This provisional structure was confirmed in phase III. Generally, the items included in the factors benefits and concerns correspond well to the body of qualitative research which mostly stems from patients with cardiovascular disease. Common themes from the literature that were also rated as important by cerebrovascular patients in this study were possible therapy side effects [28,35], the polypill's impact on patients' medication intake schedule [29,35] and worries about the dosage personalization and adjustments [28,30,31,33]. The latter were not only prominent in the literature but were also the highest rated concerns in our study (items 7 and 12). For the factor benefits, emerging themes were the simplification of the intake schedule [28,31,33], benefits of ensuring the correct medication [29,31,33] and potential cost-related benefits [30,31,33]. The highest rated benefits were cost-related aspects and the simplification of the intake schedule.

### Application of the questionnaire

In recent years, multiple international projects were able to show the potential of a polypill therapy for cardiovascular disease

[20,37], especially in underserved populations [19]. The World Stroke Organization has emphasized the potential benefits of a polypill approach for stroke and outlined possible large-scale implementations [21,38]. Considering that medication adherence is dependent on patients' attitudes towards and their informed understanding of the therapy [23,24], our questionnaire fills an important knowledge gap. The issues covered by the APPQ, especially the 'barriers', may help to inform on patients' worries and their extent.

The potential drawbacks of a dosage simplification should be examined carefully from the patient perspective, as they might lead to a neglect of other risk factors [39]. Consequently, our questionnaire may be used in any implementation of a polypill therapy for patients with cerebrovascular disease in clinical trials or practice.

### Strengths and limitations

A major strength of this article is the rigorous development process of the questionnaire, which involved patient and HCP input early in the process via a standardized method to ensure relevance of the issues. Another strength of the study is the large validation sample of patients with cerebrovascular disease.

The limitations of this study are that only a modified phase I–III questionnaire development process was conducted and that the factor structure has not yet been confirmed in an independent sample. These would be next steps in the questionnaire development process (phase IV of the EORTC questionnaire development guidelines).

Second, the test–retest reliability for both APPQ scales was low. Whilst this might be an indication that patients' attitudes towards polypills are not stable over time, an alternative more likely explanation is offered. Forming and reporting an attitude towards a hypothetical medication is a challenging cognitive task. As shown in our analysis, the low test–retest reliability was induced by a small subsample (<10%) who gave almost polar opposite ratings of benefits or concerns at the two study time points. Exclusion of those patients considerably improved test–retest reliability. It is possible that patients did not fully understand the concept of the polypill at one of the two assessments, which were also conducted in different settings. This indicates a need for an improved plain version of the introduction to the questionnaire and the concept of the polypill. Such an improved version is provided in Supplementary File 4. For further usage and validation of the questionnaire, it is recommended that patients are supported in understanding and reflecting on the polypill concept to ensure the optimal usage of the questionnaire by offering comprehensive information.

Finally, the constructed questionnaire only asked for attitudes towards an individualized polypill (or multicompartment pill) and only patients who had already suffered a stroke or TIA were included. Other use cases of a polypill, such as a fixed-dose combination pill, which can be used in low to medium risk persons, were not covered by the questionnaire. The findings from this study and the use of the questionnaire are therefore restricted to attitudes towards individualized polypills and to patients with cerebrovascular disease (i.e., secondary prevention).

## CONCLUSION

The developed APPQ can be used to assess the attitudes of German-speaking patients with cerebrovascular disease towards a polypill therapy. The data from our validation sample show that patients are open towards this form of medication, but also demonstrate what kind of concerns patients have. Further validation and testing of the questionnaire in different populations (e.g., in populations for primary prevention) are advised.

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### CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

### AUTHOR CONTRIBUTIONS

Jens Lehmann: Conceptualization (supporting); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); writing—original draft (lead); writing—review and editing (lead). David Riedl: Conceptualization (equal); data curation (equal); formal analysis (supporting); investigation (equal); methodology (equal); project administration (supporting); writing—review and editing (equal). Monika Sztankay: Conceptualization (equal); data curation (supporting); formal analysis (equal); investigation (equal); methodology (equal); writing—review and editing (equal). Christian Boehme: Investigation (equal); project administration (equal); writing—review and editing (equal). Julian Fischnaller: Investigation (equal); project administration (supporting); writing—review and editing (supporting). Stefan Kiechl: Conceptualization (equal); funding acquisition (equal); supervision (equal); writing—review and editing (equal). Bernhard Holzner: Conceptualization (lead); data curation (supporting); formal analysis (equal); methodology (equal); project administration (equal); supervision (lead); writing—review and editing (equal). Michael Knoflach: Conceptualization (equal); funding acquisition (equal); investigation (equal); project administration (equal); supervision (equal); writing—review and editing (equal). Gerhard Rumpold: Conceptualization (lead); formal analysis (equal); funding acquisition (equal); methodology (equal); project administration (equal); supervision (lead); writing—review and editing (equal).

## PATIENT AND OTHER CONSENTS

The use of patient data for this study is covered by an ethics approval of the ethics committee of the Medical University of Innsbruck (app. number 1125/2018).

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplementary Material

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