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Stroke survivors', caregivers' and GPs' attitudes towards a Polypill for the secondary prevention of stroke: A qualitative interview study

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ABSTRACT

Objectives

To understand survivors of stroke or transient ischaemic attack, caregivers and GPs perspectives and beliefs on a polypill approach, consisting of blood pressure lowering and cholesterol lowering therapies, with or without aspirin, for the secondary prevention of stroke.

Methods

A qualitative interview study was undertaken within GP surgeries in the East of England. Twenty-eight stroke survivors were interviewed, 14 jointly with a caregiver, along with 5 GPs responsible for their care. Interview topic guides explored attitudes to a polypill, factors likely to influence uptake and long term use, management of polypill medication and factors influencing the decision to prescribe polypill. Data were analysed using a grounded theory approach. Key themes are presented and augmented with verbatim quotes.

Results

Overall study participants were positive about the polypill concept and considered it acceptable in the treatment of stroke. Benefits of polypill identified included convenience leading to improved adherence and reduced burden of treatment. Caregivers felt it would improve medication taking practices and GP were open to prescribing it to those at risk. However, concerns raised included whether a polypill providing equivalent therapeutic benefit, side effects through combining medications, consequences of nonadherence, lack of flexibility in regulating dosage, disruption to current treatment and suitability to the wider stroke population.

Conclusion

Participants supported this treatment approach for the secondary prevention of stroke, however, significant concerns around a polypill strategy remain. Further research on the efficacy of polypill is needed to reassure practitioners whose concerns around inflexibility and the suitability of treatment are likely to influence the decision to prescribe a polypill for secondary stroke prevention. Acceptability of this treatment approach among patients, caregivers and GPs is likely to determine the uptake and subsequent use of a polypill as a treatment for stroke in the future.

Key words: Polypill, Stroke, Qualitative research, Semi-structured interview

Abbreviations: FDC: Fixed-dose combination; CVD: Cardiovascular disease.

Article summary

Article focus

- Cholesterol lowering and blood pressure lowering therapies as well as aspirin, can substantially reduce long term risk following a stroke event.
- A polypill consisting of multiple medications in a single tablet has been advocated as a treatment for the prevention of cardiovascular disease including stroke.
- The aim of this investigation was to explore the views and attitudes of survivors, caregivers and general practitioners, towards a polypill approach for the secondary prevention of stroke.

Key messages

- A polypill was considered acceptable, offering greater convenience and the potential to improve medication adherence in stroke survivors.
- Participants expressed concerns around treatment inflexibility, the suitability of polypill for everyone and the potential for medication side effects.
- Addressing the concerns of survivors, caregivers and GPs will be key to implementing a polypill approach in the future.

Strengths and limitations

- This research adds to an important body of work exploring cardiovascular polypills and is the first study to focus on attitudes to a polypill for stroke prevention.
- The findings are strengthened by the inclusion of caregivers who have an important role to play in managing the medication of stroke survivors.
- Conducting a qualitative assessment of individual perspectives allowed an in-depth and robust examination of the subject area.
- Due to the limited sample size findings may not generalise to the wider stroke population or necessarily represent the views of all health professionals.
- Future research should consider harder to reach groups such as those who need support to manage medication and who may benefit most from the polypill approach.

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INTRODUCTION

Stroke is the fourth most common cause of death in the UK, responsible for approximately 40,000 deaths every year [1] and is also a significant cause of acquired adult disability [2], with about half of all survivors experiencing some degree of physical or cognitive impairment [3] and left dependent on others [4].

People who have had a stroke or a transient ischaemic attack (TIA) also known as a mini-stroke are at high long term risk of a further event [5-6], however, this can be substantially reduced through the use of preventative medications such as anti-platelet agents [7] or anticoagulants [8], as well as cholesterol lowering [9-10] and blood pressure (BP) lowering therapies[11].

Despite evidence based guidelines, treatment for stroke often falls below recommended standards [12-13] and significant deficiencies in secondary prevention care have been reported[14]. The use of multiple medications to treat CVD is often associated with inappropriate medication use (e.g. under use or use of non-appropriate medicines), under prescription and reduced adherence [15]. A polypill consisting of cholesterol lowering and blood pressure lowering therapies, with or without aspirin in a single pill for the treatment of CVD [16] has been proposed.

Wald and Law (2003) introduced the concept and estimated a theoretical 88% reduction in ischaemic heart disease and 80% reduction in stroke, if taken by everyone over 55 [17]. Since then a growing body of literature has developed around fixed-dose combination (FDC) or polypill strategy for the prevention of cardiovascular disease [18-19].

However less is known about patients or practitioners attitudes towards a polypill strategy. To date a small number of investigations have been completed. Although patients considered it

convenient, there were concerns around inflexibility of treatment [20] and GPs would consider prescribing it to those in need if it was shown to be effective. [21-24] With adherence to medication in stroke survivors known to be suboptimal [25], this group may be particularly suited to treatment via a FDC polypill.

The aim of this study was to explore the attitudes and perspectives of stroke/TIA survivors, carers and GPs towards a polypill approach for the secondary prevention of stroke including the benefits and consequences of using a polypill, factors likely to influence polypill uptake, the caregiver role in managing medication and GPs views and attitudes towards prescribing a polypill in the future.

METHODS

Study Design and Participants

A qualitative study using semi-structured interviews. Purposive sampling was used to recruit participants with maximum variety characteristics representing a spread of socio-economic status [26], age, gender, and disability[27]. A search of the GP practice stroke register identified all patients over the age of 55, with a stroke or TIA. Every 3rd patient was selected from the practice, screened for suitability and approached by letter in batches of 25. Interview saturation was reached when no new information emerged from discussions. Carers were approached via stroke survivor and interviews were arranged by phone with the lead GP at each practice. Ethical approval was granted by NHS South Yorkshire Research Ethics Committee, Ref 13-YH-0067.

Data Collection

Data was collected through semi-structured interviews with open ended questions that defined the area to be explored [28]. Topic guides were piloted with 2 stroke survivors and

checked by a GP and appropriate recommendations implemented. All interviews were conducted by the lead author, JJ, who has considerable experience in qualitative research analysis. Field notes were also taken by the interviewer. The schedule of questions was refined and finalised after the 5th interview. Topics discussed were perceived benefits and consequences of a polypill, factors influencing polypill uptake, caregiver views and GPs beliefs and attitudes towards prescribing polypill. Interviews were audiotaped, lasted 1- 1.5 hours and were transcribed verbatim.

Data analysis

Analysis followed a grounded theory approach with constant comparative analysis [29]. A set of codes representing initial themes were developed and refined throughout the data analysis phase. Codes were grouped into similar concepts and from these codes categories were formed. The process of identification and refinement of categories continued until the final themes emerged. Nvivo 9 (QSR Intl, Melbourne, Victoria, Australia) was used to organise, code and manage the data. Transcripts were entered in to the program and coded by JJ, with 20% double coded independently by SS. Queries arising from coded transcripts were settled through discussion. Communication with a third author (JG) enabled clarification and refinement of categories until a consensus on the final themes was reached.

RESULTS

Twenty-eight stroke survivors participated. Fourteen were interviewed alone and 14 with the caregiver present, who was either a spouse (n=12) or family member (n=2). Characteristics of stroke survivors are displayed in Table 1 below. Three male GPs and two female GPs were also interviewed. One GP was white British, one was Chinese and three were of south Asian origin.

Table 1 here.

Polypill benefits

Convenience

Participants were enthusiastic about one tablet combining all stroke medication and reducing treatment burden through minimising the inconvenience of managing multiple medications.

> That is the best thing I've read when it said you might have to take one pill to cover the lot. Super, because that is just a bugbear, it's a bugbear in life. (pp 11, Male, 73yrs).

A single tablet was considered easier to remember and likely to improve overall medication taking behaviour.

> I think it's brilliant because erm I, I've got more chance of remembering to take one tablet than I have of remembering two different times of the day if you like. (pp10, Male, 66 yrs)

While GPs also felt polypill had the potential to improve medication adherence.

> I think that would reduce the pill burden to our patients and I think that's very good idea [ ]...[ ] I think he would be very compliant with it, because he is thinking that he is going to be taking 1 tablet and not 5 tablets….(GP 02, Female).

The potential for 'cross-over' treatment in individuals with multiple existing cardiovascular co-morbidities was mentioned.

> if you're giving polypill in the form of one pill, even with people with comorbidities (you're) maybe reducing their number [ ] and might improve overall compliance and it may have the side effect of improving their comorbidity as well (GP 05, Male).

Carers agreed that a polypill made the medication taking process less demanding.

> It's logic to me and I think it's an excellent idea if it could be done, certainly instead of Jean fiddling about in a saucer trying to pick up tablets.. (pp28, Male, carer).

They also felt that the process of obtaining and managing medication was better compared with using multiple medications.

> One tablet is good really isn't it, because it means that you if you've taken that one you've taken them all. Whereas sometimes if you run short, you think oh I'll just take that and forget about the other one until you go the doctors and get the refill. (pp02, Female, Carer)

Benefits of correct treatment

Polypill offered the benefit of correct medication and it ensured the patient received all of their recommended medications.

> It could protect, once you had polypills that contained a mixture of medications which are known not to have…contradictory side-effects…then you would feel very safe. (pp03, Male, 86 yrs)

There was also confidence that components were safe, tested and therefore provided the most appropriate treatment.

> I'm all for these things..[ ] it might not be good for you, It might not, I don't know I can't see how because if they're now gonna put four different pills into one they musta investigated a, b, c and d to put them in one so therefore it's going to be beneficial to me and anybody else that wants those four in one (pp11, Male, 73yrs).

Polypill concerns

Appropriateness of treatment

For many survivors an important polypill characteristic was its ability to sustain equivalent therapeutic benefit while reducing treatment burden.

> It's a no brainer as far as I'm concerned you've got one tablet with all the ingredients of the others.. if I've got the same erm dosage of statin and if it didn't disturb my readings then yeah I mean erm what are the objections to it? (pp05, Male, 64 yrs)

However, the prospect of a 'pill for all', inability to alter dosage and being less amenable to dose titration, if that was required, was frequently questioned.

> Would the polypill be in different strengths because like for blood pressure at the moment I'm taking…12 and a half, and then me cl- clopridogrel is 75 [ ], maybe six

months down the line my blood pressure can reduce, what would that do with the polypill? (pp21, Female, 68 yrs)

Survivors accustomed to scheduled medication regimens also questioned how drugs could now be combined and taken at a single time point.

if you've got them altogether and you're supposed to take those tablets at different times of the day, how's it going to work? Is it going to upset your system? (pp22, Female, 71 yrs).

Suitability of the polypill strategy

Patients questioned the ease of managing treatment if one or more component was no longer required.

Would it only be suitable for somebody who's taking four of that particular medication? But what would happen if say the Dr said, you're not so bad so you don't need to take that particular tablet? (pp16, Female, 82 yrs)

A few expressed concerns around the inclusion of statins in any combination pill.

Yes has that got anything to do with statins? I've read a lot about statins and I'm afraid I feel I wouldn't want to take them. Because the side effects and everything. (pp19, Female, carer)

GPs were cautious, suggesting polypill could be better suited to those on similar medications whose treatment was well-established.

> I think the right drugs in the right combinations there, it, would potentially be helpful for a cohort of people. I don't think it will be for everyone but there will be a cohort of people who will probably be on very similar drugs..[ ] (GP03, Male)

Patients and carers were also concerned that poor adherence would lead to patients missing all of their secondary prevention drugs.

> if you're gonna give them a polypill that is three or four tablets and they don't bother taking that..They're gonna be worse off (pp14, Male, Carer)

Given the unique needs of stroke patients, some survivors suggested multiple polypills may be needed.

> They don't give me three separate ones for no reason, there must be a reason for it. You can't do that with a polypill unless you have a hundred polypills all different medications and different combinations (pp18, Male, 88 yrs).

Polypill side effects

The likelihood of polypill side effects led many to question the suitability of single pill treatment.

> The fine tuning takes a bit of doing so w- with the one pill I got my bit of a doubt that it might work for some people but it might not work for everybody you see (pp04, Male, 80 yrs).

For GPs, a further problem resulting from this was the potential difficulty in identifying the polypill component responsible for side effects.

> My personal anxiety is about side effects when you club two, three medicines together, if one of them, one of the components is, is causing the side effect then you'll not know, you may have to again change.. (GP 05, Male)

Medication adjustment

GPs questioned the benefit in altering established medication routines, to accommodate a polypill, in those who were already taking their medication as directed.

> If you've got , as I said, a very motivated patient they are happy with what they are taking, then we don't probably have to intervene, but we may have to give to people who are not that motivated or compliant. (GP 05, Male)

They also expressed concern around the inconvenience of having to re-adjust future treatment if polypill components were no longer required.

> If somebody has a problem ok well we'll just stop using the polypill and give them the individual ones but with that stopping and chopping and changing people will say they've changed my tablets again, that becomes an issue. (GP 04, Male)

However inflexibility of polypill and the inability to manipulate dosage was perhaps the greatest concern among GPs.

> We do switch around quite a bit different brands, different sizes, statins and sometimes it may not be the right dose but you kind of slowly edge it in..[ ] It would

be advantageous if it was a single pill but that would be maybe a bit difficult with polypill..[ ] It's the fine tuning that's difficult..(GP 01, Female)

Size of polypill

Health professionals raised concerns that a large pill could actually discourage patients from taking their medications.

Yeah is it a horse tablet? …that's going to have the other, the opposite effect on compliance that we want.[ ] People are going to start breaking it having half now and half twelve hours later..(GP 04, Male).

Cost of polypill

The burden of polypill on NHS resources was also raised with a number of GPs suggesting a more expensive pill could be difficult to prescribe.

If it is cheaper then there won't be an issue at all. if it comes out to be more expensive than the four tablets which you are giving individually to the patient then it comes to be an issue (GP 02, Female)

Cost implications for practices and pharmacies dispensing polypill were also considered with GPs acknowledging the likelihood of reduced revenues associated with a single pill.

They get an item fee for each thing they prescribe so if you have 4 drugs you get a fee for each, if you put it in 1 pill that will account for one (GP 04, Male)

Polypill lessons for implementation

Although stroke survivors were generally positive about the polypill approach, many were non-committal on its future use, largely due to a lack of existing polypill evidence.

Polypill recommendation

Many patients felt future polypill use was likely to depend on their doctor recommending the treatment.

> It sounds good but w- we've got to, we would have to weigh up, listen to what the doctors say and the consultants and see what history, because this polypill, from what we've hear. Very, very little, it's quite new, that's all we know. (pp22, Male, carer)

Satisfied with current medication

Being content with their current medication also made survivors less enthusiastic given that potentially negative impacts of polypill use were largely unknown.

> Why take a tablet that perhaps will affect you. Plus the fact I'm perfectly happy with what I'm on, you know, at the moment anyway (pp01, Female, 71 yrs).

Endorsement of polypill

GPs agreed that if they endorsed polypill, stroke survivors were likely to accept it as a treatment for secondary stroke and commit to using it in the future.

> I think the majority of our current patients if we told them we think this is the right thing to do would probably be happy with that. It's a fairly easy argument (GP 03, Male).

And there was an obligation to try new and innovative treatments like the polypill, if its potential benefits were proven.

> I welcome change and innovation I'm excited by it… you don't know until you've tried it. [ ] We have to try it if there was a potential benefit there for people (GP04, Male)

DISCUSSION

Summary of main findings

Participants were largely enthusiastic about the polypill concept, representing an improvement in the medication taking process and management of treatment, greater convenience, reduced the pill burden and was likely to lead to better medication adherence. Polypill also ensured patients received the correct treatment and that medications were safe. Concerns around suitability for everyone, the potential for side effects and limitations of adjusting dosage and polypill inflexibility, persisted. GPs felt a more expensive pill would be problematic and acknowledged their endorsement was key to it being accepted by patients. For survivors the decision to use a polypill depended on the GPs recommendation, however, those who were satisfied with their current treatment regimen felt less inclined to change to a polypill approach.

Strengths and Limitations

A strength of this study is that it adds to a growing and important body of research on attitudes towards a cardiovascular polypill with a focus on secondary prevention of stroke. Secondly, this study benefits from a robust methodological approach using semi-structured interviews which permits a robust and in depth assessment of individual perspectives. A further strength is the inclusion of caregivers, who can make a significant contribution in the future management of polypill treatment. We believe the completion of interviews by a qualitative researcher rather than a health professional facilitated a willingness among patients to engage in discussion with survivors welcoming the opportunity to discuss experiences around stroke and preventative treatment. However limitations to consider include a relatively small sample recruited from 5 general practice surgeries. Whilst every effort was made to recruit a representative sample with varied disability, participants were largely a convenience sample consisting of those who responded to our request to participate. In addition, survivors were almost exclusively White British. With some ethnic groups, particularly south Asians, known to be at considerably higher risk of cardiovascular disease[30], the study may have benefited from the views and attitudes of those individuals who are considered to be at a greater potential risk from stroke and likely to be prospective users of polypill therapy. As a result, study participants may not necessarily represent the wider population. With all caregivers interviewed in the presence of a survivor, this may have contributed to individuals responding in a socially desirable manner. Our aim was to recruit a maximum variety sample however most participants were able bodied and independently managed their own medication. Investigating a polypill among survivors with significant symptoms and dependent on others to organise tablets may be an area for future research in the field. Finally, with a recruitment rate of 6% in the most deprived area we visited further

research should aim for those harder to reach groups of survivors who may benefit most from a polypill treatment approach.

Comparisons with existing literature

The inflexibility of treatment and the potential for side effects were considered key challenges for the polypill approach. Concerns around side effects are well founded, having previously been identified as influencing medication taking behaviour [31] and recognised as a significant barrier to adherence in cardiovascular disease medication [32]. Our findings are also in line with a recent UK primary care investigation in which patients considered a secondary prevention polypill acceptable, but were concerned about components interacting and inflexibility of treatment [33]. The inability to adapt polypill dosage and the suitability of fixed dose treatment for stroke survivors was a key concern for GPs in our study and has been previously reported in studies exploring polypill attitudes among GPs elsewhere. A small survey of 17 practitioners in New Zealand reported that having no choice of polypill components or doses was the thing GPs disliked most about the concept of a polypill [21]. In another UK study of primary healthcare professionals, inability to titrate dosage was considered a major disadvantage of polypill [24].

GPs agreed that cost was a potential impediment to prescribing polypill in the future. Compared with free combination medications, FDC therapy has the potential to be relatively inexpensive due to cheaper drug costs and reduced monitoring [34], and there is increasing evidence in the literature supporting the cost-effectiveness of a polypill strategy [35-36]. With modest costs considered a cornerstone of combination therapy [37], undertaking cost-effective evaluations to determine the feasibility of using polypills is urgently needed.

Study participants identified improved compliance as a key advantage and acknowledged a single medication episode was easier to remember. With frequent dosing

regimens [38] and polypharmacy associated with poor patient compliance to cardiovascular medications [39-40], a polypill approach offering a simplified medication regimen has the potential to improve adherence in the treatment of cardiovascular disease [41] [20]. Our study corroborates observations from a patient perspective on whether a polypill could improve adherence, which highlighted concerns around the efficacy of polypill compared with current medications and the potential for side-effects [20].

For caregivers, benefits of polypill included simplifying the medication taking process and ease in organising pill boxes. In a recent study on factors that influenced caregiving and medication management, participants recognised complex medication needs as an impediment to care by increasing the demands placed on the caregiver [42]. Caregivers in our study recognised that the polypill approach was potentially more convenient for the pharmacy, an observation which has been confirmed in a recent qualitative investigation exploring pharmacists views towards a cardiovascular polypill [43].

Stroke survivors expressed a reluctance to adopt a future polypill strategy, citing GP approval as a key factor. This not only supports the view that cardiovascular patients were inclined to do what their GPs told them [44] but also highlights the key role health professionals can play in promoting a polypill approach. Exploring the perspectives of those with direct experience of the polypill can also contribute to the wider acceptability of a polypill strategy and should be a priority of future research in the field. A recent investigation of the views of patients and providers who participated in a polypill trial identified similar advantages and concerns as our own [45] suggesting that polypill perspectives translate to other regions and health care settings.

With research suggesting that health practitioners often fail to fully explain the important elements of medication when first prescribing treatment, [46] uptake of polypill may

depend not only on the health professional prescribing therapy, but also informing and encouraging acceptance of the approach among stroke survivors and their caregivers.

Implications for clinical practice

Results of this investigation confirm acceptability of a polypill for the secondary prevention of stroke. However, greater efforts to reassure patients and the willingness of GPs to endorse such treatment is likely to determine acceptability of this approach over the long term, particularly as inadequate information and difficulties with new medications are associated with poor adherence [47]. With adherence to medication in stroke survivors known to be suboptimal [25], this patient group may be particularly suited to receiving treatment using fixed-dose combination polypill therapy. Further research on the efficacy of polypill will also reassure practitioners whose concerns around inflexibility and the suitability of treatment are likely to influence the decision to prescribe a polypill for stroke patients.

Conclusion

A growing body of evidence suggests a fixed-dose combination polypill may have an important part to play in the prevention of cardiovascular disease. Our findings contribute to this knowledge base and offer a unique insight into a potentially exciting role for polypill in the secondary prevention of stroke. The views of stroke survivors, caregivers and GPs reported here can play an important role in realising this process, however addressing patients and practitioners concerns and intensifying efforts to increase acceptability of the polypill approach are needed. Robustly designed randomised controlled trials can contribute to the successful implementation and uptake of a polypill strategy for the secondary prevention of stroke.

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Competing Interests

None

Author/s contribution

Jonathan Mant conceived of the study, is the chief investigator on the polypill programme and commented on the final draft of the manuscript. Jonathan Graffy is a co-investigator on the polypill programme, contributed to the data analysis and commented on the manuscript. Ricky Mullis is a co-investigator on the polypill programme, contributed to developing the study protocol and commented on the manuscript. Stephen Sutton is a co-investigator on the polypill programme, contributed to the data analysis and commented on the manuscript. James Jamison contributed to developing the study protocol, conducted the interviews and data analysis and prepared the manuscript for submission.

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Gender	Male: n=21 (75%) Female: n=7 (25%)
Age (Mean: 74yrs)	60-69yrs: n=10 (36%) 70-79yrs: n=11 (39%) 80-89yrs: n=7 (25%)
Ethnicity	White: n=27 (97%), South Asian: n=1 (3%)
Stroke classification	Stroke: n=14 (50%) TIA: n=14 (50%)
Time since stroke	6 mths-2 yrs; n=10 (35%) 3-5 yrs: n=8 (29%)

	6-10 yrs: n=5 (18%) >10 yrs: n=5 (18%)
Diabetes status	Yes: n=9 (32%) No: n=19 (68%)
Smoking status	Non-smoker: n=15 (54%) Ex-smoker: n=11 (39%) Smoker: n=2 (7%)
Interview status	Survivor and caregiver: n=14 (50%) Survivor only: n=14 (50%)
Rankin score **MrS-9Q(44)**	No symptoms: (0) n=6 (21%) No sig. disability: (1) n=4 (14%) Slight disability: (2) n=6 (21%) Moderate disability: (3) n=4 (14%) Mod severe/ severe disability: (4-5) n=8 (29%)

Table 1. Stroke survivor characteristics

BMJ Open

Stroke survivors', caregivers' and GPs' attitudes towards a Polypill for the secondary prevention of stroke: A qualitative interview study

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Stroke survivors', caregivers' and GPs' attitudes towards a Polypill for the secondary prevention of stroke: A qualitative interview study

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ABSTRACT

Objectives

To understand the perspectives of stroke survivors, caregivers and GPs on a polypill approach, consisting of blood pressure and cholesterol lowering therapies, with or without aspirin, for the secondary prevention of stroke.

Methods

A qualitative interview study was undertaken in five GP surgeries in the East of England. Twenty-eight survivors of stroke/TIA were interviewed, 14 jointly with a caregiver, along with a convenience sample of five GPs, to assess attitudes towards a polypill and its future use. Topic guides explored attitudes to a polypill, factors likely to influence uptake and long-term use, management of polypill medication and factors influencing the decision to prescribe. Data were analysed using a grounded theory approach. Key themes are presented and illustrated with verbatim quotes.

Results

The analysis identified three key themes: polypill benefits, polypill concerns and polypill lessons for implementation. Stroke/TIA survivors were positive about the polypill concept and considered it acceptable in the secondary prevention of stroke. Benefits of a polypill included convenience resulting in improved adherence and reduced burden of treatment. Caregivers felt that a polypill would improve medication taking practices, and GPs were open to prescribing it to those at increased cardiovascular risk. However, concerns raised included whether a polypill provided equivalent therapeutic benefit, side-effects through combining medications, consequences of nonadherence, lack of flexibility in regulating dosage, disruption to current treatment and suitability to the wider stroke population.

Conclusion

Participants supported a polypill approach for secondary prevention of stroke, but significant concerns remain. Further research on the efficacy of a polypill is needed to reassure practitioners whose concerns around inflexibility and treatment suitability are likely to influence the decision to prescribe a polypill for secondary prevention of stroke. Acceptability among survivors, caregivers and GPs is likely to determine the uptake and subsequent use of a polypill in the future.

Key words: Polypill, Stroke, Qualitative research, Semi-structured interview

Abbreviations: FDC: Fixed-dose combination; CVD: Cardiovascular disease.

Article summary

Strengths and limitations

- This research adds to an important body of work exploring cardiovascular polypills and is the first study to focus on attitudes to a polypill for secondary prevention of stroke.
- The findings are strengthened by the inclusion of caregivers who have an important role to play in managing the medication of stroke/TIA survivors.
- Conducting a qualitative assessment of individual perspectives allowed an in-depth examination of the subject area.
- Due to the limited sample size findings may not generalise to the wider stroke population or necessarily represent the views of all GPs

- Future research should consider harder to reach groups such as those who need support to manage medication and may benefit most from a polypill approach.

INTRODUCTION

Stroke is the fourth most common cause of death in the UK, responsible for approximately 40,000 deaths every year [1] and is also a significant cause of acquired adult disability [2], with about half of all survivors experiencing some degree of physical or cognitive impairment [3] and left dependent on others [4].

People who have had a stroke or a transient ischaemic attack (TIA; also known as a mini-stroke) are at higher long-term risk and therefore exposed to the increased possibility of having a further event [5-6]. However, this risk can be substantially reduced through the use of preventative medications such as anti-platelet agents [7] or anticoagulants [8], as well as cholesterol lowering [9 10] and blood pressure (BP) lowering therapies[11].

Despite evidence-based guidelines, treatment for stroke often falls below recommended standards [12 13], and significant deficiencies in secondary prevention care have been reported[14]. The use of multiple medications to treat CVD is often associated with inappropriate medication use (e.g. under-use, or use of non-appropriate medicines), under-prescription and reduced adherence [15]. A polypill consisting of cholesterol lowering and blood pressure lowering therapies, with or without aspirin in a single pill for the treatment of CVD [16] has been proposed.

Wald and Law (2003) introduced the polypill concept and estimated a theoretical 88% reduction in ischaemic heart disease and 80% reduction in stroke, if taken by everyone over 55 [17]. Since then a growing body of literature has developed around a polypill, otherwise

known as a fixed-dose combination (FDC) pill, for the prevention of cardiovascular disease [18] [19]. A series of recently completed trials investigating the role of a fixed-dose combination pill on adherence to medication for secondary prevention demonstrated improved adherence for the polypill strategy compared with standard care [20-22]. Elsewhere FOCUS found improved adherence for patients with myocardial infarction in the polypill group compared to the group given the 3 drugs separately[23].

To date a small number of studies have investigated the perspectives of patients and health care professionals towards a theoretical polypill. Although cardiovascular patients considered it convenient, they had concerns around the inflexibility of a polypill [24], however, GPs would consider prescribing it to those who needed secondary prevention medication if it was shown to be effective. [25-28] With adherence to medication in stroke survivors known to be suboptimal [29], this group may be particularly suited to treatment with an FDC polypill.

The aim of this study was to explore the attitudes and perspectives of stroke/TIA survivors, carers and GPs towards a polypill approach for the secondary prevention of stroke, including the benefits and consequences of using a polypill, factors likely to influence uptake, the caregiver role in managing medication and GPs' views and attitudes towards prescribing a polypill in the future.

METHODS

Study Design and Participants

A qualitative study using semi-structured interviews was undertaken. The stroke registers of 5 GP practices in the East of England were searched. In each practice, a list of prospective participants over the age of 55 with a diagnosis of stroke or TIA was generated and screened by a GP. Anyone deemed unsuitable for the study was excluded. Purposive sampling was used to recruit stroke/TIA survivors with maximum variation characteristics representing a spread of socio-economic status [30], age, gender, and disability[31]. Survivors were sent a study information pack and invited to interview. Caregivers were approached through the survivor and both were interviewed together, due to time and logistical constraints. All interviews were conducted in the stroke survivors' homes. We also sought the views of a convenience sample of GPs, each of whom was the study lead for their practice. The GP was contacted by phone and an interview arranged at their place of work. The number of interviews conducted was determined by data saturation, the point where no new information emerged from discussions. Interviews were face to face and consent was taken in person before any discussion commenced. Ethical approval was granted by NHS South Yorkshire Research Ethics Committee, Ref 13-YH-0067.

Data Collection

Data was collected through semi-structured interviews with open ended questions that defined the area to be explored [32]. Topic guides were developed by the authors and informed by current literature in the field and expertise within the study team which included a GP, a qualitative researcher and a stroke expert. To ensure ease of understanding and suitability, topic guides were piloted with two stroke survivors and checked by a GP. Any appropriate recommendations were considered and implemented. Data from the two pilot interviews was included in the final analysis. All interviews were conducted by the lead author, JJ, who has considerable experience in qualitative research analysis. Field notes were also taken by the interviewer. Topics discussed were perceived benefits and consequences of a polypill, factors

influencing polypill uptake, caregiver views and GPs' beliefs and attitudes towards prescribing a polypill. The schedule of questions was refined and finalised after the fifth interview to include questions on the wider experience of stroke as well as understanding of the polypill approach and the GP relationship. Interviews were audiotaped, lasted 1- 1.5 hours and were transcribed verbatim.

Data analysis

We followed the Strauss and Corbin Grounded Theory approach using constant comparative analysis [33]. This method permits key points to emerge from the data and to then be coded individually. A set of codes, representing initial themes, were developed from chunks of data. Codes were then further refined, and those representing similar concepts were grouped together to form categories. The identification and refinement of categories continued until the final themes emerged. Nvivo 9 (QSR Intl, Melbourne, Victoria, Australia) was used to organise, code and manage the data. Transcripts were entered into the program and coded by JJ, with 20% double coded independently by SS. Queries arising from coded transcripts were settled through discussion. Communication with a third author (JG) enabled clarification and refinement of categories until a consensus was reached.

RESULTS

A total of twenty-eight stroke/TIA survivors participated. Fourteen were interviewed alone and 14 with the caregiver present, who was either a spouse (n=12) or family member (n=2). Characteristics of survivors are displayed in Table 1 below. Three male GPs and two female GPs were also interviewed. One GP was white British, one was Chinese and three were of south Asian origin. Key themes identified reflected the positive and negative aspects of the polypill approach as well as future use. Sub-themes highlighted benefits and concerns associated with a polypill approach and factors likely to influence stroke survivors using a polypill.

Table 1 here.

Polypill benefits

The concept of a polypill was broadly acceptable to survivors and caregivers. Greater convenience leading to better adherence, confidence that a polypill was providing the appropriate treatment, reduced treatment burden, ease of use, and improved medication management were all considered benefits. For GPs, a polypill facilitated medication taking and provided flexibility in treatment and convenience around prescribing practices.

Convenience

Survivors were enthusiastic about one tablet combining all stroke medication and reducing treatment burden through minimising the inconvenience of managing multiple medications.

> That is the best thing I've read when it said you might have to take one pill to cover the lot. Super, because that is just a bugbear, it's a bugbear in life. (pp 11, Male, 73yrs).

A single tablet was considered easier to remember and likely to improve overall medication taking behaviour.

> I think it's brilliant because erm I, I've got more chance of remembering to take one tablet than I have of remembering two different times of the day if you like. (pp10, Male, 66 yrs)

Caregivers also endorsed the view that a polypill improved compliance and that it ensured the appropriate medications were being taken.

> It means that if you've taken that one you've taken them all. Whereas sometimes if you run short, you think oh I'll just take that one and forget about the other one until you go to the doctors and get the refill (pp02, Female, carer).

GPs also felt that a polypill had the potential to improve medication adherence.

> I think that would reduce the pill burden to our patients and I think that's very good idea... I think he would be very compliant with it, because he is thinking that he is going to be taking 1 tablet and not 5 tablets….(GP 02, Female).

The potential for 'cross-over' treatment in individuals with multiple existing cardiovascular co-morbidities was mentioned.

> If you're giving polypill in the form of one pill, even with people with comorbidities (you're) maybe reducing their number…and might improve overall compliance and it may have the side effect of improving their comorbidity as well (GP 05, Male).

Carers agreed that a polypill made the medication taking process less demanding.

> It's logic to me and I think it's an excellent idea if it could be done, certainly instead of *[patient]* fiddling about in a saucer trying to pick up tablets.. (pp28, Male, carer).

They also felt that the process of obtaining and managing medication was better compared with using multiple medications.

> One tablet is good really isn't it, because it means that you if you've taken that one you've taken them all. Whereas sometimes if you run short, you think oh I'll just take that and forget about the other one until you go the doctors and get the refill. (pp02, Female, Carer)

Benefits of correct treatment

A polypill offered the benefit of correct medication and it ensured that the patient received their recommended medications.

> It could protect, once you had polypills that contained a mixture of medications which are known not to have…contradictory side-effects…then you would feel very safe. (pp03, Male, 86 yrs)

There was also confidence that components were safe, tested and therefore provided the most appropriate treatment.

> I'm all for these things….it might not be good for you, It might not, I don't know I can't see how because if they're now gonna put four different pills into one they

musta investigated a, b, c and d to put them in one so therefore it's going to be beneficial to me and anybody else that wants those four in one (pp11, Male, 73yrs).

Polypill concerns

Survivors' and caregivers' concerns included polypill noncompliance resulting in missing all medications, inability to adjust dosage, whether a polypill could maintain the benefits of the survivors' current secondary prevention medication, timing of a polypill, identifying the source of polypill side effects and modifying treatment if a component was no longer required. GPs questioned whether a single pill could treat the entire stroke population, the cost implications of treatment and the wisdom in modifying a patient's stable treatment regimen.

Appropriateness of treatment

Several survivors expressed concern that a polypill may not sustain equivalent therapeutic benefit of secondary prevention treatment.

As far as I'm concerned you've got one tablet with all the ingredients of the others… if I've got the same erm dosage of statin and if it didn't disturb my readings then yeah I mean erm what are the objections to it? (pp05, Male, 64 yrs)

Several survivors had concerns about the prospect of a 'pill for all', inability to alter dosage and being less amenable to dose titration, if that was required..

> Would the polypill be in different strengths because like for blood pressure at the moment I'm taking…12 and a half, and then me cl- clopridogrel is 75…, maybe six months down the line my blood pressure can reduce, what would that do with the polypill? (pp21, Female, 68 yrs)

Survivors accustomed to scheduled medication regimens also questioned how drugs could now be combined and taken at a single time point.

> if you've got them altogether and you're supposed to take those tablets at different times of the day, how's it going to work? Is it going to upset your system? (pp22, Female, 71 yrs).

Suitability of the polypill strategy

Survivors questioned the ease of managing treatment if one or more components were no longer required.

> Would it only be suitable for somebody who's taking four of that particular medication? But what would happen if say the Dr said, you're not so bad so you don't need to take that particular tablet? (pp16, Female, 82 yrs)

A few expressed concerns around the inclusion of statins in any combination pill.

> Yes has that got anything to do with statins? I've read a lot about statins and I'm afraid I feel I wouldn't want to take them. Because the side effects and everything. (pp19, Female, carer)

GPs were cautious, suggesting a polypill could be better suited to those on similar medications whose treatment was well-established.

> I think the right drugs in the right combinations there, it, would potentially be helpful for a cohort of people. I don't think it will be for everyone but there will be a cohort of people who will probably be on very similar drugs… (GP03, Male)

Survivors and carers were also concerned that poor adherence would lead to missing all their secondary prevention drugs.

> If you're gonna give them a polypill that is three or four tablets and they don't bother taking that..They're gonna be worse off (pp14, Male, Carer)

Given the unique needs of stroke survivors, some suggested that multiple polypills may be needed.

> They don't give me three separate ones for no reason, there must be a reason for it. You can't do that with a polypill unless you have a hundred polypills all different medications and different combinations (pp18, Male, 88 yrs).

Polypill side effects

The likelihood of polypill side effects led many to question the suitability of single pill treatment.

> The fine tuning takes a bit of doing so w- with the one pill I got my bit of a doubt that it might work for some people but it might not work for everybody you see (pp04, Male, 80 yrs).

For GPs, a further problem resulting from this was the potential difficulty in identifying the component of a polypill responsible for side effects.

> My personal anxiety is about side effects when you club two, three medicines together, if one of them, one of the components is, is causing the side effect then you'll not know, you may have to again change.. (GP 05, Male)

Medication adjustment

GPs questioned the benefit in altering established medication routines to accommodate a polypill in those who were already taking their medication as directed.

> If you've got, as I said, a very motivated patient they are happy with what they are taking, then we don't probably have to intervene, but we may have to give to people who are not that motivated or compliant. (GP 05, Male)

They also expressed concern about the inconvenience of having to re-adjust future treatment if polypill components were no longer required.

> If somebody has a problem ok well we'll just stop using the polypill and give them the individual ones but with that stopping and chopping and changing people will say they've changed my tablets again, that becomes an issue. (GP 04, Male)

However, inflexibility of a polypill and the inability to manipulate dosage was perhaps the greatest concern among GPs.

> We do switch around quite a bit different brands, different sizes, statins and sometimes it may not be the right dose but you kind of slowly edge it in... It would be advantageous if it was a single pill but that would be maybe a bit difficult with polypill…It's the fine tuning that's difficult..(GP 01, Female)

Caregivers also expressed concern around the inflexibility of a polypill and the potential difficulties in adjusting dosage.

> You would have to get the right strengths of each tablet. "Where you were on atenolol 50 you are now on 25". Sometimes they change the strength of the tablet. That's where it would be harder to change with the polypill (pp25, Female, carer)

Size of polypill

GPs raised concerns that a large pill could actually discourage medication taking.

> Yeah is it a horse tablet? …that's going to have the other, the opposite effect on compliance that we want… People are going to start breaking it having half now and half twelve hours later..(GP 04, Male).

Cost of polypill

The burden of the polypill on NHS resources was also raised with a number of GPs suggesting that a more expensive pill could be difficult to prescribe.

> If it is cheaper then there won't be an issue at all. if it comes out to be more expensive than the four tablets which you are giving individually to the patient then it comes to be an issue (GP 02, Female)

Cost implications for practices and pharmacies dispensing a polypill were also considered with GPs acknowledging the likelihood of reduced revenues associated with a single pill.

> They get an item fee for each thing they prescribe so if you have 4 drugs you get a fee for each, if you put it in 1 pill that will account for one (GP 04, Male)

Polypill lessons for implementation

Survivors thought that whether they used a polypill in the future would depend on their doctor's recommendation, but they also questioned the need for a polypill given their satisfaction with current treatment. GPs acknowledged that their support was likely to be influential in the decision to use a polypill and believed the approach should be adopted if it was found to be beneficial to the patient. While stroke/ TIA survivors were generally positive about the polypill approach, many were non-committal on its future use, largely due to the lack of existing evidence.

Polypill recommendation

Many survivors felt that whether they used a polypill in the future was likely to depend on their doctor recommending the treatment.

> It sounds good but w- we've got to, we would have to weigh up, listen to what the doctors say and the consultants and see what history, because this polypill, from what we've hear. Very, very little, it's quite new, that's all we know. (pp22, Male, carer)

Satisfied with current medication

Being content with their current medication also made survivors less enthusiastic about taking a polypill which may have unwanted side-effects.

> Why take a tablet that perhaps will affect you. Plus the fact I'm perfectly happy with what I'm on, you know, at the moment anyway (pp01, Female, 71 yrs).

Endorsement of the polypill

GPs agreed that if they endorsed polypill, stroke/TIA survivors were likely to accept it as a treatment for secondary stroke and commit to using it in the future.

> I think the majority of our current patients if we told them we think this is the right thing to do would probably be happy with that. It's a fairly easy argument (GP 03, Male).

Furthermore, there was an obligation to try new and innovative treatments like the polypill, if its potential benefits were proven.

I welcome change and innovation I'm excited by it… you don't know until you've tried it... We have to try it if there was a potential benefit there for people (GP04, Male)

DISCUSSION

Summary of main findings

Stroke/TIA survivors and caregivers were positive about the polypill concept which they saw as offering greater convenience, reducing the burden of treatment and improving adherence. A polypill would also ensure that patients received the correct treatment and that medications were safe. There were concerns among survivors around the suitability of a polypill if not already using the components or if one component was no longer needed. Other limitations included the potential for side-effects and the inflexibility of a single pill approach. GPs felt that a more expensive pill would be problematic and acknowledged that their endorsement was key to it being accepted. For survivors, the decision to use a polypill would depend on the GP's recommendation, but those who were satisfied with their current treatment regimen felt less inclined to change to a polypill.

Strengths and Limitations

A strength of this study is that it adds to a growing and important body of research on attitudes towards a cardiovascular polypill with a focus on secondary prevention of stroke. Second, the use of semi-structured interviews enabled an in-depth assessment of individual perspectives. A further strength is the inclusion of caregivers, who can make a significant contribution in the future management of polypill treatment. We believe that being

interviewed by a qualitative researcher rather than a health care professional encouraged survivors' to be open and to engage in discussion.

However, limitations include a relatively small sample of GPs' recruited from five general practice surgeries. Although every effort was made to recruit a representative sample with varied disability, most survivors who responded to our request to participate were primarily able bodied with no significant stroke symptoms and independently managed their own medication. In addition, survivors were almost exclusively White British. With some ethnic groups, particularly south Asians, known to be at considerably higher risk of cardiovascular disease[34], the study may have benefited from the including individuals who are considered to be at a greater risk from stroke and likely to be prospective users of polypill therapy. As a result, survivors in our study may not represent the wider stroke population. Furthermore, only five GPs were interviewed, and their opinions may not reflect those of the GP population at large. With all caregivers interviewed in the presence of a survivor, this may have contributed to individuals responding in a socially desirable manner and understating their true views on secondary prevention and the polypill. Investigating a polypill among survivors with significant symptoms and dependent on others to organise their tablets may be an area for future research in the field. Finally, future research should aim to include those harder to reach groups of survivors who may benefit most from a polypill approach.

Comparisons with existing literature

The inflexibility of treatment and the potential for side-effects were considered key challenges of a polypill approach. Concerns about side-effects have previously been identified as influencing medication taking behaviour [35] and recognised as a significant barrier to adherence in cardiovascular disease medication [36]. Our findings are also in line with a recent UK primary care investigation in which patients considered a secondary prevention

polypill acceptable, but were concerned about components interacting and inflexibility of treatment [37]. The inability to adapt polypill dosage and the suitability of fixed dose treatment was a key concern for GPs in our study and has been previously reported in studies exploring polypill attitudes among GPs elsewhere. A small survey of 17 practitioners in New Zealand reported that having no choice of polypill components or doses was the thing GPs disliked most about the concept of a polypill [25]. In another UK study of primary healthcare professionals, inability to titrate dosage was considered a major disadvantage of the polypill [28].

The GPs in our study agreed that cost was a potential impediment to prescribing a polypill in the future. Compared with free combination medications, FDC therapy has the potential to be relatively inexpensive due to cheaper drug costs and reduced monitoring [38], and there is increasing evidence in the literature supporting the cost-effectiveness of a polypill strategy [39-40]. With modest costs considered a cornerstone of combination therapy [41], evaluations of the cost-effectiveness of using polypills is urgently needed.

Improved adherence was recognised as a key advantage of a polypill, and survivors acknowledged that a single medication episode was easier to remember. With frequent dosing regimens [42] and polypharmacy associated with poor patient compliance to cardiovascular medications [43 44], a polypill approach offering a simplified medication regimen has the potential to improve adherence in the treatment of cardiovascular disease [45 24]. Our study corroborates observations from a patient perspective on whether a polypill could improve adherence, which highlighted concerns around the efficacy of a polypill compared with current medications and the potential for side-effects [24].

For caregivers, benefits of a polypill included simplifying the medication taking process and ease in organising pill boxes. In a recent study on factors that influenced

caregiving and medication management, participants recognised complex medication needs as an impediment to care by increasing the demands placed on the caregiver [46]. Caregivers in our study recognised that a polypill approach was potentially more convenient for the pharmacy, an observation which has been confirmed in a recent qualitative investigation exploring pharmacists' views towards a cardiovascular polypill [47].

Stroke/TIA survivors expressed a reluctance to adopt a future polypill strategy, citing GP approval as a key factor. This not only supports the view that cardiovascular patients were inclined to do what their GPs told them [48] but also highlights the key role GPs can play in promoting a polypill approach. Exploring the perspectives of those with direct experience of the polypill can contribute to the wider acceptability of a polypill strategy and should continue to be a priority of future research. While a polypill was acceptable to most patients of the UMPIRE trial, some felt that fixed-dose combination therapy was less tailored to individual patient needs [49]. A recent investigation of the views of cardiovascular patients and providers who participated in polypill trials reported similar advantages and concerns to those identified in our study [50], suggesting that polypill perspectives translate to other regions and health care settings.

With research suggesting that health practitioners often fail to fully explain the important elements of medication when first prescribing treatment, [51] uptake of a polypill may depend not only on the GP prescribing therapy but also on informing and encouraging acceptance of the approach among stroke/TIA survivors and their caregivers.

Implications for clinical practice

Our findings suggest that survivors, caregivers and GPs were positive about a polypill but also had concerns around this approach for stroke prevention. Greater efforts are needed to reassure survivors and caregivers while GPs' willingness to endorse a polypill may determine long-term acceptability of this approach, particularly as inadequate information and difficulties with new medications are associated with poor adherence [52]. Further studies are also needed with a broader sample of GPs to corroborate the findings reported. With adherence among stroke survivors known to be suboptimal [29], this patient group may be particularly suited to receiving treatment using fixed-dose combination polypill therapy. Further research on the efficacy of a polypill will also reassure practitioners whose concerns around inflexibility and the suitability of treatment are likely to influence the decision to prescribe a polypill to stroke/TIA survivors.

Conclusion

A growing body of evidence suggests that a fixed-dose combination polypill may have a role in the prevention of cardiovascular disease. Our findings contribute to the growing literature on cardiovascular polypills, offer a unique insight around stroke and may inform future research and clinical practice in the area of secondary stroke prevention in the UK. A polypill may also have a role to play in improving adherence among stroke survivors. The findings have informed the development of PROPS - Preventative Role of a fixed dose combination Pill in Stroke -, a multi-centre open label randomised controlled trial of a fixed dose combination pill versus standard care for secondary prevention of stroke in a primary care setting. (EudraCT number: 201300472229). However, addressing patients' and practitioners' concerns and intensifying efforts to increase the acceptability of this treatment approach is likely to determine future use of a cardiovascular polypill for the secondary prevention of stroke.

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Author/s contribution: Jonathan Mant conceived the study, is the chief investigator on the polypill programme and commented on the final draft of the manuscript. Jonathan Graffy is a co-investigator on the polypill programme, contributed to the data analysis and commented on the manuscript. Ricky Mullis is a co-investigator on the polypill programme, contributed to developing the study protocol and commented on the manuscript. Stephen Sutton is a co-investigator on the polypill programme, contributed to the data analysis and commented on the manuscript. James Jamison contributed to developing the study protocol, conducted the interviews and data analysis and prepared the manuscript for submission.

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Gender	Male: n=21 (75%) Female: n=7 (25%)
Age (Mean: 74yrs)	60-69yrs: n=10 (36%) 70-79yrs: n=11 (39%) 80-89yrs: n=7 (25%)
Ethnicity	White: n=27 (97%), South Asian: n=1 (3%)
Stroke classification	Stroke: n=14 (50%) TIA: n=14 (50%)
Time since stroke	6 mths-2 yrs; n=10 (35%) 3-5 yrs: n=8 (29%) 6-10 yrs: n=5 (18%) >10 yrs: n=5 (18%)
Diabetes status	Yes: n=9 (32%) No: n=19 (68%)
Smoking status	Non-smoker: n=15 (54%) Ex-smoker: n=11 (39%) Smoker: n=2 (7%)
Interview status	Survivor and caregiver: n=14 (50%) Survivor only: n=14 (50%)
Rankin score* MrS-9Q	No symptoms: (0) n=6 (21%) No sig. disability: (1) n=4 (14%) Slight disability: (2) n=6 (21%)

	Moderate disability: (3) n=4 (14%) Mod severe/ severe disability: (4-5) n=8 (29%)

Table 1. Stroke survivor characteristics. *Rankin score is derived from a scale that measures the degree of disability in the daily activities of people who may have suffered a stroke

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	Item	Guide questions/description	
Domain 1: Research team and reflexivity			
Personal Characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	JJ was the interviewer
2.	Credentials	What were the researcher's credentials? *E.g. PhD, MD*	BSc, MSc
3.	Occupation	What was their occupation at the time of the study?	Research Assistant/ PhD Student
4.	Gender	Was the researcher male or female?	Male
5.	Experience and training	What experience or training did the researcher have?	JJ is a researcher with experience in undertaking qualitativeresearch.
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	No
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. *personal goals, reasons for doing the research*	Participants were informed that the researcher was a PhD student who worked for the University of Cambridge
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	Participants know that the researcher works in a primary care unit and is investigating as new approach to secondary stroke prevention using a Polypill
Domain 2: study design			
Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content*	Grounded Theory

No	Item	Guide questions/description	
		analysis	
Participant selection			
10.	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	Purposive/ convenience sampling –stroke survivors were selected purposively in order to achieve a range of gender, socio economic status, stroke severity. Caregivers and GPs were a convenience sample recruited through the survivors and as the GP leading the study within the practice, respectively.
11.	Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	Stroke survivors were approached by letter. Carers were approached directly through the stroke survivor. GPs were approached by phone.
12.	Sample size	How many participants were in the study?	28 stroke survivors, 14 caregivers, 5 GPs
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	No one refused to participate
Setting			
14.	Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	Data was collected in the patients/caregivers home and in the GPs place of work
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	Other than the caregiver who participated in joint interviews, no-one else was present during the interview..
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	Gender, stroke status, age
Data collection			
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Yes. An interview guide was developed for survivors, caregivers and GPs. Guides were tested by 2 stroke survivors and a clinical researcher commented on the GP guide.
18.	Repeat interviews	Were repeat interviews carried out? If yes, how	No

No	Item	Guide questions/description	
		many?	
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	Yes. All interviews were audio recorded.
20.	Field notes	Were field notes made during and/or after the interview or focus group?	Yes. Field notes were taken during interviews.
21.	Duration	What was the duration of the interviews or focus group?	Interviews lasted between 1 and 1.5 hours
22.	Data saturation	Was data saturation discussed?	Yes
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings			
Data analysis			
24.	Number of data coders	How many data coders coded the data?	2 authors contributed to the coding process. JJ coded all of the interviews. 20% were also coded independently by SS.
25.	Description of the coding tree	Did authors provide a description of the coding tree?	Not explicitly
26.	Derivation of themes	Were themes identified in advance or derived from the data?	Themes were generated from the data
27.	Software	What software, if applicable, was used to manage the data?	Nvivo 9
28.	Participant checking	Did participants provide feedback on the findings?	No.
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	Yes, quotations were presented in the text to illustrate the themes.. Participants were identified by a number.
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31.	Clarity of major	Were major themes clearly	Yes

No	Item	Guide questions/description	
	themes	presented in the findings?	
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes. Both key themes and sub-themes are reported. Restrictions on word count prevented themes being discussed extensively

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Stroke survivors', caregivers' and GPs' attitudes towards a Polypill for the secondary prevention of stroke: A qualitative interview study

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Stroke survivors', caregivers' and GPs' attitudes towards a Polypill for the secondary prevention of stroke: A qualitative interview study

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ABSTRACT

Objectives

To understand the perspectives of stroke survivors, caregivers and GPs on a polypill approach, consisting of blood pressure and cholesterol lowering therapies, with or without aspirin, for the secondary prevention of stroke.

Methods

A qualitative interview study was undertaken in five GP surgeries in the East of England. Twenty-eight survivors of stroke/TIA were interviewed, fourteen of them with a caregiver present, along with a convenience sample of five GPs, to assess attitudes towards a polypill and future use. Topic guides explored participants attitudes, potential uptake and long-term use, management of polypill medication and factors influencing the decision to prescribe. Data were analysed using a grounded theory approach. Key themes are presented and illustrated with verbatim quotes.

Results

The analysis identified three key themes: polypill benefits, polypill concerns and polypill lessons for implementation. Stroke/TIA survivors were positive about the polypill concept and considered it acceptable in the secondary prevention of stroke. Perceived benefits of a polypill included convenience resulting in improved adherence and reduced burden of treatment. Caregivers felt that a polypill would improve medication taking practices, and GPs were open to prescribing it to those at increased cardiovascular risk. However, concerns raised included whether a polypill provided equivalent therapeutic benefit, side-effects through combining medications, consequences of nonadherence, lack of flexibility in

regulating dosage, disruption to current treatment and suitability to the wider stroke population.

Conclusion

Participants acknowledged potential advantages in a polypill approach for secondary prevention of stroke, however, significant concerns remain. Further research on the efficacy of a polypill is needed to reassure practitioners whose concerns around inflexibility and treatment suitability are likely to influence the decision to prescribe a polypill for secondary prevention of stroke. Acceptability among survivors, caregivers and GPs is likely to determine the uptake and subsequent use of a polypill in the future.

Key words: Polypill, Stroke, Qualitative research, Semi-structured interview

Abbreviations: FDC: Fixed-dose combination; CVD: Cardiovascular disease.

Article summary

Strengths and limitations

- This research adds to an important body of work exploring cardiovascular polypills and is the first study to focus on attitudes to a polypill for secondary prevention of stroke.
- The findings are strengthened by the inclusion of caregivers who have an important role to play in managing the medication of stroke/TIA survivors.

- Conducting a qualitative assessment of individual perspectives allowed an in-depth examination of the subject area.
- Due to the limited sample size findings may not generalise to the wider stroke population or necessarily represent the views of all GPs
- Future research should consider harder to reach groups such as those who need support to manage medication and may benefit most from a polypill approach.

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Data sharing statement: No additional data available.

INTRODUCTION

Stroke is the fourth most common cause of death in the UK, responsible for approximately 40,000 deaths every year [1] and is also a significant cause of acquired adult disability [2], with about half of all survivors experiencing some degree of physical or cognitive impairment [3] and left dependent on others [4].

People who have had a stroke or a transient ischaemic attack (TIA; also known as a mini-stroke) are at higher long-term risk and therefore exposed to the increased possibility of having a further event [5-6]. However, this risk can be substantially reduced through the use of preventative medications such as anti-platelet agents [7] or anticoagulants [8], as well as cholesterol lowering [9 10] and blood pressure (BP) lowering therapies[11].

Despite evidence-based guidelines, treatment for stroke often falls below recommended standards [12 13], and significant deficiencies in secondary prevention care have been reported[14].

The use of multiple medications to treat CVD is often associated with inappropriate medication use (e.g. under-use, or use of non-appropriate medicines), under-prescription and reduced adherence [15]. A polypill consisting of cholesterol lowering and blood pressure lowering therapies, with or without aspirin in a single pill for the treatment of CVD [16] has been proposed.

Wald and Law (2003) introduced the polypill concept and estimated a theoretical 88% reduction in ischaemic heart disease and 80% reduction in stroke, if taken by everyone over 55 [17]. Since then a growing body of literature has developed around a polypill, otherwise known as a fixed-dose combination (FDC) pill, for the prevention of cardiovascular disease [18] [19]. A series of recently completed trials investigating the role of a fixed-dose combination pill on adherence to medication for secondary prevention demonstrated improved adherence for the polypill strategy compared with standard care [20-22]. Elsewhere FOCUS found improved adherence for patients with myocardial infarction in the polypill group compared to the group given the 3 drugs separately[23].

To date a small number of studies have investigated the perspectives of patients and health care professionals towards a theoretical polypill. Although cardiovascular patients considered it convenient, they had concerns around the inflexibility of a polypill [24], however, GPs would consider prescribing it to those who needed secondary prevention medication if it was shown to be effective. [25-28] With adherence to medication in stroke survivors known to be suboptimal [29], this group may be particularly suited to treatment with an FDC polypill.

The aim of this study was to explore the attitudes and perspectives of stroke/TIA survivors, carers and GPs towards a polypill approach for the secondary prevention of stroke, including the benefits and consequences of using a polypill, factors likely to influence uptake, the

caregiver role in managing medication and GPs' views and attitudes towards prescribing a polypill in the future.

METHODS

Study Design and Participants

A qualitative study using semi-structured interviews was undertaken. The stroke registers of 5 GP practices in the East of England were searched. The criteria for inclusion of stroke survivors was being over the age of 55, with a diagnosis of stroke or TIA and able to speak English. Based on these criteria, a list of prospective participants was generated by the practice administrator. The list was then screened by the practice GP and anyone deemed unsuitable, such as those unable to provide informed consent or who were terminally or seriously ill, was removed. Purposive sampling was used to recruit stroke/TIA survivors with maximum variation characteristics representing a spread of socio-economic status [30], age, gender, and disability[31]. Survivors were sent a study information pack and invited to interview. Caregivers were approached by the stroke survivor with a study information pack and invited to participate. All caregivers were subsequently interviewed in the presence of a stroke survivor. Due to time constraints we chose not to interview caregivers separately. All interviews were conducted in the stroke survivors' homes. We also sought the views of a convenience sample of GPs, each of whom was the study lead for their practice. The GP was contacted by phone and an interview arranged at their place of work. The number of interviews conducted was determined by data saturation, the point where no new information emerged from discussions. Interviews were face to face and consent was taken in person before any discussion commenced. Ethical approval was granted by NHS South Yorkshire Research Ethics Committee, Ref 13-YH-0067.

Data Collection

Data was collected through semi-structured interviews with open ended questions that defined the area to be explored [32]. Topic guides were developed by the authors and informed by current literature in the field and expertise within the study team which included a GP, a qualitative researcher and a stroke expert. To ensure ease of understanding and suitability, topic guides were piloted with two stroke survivors and checked by a GP. Any appropriate recommendations were considered and implemented. Data from the two pilot interviews was included in the final analysis. All interviews were conducted by the lead author, JJ, who has considerable experience in qualitative research analysis. Field notes were also taken by the interviewer. Topics discussed were perceived benefits and consequences of a polypill, factors influencing polypill uptake, caregiver views and GPs' beliefs and attitudes towards prescribing a polypill. See Supplementary file 1 for the interview schedule. The schedule of questions was refined and finalised after the fifth interview to include questions on the wider experience of stroke as well as understanding of the polypill approach and the GP relationship. Interviews were audiotaped, lasted 1- 1.5 hours and were transcribed verbatim.

Data analysis

We followed the Strauss and Corbin Grounded Theory approach using constant comparative analysis [33]. This method permits key points to emerge from the data and to then be coded individually. A set of codes, representing initial themes, were developed from chunks of data. Codes were then further refined, and those representing similar concepts were grouped together to form categories. The identification and refinement of categories continued until the final themes emerged. Nvivo 9 (QSR Intl, Melbourne, Victoria, Australia) was used to organise, code and manage the data. Transcripts were entered into the program and coded by JJ, with 20% double coded independently by SS. Queries arising from coded transcripts were settled through discussion. Communication with a third author (JG) enabled clarification and refinement of categories until a consensus was reached.

RESULTS

A total of twenty-eight stroke/TIA survivors participated. Fourteen were interviewed alone and 14 with the caregiver present, who was either a spouse (n=12) or family member (n=2). Characteristics of survivors are displayed in Table 1 below. Three male GPs and two female GPs were also interviewed. One GP was white British, one was Chinese and three were of south Asian origin. Key themes identified reflected the positive and negative aspects of the polypill approach as well as future use. Sub-themes highlighted benefits and concerns associated with a polypill approach and factors likely to influence stroke survivors using a polypill.

Table 1 here.

Polypill benefits

The concept of a polypill was broadly acceptable to survivors and caregivers. Greater convenience leading to better adherence, confidence that a polypill was providing the appropriate treatment, reduced treatment burden, ease of use, and improved medication management were all considered benefits. For GPs, a polypill facilitated medication taking and provided flexibility in treatment and convenience around prescribing practices.

Convenience

Survivors were enthusiastic about one tablet combining all stroke medication and reducing treatment burden through minimising the inconvenience of managing multiple medications.

> That is the best thing I've read when it said you might have to take one pill to cover the lot. Super, because that is just a bugbear, it's a bugbear in life. (pp 11, Male, 73yrs).

A single tablet was considered easier to remember and likely to improve overall medication taking behaviour.

> I think it's brilliant because erm I, I've got more chance of remembering to take one tablet than I have of remembering two different times of the day if you like. (pp10, Male, 66 yrs)

Caregivers also endorsed the view that a polypill improved compliance and that it ensured the appropriate medications were being taken.

> It means that if you've taken that one you've taken them all. Whereas sometimes if you run short, you think oh I'll just take that one and forget about the other one until you go to the doctors and get the refill (pp02, Female, carer).

GPs also felt that a polypill had the potential to improve medication adherence.

> I think that would reduce the pill burden to our patients and I think that's very good idea... I think he would be very compliant with it, because he is thinking that he is going to be taking 1 tablet and not 5 tablets….(GP 02, Female).

The potential for 'cross-over' treatment in individuals with multiple existing cardiovascular co-morbidities was mentioned.

> If you're giving polypill in the form of one pill, even with people with comorbidities (you're) maybe reducing their number…and might improve overall compliance and it may have the side effect of improving their comorbidity as well (GP 05, Male).

For carers, the polypill approach made the medication taking process less demanding.

> It's logic to me and I think it's an excellent idea if it could be done, certainly instead of *[patient]* fiddling about in a saucer trying to pick up tablets.. (pp28, Male, carer).

They also felt that the process of managing medication was better, compared with using multiple medications.

> Well if it's only one tablet a day it would be quicker, wouldn't it? for a start. I mean I usually sit on a night-time and do that (pillbox) when I'm watching telly. There's a few times I've missed out the odd tablet or put a double in or put too many in so I mean that would be easier. (pp02, Female, carer)

Benefits of correct treatment

A polypill offered the benefit of correct medication and it ensured that the patient received their recommended medications.

> It could protect, once you had polypills that contained a mixture of medications which are known not to have…contradictory side-effects…then you would feel very safe. (pp03, Male, 86 yrs)

> And as long as it's whether it's one pill or four pills so you know this is my point of view I don't think it's going to affect I mean other people might oh yeah I could have four pills instead of one and they'll start worrying about it but no I erm I just accept that, that the people are doing their job properly and getting their facts right… as I say as long as the scientists have got it alright you know you've got to have faith in them (pp08, Male, 87 yrs)

There was also confidence that components were safe, tested and therefore provided the most appropriate treatment.

> I'm all for these things….it might not be good for you, It might not, I don't know I can't see how because if they're now gonna put four different pills into one they musta investigated a, b, c and d to put them in one so therefore it's going to be beneficial to me and anybody else that wants those four in one (pp11, Male, 73yrs).

Polypill concerns

Survivors' and caregivers' concerns included polypill noncompliance resulting in missing all medications, inability to adjust dosage, whether a polypill could maintain the benefits of the survivors' current secondary prevention medication, timing of a polypill, identifying the source of polypill side effects and modifying treatment if a component was no longer

required. GPs questioned whether a single pill could treat the entire stroke population, the cost implications of treatment and the wisdom in modifying a patient's stable treatment regimen.

Appropriateness of treatment

Several survivors expressed concern that a polypill may not sustain equivalent therapeutic benefit of secondary prevention treatment.

> As far as I'm concerned you've got one tablet with all the ingredients of the others… if I've got the same erm dosage of statin and if it didn't disturb my readings then yeah I mean erm what are the objections to it? (pp05, Male, 64 yrs)

Others also had concerns about the prospect of a 'pill for all', inability to alter dosage and being less amenable to dose titration, if that was required.

> Would the polypill be in different strengths because like for blood pressure at the moment I'm taking…12 and a half, and then me cl- clopridogrel is 75…, maybe six months down the line my blood pressure can reduce, what would that do with the polypill? (pp21, Female, 68 yrs)

Survivors accustomed to scheduled medication regimens also questioned how drugs could now be combined and taken at a single time point.

> if you've got them altogether and you're supposed to take those tablets at different times of the day, how's it going to work? Is it going to upset your system? (pp22, Female, 71 yrs).

Suitability of the polypill strategy

Survivors questioned the ease of managing treatment if one or more components were no longer required.

> Would it only be suitable for somebody who's taking four of that particular medication? But what would happen if say the Dr said, you're not so bad so you don't need to take that particular tablet? (pp16, Female, 82 yrs)

A few expressed concerns around the inclusion of statins in any combination pill.

> Yes has that got anything to do with statins? I've read a lot about statins and I'm afraid I feel I wouldn't want to take them. Because the side effects and everything. (pp19, Female, carer)

GPs were cautious, suggesting a polypill could be better suited to those on similar medications whose treatment was well-established.

> I think the right drugs in the right combinations there, it, would potentially be helpful for a cohort of people. I don't think it will be for everyone but there will be a cohort of people who will probably be on very similar drugs… (GP03, Male)

Survivors and carers were also concerned that poor adherence would lead to missing all their secondary prevention drugs.

> If you're gonna give them a polypill that is three or four tablets and they don't bother taking that..They're gonna be worse off (pp14, Male, Carer)

Given the unique needs of stroke survivors, some suggested that multiple polypills may be needed.

> They don't give me three separate ones for no reason, there must be a reason for it. You can't do that with a polypill unless you have a hundred polypills all different medications and different combinations (pp18, Male, 88 yrs).

Polypill side effects

The likelihood of polypill side effects led many to question the suitability of single pill treatment.

> The fine tuning takes a bit of doing so w- with the one pill I got my bit of a doubt that it might work for some people but it might not work for everybody you see (pp04, Male, 80 yrs).

For GPs, a further problem resulting from this was the potential difficulty in identifying the component of a polypill responsible for side effects.

> My personal anxiety is about side effects when you club two, three medicines together, if one of them, one of the components is, is causing the side effect then you'll not know, you may have to again change.. (GP 05, Male)

Medication adjustment

GPs questioned the benefit in altering established medication routines to accommodate a polypill in those who were already taking their medication as directed.

> If you've got, as I said, a very motivated patient they are happy with what they are taking, then we don't probably have to intervene, but we may have to give to people who are not that motivated or compliant. (GP 05, Male)

They also expressed concern about the inconvenience of having to re-adjust future treatment if polypill components were no longer required.

> If somebody has a problem ok well we'll just stop using the polypill and give them the individual ones but with that stopping and chopping and changing people will say they've changed my tablets again, that becomes an issue. (GP 04, Male)

However, inflexibility of a polypill and the inability to manipulate dosage was perhaps the greatest concern among GPs.

> We do switch around quite a bit different brands, different sizes, statins and sometimes it may not be the right dose but you kind of slowly edge it in... It would be advantageous if it was a single pill but that would be maybe a bit difficult with polypill…It's the fine tuning that's difficult..(GP 01, Female)

Caregivers also expressed concern around the inflexibility of a polypill and the potential difficulties in adjusting dosage.

> You would have to get the right strengths of each tablet. "Where you were on atenolol 50 you are now on 25". Sometimes they change the strength of the tablet. That's where it would be harder to change with the polypill (pp25, Female, carer)

Size of polypill

GPs raised concerns that a large pill could actually discourage medication taking.

> Yeah is it a horse tablet?…that's going to have the other, the opposite effect on compliance that we want…People are going to start breaking it having half now and half twelve hours later (GP 03, Male).

The size was also highlighted by caregivers who expressed concerns around a prospective polypill being very large.

> Not going to be horse pills are they.. as we call them, 500 mg.
> (pp07,Female, carer)

For some stroke survivors, a single pill was considered much easier given the potential problems associated with multiple medications which could be larger and more difficult to swallow.

> If you can get it into one, it's so much better, you haven't got to put all these tablets down your throat. I mean like this might get stuck, and one of my tablets, if it gets stuck it burns my throat so much so the other week I lost my voice (pp06, Male, 61 yrs)

Cost of polypill

The burden of the polypill on NHS resources was also raised with a number of GPs suggesting that a more expensive pill could be difficult to prescribe.

> If it is cheaper then there won't be an issue at all. if it comes out to be more expensive than the four tablets which you are giving individually to the patient then it comes to be an issue (GP 02, Female)

Cost implications for practices and pharmacies dispensing a polypill were also considered with GPs acknowledging the likelihood of reduced revenues associated with a single pill.

> They get an item fee for each thing they prescribe so if you have 4 drugs you get a fee for each, if you put it in 1 pill that will account for one (GP 04, Male)

Polypill lessons for implementation

Survivors thought that whether they used a polypill in the future would depend on their doctor's recommendation, but they also questioned the need for a polypill given their satisfaction with current treatment. GPs acknowledged that their support was likely to be influential in the decision to use a polypill and believed the approach should be adopted if it was found to be beneficial to the patient. While stroke/ TIA survivors were generally positive about the polypill approach, many were non-committal on its future use, largely due to the lack of existing evidence.

Polypill recommendation

Caregivers felt that whether they used a polypill in the future was likely to depend on their doctor recommending the treatment.

> It sounds good but w- we've got to, we would have to weigh up, listen to what the doctors say and the consultants and see what history, because this polypill, from what we've hear. Very, very little, it's quite new, that's all we know. (pp22, Male, carer)

While GP's felt comfortable with the polypill approach, there was a preference for recommending a polypill to those who were already using the medication components.

> I don't think I'd be comfortable saying here's a new stroke patient, just start them with a polypill as a starting point, I think I'd feel uncomfortable with that.
> If I had patients that are on the four drugs that are in there erm I think I'd probably feel fairly comfortable saying well here's one tablet that's got all of those things you're on already (GP 04, Male)

Satisfied with current medication

Being content with their current medication also made survivors less enthusiastic about taking a polypill which may have unwanted side-effects.

> Why take a tablet that perhaps will affect you. Plus the fact I'm perfectly happy with what I'm on, you know, at the moment anyway. Perhaps if I go a bit doo-lally or you know erm….I would consider it (pp01, Female, 71 yrs).

While a concern raised among some study participants was that there was as yet, little scientific evidence in support of a polypill approach.

> No, I don't think I'd like to be a guinea pig with it though…. I don't know, I think I would rather continue with what I've got until it's absolutely perfected the polypill. Get somebody else (pp23, Female, 74 yrs)

Endorsement of the polypill

GPs agreed that if they endorsed polypill, stroke/TIA survivors were likely to accept it as a treatment for secondary stroke and commit to using it in the future.

> I think the majority of our current patients if we told them we think this is the right thing to do would probably be happy with that. It's a fairly easy argument (GP 03, Male).

Furthermore, there was an obligation to try new and innovative treatments like the polypill, if its potential benefits were proven.

> I welcome change and innovation I'm excited by it… you don't know until you've tried it... We have to try it if there was a potential benefit there for people (GP04, Male)

DISCUSSION

Summary of main findings

Stroke/TIA survivors and caregivers felt a polypill offered greater convenience, reduced the burden of treatment and improved adherence to medication. A polypill also ensured that patients received the correct treatment and that medications were safe. However, survivors

expressed significant concerns around the suitability of a polypill if not already using its individual components, the size of a polypill and the implication for using a polypill if any component was no longer needed. Other important limitations identified by participants included the potential for side-effects and the inflexibility of the single pill approach. GPs felt that a more expensive pill would be problematic and acknowledged that their endorsement was key to it being accepted. For survivors, the decision to use a polypill would depend on the GP's recommendation, but those who were satisfied with their current treatment regimen felt less inclined to change to a polypill.

Strengths and Limitations

A strength of this study is that it adds to a growing and important body of research on attitudes towards a cardiovascular polypill with a focus on secondary prevention of stroke. Second, the use of semi-structured interviews enabled an in-depth assessment of individual perspectives. A further strength is the inclusion of caregivers, who can make a significant contribution in the future management of polypill treatment. We believe that being interviewed by a qualitative researcher rather than a health care professional encouraged survivors' to be more open and to engage in discussion.

However, limitations include a relatively small sample of GPs' recruited from five general practice surgeries. Although every effort was made to recruit a representative sample with varied disability, most survivors who responded to our request to participate were primarily able bodied with no significant stroke symptoms and independently managed their own medication. In addition, survivors were almost exclusively White British. With some ethnic groups, particularly south Asians, known to be at considerably higher risk of cardiovascular disease[34], the study may have benefited from the including individuals who are considered to

be at a greater risk from stroke and likely to be prospective users of polypill therapy. As a result, survivors in our study may not represent the wider stroke population. Furthermore, only five GPs were interviewed, and their opinions may not reflect those of the GP population at large. With all caregivers interviewed in the presence of a survivor, this may have contributed to individuals responding in a socially desirable manner and understating their true views on secondary prevention and the polypill. Investigating a polypill among survivors with significant symptoms and dependent on others to organise their tablets may be an area for future research in the field. Finally, future research should aim to include those harder to reach groups of survivors who may benefit most from a polypill approach.

Comparisons with existing literature

The inflexibility of treatment and the potential for side-effects were considered key challenges of a polypill approach. Concerns about side-effects have previously been identified as influencing medication taking behaviour [35] and recognised as a significant barrier to adherence in cardiovascular disease medication [36]. Our findings are also in line with a recent UK primary care investigation in which patients considered a secondary prevention polypill acceptable, but were concerned about components interacting and inflexibility of treatment [37]. The inability to adapt polypill dosage and the suitability of fixed dose treatment was a key concern for GPs in our study and has been previously reported in studies exploring polypill attitudes among GPs elsewhere. A small survey of 17 practitioners in New Zealand reported that having no choice of polypill components or doses was the thing GPs disliked most about the concept of a polypill [25]. In another UK study of primary healthcare professionals, inability to titrate dosage was considered a major disadvantage of the polypill [28].

The GPs in our study agreed that cost was a potential impediment to prescribing a polypill in the future. Compared with free combination medications, FDC therapy has the potential to be relatively inexpensive due to cheaper drug costs and reduced monitoring [38], and there is increasing evidence in the literature supporting the cost-effectiveness of a polypill strategy [39-40]. With modest costs considered a cornerstone of combination therapy [41], evaluations of the cost-effectiveness of using polypills is urgently needed.

Improved adherence was recognised as a key advantage of a polypill, and survivors acknowledged that a single medication episode was easier to remember. With frequent dosing regimens [42] and polypharmacy associated with poor patient compliance to cardiovascular medications [43 44], a polypill approach offering a simplified medication regimen has the potential to improve adherence in the treatment of cardiovascular disease [45 24]. Our study corroborates observations from a patient perspective on whether a polypill could improve adherence, which highlighted concerns around the efficacy of a polypill compared with current medications and the potential for side-effects [24].

For caregivers, benefits of a polypill included simplifying the medication taking process and ease in organising pill boxes. In a recent study on factors that influenced caregiving and medication management, participants recognised complex medication needs as an impediment to care by increasing the demands placed on the caregiver [46]. Caregivers in our study recognised that a polypill approach was potentially more convenient for the pharmacy, an observation which has been confirmed in a recent qualitative investigation exploring pharmacists' views towards a cardiovascular polypill [47].

Stroke/TIA survivors expressed a reluctance to adopt a future polypill strategy, citing GP approval as a key factor. This not only supports the view that cardiovascular patients were inclined to do what their GPs told them [48] but also highlights the key role GPs can play in

promoting a polypill approach. Exploring the perspectives of those with direct experience of the polypill can contribute to the wider acceptability of a polypill strategy and should continue to be a priority of future research. While a polypill was acceptable to most patients of the UMPIRE trial, some felt that fixed-dose combination therapy was less tailored to individual patient needs [49]. A recent investigation of the views of cardiovascular patients and providers who participated in polypill trials reported similar advantages and concerns to those identified in our study [50], suggesting that polypill perspectives translate to other regions and health care settings.

With research suggesting that health practitioners often fail to fully explain the important elements of medication when first prescribing treatment, [51] uptake of a polypill may depend not only on the GP prescribing therapy but also on informing and encouraging acceptance of the approach among stroke/TIA survivors and their caregivers.

Implications for clinical practice

This study identified some positive aspects of a cardiovascular polypill for the secondary prevention of stroke. However greater efforts are needed within the clinical practice setting to reassure patients of the benefits of a polypill. Health professionals endorsement when prescribing a polypill could also lead to greater acceptance of this treatment approach and its use among stroke survivors, particularly as inadequate information and difficulties with new medications are associated with poor adherence [52]. Further studies are needed with a broader sample of GPs to corroborate the findings reported here. With adherence among stroke survivors known to be suboptimal [29], this patient group may be particularly suited to receiving treatment using fixed-dose combination polypill therapy. Further research on the efficacy of a polypill will also reassure practitioners whose concerns

around inflexibility and the suitability of treatment are likely to influence the decision to prescribe a polypill to stroke/TIA survivors.

Conclusion

A growing body of evidence suggests that a fixed-dose combination pill may have a role to play in the prevention of cardiovascular disease. This study contributes to the growing literature on cardiovascular polypills, offers a unique insight into the field of stroke, and may inform future research and clinical practice on secondary prevention in the UK. A polypill may also have a role to play in improving adherence among stroke survivors. The findings have informed the development of PROPS - Preventative Role of a fixed dose combination Pill in Stroke -, a multi-centre open label randomised controlled trial of a fixed dose combination pill versus standard care for secondary prevention of stroke in a primary care setting. (EudraCT number: 201300472229). However, addressing patients' and practitioners' concerns and intensifying efforts to increase the acceptability of this treatment approach is likely to determine future use of a cardiovascular polypill for the secondary prevention of stroke.

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Competing Interests

None declared.

Author/s contribution

Jonathan Mant conceived the study, is the chief investigator on the polypill programme and commented on the final draft of the manuscript. Jonathan Graffy is a co-investigator on the polypill programme, contributed to the data analysis and commented on the manuscript. Ricky Mullis is a co-investigator on the polypill programme, contributed to developing the study protocol and commented on the manuscript. Stephen Sutton is a co-investigator on the polypill programme, contributed to the data analysis and commented on the manuscript. James Jamison contributed to developing the study protocol, conducted the interviews and data analysis and prepared the manuscript for submission.

Data sharing

No additional data available.

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Gender	Male: n=21 (75%) Female: n=7 (25%)
Age (Mean: 74yrs)	60-69yrs: n=10 (36%) 70-79yrs: n=11 (39%) 80-89yrs: n=7 (25%)
Ethnicity	White: n=27 (97%), South Asian: n=1 (3%)
Stroke classification	Stroke: n=14 (50%) TIA: n=14 (50%)
Time since stroke	6 mths-2 yrs; n=10 (35%) 3-5 yrs: n=8 (29%) 6-10 yrs: n=5 (18%) >10 yrs: n=5 (18%)
Diabetes status	Yes: n=9 (32%) No: n=19 (68%)
Smoking status	Non-smoker: n=15 (54%) Ex-smoker: n=11 (39%) Smoker: n=2 (7%)
Interview status	Survivor and caregiver: n=14 (50%) Survivor only: n=14 (50%)
Rankin score* MrS-9Q	No symptoms: (0) n=6 (21%) No sig. disability: (1) n=4 (14%)

	Slight disability: (2) n=6 (21%) Moderate disability: (3) n=4 (14%) Mod severe/ severe disability: (4-5) n=8 (29%)

Table 1. Stroke survivor characteristics. *Rankin score is derived from a scale that measures the degree of disability in the daily activities of people who may have suffered a stroke

Supplementary File 1

Topic guide for semi-structured interviews

Stroke survivors

Can you tell me a bit about your experience of having a stroke?
What were you advised to do? What do you know about the risk factors for having another stroke?

Taking your medication?
Can you tell me about your current medication taking experience? Anydifficulties?

Do you know what a polypill is?
What do you think of being able to take a single pill (containing a combination of different stroke medications in one pill) instead of your usual medication?
How do you think this would change the experience of taking medication?
What would you consider to be the advantages of taking a polypill?
Can you think of any reasons why taking a polypill might not be a good thing?
Would you consider taking a polypill in the future?

Can you tell me about your relationship with your GP?

Carers

Can you tell me about your experience of being a carer?
How informed do you feel you are? about your stroke survivors condition?

Do you manage the medication? Can you tell me about this?
Are there any specific difficulties related to patient taking the stroke medication?
Can you think of any ways in which the medication taking process could be made easier/improved?

Have you heard of a polypill?
What do you think of the idea of a 'polypill'
What do you think of the patient taking a single polypill instead of their usual stroke medications?
How do you think this would benefit patient's medication taking behaviour?
Can you think of any reasons why taking a polypill may not be a good idea?
How do you think a polypill would enable better management of medication?
Can you think of any ways taking polypill would be a disadvantage?
What do you think about using a polypill in the future?

GPs

Current Practice
Can you tell me about current practice for secondary prevention of stroke?
Can you think of any limitations associated with current practice?

Polypill
What do you know about polypill therapies?- for treating cardiovascular disease?
Are you familiar with these?
What do you think about using a polypill for secondary prevention? Do you think it's feasible?
What would be the difficulties (if any) with using polypill for secondary prevention?
If a polypill became available for secondary prevention, is it something you would consider using?

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	Item	Guide questions/description	
Domain 1: Research team and reflexivity			
Personal Characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	JJ was the interviewer
2.	Credentials	What were the researcher's credentials? *E.g. PhD, MD*	BSc, MSc
3.	Occupation	What was their occupation at the time of the study?	Research Assistant/ PhD Student
4.	Gender	Was the researcher male or female?	Male
5.	Experience and training	What experience or training did the researcher have?	JJ is a researcher with experience in undertaking qualitativeresearch.
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	No
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. *personal goals, reasons for doing the research*	Participants were informed that the researcher was a PhD student who worked for the University of Cambridge
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	Participants know that the researcher works in a primary care unit and is investigating as new approach to secondary stroke prevention using a Polypill
Domain 2: study design			
Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content*	Grounded Theory

No	Item	Guide questions/description	
		analysis	
Participant selection			
10.	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	Purposive/ convenience sampling –stroke survivors were selected purposively in order to achieve a range of gender, socio economic status, stroke severity. Caregivers and GPs were a convenience sample recruited through the survivors and as the GP leading the study within the practice, respectively.
11.	Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	Stroke survivors were approached by letter. Carers were approached directly through the stroke survivor. GPs were approached by phone.
12.	Sample size	How many participants were in the study?	28 stroke survivors, 14 caregivers, 5 GPs
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	No one refused to participate
Setting			
14.	Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	Data was collected in the patients/caregivers home and in the GPs place of work
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	Other than the caregiver who participated in joint interviews, no-one else was present during the interview..
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	Gender, stroke status, age
Data collection			
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Yes. An interview guide was developed for survivors, caregivers and GPs. Guides were tested by 2 stroke survivors and a clinical researcher commented on the GP guide.
18.	Repeat interviews	Were repeat interviews carried out? If yes, how	No

No	Item	Guide questions/description	
		many?	
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	Yes. All interviews were audio recorded.
20.	Field notes	Were field notes made during and/or after the interview or focus group?	Yes. Field notes were taken during interviews.
21.	Duration	What was the duration of the interviews or focus group?	Interviews lasted between 1 and 1.5 hours
22.	Data saturation	Was data saturation discussed?	Yes
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings			
Data analysis			
24.	Number of data coders	How many data coders coded the data?	2 authors contributed to the coding process. JJ coded all of the interviews. 20% were also coded independently by SS.
25.	Description of the coding tree	Did authors provide a description of the coding tree?	Not explicitly
26.	Derivation of themes	Were themes identified in advance or derived from the data?	Themes were generated from the data
27.	Software	What software, if applicable, was used to manage the data?	Nvivo 9
28.	Participant checking	Did participants provide feedback on the findings?	No.
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	Yes, quotations were presented in the text to illustrate the themes.. Participants were identified by a number.
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31.	Clarity of major	Were major themes clearly	Yes

No	Item	Guide questions/description	
	themes	presented in the findings?	
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes. Both key themes and sub-themes are reported. Restrictions on word count prevented themes being discussed extensively