Patient Acceptance and Adherence to the COMPASS Trial Drug Recommendations Following Symptomatic Carotid Endarterectomy

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Background: The COMPASS trial demonstrated that in patients with atherosclerotic diseases, low-dose rivaroxaban and aspirin provides greater protection against subsequent major adverse cardiovascular events (MACEs) than mono-antiplatelet therapy (MAPT) alone. Drug acceptance and adherence maximizes this benefit. We have assessed drug acceptance and adherence to the COMPASS drug regime in patients following carotid endarterectomy (CEA) for symptomatic carotid artery stenosis.

Methods: Following CEA, the views of 63 patients on the COMPASS drug regime were assessed using the Beliefs about Medicine Questionnaire and drug adherence was determined using the Sidorkiewicz scoring system. These views were compared with those of 54 patients on MAPT. Side effects (bleeding and drug reactions) and new MACE were recorded.

Results: Post-CEA patients on the COMPASS drug regimen had strong positive views on the necessity to take these drugs (necessity scale 19.6 ± 3.6). Although there were some concerns about the COMPASS drug regimen, these were not strongly held (concern cscale 11.8 ± 4.9) and the necessity−concerns differential was positive (7.8 ± 6.2). The Drug Adherence Score was "High" to "Good" (level of drug adherence 1.7 ± 1.0). The Beliefs about Medicine Questionnaire scales and Drug Adherence Score of post-CEA patients on the COMPASS drug regimen were similar to those on MAPT. The incidence of post-CEA MACE and side effects were similar for those on the COMPASS drug regimen and MAPT.

Conclusions: Post-CEA patients on the COMPASS drug regimen had positive views on taking the drugs and drug adherence was high. We did not identify any patient-related barriers to the use of the COMPASS drug regimen to further reduce cardiovascular events.

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INTRODUCTION

The COMPASS trial demonstrated that for patients with atherosclerosis, low-dose rivaroxaban taken twice a day with aspirin once a day reduced major adverse cardiovascular events (MACEs) more effectively than aspirin alone.[1,2] Our department has successfully introduced the COMPASS drug regimen following carotid endarterectomy (CEA) for symptomatic disease[3] on the assumption that such patients have a high atherosclerotic burden and are at risk of subsequent MACE.[1,2,4–7] Success in changing clinical practice is dependent on patient acceptance. The COMPASS drug regime involves more drugs, taken at different times of the day and with more potential side effects than mono-antiplatelet therapy (MAPT) alone.[1] These factors may influence patient drug acceptance and adherence. This paper assesses patient acceptance and adherence to the COMPASS drug regime and compares this with MAPT following CEA for symptomatic carotid disease.

MATERIALS AND METHODS

Patients

From March 2020, following CEA undertaken within 14 days of a TIA or minor stroke, for a carotid artery stenosis >50% the initial dual antiplatelet treatment[8,9] was converted to the COMPASS drug regime of 2.5 mg of Rivaroxaban twice a day and Aspirin 75 mg once a day. This drug regimen preferentially replaced MAPT (aspirin 75 mg or clopidogrel 75 mg once a day) which had been implemented up to this point. Perioperative data, such as the indications for surgery and preoperative comorbidities were obtained from the prospectively collected National Vascular Registry.[10]

Questionnaire

While attending a follow-up clinic, the drug adherence views of 63 post-CEA patients on the COMPASS drug regime were obtained through a structured interview. Any potential drug side effects and MACE were also determined. These views were compared with those of 54 post-CEA patients on MAPT.

The patients' views on drug adherence were assessed with 22 questionnaires. The *Beliefs about Medicine Questionnaire*—Specific[11,12] assessed their views on taking the drugs and the *Sidorkiewicz scoring system*[13] assessed actual drug adherence. The *Beliefs about Medicine Questionnaire*—Specific (Table I), consists of 22 5-item scales assessing patients' beliefs about the necessity of prescribed drugs for controlling their disease and their concerns about potential adverse consequences of taking them. The degree of agreement with each statement is recorded on a 5-point Likert scale, ranging from 1 strongly disagree to 5 strongly agree. Scores obtained for individual items within both scales are added. This gives total scores for both the n*ecessity scale* and c*oncerns scale* ranging from 5 to 25. Higher scores indicate stronger beliefs. A n*ecessity—concerns differential* is calculated as the difference between the necessity scale and the concerns scale, with a possible range of −20 to +20. The *Sidorkiewicz scoring system*[13] to assess patient drug adherence consists of 5 questions from which a 6-point adherence level (1: high, 2: good, 3: moderate, 4: poor, 5: very poor, and 6: discontinued) is determined.

Analysis

Questionnaire and clinical data were entered into a hospital secure computer spreadsheet. The IBM SPSS Statistics package 25, nonparametric Man-Whiney *U* test for 22 independent groups was used to determine a difference between the 22 treatment groups of $P < 0.01$.

Statement of Ethics

The study protocol including the patient questionnaire was reviewed and approved by the Reseach, Audit and Project Committee of the Royal Free London NHS Foundation Trust Hospital (Approval Reference number RFHBU_62222/23). It was deemed to be part of a Quality Improvement Program.

RESULTS

Patient Views on Taking Drugs and Drug Adherence (Table II)

Patients taking the COMPASS drug regime following their CEA held strong positive views on the necessity to take these drugs (necessity scale 19.6 ± 3.6). Although there were some concerns these were not strongly held (concern scale 11.8 ± 4.9). The necessity-concerns differential was positive (7.8 ± 6.2). The Drug Adherence Score was between ''High'' and ''Good'' (level of drug adherence 1.7 ± 1.0, mode 1). The necessity scale, concerns scale and necessity—concerns differential for those taking the COMPASS drug regime were similar to those taking MAPT. Drug adherence was also similar between the groups.

Table I. Belief about Medicine Questionnaire—specific ques tions[11,12]

Necessity scales
Without my medicines I would be very ill (1—5)
My life would be impossible without my medicines (1—5)
My health, at present, depends on my medicines (1—5)
My health in the future will depend on my medicines (1—5)
My medicines protect me from becoming worse (1—5)
Concerns scales
I sometimes worry about becoming too dependent on my medicines (1—5)
My medicines disrupt my life (1—5)
My medicines are a mystery to me (1—5)
Having to take medicines worries me (1—5)
I sometimes worry about long-term effects of my medicines (1—5)

Table II. Post-CEA patient views and adherence to taking the COMPASS drug regime and MAPT

	COMPASS	MAPT	*P*
Beliefs about Medicine Questionnaire			
Necessity scales (range 5—25) (Mean and SD)	19.6 ± 3.6	19.1 ± 4.6	0.91
Concerns scales (range 5—25) (Mean and SD)	11.8 ± 4.9	12.0 ± 4.4	0.76
Necessity—concerns differential (range −20 to +20) (Mean and SD)	7.8 ± 6.2	7.1 ± 6.4	0.83
Level of drug adherence: (range 1—6: 1: high, 2: good, 3: moderate, 4: poor, 5: very poor, and 6: discontinued) (Mean and SD)	1.67 ± 0.95 Mode = 1	1.58 ± 0.96 Mode = 1	0.5

Patient Demographic and Clinical Data (Table III)

Patients taking the COMPASS drug regime were on average 70 years old and 2-thirds were male. Half had had a stroke and the rest a TIA, the modified Rankin Score was between 0 and 1. The MAPT group were of a similar age, gender and social deprivation indices distribution, but with more severe strokes. As expected from the study design, the duration on the thromboembolic reducing drugs was longer in the MAPT group ($P < 0.01$). Preoperative comorbidities were similar in patients subsequently on the COMPASS drug regimen or MAPT (hypertension 40/63 vs. 40/54 $P = 0.83$, ischemic heart disease 12/63 vs. 16/54 $P = 0.41$, diabetes 18/63 vs. 11/52 $P = 0.18$ and current or ex-smoker smokers 40/63 vs. 38/53 $P = 0.18$).

On average, at the follow-up interview, those on the COMPASS drug regime were taking a total of 6 MACE-reducing drugs and in the MAPT group 5. This was due to the added antithrombotic drugs in the COMPASS drug regimen group. In the MAPT group, 8 were taking Aspirin and 46 clopidogrel. In both groups, over 90% were taking blood lipid regulating drugs (mainly atorvastatin). Seventy-five percent in the COMPASS drug regimen group were taking antihypertensive drugs and 85% in the MAPT group ($P = 0.41$). Most were on medications to protect against gastric side effects.

Table III. Patient demographic and clinical details

	COMPASS	MAPT	*P*
Patient demographics at CEA			
Number of patients	63	54	
Age (mean, SD) in years	70.4 ± 7.4	70.8 ± 9.5	0.78
Sex (male: female)	43:20	33:21	0.42
Index of multiple deprivation decile[14] (mode, range)	6 (1−10)	6 (1−10)	0.13
Prestroke frailty score[10] (range 1−4) (mean range)	1.35 (1−3)	1.5 (1−3)	0.07
CEA indication (transient ischaemic eventTIA: stroke) number	31:32	28:26	0.78
Modified Rankin Score[10] at CEA (range 0−6) (mean, range)	0.82 (0−3)	1.2 (0−3)	0.024
Drug history (at interview)			
Duration on COMPASS/MAPT Drugs (mean, standard deviation in months)	20 ± 11.4	46 ± 17.5	0.001
Number of MACE reducing drugs taken (including thromboembolic drugs) per patient (mean, standard deviation)	5.8 ± 1.6	4.8 ± 1.9	0.001
Plasma lipid regulating drugs (number, %)	63 (98%)	50 (93%)	0.12
Antihypertensive drugs (number, %)	50 (79%)	46 (85%)	0.41
Diabetes regulating drugs (number, %)	18 (29%)	9 (17%)	0.13
Drugs to control gastric side effects (number, %)	54 (86%)	36 (67%)	0.015

Effectiveness of Treatment (Table IV)

In the COMPASS drug regime group at follow-up, 5 patients reported new MACE (3 new strokes and 2 new ischemic cardiac events). This is comparable to the MAPT group of 7 new strokes and 2 new ischemic cardiac events ($P > 0.05$).

At the follow-up, patients taking the COMPASS drug regimen were on average, aware of at least 1 of 5 minor symptoms of an increased bleeding tendency (bruising, gum bleeding, nose bleeds, prolonged oozing and slower healing of cuts). Few had shown symptoms of a major bleed (melena, hematemesis, uncontrollable bleeding, medical

Table IV. Treatment side effects

	COMPASS	MAPT	*P*
Minor bleeding			
Number of symptoms (range 0−5: burse easily, gums bleed, nose bleeds, cuts bleed longer and heal slowly (mean ± SD)	1.7 ± 1.4	1.3 ± 1.2	0.08
Major bleeding			
Number of symptoms (range 0−5: Blood in stool, hematemesis, bleed uncontrollably, seen a doctor, admitted to hospital due to bleeding) (mean ± SD)	0.3 ± 0.6	0.3 ± 0.5	0.45
Minor drug reactions			
Number of symptoms (range 0−2: drug related rash, itching) (mean ± SD)	0.2 ± 0.5	0.5 ± 0.7	0.02
Major drug reactions			
Number of symptoms (range 0−2: drug related body swelling or difficulty breathing) (mean ± SD)	0.2 ± 0.5	0.3 ± 0.5	0.55

review, hospital admission). Of those who did report a major symptom, only 1 had required medical attention. This was similar in the MAPT group where 1 patient had been admitted to hospital to manage bleeding.

Two patients in the COMPASS drug regimen group reported probable drug reaction symptoms (1 major and 1 minor). This was lower than the MAPT group where there was 1 reported major and 4 minor probable drug-related reactions. The questionnaire was not aimed to distinguish between different drug reactions.

DISCUSSION

In a cohort of patients who underwent CEA following a minor stroke or TIA, those commenced on the COMPASS drug regime had strong positive views on the necessity to take these drugs. Although they had some concerns about the COMPASS drug regimen these were not greatly held and drug adherence was very good. Despite taking more drugs and at different times of the day, the acceptance and adherence to the COMPASS drug regimen appeared similar to post-CEA patients taking MAPT. Post-CEA MACE and drug reactions were similar for those taking the COMPASS drug regimen and MAPT.

Drug nonadherence is a major public health problem. There is up to 50% nonadherence in chronic disorders costing the European economy 1.25 billion euros per annum.[15] For stroke patients, nonadherence to drugs has an increased risk of further stoke and death.[16,17] Drug adherence varies with the recommended treatment.[15] Adopting the COMPASS drug regimen over MAPT involves taking more drugs, at different times of the day, and with a worse drug side

effect profile.[1] This could adversely influence drug adherence.[18] However, our study demonstrates (Table II) a high level of adherence to the COMPASS drug regime which is likely due to the patients' favorable perception of the necessity over the concerns of taking the extra drugs. The necessity—concerns differential for patients taking the COMPASS drug regimen in this study (mean greater than +7) is generally higher than that reported for patients with other chronic medical problems.[19] Reasons for drug nonadherence are multifactorial.[15] It is not only influenced by the recommended treatment, but also the health-care system, disease condition, socioeconomic-related factors, and patient demographics (age, sex, frailty).[20] In this study, the health-care system, the disease condition, socioeconomic factors, as measured by the Indices of deprivation[14] and patient factors, have not changed with the introduction of the COMPASS drug regimen (Table III).

Contrary to the views of some, that further studies are needed before the potential poststroke benefits could be embraced,[21,22]in March 2020 we adopted the COMPASS drug regimen as part of our post-CEA MACE reducing drug protocol. This was because the COMPASS trial demonstrated a nonsignificant benefit in the carotid subgroup (MACE reduction from 6 to 3.9%, $P = 0.07$)[2] with no increase in major bleeding side effects (1.9—2.3% $P = 0.67$)[2] We also adopted the COMPASS trial[1,2,23] recommendations as it demonstrated reduced MACE (stoke, cardiac, and peripheral vascular) in patients with known atherosclerotic disease (stable coronary artery or peripheral artery disease). Atherosclerosis is a systemic disease and patients who have ischemic atherosclerotic-related strokes are at a 5 times higher risk of nonstroke MACE at 5 years.[5] A third of atherosclerotic-related stroke patients will subsequently die from nonstroke MACE irrespective of whether they underwent a CEA.[4,6,7] Reducing nonstroke MACE in post-CEA patients is therefore a priority and the COMPASS drug regimen appears more effective than MAPT at achieving this. Extrapolating the COMPASS data on carotid disease patients,[2] 48 post-CEA patients need to be on the COMPASS drug regimen to further reduce 1 MACE when compared to taking Aspirin alone. In the UK, where 4000 CEA are undertaken a year, this regimen would reduce further 48 MACEs within 2 years post-CEA compared to those on aspirin alone.

The strength of the study is that the data sets for each patient are complete and the questionnaires used to assess views on drug acceptance and adherence are published and validated. Limitations to this study include its nonrandomized, single-center, small sample size and longitudinal nature. As a consequence, comparing the effects of the MAPT antithrombotic drug regimens applied before the introduction of the COMPASS Drug regimen with outcomes after its introduction must be undertaken with caution. The patients on MAPT have been taken the medications for a significantly longer time period and therefore had longer to develop further MACE and drug side effects. Although this may also influence views on drug acceptance and drug adherence, the lack of difference between the treatment groups suggests this was not the case. The post-CEA MACE and treatment side effects (Table IV) affecting our patients on the COMPASS drug regimen should not be equated to the findings of the actual COMPASS trail.[1,2]

CONCLUSIONS

Despite the increased number of drugs taken at different times of the day, this study demonstrates that following CEA, patients have strongly positive views on the necessity to take the COMPASS drug regime and their adherence is very good. Patient attitudes and their adherence to taking the COMPASS drug regime is unlikely to be a barrier to its wider introduction in patients with symptomatic atherosclerotic carotid artery disease.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Daryll Baker: Writing — review & editing, Writing — original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lucinda Cruddas:** Data curation. **Tom Eveson:** Data curation. **Ameet Bakhai:** Methodology, Conceptualization. **Justin Penge:** Methodology, Conceptualization.

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