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Fixed dose combination drugs for cardiovascular disease in a prolonged humanitarian crisis in Lebanon: an implementation study

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ABSTRACT

Objectives This pre–post implementation study evaluated the introduction of fixed dose combination (FDC) medications for atherosclerotic cardiovascular disease (ASCVD) secondary prevention into routine care in a humanitarian setting.

Setting Two Médecins sans Frontières (MSF) primary care clinics serving Syrian refugee and host populations in north Lebanon.

Participants Consenting patients ≥18 years with existing ASCVD requiring secondary prevention medication were eligible for study enrolment. Those with FDC contraindication(s) or planning to move were excluded. Of 521 enrolled patients, 460 (88.3%) were retained at 6 months, and 418 (80.2%) switched to FDC. Of these, 84% remained on FDC (n=351), 8.1% (n=34) discontinued and 7.9% (n=33) were lost to follow-up by month 12.

Interventions Eligible patients, enrolled February–May 2019, were switched to Trinomia FDC (atorvastatin 20 mg, aspirin 100 mg, ramipril 2.5/5/10 mg) after 6 months' usual care. During the study, the COVID-19 pandemic, an economic crisis and clinic closures occurred.

Outcome measures Descriptive and regression analyses compared key outcomes at 6 and 12 months: medication adherence, non-high density lipoprotein cholesterol (non-HDL-C) and systolic blood pressure (SBP) control. We performed per-protocol, intention-to-treat and secondary analyses of non-switchers.

Results Among 385 switchers remaining at 12 months, total adherence improved 23%, from 63% (95% CI 58 to 68) at month 6, to 86% (95% CI 82 to 90) at month 12; mean non-HDL-C levels dropped 0.28 mmol/L (95% CI −0.38 to −0.18; p<0.0001), from 2.39 (95% CI 2.26 to 2.51) to 2.11 mmol/L (95% CI 2.00 to 2.22); mean SBP dropped 2.89 mm Hg (95% CI −4.49 to −1.28; p=0.0005) from 132.7 (95% CI 130.8 to 134.6) to 129.7 mm Hg (95% CI 127.9 to 131.5). Non-switchers had smaller improvements in adherence and clinical outcomes.

Conclusion Implementing an ASCVD secondary prevention FDC improved adherence and CVD risk factors in MSF clinics in Lebanon, with potential for wider implementation by humanitarian actors and host health systems.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This pragmatic implementation study examined the introduction of a fixed dose combination (FDC) medication for cardiovascular secondary prevention in a humanitarian setting, for the first time.
⇒ We followed a cohort of patients with established atherosclerotic cardiovascular disease in two primary care clinics serving Syrian refugees and the host population in Lebanon, for 6 months before (to account for the expected Hawthorne effect) and for 6 months after FDC implementation.
⇒ Our pre–post intervention study evaluated multiple outcomes related to the FDC intervention, including medication adherence and related biomarkers (systolic blood pressure and non-high density lipoprotein).
⇒ Despite being conducted in a very challenging conflict setting and in the middle of the COVID-19 pandemic, a high percentage of patients (84%) continued with the intervention (FDC).
⇒ While most study outcomes improved, our approach could not attribute causality to the FDC because of the nature of the pre–post study design and the potential confounders.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide (Global Burden of Disease 2019). Atherosclerotic CVDs (ASCVDs), including coronary heart disease, stroke and peripheral vascular disease, are the most common types of CVD. There are approximately 18 million deaths due to CVD annually, and the prevalence of these conditions is estimated at over 422 million cases worldwide.[1] People with existing ASCVD are at high risk of new CVD events.[2] The majority (80%) of the global CVD burden occurs in low- and middle-income countries (LMICs), where it affects younger people, with major social and economic consequences.[1]

High-quality evidence has demonstrated the cost-effectiveness of pharmacological treatments for secondary prevention of CVD events in patients with ASCVD, including β-blockers, ACE inhibitors (ACE-i), statins and aspirin. These treatments are recommended by all major international guidelines.[3–5] However, their use is worryingly low worldwide. Access remains a critical issue, particularly in LMICs, where up to 80% of patients with ASCVD cannot access any of the recommended drugs.[6 7]

Identifying and treating ASCVD can be challenging, even in high income, stable settings with ready access to medications and diagnostics.[8] Challenges around patients' limited adherence to medications proven to lower CVD mortality have been well documented. Recent studies indicate that cardiovascular fixed dose combination (FDC) therapy, which combines several medications in one pill, effectively increases adherence, reduces lipids and blood pressure, is well tolerated and improves outcomes.[9–15] Despite years of advocacy from their proponents and specific FDCs—or polypills—being approved in over thirty countries (including Lebanon), uptake and implementation have been slow globally. Reasons for this occur at patient, provider and manufacturer level.[15 16]

As the global non-communicable disease (NCD) burden has increased, medical humanitarian organisations have been increasingly faced with patients needing care for NCDs, including ASCVD. While there is growing evidence on the burden and gaps in access to care for NCDs in humanitarian crisis settings, there is little evidence on the implementation of effective interventions to manage people with NCDs in these contexts, and even less on the management of people with ASCVD.[17–21] This is a significant gap, especially given that limited evidence shows that crises may increase CVD mortality, morbidity and risk factors.[18 22–24]

The Syrian crisis has continued to take an enormous toll on the Syrian population since 2011. Over 6.9 million people have been internally displaced, while over 6.8 million people have fled as refugees, mainly into Syria's neighbouring countries, Jordan, Lebanon and Turkey.[25 26] Relative to its national population, Lebanon hosts the highest number of refugees globally.[27 28] Host country and humanitarian health systems in these countries have adapted to new realities in responding to the Syrian crisis. These involved tackling a high NCD burden and reaching a mainly urban-based (rather than camp-based) refugee population in the context of stressed local health systems.[21 29–33] CVD was responsible for 44% of mortality in Syria preconflict,[33] and almost 11% of Syrian refugee households in Lebanon include a person living with CVD.[31] In 2020, Lebanon faced two further crises, the COVID-19 pandemic and a crippling political and economic crisis.

In a previous study of patients with ASCVD in Lebanon, we showed that self-reported adherence to a package of ASCVD secondary prevention drugs was low, despite prescription rates being acceptable, with only approximately 40% of patients taking all three of aspirin/statin/ACEi or angiotensin receptor blocker (ARB).[34] An FDC approach may support medication adherence for people with ASCVD in humanitarian settings and may offer multiple additional benefits through the simplification of management from logistics, healthcare provider and patient perspectives. However, such an approach has yet to be implemented or evaluated in these settings.

Within a comprehensive study using different methodological approaches, Médecins sans Frontières (MSF) aimed to evaluate the implementation of an FDC treatment strategy (including aspirin, statin and ACEi) for patients with ASCVD in a humanitarian refugee setting. The overall study aimed to assess impact on adherence, CVD risk factor levels, and acceptability, sustainability and costs of this strategy. Here, we report on adherence measures, including self-reported medication adherence, changes in CVD risk factor levels (systolic blood pressure (SBP) and non-high density lipoprotein (HDL) cholesterol) and adverse events. The implementation outcomes, acceptability and sustainability, are reported in our related qualitative paper, and costs will be reported separately.[35]

METHODS

Study design

This mixed methods pre–post intervention study included quantitative, qualitative and costing components. The quantitative component, reported here, evaluated adherence and CVD risk factor levels. We used a prospective design following a cohort of patients with ASCVD in two clinics for 6 months before, and 6 months after switching to FDC. We report our methods guided by the StaRi checklist for implementation studies.

Setting

Syrian refugees and vulnerable Lebanese were treated free-of-charge at Dar al Zahara (DAZ) and Abdeh clinics in North Lebanon where MSF provided NCD outpatient care. This included delivery of essential medications, access to basic investigations and laboratory tests, and when necessary, specialist referral. Consultations were by appointment, provided by non-specialist general practitioners, supported by a supervising family medicine or internal medicine specialist NCD doctor. Routine follow-up for stable patients was provided by nurses. Patients were seen by the NCD doctor at least every third visit or in case of complications. Patient education was provided by NCD nurses and doctors, and by health promotion staff.

Health system context

The Lebanese Ministry of Public Health (MoPH) leads the public health response to the Syrian crisis in Lebanon, working closely with the United Nations High Commissioner for Refugees (UNHCR) and the WHO. These organisations work with a complex network of partner and non-partner healthcare providers to serve Syrian

refugees. The Lebanese healthcare system is highly privatised and pluralistic.[36 37] There are over 800 primary care clinics and dispensaries, and UNHCR-registered Syrian refugees are entitled to access the 245 MoPH-accredited primary care centres.[21 38 39] However, they are required to make highly variable subsidised copayments for consultations, medications and referral for hospital treatment. Hence, accessibility varies between areas, and access to hospital-based services is extremely limited.[21 40] Registration of Syrian refugees by UNHCR was suspended in May 2015, following Lebanese government instruction, and unregistered refugees are limited to attending facilities funded by private donors or humanitarian organisations, such as MSF.[21 41] MSF has been providing free-of-charge healthcare to Syrian refugees and the vulnerable host community in Lebanon, complementing the MoPH system in North Lebanon and the Bekaa Valley, since 2012. The two facilities included in this study were managed by MSF and were not part of the MoPH primary healthcare network.

Participants

Patients were eligible for enrolment in the study if they were (A) aged 18 years and older, (B) attending either DAZ or Abdeh MSF clinic, with established ASCVD (history of coronary heart disease, ischaemic cerebrovascular disease or peripheral artery disease) and (C) were receiving (or were eligible to receive) a multiple pill treatment regimen for secondary prevention (aspirin, statin, antihypertensive medication). Patients were not eligible for enrolment if they had a contraindication to any FDC component or if they planned to stop attending the clinic during the study period. Patients with ASCVD were identified using database and file review, using documented ASCVD and/or current prescription of aspirin as initial screening criteria.

Intervention

Patients with ASCVD were enrolled on a rolling basis while attending routine appointments during a 4-month period from February to May 2019 (online supplemental material 1). Their treatment was reviewed and adapted as needed, according to the MSF NCD guidelines (online supplemental material 2), which recommend aspirin, a statin and at least one antihypertensive medication for patients with established ASCVD. Usual care continued for 6 months after final patient enrolment (period 1; June–November 2019; figure 1). This 6-month period was included to minimise any possible 'Hawthorne effect' leading to improvement in adherence, non-HDL cholesterol and SBP, due to study participation. After period 1, an FDC was introduced into routine care to replace the multiple tablet combinations of ASCVD secondary prevention drugs for study participants (period 2; December 2019–May 2020; figure 1). Eligible patients with ASCVD without contraindications were switched from usual care to Trinomia (Ferrer), (atorvastatin 20 mg, aspirin 100 mg and ramipril 2.5, 5 or 10 mg), a cardiovascular polypill that has been granted regulatory approval in 15 countries in the EU and of a total of 28 countries worldwide.[42] Patients' other treatments were prescribed as usual.

Trinomia was locally purchased and managed through the MSF supply chain in accordance with MSF's robust quality assurance measures. At local purchase prices, the cost of Trinomia was similar to the combined cost of the individual generic constituents.

A treatment protocol (online supplemental material 3) was developed and healthcare providers were trained in initiation, maintenance and adjustment (if necessary) of the FDC and other concomitant drugs. Top-up doses of the FDC's components or of additional ASCVD secondary prevention drugs, including other antihypertensive drug classes, were prescribed according to patient need. As

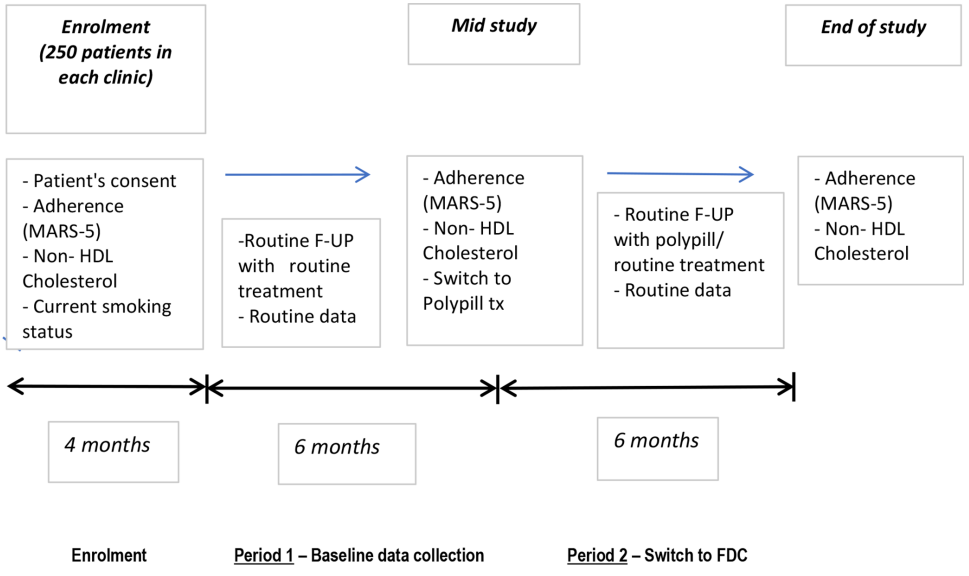

Figure 1 Flow chart of the study procedure.

Table 1 Domains, outcomes, methods and timing of measurement

Domains	Outcomes	Methods/data collection	Timing from start of data collection
Adherence	Self-reported adherence	MARS-5 Scale	Baseline, 6 and 12 months
	CVD risk factor levels		
	Systolic blood pressure	Existing information system	Baseline, 6 and 12 months
	Total/non-HDL cholesterol	Case report form	Baseline, 6 and 12 months
Tolerability	Major cardiovascular events	Existing information system	At each routine visit
	Drug discontinuation and side effects	Existing information system	At each routine visit

CVD, cardiovascular disease; HDL, high-density lipoprotein; MARS-5, Medication Adherence Report Scale.

is standard MSF practice, the FDC was provided free-of-charge for patients.

Biological sampling

To determine non-HDL cholesterol levels, non-fasting EDTA blood samples were drawn by an MSF nurse, stored onsite and analysed same-day using a point-of-care clinical chemistry analyser, Reflotron. Plasma non-fasting total cholesterol, triglycerides and HDL cholesterol measurements were determined and used to calculate non-fasting LDL cholesterol, using the Friedewald calculation. Blood pressure was measured using an digital Omron sphygmomanometer.

Contextual changes

Two major operational changes occurred during the second 6-month study period (period 2). MSF decided to end the project in North Lebanon and transfer patients to local MoPH registered primary care clinics, and the COVID-19 pandemic struck, necessitating a period of adaptation to service delivery to minimise patients' attendance at facilities (online supplemental material 4).

Variables

The main outcomes of interest reported in this paper are shown in table 1.

Definitions

Adherence

Adherence was defined as the extent patients' medication-taking behaviour corresponded with healthcare provider recommendations. We measured self-reported adherence using the Medication Adherence Report Scale (MARS-5), validated in Arabic.[43] The scale was applied to each individual FDC component (statin, aspirin and ACEi/ARB) and to the FDC post intervention.

CVD risk factor levels

We reported on biomarkers that may be considered proxy adherence measures, including SBP and non-fasting total and non-HDL-C.[44–46]

Major cardiovascular events

This study evaluated the implementation of a proven (FDC) treatment with a well-documented safety profile. It was conducted in a population for whom the FDC components were clinically indicated, which is at higher risk of major cardiovascular events (MCEs) (fatal or non-fatal cardiovascular events, including cardiovascular death, acute coronary syndrome, stroke, revascularisation or cardiovascular hospitalisation) than the general population. While the study was not powered to detect a difference in MCE between the two groups, we report them for descriptive purposes.

Drug discontinuation

Drug discontinuation and side effects were monitored at each consultation as per usual care.

Data collection and management

Routine data, collected at routine clinic visits, were maintained in paper-based, MSF NCD files stored securely at each clinic. Each week, MSF data clerks entered data into a password-protected Macro-based Microsoft Excel software database, initially Gecko, then District Health Information Software 2, as per usual care. Routine data from study patients were double-entered into a separate Microsoft Excel database created for the study. A case report form was designed to capture non-routine data collected at each of three study visits (enrolment, 6-month and 12-month visit) and these data were double entered into a bespoke Excel database. Data from both clinics were analysed separately and in aggregate, using statistical software R V.3.6.1 (2019-07-05) (R, Boston, MA 02210, USA).

Sample size

We assumed that if improvement in patient and provider acceptability and in workload was demonstrated, MSF may be encouraged to implement an FDC strategy more broadly, providing that adherence did not deteriorate after switching to the FDC. Thus, our primary measurement of interest was impact on adherence (which has been shown to improve in research-controlled conditions). We estimated that, with a sample size of 500 patients, we had 97.8% power to detect a reduction of 10% in adherence from a baseline of 80% (online supplemental material 5).

Data analysis and reporting

Descriptive statistics were used to explore patient demographics at baseline and among those who remained in care after the first 6 months and/or 12 months post enrolment.

Categorical variables were described with proportions, and continuous variables were summarised with means, SD and quartiles (after being transformed if excessive skewness was found).

We performed an intention-to-treat (ITT) analysis (analysing as having switched to FDC even if the patient later returned to the multiple pill regimen) to evaluate the differences in MARS5 score, SBP and non-HDL-C levels between the 6-month (switch to FDC) and 12-month study visits. MARS5 was reported as a binary outcome, dichotomising into two groups, with a full score of 25 representing adherence and less than 25 representing non-adherence. SBP and non-HDL-C were reported as continuous variables (in mm Hg and mmol/L, respectively) and as binary variables when reporting if they were at target (<140/90 mm Hg for SBP and <2.2 mmol/L for non-HDL-C).

For each of the two continuous outcomes (SBP and non-HDL-C), we performed a linear regression model of the difference between 6-month and 12 month visit outcomes, to estimate the expected change between the two visits, adjusted for the value at 6 months (centred on the mean). For each binary outcome (complete adherence to medication, SBP control and non-HDL-C control), we used a logistic regression model to estimate the probability of a patient achieving a poorer outcome at 12 months, if they had previously been adherent or were achieving risk factor control at 6 months, (eg, the probability of changing from having controlled blood pressure at 6 months to uncontrolled at 12 months), and, conversely, to estimate the probability of a patient achieving a better outcome at 12 months, if they had previously been non-adherent or were not achieving risk factor control at 6 months (eg, the probability of becoming fully adherent at 12 months if they had not been at 6 months). The model allowed us to test if the difference between the two probabilities was significant.

Our intended interrupted time series analysis of SBP (using measures at every visit) was not possible due to the disruption of face-to-face appointments during the COVID-19 pandemic-related lockdown. This disruption led to a paucity of clinical measurement data during study period 2.

Sensitivity analyses

We performed sensitivity analyses, repeating the descriptive and regression analyses for total adherence, non-HDL-C and SBP level, using data from 35 people who had not switched to the FDC and were retained at 12 months, as a natural control group, and among people who switched and then discontinued the FDC before 12 months (n=34). Reasons for not switching or for discontinuing are listed in figure 2. The specific statistical models were not prespecified. We have reported our results in accordance with the STROBE checklist (S1 STROBE Checklist).

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research. The research methods, choice of outcome measures and methods of recruitment were informed by discussions with local clinical and research staff. Patients with ASCVD enrolled in the MSF clinics were informed of the study through clinic posters. The MSF clinics have closed since the study's completion; therefore, findings will be disseminated through MSF and MoPH networks in Lebanon.

RESULTS

Among 653 patients from both clinics initially identified as having known ASCVD, 521 (79.8%) were enrolled in the study (figure 2).

Of the 521 included patients, 265 were enrolled in DAZ and 256 were enrolled in Abdeh. Patient characteristics were similar between the two groups, other than levels of hypertension (76.2% in Abdeh and 58.5% in DAZ, p<0.0001) and education (78.5% primary/none in Abdeh and 69.5% primary/none in DAZ, p=0.03). Patients' prescriptions at the time of enrolment included the following: all patients were prescribed a statin and an anti-platelet agent, 94% were prescribed an ACEi, 79% were prescribed a beta-blocker, and 27% were prescribed a calcium channel blocker.

Of 521 enrolled patients, 460 were retained at the 6-month study visit, when 418 switched from multi-drug treatment to the FDC and 42 remained on usual care. Among those not switching, over half had a new or previously unrecognised contraindication (n=27). These included history of cough with ACEi (n=14), low blood pressure (n=5), new contraindication to aspirin (bleeding or need for alternative anticoagulant) (n=5) and hyperkalaemia (n=3). Patient preference (n=11), gastrointestinal symptoms (n=1), dizziness (n=1) and other reasons (n=2) accounted for the rest.

During period 2, among those that switched, 84.0% (n=351) remained on the FDC, 8.1% (n=34) discontinued it and 7.9% (n=33) were lost to follow-up. Among the 34 patients who discontinued, the average duration on the FDC was 1.1 months. Reasons for discontinuation included contraindication/side effect (n=16), patient preference (n=11), MSF doctor's recommendation (n=2) or other (n=5) (figure 2). Overall, retention in the study was 80.6% (n=420) at 12-month study visit. The demographics of those who remained on the FDC throughout the study (n=351) were similar to those of the overall cohort enrolled (n=521) (table 2).

The main study outcomes for different patient groups at different times are available in online supplemental material 6 and are described below.

Medication adherence

At enrolment, 45% of 521 patients were considered adherent (MARS5 score=25). Figure 3 shows adherence to the multiple individual medications (aspirin, statin, ramipril/losartan) at the 6-month (switching visit), and adherence to either the FDC or the multiple medication regimen (for those who discontinued) at the 12-month study visit. At 6 months, 63% (95% CI 58% to 68%) of 385 patients who were switched to the FDC and retained

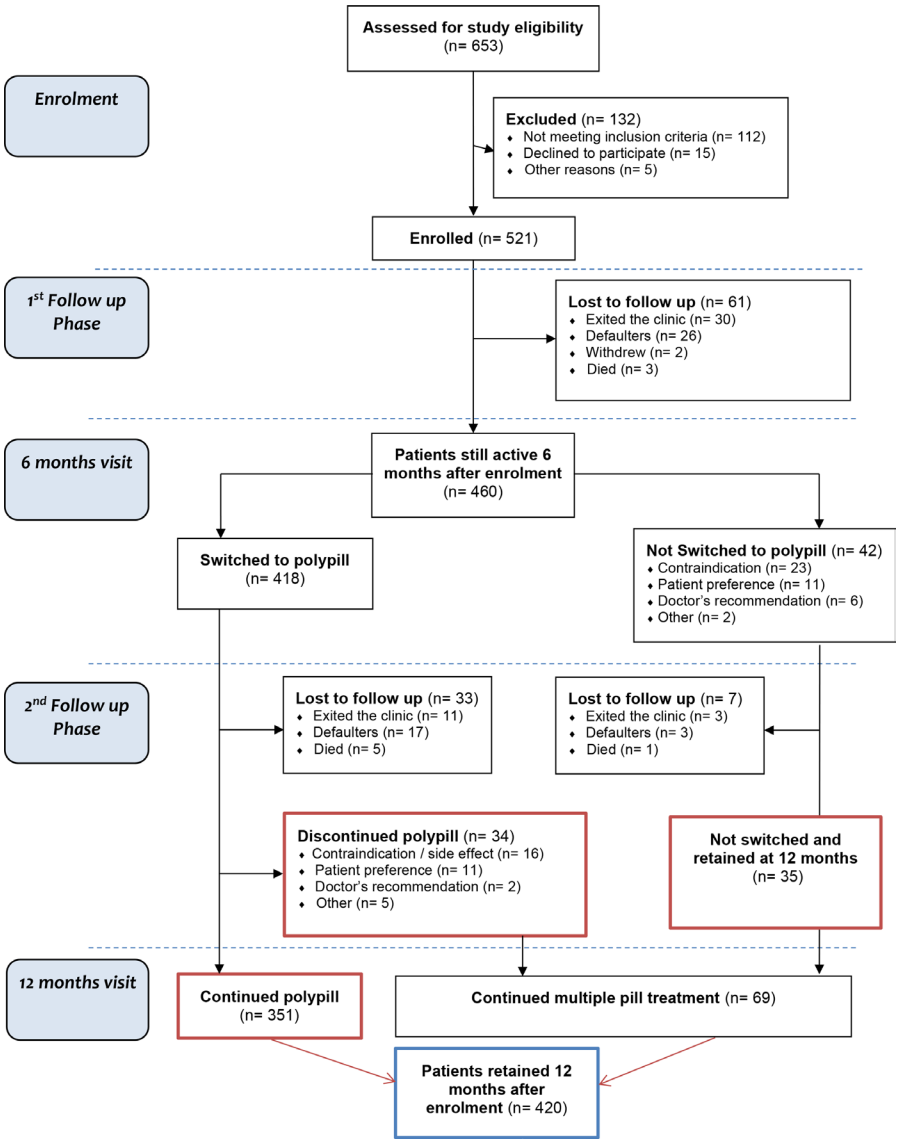

Figure 2 Study enrolment and retention flow diagram reasons for not switching to FDC or for discontinuation: 'contraindication/side effect': any medical reported side effect [by MSF general practitioner (GP) or private physician outside MSF clinic] or any specific reported side effects from patients. 'Patient preference': any non-specific reason for discontinuation provided by the patient for example, 'patient feels bad and wants to stop the medication'. 'Doctor recommendation': any recommendation by MSF GP to discontinue.'Other': any non-MSF guided intervention (ie, private doctor advised to stop, without mentioning reason) or any reason that does not fit the above categories. FDC, fixed dose combination; MSF, Médecins sans Frontières.

throughout the study period were fully adherent to the multiple medications. At 12 months, this improved to 86% (95% CI 82% to 90%) in the ITT analysis. In a per-protocol (PP) analysis, excluding those that discontinued the FDC (n=34), adherence at 12 months was slightly higher at 89% (95% CI 85% to 92%). Logistic regression analyses showed strong evidence that switchers (n=385) who were not fully adherent at 6 months had a 78.2% chance of improving their adherence by the 12-month visit, whereas those who were already fully adherent (MARS5 score=25) had only a 9.1% chance of worsening adherence (p<0.0001).

Non-HDL cholesterol control

Baseline non-HDL cholesterol was 2.83 mmol/L among all enrolled patients (n=521) (95% CI 2.73 to 2.92). It dropped to 2.39 mmol/L (95% CI 2.26 to 2.51) at the 6-month visit among the 385 patients who would switch to FDC and were retained in the study by 12 months (figure 4). In this group, by 12 months, non-HDL-C levels were reduced further by 0.28 mmol/L (95% CI −0.38 to −0.18; p<0.0001) to 2.11 mmol/L (95% CI 2.00 to 2.22) in the ITT analysis (figure 4) and by 0.30 mmol/L, to 2.05 mmol/L (95% CI 1.94 to 2.16) in the PP analysis (n=351). Less than half (46%; 95% CI 41% to 51%) of the 385 patients who switched to FDC were meeting non-HDL targets at the 6-month switching visit. This improved to 57% (95% CI 52% to 62%) at the 12-month visit in the ITT analysis and to 59% (95% CI 54% to 64%) in the PP analysis.

Table 2 Characteristics of patients at enrolment and among those remained on FDC and were retained throughout the study period

	Baseline		12-month final visit	
	Patients enrolled in study		Patients remaining on FDC	
Variable	N=521	%	N=351	%
Age group (years)				
18–40	9	1.7	8	2.3
41–65	364	69.9	253	72.1
66–80	141	27.1	86	24.5
>80	7	1.3	4	1.1
Sex				
Female	183	35.1	120	34.2
Male	338	64.9	231	65.8
Origin				
Lebanese	3	0.6	1	0.3
Syrian	518	99.4	350	99.7
Marital status				
Divorced	2	0.4	1	0.3
Married	467	89.6	315	89.7
Single	5	1.0	2	0.6
Widowed	47	9.0	33	9.4
Education				
None	133	25.5	90	25.6
Primary	252	48.4	168	47.9
Secondary	108	20.7	76	21.7
University	28	5.4	17	4.8
Smoking				
Ex	133	25.5	92	26.2
Never	182	34.9	120	34.2
Yes	206	39.5	139	39.6
Hypertension				
Yes	350	67.2	236	67.2
Diabetes type 1				
Yes	2	0.4%	1	0.3
Diabetes type 2				
Yes	258	49.5	177	50.4

% refers to the proportions of patients in that visit.
FDC, fixed dose combination.

SBP control

The mean baseline SBP at enrolment was 128.73 mm Hg (95% CI 126.73 to 130.73). Mean SBP increased between the baseline and 6-month study visits by 3.3 mm Hg to 132.0 mm Hg (95% CI 129.90 to 134.10). Specifically, among those patients who switched to FDC, the mean SBP was 132.68 (95% CI 130.75 to 134.61) at 6 months. We observed a reduction of 2.89 mm Hg (95% CI 4.49 to 1.28, p=0.0005) to 129.73 mm Hg (127.92–131.54) in ITT analysis and a similar reduction of 3.07 mm Hg (−4.76 to −1.38) to 129.46 mm Hg (95% CI 127.58 to 131.35) at 12 months in PP analysis (figure 4).

Secondary analyses

We performed secondary analyses examining the outcomes of interest among the 35 people who were not switched to the FDC at the 6-month switching visit and who were retained in the study at 12 months, and among the 34 people who were switched but discontinued the FDC and who were retained at 12 months.

Among the non-switching group (n=35), at the 6-month visit, total adherence was much lower (26%; 95% CI 12% to 43%) than among those who would switch to the FDC (63%; 95% CI 58% to 68%; n=385) and adherence improved to a lesser degree by the 12-month visit in the non-switching group (by 17% to 43%; 95% CI 26% to 61%) compared with those who switched (by 23% to 86%; 95% CI 82% to 90%). The non-switching group also showed improvement in non-HDL-C, with mean levels improving by 0.24 mmol/L (95% CI −0.62 to 0.15) from 2.66 at 6 months to 2.43 mmol/L at 12 months, and 40% (95% CI 0.24% to 0.58%) achieving control by 12 months. Improvement in SBP was also found, with SBP dropping by 3.29 mm Hg (95% CI −8.99 to 2.42) from 128.74 (a lower baseline than among the switchers) to 125.91 mm Hg, and 62% achieving control (95% CI 44% to 78%). However, the small sample size meant that confidence intervals were wide and crossed zero.

Among those who switched but then discontinued the FDC (n=34), returning to the constituent medications, the proportion self-reporting total adherence to the constituent medications dropped from 65% (95% CI 46% to 80%) at 6 months to 56% (95% CI 38% to 73%) at 12 months. Of note, at the 6-month visit, study participants were asked about their adherence to medications taken leading up to that visit, meaning the medications equivalent to the components of the FDC. At the 12-month visit, those that discontinued were asked about what they were taking leading up to that visit (again the constituent or equivalent medications to the FDC). The proportion at target for non-HDL-C deteriorated from 38% (95% CI 22% to 56%) to 33%, dropping 0.09 mmol/L (95% CI −0.47 to 0.29; p=0.625) from a mean of 2.78 at 6 months. SBP control remained stable, with 56% (95% CI 38% to 73%) achieving control at 6 months, vs 55% (95% CI 36% to 72%) at 12 months.

Major cardiovascular events

During the study period, nine enrolled patients died. Three deaths occurred during the baseline data collection period and six after the 6-month switching visit. Of the latter, five occurred among patients switched to the FDC at 6 months (n=418) and one occurred among those not switched (n=42). Four deaths were reportedly due to heart attacks. Cause of death for the other five patients was unknown.

DISCUSSION

To our knowledge, this is the first study describing the implementation of an FDC medication for secondary

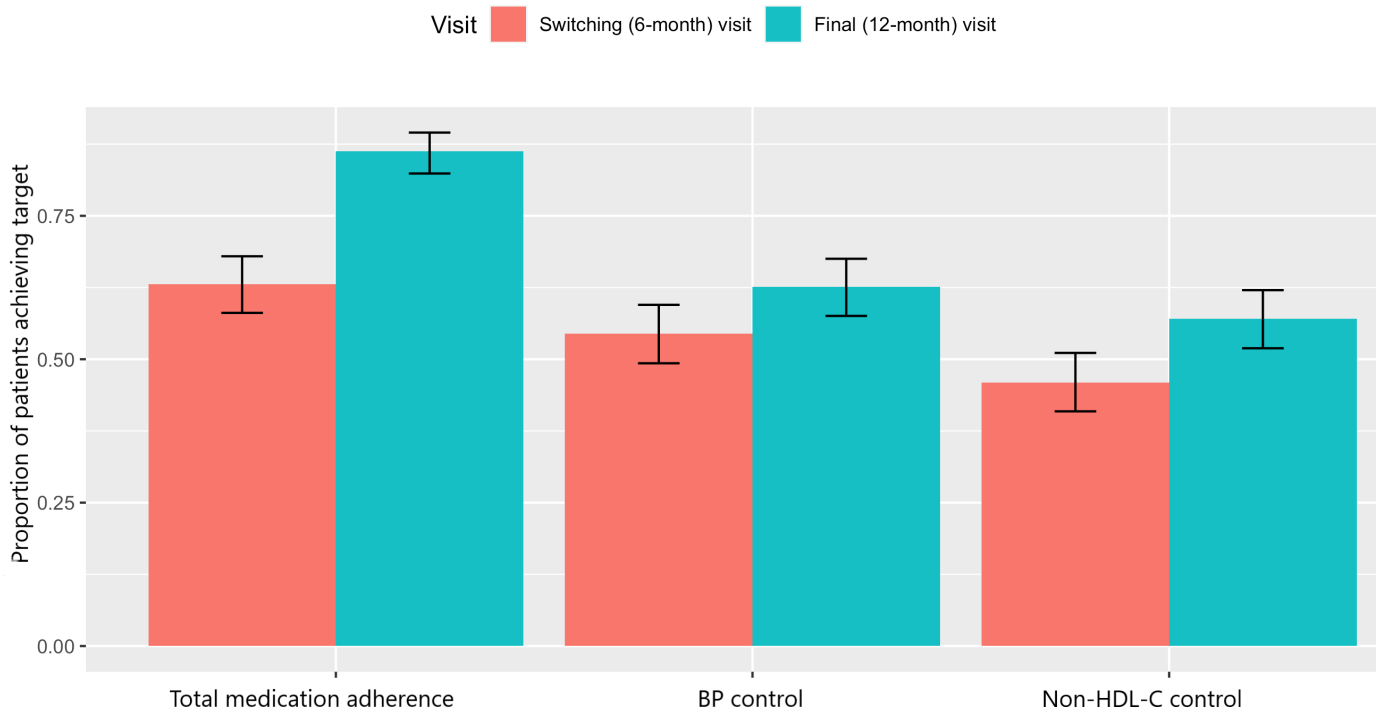

Figure 3 Proportion of patients achieving full adherenceˆ, non-HDL cholesterol and systolic blood pressure control at 6 month (switching) and 12 month visits*. ˆAdherence was defined as self-reported MARS5 score of 25, regarding all of the FDC equivalent medications at 6 months (atorvastatin, rampiril/losartan, aspirin) and regarding the FDC for those patients who switched and were maintained on the FDC (n=351), or all the equivalent medications in the case of those discontinuing the FDC at 12 months (n=34). *6 month visit data include all patients switched to the FDC, and 12 month visit data include all patients switched to the FDC and retained in the study at 12 months, in an intention to treat analysis. BP, blood pressure; FDC, fixed dose combination; non HDL-C, non-high density lipoprotein cholesterol.

prevention of CVD in a humanitarian setting. We implemented an FDC in an MSF-run NCD clinic serving Syrian refugees and vulnerable Lebanese in North Lebanon to explore whether this approach could address some of the challenges of delivering chronic disease care in crisis-affected settings.

Our findings showed an improvement in self-reported adherence in patients taking the FDC. Adherence at enrolment was 50% and improved, as expected, during the first 6-month period of baseline data collection, which may be due to the Hawthorne effect. About two-thirds were already fully adherent before the switch to

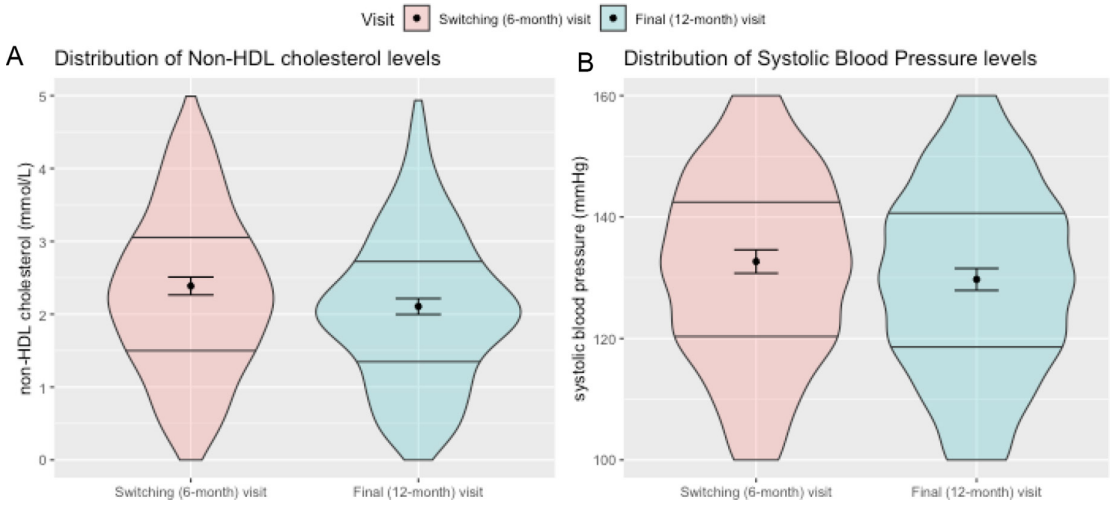

Figure 4 Distribution of continuous outcomes, non-HDL cholesterol and systolic blood pressure levels, at 6-month (switching) and 12-month visits*. *6-month visit data include all patients switched to the FDC and 12-month study visit include all patients switched to FDC and retained in the study at 12 months, in an intention-to-treat analysis. FDC, fixed dose combination; non-HDL, non high-density lipoprotein.

FDC at 6 months, but we observed further improvement to almost 90% full adherence at 12 months, among those who remained on the FDC. Aligned with improved adherence, we observed an improvement in the biomarkers (non-HDL-C and SBP), which are affected by these medications.

It is noteworthy that we found these positive results despite the switch to FDC coinciding with the COVID-19 lockdown period (March–May 2020), when these outcomes might have been expected to deteriorate. Data from the UK have shown poorer rates of diagnosis, control and up-titration of medications among patients with diabetes, while research from Italy has highlighted poorer CVD outcomes due to decreased access to care during the pandemic.[47–49] However, this was not the case among this cohort, which potentially points to the added utility of an FDC approach during periods of service disruption. Although our study was not powered to detect a difference in clinical outcomes, based on trial evidence, we can infer that improved non-HDL-C and SBP levels would result in potentially reduced CVD events and mortality.[44 45]

Our secondary analyses of patients who did not switch or who discontinued the FDC, while not prespecified and involving small numbers of patients, supported our main findings. While these groups also demonstrated improved adherence and non-HDL control, this was from a lower baseline and to a lesser degree than the group that switched to the FDC. We noted that reasons for not switching were largely clinician-led, relating to known side effects of the individual medication components, such as ACE-i-related cough and bleeding issues, rather than adherence issues. However, reasons for discontinuation may have been more patient driven and linked to adherence, since eleven patients stopped the FDC because they felt unwell. Data from randomised controlled trials (RCTs) have shown that rates of adverse effects were similar with use of the Trinomia cardiovascular FDC polypill compared with concurrent use of the individual components.[16 42]

Our qualitative analysis, reported separately, also supports our main findings, with the majority of patients reporting that it was easier to adhere to taking the FDC than to taking the three component drugs separately.[35] We note that medication was also provided free-of-charge to patients by MSF, which would have facilitated retention in care and adherence. There is ample evidence showing that NCD patients in Lebanon and Jordan prioritise a regular medication supply over other elements of care, and that access to consistent, affordable NCD medications remains challenging.[50 51] In addition, during the study period, MSF decided to close their clinics for operational reasons, and to transfer the patient cohort to MoPH-accredited primary care clinics receiving NCD medications via the YMCA (Young Men's Christian Association, which was working with the MoPH and WHO to supply medications to the MoPH-accredited primary care network). The process began during the study period, although study patients were retained in MSF care until study completion. This meant that patients were likely to have switched back to multipill regimens on concluding the study, since Trinomia was not available in public clinics and could only be purchased through private pharmacies. This issue raises the importance of integrating a strong advocacy agenda into study design when humanitarian actors are implementing a treatment that is not consistent with care offered to the host population through the national public health system. This is particularly relevant when future scale-up within public systems may be considered.

Strengths and limitations

A key strength of this research is its pragmatic implementation study design. The study took place in a resource-constrained humanitarian setting among populations with limited finances and healthcare access, during a global pandemic and a national economic crisis. Despite these challenges, we successfully followed up most participants, we had few missing data and the 6-month baseline period allowed us to minimise the expected Hawthorne effect. Limitations included use of a pre/post design, making it difficult to draw conclusions about causation. However, given that the impact of FDC for secondary prevention is well established, and the challenging study setting, this pragmatic design was appropriate to answer a 'real-life' implementation question. The study also involved small numbers of patients. Our intended interrupted time series analysis was not possible given the confounders of the COVID-19 pandemic, the Lebanese economic crisis and the MSF clinic closure. In addition, our results were achieved in a well structured, multidisciplinary clinic run by MSF with appointment times, patient reminders and follow-up of defaulters, which does not reflect the capacity and quality of many other primary care centres in Lebanon. Therefore, our findings may not be readily translatable or scalable in Lebanon's public system. Conversely, the findings may be especially relevant given Lebanon's current crises. Where health systems are struggling, a public health approach that simplifies treatment and facilitates adherence may be of particular benefit. FDCs may also offer benefits where regular clinical contact is challenging. Managing fewer pills may facilitate procurement and supply and may bring cost benefits.

Implications for practice, policy and research

We have shown that the use of a CVD secondary prevention FDC improves adherence and CVD risk factor levels in a humanitarian setting. Further research is needed to determine if such an approach would be acceptable and cost-effective within a national public health system in a crisis-affected country and/or within NGO-run or supported clinics in other humanitarian settings with less developed primary care systems and greater human resource limitations than Lebanon. We note that, while the proportion achieving non-HDL-C targets improved with FDC, approximately half were still not achieving

non-HDL-C treatment targets at 12 months using a moderate intensity statin dose (atorvastatin 20 mg). Thus, there may be room for further improvement, for example, with a high intensity statin.

Since this study was initiated, further studies have shown the effectiveness of an FDC strategy for primary prevention, and the WHO EML has included FDC antihypertensive drugs in its recommendations.[9 10] MSF has recently included antihypertensive FDCs, combining telmisartan and amlodipine, in their clinical guidance and pilot implementations of similar combinations have begun. Further work is needed to determine how a CVD secondary prevention FDC could be combined with FDCs for hypertension and diabetes. The use of single pill FDCs for HIV (Human Immunodeficiency Viruses), enabled simplification of treatment regimens, improving outcomes and tolerability, and facilitated a public health management approach, including community-based management by non-physician health workers.[52 53] Such an approach could help address the large gap in use of secondary prevention medications in those at high risk of CVD, particularly in humanitarian and low-resource settings.

Lessons learnt around the implementation of this FDC medication may be useful for other humanitarian actors engaged in NCD care and for the Lebanese MoPH as they seek to strengthen primary level NCD care within their public system.

CONCLUSION

We have shown that introducing a CVD secondary prevention FDC was feasible in a humanitarian setting and led to improved adherence and CVD risk factor levels during a 6-month follow-up period, despite contextual challenges. A broader application of this approach could facilitate increased use of secondary prevention medications for CVD in humanitarian and low-resource settings, and thus contribute to decreased morbidity and mortality. Further work is needed to determine how these medications could best be integrated into national health systems.

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