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Supervisors: Assoc. Prof. Iva Mucalo, PhD
Prof. Djenane Ramalho de Oliveira, PhD

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UTJECAJ USLUGE UPRAVLJANJA FARMAKOTERAPIJOM NA KLINIČKE ISHODE U PACIJENATA S KARDIOVASKULARNIM BOLESTIMA NA RAZINI PRIMARNE ZDRAVSTVENE ZAŠTITE

DOKTORSKI RAD

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SUMMARY

Patients with established cardiovascular diseases (CVDs) often use multiple medications that increase the risk of irrational drug use, subsequently leading to unfavourable clinical and health outcomes. New pharmacist's intervention named Comprehensive Medication Management (CMM) services provided at the primary care level could address the abovementioned problem by optimizing patients' therapy and improving their outcomes. Hence, the main aim of this dissertation was to evaluate the impact of CMM services on healthcare utilisation, cardiovascular risk factors, and health-related quality of life (HRQoL) among older patients with established CVDs. Moreover, the study aimed to describe the newly implemented practice management system of CMM services at the Croatian county health care centre and to predict CMM's budget impact on Croatian health insurance fund. To determine the clinical and humanistic impact of provided CMM services, quasi-experimental study that was conducted from January 2018 to December 2020 included patients aged 65 to 80 years divided into intervention (65 patients) and control group (68 patients) and followed-up for one year. Results showed that the intervention group patients had significantly lower systolic ($p = 0.038$) and diastolic blood pressure ($p = 0.001$), total cholesterol ($p = 0.014$), low-density lipoprotein cholesterol ($p = 0.005$), and glycosylated haemoglobin ($p = 0.045$) in comparison to the control group. Moreover, patients in the control group had 3.35 (95% CI 1.16–10.00) and 2.34 (95% CI 1.52–3.57) times higher number of hospital admissions and unplanned GPs visits compared to the intervention group, respectively. At the initial visit and 12 months following CMM intervention, HRQoL was measured in the intervention group by using the EQ-5D-5L questionnaire. A significant improvement in dimensions "self-care" ($p = 0.011$) and "usual activities" ($p = 0.003$) was found, with no significant change in the "mobility", "pain/discomfort" and "anxiety/depression" dimensions, as well as the self-rated visual analogue scale. An action research methodology was used to assess the process of the implementation of CMM services. The implementation process included two stages: a pre-implementation stage that set the groundwork for the early implementation stage, in which the practice was set up, the patients' recruitment established, and an array of challenges determined. The budget impact analysis employed in this research led to a CMM's net budget impact of EUR 92,869 and EUR 0.67 incremental cost per patient within a 3-year horizon, rendering CMM an affordable intervention for the Croatian healthcare system. The results of this dissertation add to the evidence base supporting the CMM's full implementation in the Croatian health care system by demonstrating that CMM interventions can significantly

contribute to better clinical outcomes and lower healthcare utilisation, may improve patients' HRQoL, thus serving as a viable solution for safety management in older patients with hypertension and established CVDs at the primary care level.

KEYWORDS: comprehensive medication management services; pharmaceutical care; nonrandomised; primary health care; cardiovascular diseases; older patients; clinical outcomes; health-related quality of life; implementation stage; budget impact analysis

SAŽETAK

Uvod: Kardiovaskularne bolesti (KVB) vodeći su uzrok smrti širom svijeta, uključujući i Hrvatsku; samo u 2019. godini je zbog KVB u svijetu umrlo oko 17,9 milijuna ljudi. Pacijenti s kardiovaskularnim (KV) rizikom ili postojećom KVB često boluju i od ostalih komorbiditeta što često zahtjeva višestruku uporabu lijekova i složene terapijske režime te posljedično doprinosi nepovoljnim kliničkim ishodima, smanjenju kvalitete života i povećanju troškova u zdravstvu. Stoga se kao posljedica spomenutog pojavila potreba za uvođenjem nove usluge usmjerene optimizaciji terapije pacijenta i poboljšanju ishoda - usluge upravljanja farmakoterapijom (UFT) (engl. *Comprehensive Medication Management, CMM*). Pružanjem ove usluge ljekarnik preuzima odgovornost za pacijentove terapijske potrebe te u suradnji s liječnikom obiteljske medicine (LOM) i ostalim članovim multidisciplinarnog tima doprinosi poboljšanju kliničkih ishoda i kvalitete života pacijenata te dugoročno uštedama u zdravstvu. Glavni cilj ovog doktorskog rada bio je utvrditi utjecaj usluge UFT na KV rizične čimbenike, utilizaciju zdravstvene skrbi i kvalitetu života povezanu sa zdravljem u pacijenata starije životne dobi s KV oboljenjima na razini primarne zdravstvene zaštite. Dodatno, cilj ovog istraživanja bio je opisati cjelokupni proces rane implementacije nove zdravstvene usluge UFT u Dom zdravlja Zagreb – Centar te identificirati i procijeniti troškove i uštede u zdravstvu povezane s pružanjem usluge UFT na razini primarne zdravstvene zaštite.

Metode i ispitanici: Kako bi se ispitao utjecaj učinkovitosti usluge UFT na kliničke i humanističke ishode provedeno je prospektivno, nerandomizirano, intervencijsko istraživanje s jednogodišnjim kontroliranim praćenjem pacijenata u Domu zdravlja Zagreb – Centar u razdoblju od siječnja 2018. do prosinca 2020. godine. U istraživanje su bili uključeni pacijenti u dobi od 65 do 80 godina koji su bolovali od hipertenzije i jedne ili više KVB. U ispitivanju je sudjelovalo 65 pacijenata kojima je bila pružena usluga UFT u obliku opsežnih konzultacija s ljekarnikom (intervencijska skupina) te 68 pacijenata kojima je bila pružena standardna zdravstvena skrb (kontrolna skupina) te čije je podatke prikupljao "kontrolni" LOM, paralelno s intervencijskom grupom. Pacijenti koji su pristali na sudjelovanje u istraživanju potpisali su informirani pristanak što je i bio preduvjet za sudjelovanje u istraživanju. U okviru usluge UFT ljekarnici identificiraju, rješavaju i sprječavaju terapijske probleme, utvrđuju terapijske ciljeve, odabiru prikladne intervencije odnosno izrađuju plan skrbi za svakog pojedinog pacijenta i prate ishode liječenja. Ovaj se kognitivni rad ljekarnika svojstven usluzi UFT naziva farmakoterapijska obrada pacijenta (engl. *Pharmacotherapy*

Workup). Učinak usluge UFT na kliničke ishode (sistolički (SAT) i dijastolički (DAT) arterijski tlak, LDL kolesterol (LDL), ukupni kolesterol (UK), trigliceride (Tg), HDL kolesterol (HDL), glikirani hemoglobin (HbA1c), broj hospitalizacija, broj nenadanih posjeta LOM-u i broj posjeta hitnoj službi) utvrđen je mjerenjem razlika početnih i krajnjih vrijednosti (nakon 12 mjeseci) između intervencijske i kontrolne skupine, dok je utjecaj na humanističke ishode (kvaliteta života vezana uz zdravlje) i broj terapijskih problema utvrđen usporedbom početnih i krajnjih vrijednosti ispitanika koji su pripadali intervencijskoj grupi. Za procjenu kvalitete života vezane uz zdravlje pacijenata korištena je hrvatska verzija validiranog upitnika EQ-5D-5L. S obzirom na složenost uvođenja nove zdravstvene usluge u hrvatski zdravstveni sustav, za njenu početnu implementaciju usluge i opis procesa pilotiranja korištena je metodologija akcijskog istraživanja (engl. *action research methodology*) koja je omogućila da istraživači ujedno budu i pružatelji same usluge. Nadalje, za procjenu troškovne učinkovitosti uvođenja nove ljekarničke intervencije-usluge UFT u zdravstveni sustav, provedena je studija utjecaja na proračun (engl. *budget impact analysis*, *BIA*).

Rezultati: Ovo je istraživanje pokazalo da su pacijenti u intervencijskoj skupini imali statistički značajno niži SAT ($p = 0,038$), DAT ($p = 0,001$), LDL ($p = 0,005$), UK ($p = 0,014$) i HbA1c ($p = 0,045$). Kod pacijenata u intervencijskog skupini došlo je do statistički i klinički značajnog sniženja SAT za 9 mmHg ($p < 0,001$) i DAT za 4.99 ($p < 0,001$) mmHg nakon godine dana praćenja. Vjerojatnost nenadanih posjeta LOM-u bila je 2,34 (95% CI 1,52-3,57) puta veća u kontrolnoj grupi u odnosu na intervencijsku, dok je vjerojatnost hospitalizacije bila 3,35 (95% CI 1,16-10,00) puta veća u kontrolnoj, što je bilo i statistički značajno (broj nenadanih posjeta LOM-u $p < 0,001$; broj hospitalizacija $p = 0,034$). Nije pronađena statistički značajna razlika u broju posjeta hitnoj službi između dviju grupa ($p = 0,545$).

U intervencijskoj grupi provedeno je sveukupno 317 konzultacija tijekom kojih je identificirano 563 terapijska problema. Prosječan broj terapijskih problema po pacijentu identificiran tijekom početne procjene iznosio je 3.8 ± 1.9. Najčešći terapijski problemi uključivali su „prenisku dozu lijeka" (35.5 %) i „potrebu za uvođenjem dodatne terapije" (25.6 %). Zabilježeno je sveukupno 596 sumnji na nuspojave lijekova (po pacijentu 9,2 ± 16,9) što je uključivalo i nuspojave koje su pacijenti doživjeli prije dolaska u Savjetovalište, a koje su također prijavili za vrijeme prikupljanja medikacijske povijesti u okviru inicijalne procjene.

Ljekarnička intervencija dovela je do statistički značajnog poboljšanja kvalitete života vezane uz zdravlje u dvije dimenzije, „skrb o sebi" ($p = 0,011$) i „uobičajene aktivnosti" ($p = 0,003$),

dok u ostalim dimenzijama (pokretljivost, bol, tjeskoba), kao ni u vizualnoj analognoj skali nije došlo do značajnih promjena. Analiza EQ-5D-5L upitnika pokazala je da je usluga UFT pozitivno utjecala na kvalitetu života pacijenata starije životne dobi s postojećim KV bolestima s obzirom da je u dvije kategorije došlo do značajnog poboljšanja. Za napomenuti je da se dio istraživanja provodio tijekom COVID-19 pandemije što je znatno utjecalo na zdravlje pacijenata, osobito na tjeskobu i pokretljivost.

Ovo je prvo istraživanje mješovitog metodološkog pristupa kojim su prikazana opažanja i iskustva pilotiranja implementacije usluge UFT na razini primarne zdravstvene zaštite. Proces inicijalne implementacije uključivao je dvije faze: pred-implementacijsku fazu (pripremna faza) koja je postavila temelje za fazu rane implementacije te početak pružanja usluge UFT. Tijekom pripremne faze definiran je proces rada ljekarnika u okviru kojeg se posebna pažnja pridavala postavljanju komunikacijskih kanala na relaciji LOM-ljekarnik, razvoju sustava upućivanja pacijenata ljekarniku, razvoju farmakoterapijskog obrasca („mišljenje za LOM-a“), sustava dokumentiranja te ostalim komponentama sustava za upravljanje ljekarničkom praksom. U fazi rane implementacije uspostavljena je ljekarnička praksa koja se započela provoditi u Farmakoterapijskom savjetovalištu DZZC-a, krenulo je upućivanje pacijenata od strane LOM-ova te su prepoznati različiti izazovi pred kojima su se našli ljekarnici koji su pružali uslugu UFT. Najveći izazov predstavljao je otpor LOM-ova prihvaćanju nove uloge ljekarnika i usluge UFT s kojom se do tada nisu susreli. Dobiveni rezultati ove studije pokazali su složenost i izazovnost uvođenja nove uslugu u rigidni i već uspostavljen zdravstveni sustav.

Multipla regresijska analiza pokazala je da bi pacijenti sa šećernom bolešću tipa 2 ($p = 0,025$) i politerapijom ($p = 0,011$), zbog većeg broja identificiranih terapijskih problema, mogli imati veću korist od ove ljekarničke intervencije te bi stoga trebali imati prioritet prilikom upućivanja ljekarniku u Farmakoterapijsko savjetovalište.

U sklopu ovog doktorskog rada provedena je prva studija utjecaja usluge UFT na proračun zdravstvenog sustava. Ukupni izravni troškovi, koji uključuju edukaciju i rad ljekarnika (2.667.098 EUR) te dodatni trošak lijekova (5.182.864 EUR) procijenjeni su na 7.849.962 EUR za trogodišnje razdoblje predstavljajući godišnji trošak od 57 EUR po liječenom pacijentu. S obzirom da se očekuje da usluga UFT smanjuje stope korištenja zdravstvenih usluga i incidenciju neželjenih kliničkih događaja, procijenjeno je da bi nakon njezinog uvođenja došlo do ukupnog trogodišnjeg smanjenja troškova zdravstvene zaštite u iznosu od 7.787.765 EUR. Stoga bi utjecaj usluge UTF na trogodišnji proračun iznosio 92.869 EUR predstavljajući pojedinačni trošak usluge UFT od 0,67 EUR po liječenom pacijentu.

Zaključak: Uspješna suradnja ljekarnika i liječnika obiteljske medicine prikazana ovim istraživanjem pokazala se učinkovitim rješenjem neracionalne i neoptimizirane terapije pacijenata starije životne dobi s politerapijom i KVB. Rezultati ovog doktorskog rada ukazuju na to da usluga UFT na razini primarne zdravstvene zaštite značajno doprinosi poboljšanju zdravstvene skrbi pacijenata starije životne dobi s hipertenzijom i postojećim kardiovaskularnim oboljenjima. Temeljem rezultata dobivenih analizom utjecaja na proračun zaključuje se da je usluga UFT cjenovno pristupačna nova zdravstvena intervencija što, uz poboljšanje kliničkih ishoda i kvalitete života vezane uz zdravlje, predstavlja dodatni dokaz o učinkovitosti ove usluge, potreban za njenu potpunu implementaciju u hrvatski zdravstveni sustav.

KLJUČNE RIJEČI: usluga upravljanja farmakoterapijom; ljekarnička skrb; nerandomizacija; primarna zdravstvena zaštita; kardiovaskularne bolesti; pacijenti starije životne dobi; klinički ishodi; kvaliteta života povezana sa zdravljem; faza implementacije; studija utjecaja na proračun

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1. INTRODUCTION

Over recent decades medical practice has changed dramatically due to an array of treatment opportunities, both prescription and over-the-counter medications, leading to an increased drug regimen complexity. Such prescribing practices for the management of mainly long-term chronic conditions contribute to drug-related morbidity and mortality, and a significant financial burden to healthcare systems. Simultaneously, the role of a pharmacist has gone through tremendous changes, from a medication expert in prescription-focused activities towards a patient-centred caregiver responsible for ensuring safe and effective medication use, capable of understanding patients' medication experience and including them in decision making process. All these factors underscored the need for the development of a standardized and rational patient-centred approach to high-quality use of medications, resulting in the 1990s with the development of a new professional pharmacy practice named pharmaceutical care practice (1). When the pharmaceutical care practice delivered by a pharmaceutical care practitioner is being organized and integrated into the clinical practice of the health care system, whereby the pharmaceutical care practitioner collaborates with general practitioners (GPs) and other health care providers, then the comprehensive medication management (CMM) services are being provided (2).

CMM services is an evidence-based and patient-centred service that involves an assessment of patient's medications to determine that each medication is appropriate, effective, safe and that the patient is able and willing to take the medications as intended. As all patient care providers need a structured, rational thought process for sound clinical decision retrieval, the Pharmacotherapy Workup was developed and adopted as a systematic problem-solving process (2). This process represents the cognitive work taking place in the mind of the practitioner and is used to identify, resolve, and prevent drug therapy problems (DTPs), establish therapy goals, select interventions, and evaluate outcomes.

It is a well-known fact that older patients with established cardiovascular diseases (CVDs) visit various health care providers and are being prescribed multiple medications. Subsequently this leads to an increased risk of experiencing DTPs which, if not resolved, have substantial unfavourable clinical repercussions and add substantial costs to the health care system (3–5). By optimizing therapeutic outcomes through improved medication use and by reducing the risk of adverse events, pharmaceutical care practitioners have been recognized as effective and scalable health care professionals capable of mitigating these avoidable costs, improving patient clinical outcomes, and enhancing health-related quality of life.

1.1 Pharmaceutical care as the new paradigm

1.1.1 Definition of pharmaceutical care practice

Pharmaceutical care practice presents the professional practice of a pharmacist whose concept was widely accepted following its definition in 1998 by Cipolle, Strand and Morley. Pharmaceutical care practice was defined as a practice in which a pharmacist-practitioner is held responsible for patient's drug-related needs and accountable for this commitment, providing rational drug therapy for the purpose of achieving positive patient outcomes and improving patient's quality of life (6). Pharmaceutical care is considered a necessary element of health care, with an emphasis on the adoption of a strong patient focus and the establishment of a therapeutic relationship with a patient (2). Like any other professional patient care practice, this practice consists of three core elements that include the philosophy of the practice, the patient care process, and the practice management system. Each of these components has its meaningful purpose for the successful provision of the pharmacist's practice and improving patient care.

1.1.2 Components of pharmaceutical care practice

The foundation of the practice is the intangible philosophy of practice, a moral compass, and a set of values for a practitioner providing CMM services. By attending patients' medication-related needs, optimizing their drug therapy, and minimizing drug-related morbidity and mortality the practitioner meets the unique social need for the practice. Furthermore, the philosophy of practice outlines the responsibilities of the practitioner that have to be fulfilled to ensure that all the goals of the practice are being completed, and commit to utilize a patient-centred approach, meaning that the care starts with meeting patients' needs and continues until all the needs are met. The last key element of the philosophy is the requirement for the pharmacist to function within the caring paradigm, through the development and maintenance of a rapport with a patient formed to optimize his or her experience (7).

The base of the patient care process is the pharmacotherapy workup. It presents a cognitive work used to make clinical decisions occurring in the mind of the practitioner. This systematic thought process unites the knowledge of pharmacology, pharmacotherapy, pharmaceutical care, and social skills necessary for solving patients' medication problems. The patient care process starts with the assessment of a patient's socio-demographic data, anthropometric data, disease data and medication data obtained directly from the patient and his or her health record, understanding his or her medication experience, and identifying,

resolving, and preventing DTPs. The second step of the patient care process is the development of the care plan to help the patient to establish the goals of therapy for each medical condition and illness, by selecting appropriate individualized interventions in agreement with the patients and their GPs. The final step is a follow-up evaluation - during each follow-up consultation, the pharmacist will determine the actual outcomes of drug therapy for the patient, compare them to the individual desired goals of therapy, determine the effectiveness and safety of drug therapy, and ascertain if the patient has developed any new problem or illness (2).

To facilitate the patient care process, establish a successful practice and sustain the long-term viability of the practice, the management system must be developed. The two most important factors that need to be satisfied are the preparedness of the practitioner and continuous patients inflow. Only with the ongoing addition of new patients on a regular basis, the practice can become economically sustainable. That requires an efficient structure that can facilitate the provision of pharmaceutical care. A practice management system, including a clear understanding of services provided, defines standards and expectations for the service, physical, financial, and human resources, including documentation, reporting and appointment processes, development of methods for evaluation of the practice (practitioner's ability to manage the patients and the practice), payment for the service and development of the business plan (8).

1.2 Comprehensive Medication Management Services

As a service, CMM services were recognized by the Federal Government of the USA in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003) (9) and by 2006 were implemented as a new service as a part of new drug benefit (Part D) within the federal insurance program of Medicare. CMM services are professional activities of the pharmacist that ensure each patient’s medication (prescription, non-prescription, alternative, traditional, vitamin, or nutritional supplement) is individually assessed as to determine that each medication is appropriate for the patient, effective and safe given the medical conditions and other medications taken, and that the patient is able to take them as expected (10). The definition and the concept that we rely on today are based on definitions proposed by the Patient Centered Primary Care Collaborative (11), American Medical Association (12), and the Minnesota State Legislature (13). The CMM services are also promoted by several organizations such as the American College of Clinical Pharmacy (14,15), Get the Medications Right Institute (16), and Patient-Centered Primary Care Collaborative (11),

which include active stakeholders in the health care system. The CMM presents professional clinical service provided by specially trained pharmacists and complements current patient care practices. When the service is delivered in a healthcare centre, it has to be delivered directly to a specific patient, either face-to-face or via telephone, on an appointment basis. The care must be comprehensive (a practitioner assesses all of the patient's medications), meaning that it includes an assessment of the patient's drug-related needs, development of the individualized care plan, outcome evaluation and coordination with GPs and other team members. The benefit of the service is likely to add unique value to all patients who are in need. To provide efficient pharmaceutical care practice, numerous steps and activities need to be carried out (Table 1).

1.2.1 Drug therapy problems

The key part of pharmaceutical care practice are drug therapy problems, as they interfere with achieving the desired goals of therapy and demand professional knowledge and experience to resolve them (6,17). The practitioner's responsibility is to bring rational clinical decision-making when identifying DTPs. For the practitioner to be able to identify, resolve or prevent any undesirable event experienced by a patient, three components have to be known: a) recognition of the problem experienced by the patient, b) identification of a medication that is linked with the problem and c) the relationship that occur or is suspected to occur between those two factors. Drug therapy problems are logically and comprehensively evaluated in the same standardized order; first, the appropriateness of the drug therapy, followed by the effectiveness of drug, then safety and, finally, adherence which represents patient's ability and willingness to use the medication as professionally recommended (17) (Figure 1). Furthermore, alongside the identification and categorization of DTPs, for better understanding and applying clinical judgment, it is important to establish its most likely cause (18). Drug therapy problems are categorized into seven basic categories and they are always related to the indication, effectiveness, safety or adherence:

1) Unnecessary drug therapy – INDICATION;
2) Needs additional drug therapy – INDICATION;
3) Ineffective drug – EFFECTIVENESS;
4) Dosage too low – EFFECTIVENESS;
5) Adverse drug reaction – SAFETY;
6) Dosage too high – SAFETY;
7) Nonadherence or noncompliance – ADHERENCE.

Table 1. Steps and activities that need to be accomplished to provide effective CMM services (11)

	STEPS AND ACTIVITIES	HEALTH PROFESSIONAL
PATIENT REFERRAL AND RECRUITMENT	Identify patients who benefit most from the service: a) Patients who have not reached their therapeutic goal b) Patients with very complex dosage regimens c) Patients who are repeatedly readmitted to the hospital d) Patients experiencing adverse drug reactions e) Patients needing preventive therapy f) Patients who are having difficulty to understand and follow their medication regimen.	GPs, medical specialists, pharmacists, self-referral, other (nurses, family/friend recommendation)
THE PATIENT CARE PROCESS		Pharmaceutical-care practitioner
ASSESSMENT OF THE PATIENT'S DRUG RELATED NEEDS	Meet the patient and uncover patient's medication experience (preferences, expectations, concerns, and beliefs). Obtain specific patient information: demographic, use of alcohol, tobacco or caffeine, and clinical information (relevant medical and medication history, prescription and over-the-counter medications, herbal remedies, supplements, and medications used for a limited period of time, and relevant laboratory values) including allergies, side-effects and immunizations. Prioritize patients' active medical conditions and DTPs.	
IDENTIFICATION OF	Identify that all the patient's medications are properly indicated, the most effective,	

DRUG-RELATED PROBLEMS	the safest possible, and that the patient is able and willing to take the medication as intended. Analyse the assessment data to determine if any drug therapy problems are present.	
CARE PLAN DEVELOPMENT	Determine goals of therapy for each indication managed with medication. Develop a care plan that includes interventions to resolve current drug therapy problems, prevent potential DTPs and achieve goals of therapy. Discuss and negotiate the care plan with the patient and his GP, ensure patient's and GP's understanding and agreement with the plan, and schedule follow-up evaluation. Document the care plan which consists of the steps and clinical status determined for every patient's medical condition.	
FOLLOW-UP EVALUATION	Provide follow-up evaluation for each patient to reassess whether any new DTPs have developed, monitor patient's progress toward the achievement of the goals of therapy, and clarify the care plan to ensure therapy goals are achieved and therapy is optimized.	
CARE COORDINATION BY ALL TEAM MEMBERS – REPEATING PROCESS-CARE	Collaborate and integrate with other health care providers such as GPs, medical specialists, other pharmacists, care managers, and others, with the purpose of achieving patient's optimal care and assuring all goals of therapy are understood by all team members.	Pharmaceutical-care practitioner, GP, medical specialists and other (e.g. nurses)

All the identified DTPs need to be prioritized to reflect patient's experience, preferences and clinical needs of the situation. This is deemed crucial in very complex patients since they often have multiple DTPs and tend to self-identify medication-related problems. That is something what every practitioner must be aware of and always take into account when DTPs are identified. Comprehensive assessment of DTPs is the unique and fundamental contribution of the pharmaceutical care practice and by identifying, resolving, and preventing DTPs pharmaceutical care practitioners help patients to achieve desired therapeutic goals, enhance health outcomes and, consequently, impact the economic burden related to adverse outcomes.

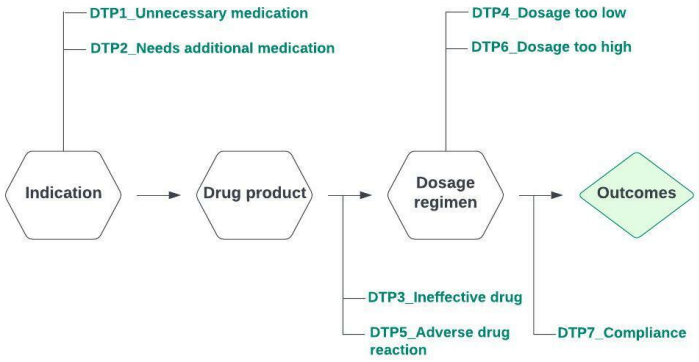

Figure 1. Identification of drug therapy problems (modified according to Cipolle RJ, Strand LM, Morley PC. Drug Therapy Problems. In: Pharmaceutical Care Practice The Patient-Centered Approach To Medication Management Services. 3E. New York: The McGraw-Hill Companies; 2012. p. 141–82)

1.3 Comprehensive Medication Management services at the primary care level

Primary care is considered the cornerstone of health care, where cost reduction and disease prevention are seen as a priority. Primary care services in Croatia are provided in individual practices, larger units comprising several offices and county Health Centres (Dom zdravlja). Health Centre provide general medical consultations, primary care gynaecology services, care for pre-school children, dental care and community nursing care. The National Health Care Strategy 2012–2020 for Croatian health system emphasized the importance of improving clinical outcomes (19), where CMM services if integrated at the primary care level, could play an important role in achieving that aim.

The United States of America (USA) were the first country that managed to integrate CMM services into its existing health care system at the primary care level, by linking it with family practices, internal medicine, and general medicine clinics (14,20–23). Funk et al. (24) have

shown that when pharmacotherapy experts able to manage complex therapies are located in the primary care clinics side by side GPs, they bring profit by mitigating pressures that GPs face due to an aging population coupled with multi-morbidity (25), providing a multi-skilled task force and enabling GPs to have more time for diagnostics and quality medical care provision.

Apart from USA, several countries outside of Europe such as Brazil (26) and Australia have recognized the importance of introducing patient-centred practices in which pharmacists are held accountable for patients' clinical outcomes (27). The situation in Europe, including Croatia is slightly different, and regardless of the support of vast scientific literature and relevant laws, pharmacists are still not recognized as professionals who can play a major role in patients' medication management at the primary care level. Despite the need to improve the mismanagement of health problems by introducing more efficient health care interventions, only small progress can be seen in a few European countries. With the support of National Health Service, Great Britain has started the integration of 400 clinical pharmacists into GP services due to a lack of GPs at the primary care level in 2015 (28–30). By 2022 approximately every fifth general practice in England had access to 1358 full-time equivalent clinical pharmacists (31). Yet, it stays uncertain whether CMM services based on the theoretical framework proposed by Cipolle et al (32) have been employed and implemented. Countries such as Ireland, Netherlands, and Slovenia introduced a non-dispensing pharmacist to the healthcare system and pointed out the significance of embracing pharmaceutical care practice in close cooperation with GPs (33–35).

Croatia is one of the countries where CMM services have only recently been introduced through the employment of the first pharmacists providing full-time CMM services as their primary pharmacy activity.

Although Croatia embraces the concept of pharmaceutical care practice, the current policies and legal framework do not specifically address CMM services. According to the current Pharmacy Act (56), Croatian pharmacists provide pharmaceutical care in cooperation with other health care workers. However, at the same time, pharmacists' activities are limited to community and hospital pharmacies, precluding them from providing pharmaceutical care at other locations where their expertise is indispensable, such as nursing homes, health care centres and hospital wards. It is expected that the planned amendments of the Pharmacy Act will introduce the specific legal framework for CMM services, which should streamline their future development.

1.4 The impact of the CMM services on patients' clinical outcomes

Since the introduction and full implementation of CMM services, numerous studies have proven its clinical benefit by improving patients' CVD risk factors and decreasing health care utilisation (23,26,36–41).

According to the largest database published until now, the total number of 88,556 DTPs was identified and resolved in 22,694 patients receiving CMM services in a 4-year period. This large number of DTPs represents an average of four DTP per patient, whereof 85% had more than one DTP, and 27% five or more. The two most frequent DTPs were the need for additional medication to prevent or treat a medical condition and dosage too low. Out of 18,866 patients' medical conditions that were not at goal at their first visit to a pharmaceutical care practitioner, 74% of conditions improved or remained the same after receiving CMM services (18). In a retrospective study from 2004, pharmaceutical care practitioners identified 3,407 DTP in 2,985 patients during their patients' first assessment, out of which 61% had one or more DTPs identified and resolved. As a result of pharmaceutical care provision, in one third of patients, medical conditions improved (23). Another retrospective analysis of electronic therapeutic records from 9,068 patients that received care-based medication management practice in the large integrated health care system "Fairview Health Services" during 10 years, showed that pharmacists identified and addressed 38,631 DTPs, whereof 80% of DTPs were directly resolved with patients, without consulting GPs. More than half of DTPs obligated the inclusion of a new medication or a dosage increase, while only 16.5% were associated with non-adherence. At the initial consultation 7,708 (85.0%) of patients had 1 or more DTPs, and 2,630 (29.0%) had 5 or more DTPs (22). In a study conducted by Isetts at al. (36), patients had an average of 2.2 DTPs, and the two most common DPTs were additional drug therapy needed and dosage too low as found in previously mentioned studies, while in two Brazilian studies the most prevalent DTP was related to patient adherence (26,42).

Considering the CV risk factors the paramount component in the prevention of the CVDs, the assessment of the impact of pharmacists' interventions on the management of chronic diseases presented a bottom line of many research. Various studies confirmed the positive impact of CMM services by improving individual CV risk factors such as patients' blood pressure (26,38–40,43–48), low-density lipoprotein cholesterol (LDL-C) (26,38,42,45,46,49) and glycated haemoglobin (HbA1c) (26,39,41,42,45–47,49).

A retrospective case-control study conducted in the patient-centred medical home “Midwest VA Medical Center” for veterans included hypertensive patients who received the hypertension care management program provided by pharmacists and their matched controls who did not receive the pharmaceutical care programme. The main goal of the study was to evaluate the effectiveness of the provided programme, with the primary outcome being the difference in systolic (SBP) and diastolic (DBP) blood pressure after 6- and 12-month follow-up. Following 12 month-period blood pressure decreased 7.1/3.2 mmHg in cases, and compared to the controls both SBP and DBP were significantly lower (43).

Carter et al. showed high effectiveness of a GP/pharmacist collaborative intervention in managing patients with uncontrolled hypertension. This prospective, cluster-randomized controlled clinical trial enrolled 402 patients (mean age 58.3 years). The blood pressure was controlled in 63.9% of patients pertaining to the intervention group compared to 29.9% of patients in the control group. Clinically and statistically significant difference was found both in the control (6.8/4.5 mmHg) and the intervention group (20.7/9.7 mmHg) (48).

CMM services can play an important role in the management of type 2 diabetes. Due to the unregulated clinical parameters and complexity of diabetic patients, optimal diabetes management is needed and CMM services showed to be effective in a population of patients with complicated type 2 diabetes (39,41,46,47).

Mourão et al. showed how a pharmaceutical care programme can enhance the quality of health care for type 2 diabetic patients by significantly reducing HbA1c, fasting plasma glucose, total cholesterol (TC), LDL-C, triglycerides, and SBP and increasing high-density lipoprotein (HDL) compared to the control group in the Brazilian public health system. All the participants of this randomized clinical trial, regardless of the group, had HbA1c ≥7%. By the end of the 6-month follow-up, patients in the intervention group had significantly lower HbA1c (-0.6%) and LDL-cholesterol (-0.59 mmol/L) compared to the control group (39). Moreover, another Brazilian 36 month-long clinical trial conducted in a Primary Health Care Unit found similar results, but on a larger patient sample. Pharmaceutical care provided for elderly diabetic and hypertensive patients improved patients' health outcomes. At the end of the study patients in the intervention group had significantly improved SBP (-23.0 mmHg), DBP (-14.8 mmHg), fasting glucose (-1.5 mmol/L), HbA1c (-0.7%), and LDL (-0.27 mmol/L) (45). The results of the study in which two pharmacists provided CMM services in a rural family medicine clinic in Hawaii added significant value to the existing evidence base with regards to how the integration of clinical pharmacists at the primary care level can improve patient outcomes related to diabetes (47).

1.5 Cardiovascular diseases

Cardiovascular diseases are a group of disorders affecting heart and blood vessels most commonly caused by atherosclerosis, i.e. change, damage and deposits on the walls of the arteries. The two most prevalent CVDs are coronary heart diseases and cerebrovascular diseases. Other CVDs include peripheral arterial disease, significant plaque on coronary angiography or carotid ultrasound, myocardial infarction, acute coronary syndrome, coronary revascularisation, transient ischaemic attack, heart failure or atrial fibrillation. Although some people are born with certain medical conditions that predispose them to developing CVDs, the majority of CVDs are caused by behavioural, socioeconomic, and environmental risk factors, including poor diet, tobacco use, physical inactivity, harmful alcohol use, air pollution, high fat intake, obesity, kidney disease, stress, family situation, ageing, as well as modifiable risk factors including hypertension, dyslipidaemia and diabetes. Albeit a high percentage of CVDs can be prevented by addressing those risk factors, atherosclerotic cardiovascular (CV) risk factors are often poorly treated, even in patients with high CV risk (22). The latest 2021 European guidelines on CVDs prevention in clinical practice emphasize the importance of CVD prevention in apparently healthy patients with CV risk, patients with specific risk conditions including diabetes mellitus, chronic kidney disease and familial hypercholesterolaemia, lifestyle improvement and reduction of risk factor levels in patients with established CVDs (50). Vast worldwide evidence data show that patients with established CVDs often have various conditions requiring multiple drug use but are inadequately treated or offered medications that are not likely to enhance their health status (51,52). Therefore, appropriate drug management and rational drug use should be ensured for these patients as to achieve better health outcomes, decrease health care utilisation and improve patients' quality of life.

1.5.1 Epidemiology of cardiovascular diseases

Hypertension is one of the most common diseases in the world, with an overall prevalence around 30 - 45% in adults, and more than 60% in people aged >60 years, irrespective of income status (53). Blood pressure has an independent and continuous relationship with the incidence of several CV events (54), alongside with CV risk factors such as dyslipidaemia and glucose intolerance (55,56). Cardiovascular diseases are a leading cause of death globally; an estimated 17.9 million people died from CVDs in 2019, representing, thus, around one third of global deaths. More than 85% of all CVD deaths are due to ischaemic heart diseases (notably heart attacks) (IHDs) and cerebrovascular diseases (strokes) (57).

European data show that around 1.7 million people died from CVDs in 2017, rendering 37% of all causes of death in European countries. In high-income European countries substantial reductions in mortality rates from CVDs were noticed in previous decades, however this trend has slowed down. Based on data from 2017, IHD and stroke mortality rates were higher in Croatia compared to the European average, with 20.7% of all deaths being caused by IHD and 11.5% by cerebrovascular diseases (58,59). In the following few years, IHD and cerebrovascular diseases remained the leading death cause, up until 2021 when COVID-19 took over first place. Ischaemic heart diseases and cerebrovascular diseases were the second and third cause of all deaths in Croatia in 2021 causing 12.5% and 8% of all deaths in Croatia, respectively (60).

1.6 Pharmaceutical expenditure in Europe and Croatia

Pharmaceuticals are one of the most common medical interventions to manage, prevent and treat diseases and illnesses, especially chronic conditions, including CVDs (61). This fact is predominantly driven by the ageing population, that is characterized by an increased incidence of chronic diseases, leading than to higher medication use. Multiple medication use in the treatment of CVDs, and inappropriate prescribing accompanied with potential adverse drug events lead to a higher risk of experiencing both medication errors and DTPs, resulting in substantial costs to the health care system (3–5).

The need for medications is growing throughout the European Union (EU), fuelling the growth of total health care expenditure, and pharmaceuticals, including prescription and over-the-counter medications, represent the third largest spending component in the European Union (EU) countries after inpatient and outpatient care. Comparable data for total spending on pharmaceuticals across countries is not readily available, but expenditure for outpatient medicines and consumables in Croatia represents 21.6% of total health expenditures, higher than the EU average of 18.1% (52). Croatian pharmaceutical spending has been growing on average 5% a year between 2014 and 2018, while the growth of other health spending categories has been slower.

All these factors, that is increased demand and expenditure on medicines, underline the need for cost-effective and value-based assessments to allow for pricing and reimbursement decision-making purposes. Increasing the cost-effectiveness of medication prescribing and use is of paramount importance, and the focus should be expanded to evaluating the cost-effectiveness of health care interventions and other services. So far, Croatia – as well as many

other countries in South-Eastern Europe - lacks in many aspects of post-listing follow-up of medicines, including rational prescribing and rational use monitoring (62).

By optimizing patients' therapy regimens, ensuring the most effective medication intake and decreasing the unnecessary and unsafe use of medicines and their consequences, these problems can be addressed (11,20,22,27). Hence, CMM services can help patients to enhance their quality of life and clinical outcomes. Another value that this service can reproduce is the economical one, important to the payers and the health care systems in general, substantiating the greatest cost savings for health care budgets. Namely, decreased hospital admissions, that is lower health care utilisation of chronic patients, are one of the most cost-effective outcomes, and the provision of medication management can play a crucial role in reaching this goal (11,63).

1.7 The economic value of the CMM services

The role of the pharmacist in the past few decades has gone through a huge transition – from the health care professional responsible for the medication dispensing process to the provision of individualised patient-centred care as a part of a multidisciplinary health care team. This transformation required development and introduction of new pharmacist-led interventions and services that became the interest of policymakers. For a broader adoption and implementation of new health care interventions, the benefits they yield for patients have to be proven through strong and comprehensive clinical and health economic assessments. The sub-discipline of health economics that focuses on the costs and benefits of specific interventions and guides health care decision-makers for optimal allocation of limited resources is named pharmacoeconomics (64).

One of the pharmacoeconomic analyses that has become an important part of a comprehensive economic evaluation of health care interventions is a budget-impact analysis (BIA). The budget impact model estimates the financial impact of adoption and implementation of a new health care intervention within a health care setting on a designated health care budget, and it assesses its affordability (64). This model has a short-term time horizon (e.g. 3 to 5 years), rendered from the payer perspective (model inputs) and the output of the analysis is the cost.

So far, several studies performed rigorous quantitative cost analyses and evaluation of pharmacist-led medication management services (22,36–38,45,49,65), but yet, no author has brought up the question about the CMMs' affordability. Furthermore, evidence demonstrating health care utilisation reduction due to CMM provision is lacking (22,37,38,45).

The economic value of CMM services is demonstrated through the return on investment (ROI), and it reflects the ability to reduce hospitalisations, GP visits, emergency department visits and the use of unnecessary and inappropriate medications (10).

Isetts et al. demonstrated the ROI of 12:1 measured for 1 year in the Fairview Health Services clinics. This implies that the provision of pharmacist-led pharmaceutical care practice can save $12 for every $1 that is invested in the CMM services provision. Total annual health expenditures per person per year decreased by 31.5% (from $11,965 to $8,197 per person per year) among the 186 MTM intervention group patients ($p < 0.001$) (36).

Furthermore, Ramalho de Oliveira et al. also examined the outcomes of the Fairview's MTM program during the 10-year period. Their direct savings included avoided medical services such as emergency department visits, GPs visits, urgent care visits, long-term care stay and hospitalisation. This study found that pharmacist-estimated cost savings totalled $86 per encounter, and that the total cost of CMM amounted $67 per encounter. The ROI of $1.29 for every dollar spent was calculated by dividing the pharmacist-estimated total health care savings by the cost of CMM visits in 2008 (22).

The Asheville project that involved a 5-year enrolment of diabetic patients that had their therapy managed by specially trained community pharmacists, showed a reduction of direct medical costs between $1200 and $1872 per patient per year, with a 4:1 ROI (49). The continuation of the Asheville project was directed to the participants across 12 community pharmacy and hospital clinic locations over a 6-year period. The study included 620 patients in the financial and 565 in the clinical cohort that were diagnosed with hypertension and/or dyslipidaemia. Significant improvements in SBP, DBP, and lipid measures were noted during the study period. Interestingly, the use of medications for the treatment of CVDs increased nearly threefold, but the medical expenses related to CV events decreased by 46.5%, mainly due to the reduced emergency department visits and hospitalizations (by 54% overall) (38).

A quasi-experimental study that was carried out at six general non-federal acute care hospitals in Hawaii with an aim of implementing a Pharm2Pharm model - a medication optimization program for high-risk older adults including collaboration between the hospital and community pharmacists, showed that the more complex patients were associated with higher medication-related hospitalization. Furthermore, this model led to the reduction of medication-related hospitalisations, thus the annual cost avoidance of future avoided hospitalisations were estimated at around $6,6 million with a ROI 2.6:1 (37).

1.8 Health-related quality of life

Quality of life represents a multidimensional assessment of patient's physical, functional, psychological and social well-being, and includes his or her subjective evaluation of both positive and negative aspects of life that can affect health (66,67). Among many components of overall quality of life, one of the most important is health. In 1990 Schipper et al. defined health-related quality of life (HRQoL) as "the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient" (68). HRQoL gives insight into how chronic diseases, that is, physical and mental health can affect patients' quality of life as well as how community-level resources, policies, and practices impact patients' health viewpoint and functional status. It is recognized that patients with CVDs, such as heart failure or myocardial infarction, often accompanied by several other chronic conditions, have reduced quality of life (69–71). Furthermore, studies have shown that the COVID-19 pandemic negatively impacted the socio-emotional well-being of older people (72,73). Therefore, measurement of the HRQoL, in the past few years, has become an important public health goal and indicator of therapeutic benefit and health outcomes in older patients with chronic diseases (69,74–76). Due to the prolonged life expectancy, ensuring a better quality of life is crucial if we are to experience beneficial aging. Hence, Fernandez-Mayoralas et al. emphasized the need to better understand HRQoL in older patients to promote the development of health and social services that are encouraging and ensuring healthy aging (75). Furthermore, the evaluation of HRQoL assists health care practitioners in clinical decision making resulting in favourable clinical outcomes (77).

Throughout the years several instruments have been developed to determine HRQoL by taking into account multiple measures to capture subjectivity and multidimensionality. The choice of the instrument depends on the study population and context, that is on the type of the study (77). Although there are several methods for HRQoL assessment available, the most commonly used method is a standardized questionnaire. Namely, other methods have shown some flaws, especially when in studies with a large number of participants. The HRQoL tools should be easy to use and understandable, comprehensive, reliable, and accurate (76), and their purpose is to show clinically meaningful changes, and not only the ones that are statistically significant (78). The most often used tools are either generic, providing a comprehensive evaluation of the health status impact or disease-specific questionnaires. Although disease-specific questionnaires are more responsive and clinically more sensitive than the generic ones (79), they can be too narrow and consequently become meaningless

(80). Due to the multidimensionality, comparability and applicability, most of the research elect generic HRQoL assessment questionnaires to allow for objective determination of subjective sensation. The most commonly used generic tools in the context of health-care decision-making are the Medical Outcomes Study Short-Form 36 (SF-36), EuroQol 5-Dimension Questionnaire (EQ-5D), 12 Item Short-Form Health Survey and Visual Analogue Scale EQ-VAS (77,81).

1.8.1 The impact of the pharmaceutical care interventions on the HRQoL

The EuroQol EQ-5D-5L is one of the most frequently applied questionnaires among the CV patients due to its briefness, clarity of administration and availability of population norms. The EQ-5D-5L instrument represents a patient reported outcome measure (PROM) used to assess a patient's health status at a particular point in time (82). Patient-reported outcomes, such as quality of life, are important part of patient-centred care as they are directly reported by patients. Improved health and functioning are positive outcomes of a well-operating health care system, and therefore PROMs represent an important key element of quality of care. PROMs can be employed by various stakeholders in the decision-making process. Alongside clinical outcome measures, HRQoL is an important outcome measure since the true value of a particular intervention can only be reported by patients. As one of the most important goals of pharmaceutical care provision is to enhance patients' quality of life, HRQoL became a crucial indicator of pharmaceutical care interventions. Several studies have assessed the impact of pharmacist-led health care on the HRQoL by using different tools (81). However, according to the available literature until now no study examined the impact of the CMM services on HRQoL in CV patients at the primary care level by using the EuroQol EQ-5D-5L instrument.

Isetts et al (2006) used the Short Form-12 (SF-12v2) instrument to measure the HRQoL in chronic patients prior to and 6 months following collaborative drug therapy management in ambulatory clinics in the Fairview system. The study showed statistically significant improvement in 3 out of 10 scales (physical component summary scale, physical role and social functioning subscale) (83). In the patient satisfaction survey administered among 317 patients, majority of patients (95.3%) agreed or strongly agreed that their overall health and well-being enhanced as a result of CMM services (22).

A systematic review and meta-analysis that reported the impact of pharmacist-led pharmaceutical care interventions on the HRQoL, by using the SF-36 measure, has found that pharmaceutical care interventions significantly improved at least one domain of HRQoL. The existing instruments had minimal to moderate sensitivity to pharmacist-led interventions, with

evidence favouring social functioning, general health, and physical functioning. Out of 10 studies that used the EQ-5D-5L instrument to assess HRQoL in different settings and study populations, only one found a significant impact on a single domain of HRQoL (81). In this study, antidepressant-naive patients pertaining to the intervention group that were educated about their illness, its treatment and the importance of adherence had statistically higher overall improvement of HRQoL compared to the control group that received the usual care (84).

The evidence about the quality of life in patients with CVDs who received pharmaceutical care alongside with the standard care is scarce. Until now, only few studies have examined HRQoL in patients with a particular CVD. A prospective study carried out in Brazil among patients with resistant hypertension showed that pharmaceutical care intervention has significantly improved patients' social functioning and their global health status (85). Hohmann et al assessed the impact of pharmaceutical care on patients who have experienced TIA or ischemic stroke and were hospitalized. The HRQoL was determined by using the SF-36 questionnaire, upon entry to the hospital and after one year. Pharmaceutical care was provided to patients pertaining to the intervention group during the hospital stay, on discharge and in the ambulatory setting for 12 months. Although no significant improvement in the HRQoL among intervention group patients was observed, there was a significant decrease in 7/8 subscales and in both summary measures of SF-36 in the control group (86). The pooled results of three randomized clinical trials that used heart failure-specific tool for HRQoL showed no significant impact of pharmacist-led care practice on the HRQoL (81). A Dutch clinical interventional randomized controlled trial assessed the influence of a medication review accompanied with a follow-up and a pharmaceutical care plan on HRQoL in CVD polymedicated patients of more than 60 years of age. This paper did not find any significant effect of the intervention on the quality of life. According to the results, higher age, female gender, increased number of episodes (interpreted as a frequency of GP visits by one patient) and a higher number of medications were associated with a lower quality of life (87).

2. Implementation of medication management services at the primary healthcare level - a pilot study

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Implementation of medication management services at the primary healthcare level – a pilot study

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This study employed a mixed-method approach to enable the implementation of comprehensive medication management (CMM) services in Croatia's primary care setting. Drug therapy problems (DTPs) and factors associated with their occurrence were determined in patients with chronic diseases from January 2018 to April 2019. The pre-implementation stage established the foundations for the early implementation stage, in which the practice was set up, the patients' recruitment initiated and various challenges identified. During the study period, 86 patients were recruited for CMM provision. Overall, 2.8 DTPs (± 1.6) per patient were identified and the majority (96.2 %) presented with at least one DTP. Multiple regression analysis showed that type 2 diabetic patients ($p = 0.025$) and patients using five or more medications ($p = 0.011$) should be prioritized to receive CMM services as potentially they have a higher number of DTPs, and could, therefore, obtain a greater benefit from the service.

Keywords: comprehensive medication management services, drug therapy problems, risk factors, pharmaceutical care, primary care, implementation stage

Pharmaceuticals are the most common medical intervention and their ability to control disease and impact overall cost, morbidity, and productivity, when appropriately used, is enormous (1, 2). According to the latest OECD publication "Health at a Glance: Europe 2018", pharmaceuticals expenditure, including prescription and over-the-counter medications, presented the third largest item of health care spending in the European Union (EU) (3). Croatia is among the EU Member States with the highest expenditure on medical goods, mainly pharmaceuticals, amounting to 28.5 %, compared to an EU average of 18.5 % (3). Moreover, mortality rates from cardiovascular diseases are almost double the EU average and mortality rates from lung, breast and colorectal cancer are among the highest in the EU, pointing to shortcomings in health care delivery and public health interventions in Croatia (3).

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In addition, a continuous increase in the prevalence of chronic medical conditions is expected alongside the accompanying polypharmacy (4). This scenario renders chronic patients at an increased risk of experiencing drug therapy problems (DTPs), hence adding substantial costs to the health care system and exceeding the amount spent on the medications themselves (5–7).

New approaches are needed at an individual and population level to provide safe and effective pharmacotherapy to patients in an ever more complex environment (8). Thus, to ensure patients' optimal medication use and improve their clinical outcomes, comprehensive and systematic management of medications is deemed crucial. Comprehensive Medication Management (CMM) services (9), officially recognized by the Federal Government of the USA in 2003 (MMA 2003) (10), address this problem. The provision of CMM involves a logical and patient-centered approach to medication optimization that ensures every medication used by a patient is appropriate, effective, safe and convenient to be taken. Almost 30 years have passed since Hepler and Strand had defined pharmaceutical care as a practice in which a pharmacist-practitioner takes the responsibility for a patient's drug-related needs by identifying, resolving and preventing DTPs (9). Collaborative practice between pharmacists and general practitioners (GPs), together with patients' active participation in the definition of treatment regimens, plays an important role in the effectiveness of CMM services (9). Apart from the USA, several countries (e.g. Great Britain, Australia, Canada and Brazil) have managed to integrate CMM services into their existing health care system at the primary care level (11–16).

In January 2018, CMM services were introduced as a pilot project in the largest county health centre in Croatia – Health Centre Zagreb – Centre, thus becoming the first and, at the moment, the only health centre in Croatia and South-Eastern Europe providing CMM by using the patient care process proposed by Cipolle *et al.* (9). However, until now little descriptive and in-depth comparative qualitative work has been published to broaden the understanding regarding the process of implementation of CMM services. Therefore, the primary aim of this study is to describe the newly implemented practice management system of CMM services at the county health centre in Croatia. In addition, various studies have demonstrated its effectiveness on clinical (14, 15, 17–24), economic (17, 22, 23, 25) and humanistic outcomes (26, 27). Other studies determined some factors associated with the occurrence of DTPs, such as polypharmacy, multimorbidity and age, yet employed methodology or clinical settings dissimilar to the present study (28–31). However, to the best of authors' knowledge, until now, no study determined the associated factors of patients with chronic diseases at the primary care level as they receive CMM services that follow the theoretical framework proposed by Cipolle *et al.* (9). Therefore, the secondary aim of the present study was to describe the DTPs and to determine the factors associated with their occurrence among general ambulatory patients receiving CMM services at the primary care level.

EXPERIMENTAL

Study design

In this paper, a mixed-method methodology, involving the use of a combination of qualitative and quantitative approaches to data gathering, was employed. The first part was a qualitative study that used an action research methodology with the aim of implementing CMM services, a new patient care service in the Croatian primary health-care

system, and describing the implementation processes involved. Action research followed the procedures proposed by Kurt Lewin (32), its founder, who assumed that human systems can only be understood and changed if their members take part in this process. Considering the complexity involved in implementing a new health service in the Croatian health system, such as CMM services, this approach was suitable for the herein present study. Within the active research strategy, the first two authors were active in implementing and providing the service, that is, being practitioners, while at the same time they were gathering and analysing data, or acting as researchers.

The implementation stages utilized previously published research as a roadmap (33, 34), which was adapted to the Croatian reality as needed. Additionally, the previously proposed implementation system assisted the piloting of the initial implementation of CMM services through two stages: pre-implementation and early implementation (34). The pre-implementation stage encompassed the following components: ensuring a usable innovation (use of a common language for the CMM philosophy of practice and patient care process), building an implementation team, developing practitioners' readiness to provide the service, identifying and ensuring essential practice management support (infrastructure necessary to ensure the capacity to implement CMM), assessing fidelity of the service and establishing a practice-policy loop.

The second part, the quantitative approach, was a prospective, observational study on CMM services provided to ambulatory patients that was conducted from January 2018 to April 2019 at the primary care clinic, Health Centre Zagreb – Centre (HCZC), with an aim of describing DTPs and determining the factors associated with their occurrence. These results are a part of a larger study designed as an open controlled pre- and post-intervention study with a 1-year patient follow-up. Thus, this paper presents a secondary subset analysis of trial data evaluating the impact generated by a CMM service in patients with chronic health conditions as a primary outcome measure (unpublished to date).

Setting

The CMM services outlined in the present study are piloted in an independent counseling unit, *Pharmacotherapy counselling service*, located in the county health centre, HCZC. This is a primary health care institution and the largest health centre in the Republic of Croatia with 101 active GPs teams. The HCZC's CMM service, developed in partnership with the University of Zagreb Faculty of Pharmacy and Biochemistry (UoZ) as a part of the joint research project, was established in January 2018 to help patients manage their chronic health conditions and optimize the therapeutic value of medicines. Until now, this is the only health centre in the country providing CMM services at the primary care level in Croatia. Two pharmacists from the UoZ Faculty of Pharmacy and Biochemistry facilitated the implementation of the CMM services in the health centre by using the same standardized patient care process (18). CMM services were provided to patients with chronic conditions taking multiple medications, but who were not meeting their therapy goals. Based on the pre-defined inclusion criteria, GPs identified patients and referred them to the pharmacist. The inclusion criteria were the following: a) patients who have not reached or are not maintaining the intended therapy goal, b) patients experiencing adverse effects from their medications, c) patients having difficulty understanding and following their medication regimen, d) patients in need of preventive therapy, and e) patients frequently readmitted to hospital. The initial assessment lasted 60–90 minutes and the follow-

up evaluations 30–60 minutes. Alternatively, patients were followed-up by telephone. The infrastructure needed for the provision of the service, including the space facilitating the delivery of quality service, access to patients, access to the patients' health care providers and administrative support, was ensured by the HCZC. Furthermore, newly implemented electronic consultation system (*Health.net PRO*) (35) at the HCZC enabled GPs to consult with both, hospital medical specialists and practising pharmacists providing CMM services, thus creating a unique platform for patient referral and care plan sharing. Aside from GPs and pharmacists, no other health care professionals were present within this setting.

Data collection

Qualitative data. – Data were collected through semi-structured interviews, group meetings (focus-groups), participant observation, and field journals with descriptions and reflections on the process of implementing and delivering comprehensive medication management services. Semi-structured interviews and group meetings were conducted with GPs and other stakeholders (health policy experts and health-system experts) for sixteen months, and a total of twenty GPs and three members of the management board of the health centre participated in this study.

Both unstructured interviews and group meetings served to introduce the service to GPs, but also to study their views on today's status of the health care system in general, their perspectives on medicine use and rational medication use, and the need for introducing medication management services in the ambulatory clinic. The group meetings allowed discussions regarding the benefits and outcomes of integrating medication management services with other existent services, the types of patients that could benefit most from the service, the value of the service, and their expectations related to the new service. Moreover, practicalities like the structure of a patient's personal medication plan and communication channels between pharmacists and GPs were examined. Since the beginning of the project, twenty-five meetings with the Head of the family medicine specialists took place to share ideas and updates on the progress of the project, and to create new solutions for the advancement of the service.

To encourage and sustain the reflectivity of the team, discussions between the two practitioners-researchers were being held on a weekly basis, and with their trainer, a highly experienced researcher, on a monthly basis. Moreover, participant observation involving journaling and reflection by the practitioners/researchers occurred during the entire implementation period to reach an in-depth understanding of experiences, feelings and actions practitioners lived through during this time. Pharmacists' experiences with the patient-caring process, descriptions of the events that depicted the project's process, ideas for project development and the vision for the CMM services in the future including the remuneration options, were being kept.

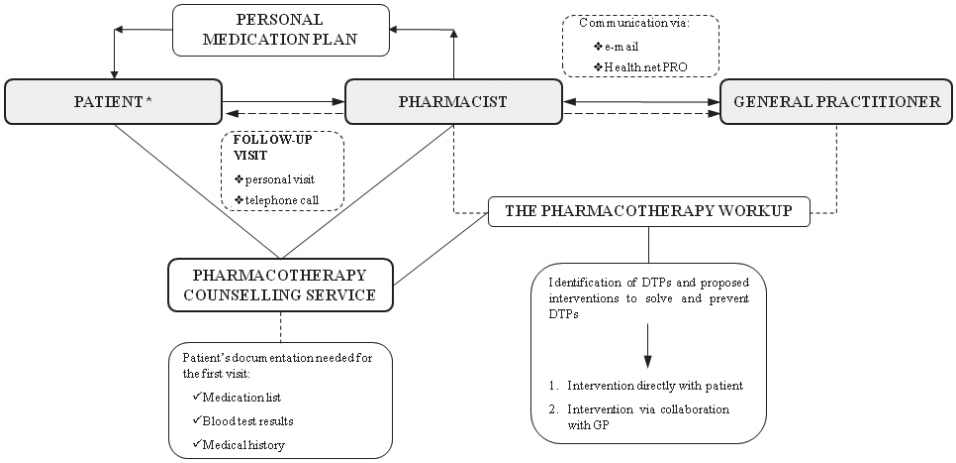
As abovementioned, in order to minimise research bias and enhance the validity of the results, triangulation of different methods of data collection and researcher reflexivity was employed. As previously emphasized, once a proposition has been confirmed by more than one independent measurement process, the level of uncertainty surrounding it is reduced (36).

Quantitative data. – Data was collected from CMM interventions with patients which ran from January 2018 to April 2019. Patients were eligible for the participation if they were aged 18 years or more with at least one regular prescription medication and were admitted fol-

lowing referral by their general practitioner or self-referral. Data were retrieved by a careful review of paper and electronic medical records, and through the interview with the patient, or a patient's family member or a caregiver, if needed. Subsequently, the data were entered into the CMM documentation system that stored all the patients' records. The extracted data contained the following fields: patients' demographics, current and previous medical conditions, number of medications taken, history of drug allergy and adverse drug reactions, number of CMM consultations, types of drug therapy problems identified and addressed, types of interventions implemented to resolve drug therapy problems and change in patients' clinical status. Prescription medications for chronic conditions and all active over-the-counter (OTC) medications, as well as herbal remedies, supplements and medications used for a limited period of time were included in the analysis. The principal diagnosis and comorbidities were coded according to the International Classification of Diseases (ICD-10 Version: 2016) and Anatomical Therapeutic Chemical (ATC) Classification codes were used to analyse the drug therapy. Patients using methadone and other patients with addiction problems, mental and behavioural disorders due to psychoactive substance use and patients with cognitive impairment were not deemed eligible and were thus excluded from the study. The study protocol was approved by the Health Centre's Ethics Committee and the Ethics Committee of the University of Zagreb Faculty of Pharmacy and Biochemistry. This study followed guidelines of the Declaration of Helsinki and Tokyo.

The patient care process

The patient care service employed in this study, namely CMM service, followed the philosophy and the standardized patient care process proposed by Cipolle *et al.* (9). Each CMM encounter was based on the rational decision-making process referred to as the Pharmacotherapy Workup (9). This process represents cognitive work taking place in the



* Type of patient's referral to Pharmacotherapy counselling service: GP referral; Self-referral; Other (family/friend recommendation, specialist referral).

Fig. 1. Workflow diagram of CMM services.

mind of the practitioner and is used to identify, resolve, and prevent DTPs, establish therapy goals, select interventions and evaluate actual outcomes. Identifying a DTP required the practitioner to establish an association between the patient's medical condition and the patient's pharmacotherapy with the purpose of determining whether the patient's drug-related needs were being met. Patients' DTPs identified and addressed by CMM pharmacists were categorized into seven groups (Appendix A) and always assessed in the same systematic order; first, the appropriateness of the drug therapy, followed by the effectiveness of drug regimen, safety and at the last place, adherence. Moreover, this standardized process is implemented in a patient-centred manner, which takes the patient's unique circumstances, needs and expectations into consideration. The workflow of the patient care process specific for Croatian primary care level is shown in Fig. 1.

Study variables and data analysis

The independent variables included demographic characteristics of a patient (age, sex and employment status), anthropometric and clinical (number of diseases, number of drugs used, diagnosis of cardiovascular disease, hypertension, dyslipidaemia or diabetes, hospitalization and emergency department visit recorded in the previous year) and smoking status. The sum of the DTPs detected during the first and second consultation was dichotomized (0–2 DTP; ≥ 3 DTP) and defined as the dependent variable. Quantitative variables were described according to their mean, standard deviation, median and interquartile range, while categorical variables were shown as frequency and percentage.

Pearson's Chi-squared test or Fisher's exact test were used to assess univariate analyses between the independent variables and the DTP presence. Independent variables with $p < 0.15$ in the univariate analyses were included in a multivariable logistic regression model to identify factors associated with the dependent variable. Taking into consideration that the univariate analysis represents the initial step to the associated factors analysis, the higher $p <$ value ($p < 0.15$) was selected to ensure that no important variable was left outside the final and multivariate analysis. To evaluate the goodness of fit of the model, the Hosmer-Lemeshow test was used and a likelihood ratio test was used to compare the models. A $p < 0.05$ was considered statistically significant in all analyses. All of the data were analysed with the IBM SPSS software, version 22.0 (SPSS Inc, Chicago, SAD).

RESULTS AND DISCUSSION

Qualitative results

Piloting the implementation of the CMM services in the county health centre. – The following description depicts observations, understandings and experiences of implementing CMM services at the primary care clinic, HCZC in Zagreb, Croatia for the first time.

Pre-implementation (preparation). – Three years prior to the commencement of the pilot project, an implementation team of five members was established, each member with a unique role and set of skills in the areas of pharmacy practice, clinical pharmacy, quality improvement, primary care, health systems in transition and health care reforms. The team assembled periodically to discuss and set the grounds for the implementation of the

new service. Firstly, the suitability of various primary care practice sites was explored to determine whether the structural (private consultation room, documentation system, access to evidence-based information) and system-level support systems (support of clinic leadership and primary care physicians) were in place to facilitate the successful implementation of the CMM services. To ascertain that, a series of interviews with health centres managers and GPs across multiple study sites were conducted over a period of one year, until an agreement with an interested health centre was reached and the availability of the practice management infrastructure was assured.

Furthermore, the identification of an 'in-house' key person interested in initiating this innovation, in this case, the Head of family medicine specialists, was of paramount importance, as he facilitated the introduction of the new service into the health centre. Utilizing the vast scientific literature already published in different countries about the impact of CMM services (18, 19, 21, 24), the perceived need and the benefits of this innovation were communicated with the Director of Health Care Centre and the Head of the family medicine specialists over four group meetings during a two-month period. Openness and eagerness of the management board to allow the piloting of the new service was seen as the rate-increasing step for the outset of the project.

Although this study describes a pilot project, and not a full-service implementation (remuneration was not ensured for practicing pharmacists), fidelity measures were undertaken through a series of steps. Bearing in mind the importance of ensuring a usable innovation, it was made sure that both pharmacists providing the service spoke a common language and delivered the same standards of care, which was achieved through a shared commitment to the philosophy of practice that underlies the CMM patient care process (9).

Furthermore, to ensure both pharmacists at the primary care clinic were prepared to engage in the implementation of the service, several learning strategies were employed. During a three-month doctoral internship at the Centre for Pharmaceutical Care Studies, Federal University of Minas Gerais in Belo Horizonte, Brazil, the philosophy of pharmaceutical care practice and the core elements of CMM services were mastered by the younger researcher (PhD student). Learning resources, such as documents overviewing CMM patient care process and the philosophy of practice (37), on-line training, coaching calls and access to real-life practice to provide a forum for sharing lessons learned, were utilised to equip both pharmacists with the skills and knowledge necessary to successfully commence with the implementation process. Additionally, a relationship with a highly experienced researcher, practitioner and trainer was established and maintained throughout the project. The trainer's continuous assistance and coaching provided through regular telephone meetings was invaluable for the piloting process. Besides the required transformation in pharmacists' attitudes and behaviours, CMM services are a multi-layered service requiring a profound knowledge-base in pharmacotherapy. Hence, a connection was established with several medical specialists who provided external support by covering multiple content areas (*e.g.* endocrinology ($N = 2$), cardiology ($N = 1$), pulmonology ($N = 1$), ophthalmology ($N = 1$) and nephrology ($N = 1$)). Finally, to keep pace with the ever-evolving field of pharmacotherapy, evidence-based literature (38–40) and clinical decision support systems (41) were consulted. Additionally, lecture-based courses covering various pharmacotherapy topics were continuously attended.

Subsequently, establishing and standardizing workflow and a management system unique to this specific health centre was a challenging assignment for the team members.

Three group meetings and two working sessions were carried out for both implementation team members and external consultants recruited to provide support. This work resulted in the development of the document describing the work process flow, namely GP-pharmacist-patient communication, the process of referring patients to a pharmacist, various channels of GP-pharmacist communication, the layout of patients' output documents and other aspects of the practice management system. Components of the practice management system adapted to Croatian primary health care setting are shown in Fig. 2.

Finally, the team engaged in sharing learnings about the implementation process through various communication strategies: publishing in peer-reviewed research manuscripts, presenting at conferences and by engaging in discussions with key stakeholders. This period was sufficient to gain a deeper understanding of the philosophy, patient care process and practice management system of pharmaceutical care practice. Altogether, during this period, visions and ideas were shared between the implementation team, challenges were identified, and potential solutions scrutinized. It is strongly believed by the authors of this paper that such a thorough and lengthy preparation laid down the grounds for the forthcoming piloting stage, namely early implementation of CMM services.

Early implementation. – Once all the pre-requirements for CMM implementation were in place, the Pharmacotherapy counselling service at the HCZC initiated its work. To reach as many GPs as possible, at the outset of the project an email inviting to engage in the CMM services was sent to all GPs (N = 101), leaflets with all the necessary information on CMM services were printed and distributed across the HCZC facilities, a new website was created and a public health campaign with a stand dedicated to CMM services was organized. Thus, all the information on the newly commenced service was made public and widely available. Additionally, a practicing pharmacist personally visited twenty GPs located in the same building as the Pharmacotherapy counselling service to prompt them to engage in the CMM initiative. Despite all of this effort, during the first six months, the response and active engagement of the family medicine specialists was rather poor, however, it increased towards the end of the first year. Regardless of the fact that pharmacists did not share the office space with other health-care providers and were thus not highly visible on a daily basis, the recruitment of patients for the CMM services almost exclusively occurred through referral by general practitioners or self-referral. Hence, the predominance of the active search of patients by the pharmacist, as previously noted (42), was not encountered in the present study. Nevertheless, as previously described in the literature (43), it can be assumed that patient recruitment and acceptance of the service would have been more prominent, had the pharmacists shared the working space with GPs, and thus had been more visible. To allow for the standardisation of the patient care process, and consistency of CMM implementation, both pharmacists were present during all patient encounters. Thus, all uncertainties were immediately discussed and a consensus, regarding the identification of DTPs and proposed interventions, was reached.

During this stage, the team faced several challenges. One of the biggest challenges was the unawareness of medical providers of the existence of the new service at the health centre or the scope and benefits of such service regardless of the fact that they were informed, which resulted in their lack of involvement. To improve GPs' active engagement, various meetings and events were organized, ranging from presenting the CMM concept at GPs' monthly assemblies at the health centre in front of a large group of GPs to multiple one-on--one meetings to explain what CMM stands for, the potential benefit of the service to patients

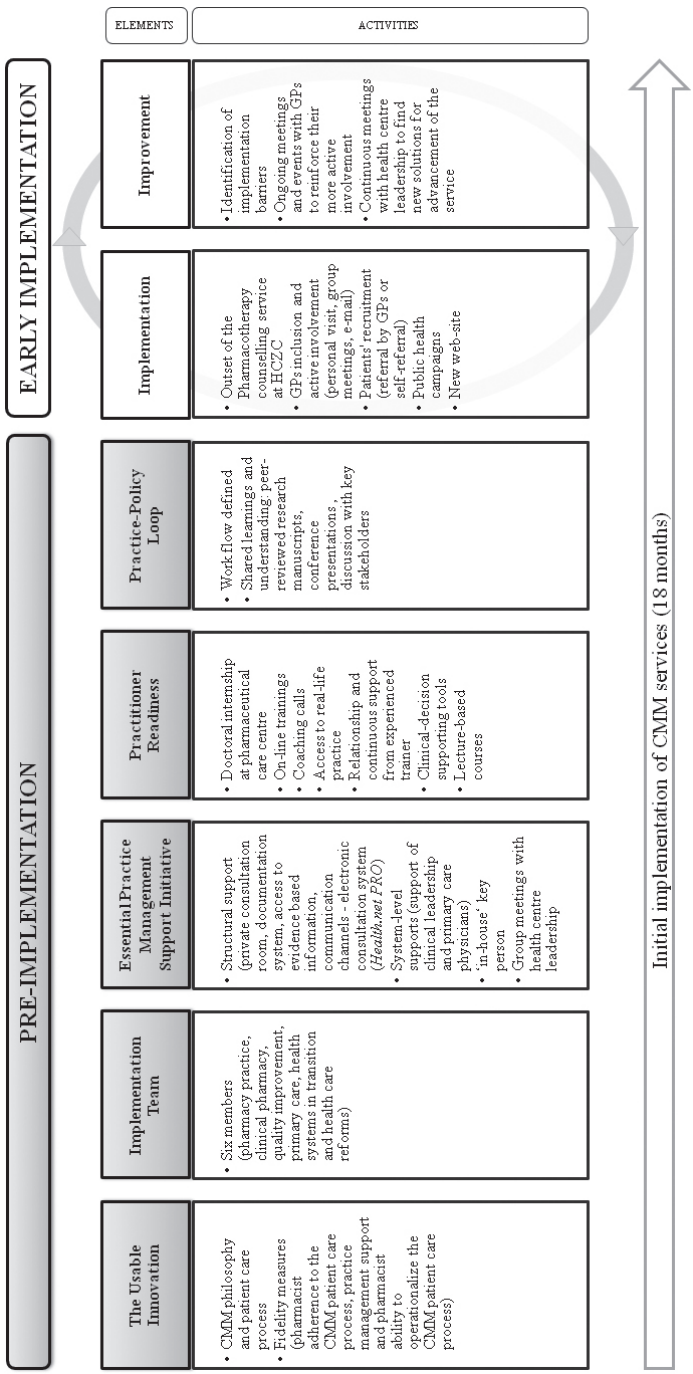


Fig. 2. Components of the practice management system of CMM services.

and GPs, and the steps for engaging the patient into the service. Overall, twenty one-on-one meetings with GPs were held within the first sixteen months of the piloting, and the response rate of GP's actually adopting this innovation was still rather low. Out of the total number of informed GPs (N = 101), only four have fully embraced the service (3.9 %) and nine have sporadically engaged with the service, that is referred 2–3 patients altogether.

Importantly, the Head of family medicine specialists was appointed by the implementation team as the 'key person' ('champion') with the role to showcase success and share the progress of the CMM initiative with clinic leadership and practicing GPs. Even though having the champion GP was very helpful, this process of getting acceptance in the clinic was found extremely demanding, time-consuming and wearing, requiring various sets of skills, mainly to do with negotiating the introduction of a new service within an already established rigid system. Without conducting a deeper qualitative study on the underlying reasons for GPs' lack of involvement, the authors suspect that lack of time, lack of interest, forgetfulness, resistance to change as well as their frequent rotations between multiple practice sites were the main factors contributing to poor response rate. The highest success was accomplished with younger GPs, particularly those with less than 5 years of professional experience in primary health care (N = 3 out of four, 75 %).

In conclusion, the action research stage of this study illustrates both pre-implementation and early implementation stages of CMM in a primary care practice with all the challenges that we came across and that needed to be taken into consideration while introducing the CMM service. Moreover, it reflects other experiences and learnings from the use of the implementation system utilized for the purpose of this initiative (early implementation) (34, 43).

Quantitative results

Data were prospectively collected from 86 patients, of which 54 (62.8 %) were female. Patients' median age (overall range) was 70.5 (32–87) years, with 73.3 % (N = 63) being 65 years or older. The median number (overall range) of medications per patient was 8 (2–19) and polypharmacy (more than 4 medications used) was recorded in 68 (79.1 %) patients. Cardiovascular medications were the most frequently prescribed group of medications (42.5 %). Accordingly, diseases of the circulatory system were the most prevalent conditions (42.5 %), with hypertension as the most commonly presenting condition (82.6 %). Overall, the median number (overall range) of medical conditions per patient was 5 (1–11), and 54.7 % had five or more comorbidities. Detailed study sample characteristics are shown in Table I.

During the initial two visits, overall 241 DTPs were identified with an average of 2.8 DTPs (± 1.6) per patient. At least one DTP was identified in 81 (96.2 %) patients, of which 30.2 % had 4 or more DTPs. The most prevalent DTP was "Needs additional therapy" (26.1 %), with "Untreated condition" being the most common cause. The second most frequent DTP category was "Dosage too low" (24.5 %), followed by "Unnecessary drug therapy" (12.4 %) and "Dosage too high" (11.6 %). Only 5.0 % of identified DTPs were related to non-adherence. Appendix A lists the prevalence of DTP categories, along with its causes and the most common examples. The medications most frequently associated with DTPs were pantoprazole, statins, and bisoprolol (Table II).

Table I. Study sample characteristics

Characteristic		Study sample (N = 86)
Age, median (range)		70.5 (32–87)
Sex, *N* (%)	Male	32 (37.2)
	Female	54 (62.8)
Smoking status, *N* (%)	Yes	11 (12.8)
Medications used at the initial visit, *N*		710
Medications used per patient at the initial visit, median (range)		8 (2–19)
Use of cardiovascular system medications, *N* (%) (ATC class C)		302 (42.5)
Use of alimentary tract and metabolism system medications, *N* (%) (ATC class A)		132 (18.6)
Use of nervous system medications, *N* (%) (ATC class N)		110 (15.5)
Diagnoses at the initial visit, *N*		361
Diagnoses per patient, median (range)		4 (1–9)
Most frequent diagnosis-related groups, *N* (%)		
Diseases of the circulatory system (ICD-10 I00-I99), *N* (%)		147 (40.7)
Endocrine, nutritional and metabolic diseases (ICD-10 E00-E99), *N* (%)		81 (22.4)
Diseases of the musculoskeletal system and connective tissue (ICD-10 M00-M99), *N* (%)		32 (12.3)

Table II. The most common drug therapy problems associated with medications

Medication	Frequency of drug therapy problems, *N* (%)	The most common drug therapy problem category, *N* (%)
Pantoprazole	14 (5.8)	Unnecessary drug therapy, 5 (2.1)
Statins	13 (5.4)	Needs additional therapy, 7 (2.9)
Bisoprolol	13 (5.4)	Dosage too low, 6 (2.5)
Amlodipine	9 (3.7)	Needs additional therapy, 3 (1.2)
Ramipril	9 (3.7)	Dosage too low, 2 (0.8)
Perindopril	7 (2.9)	Needs additional therapy, 2 (0.8)
Furosemide	7 (2.9)	Dosage too low, 2 (0.8)
Metformin	7 (2.9)	Dosage too low, 2 (0.8)
Moxonidine	7 (2.9)	Needs additional therapy, 2 (0.8)
Diazepam	6 (2.5)	Unnecessary drug therapy, 3 (1.2)

According to the univariate analysis, several factors showed significant association with the identification of three or more DTPs: age (p = 0.010), employment status (p = 0.016), number of comorbidities (p = 0.001), polypharmacy (p = 0.000), hospitalizations in previous

year (p = 0.107), hypertension (p = 0.029), type 2 diabetes (p = 0.010) and dyslipidaemia (p = 0.001) (Table III). Multivariate analysis showed that patients with polypharmacy were 8.86 times more likely to have three or more DTPs than the patients using 4 or less medications (p = 0.011). In addition, type 2 diabetes was the second most significant factor associated with the identification of three or more DTPs (p = 0.025). Detailed results of multivariable logistic regression are shown in Table IV.

CMM is a patient-centred clinical service provided by specially educated pharmacists in collaboration with general practitioners and other health care providers, designed to optimize patients' drug-therapy and improve clinical outcomes (1). However, CMM services are still fairly novel at the primary care level and, for that reason, are generally not embedded in health care systems across Europe (9). Moreover, due to implementation variability

Table III. Univariate analysis of factors associated with the DTP occurrence among patients with chronic diseases receiving CMM services

Variable		DTP (%)		OR[a] (95 % CI)[b]	p-value
		0–2	≥ 3		
Gender	Male	15.1	22.1	1	–
	Female	23.3	39.5	1.16 (0.48–2.85)	0.741
Age	< 65	16.3	10.5	1	–
	≥ 65	22.1	51.2	3.60 (1.33–9.75)	0.010
Smoking status	No	31.4	55.8	1	–
	Yes	7.0	5.8	0.47 (0.13–1.68)	0.332
Employment status	Retired	25.6	54.7	1	–
	Employed	10.5	4.7	0. 21 (0.06–0.75)	0.016
	Unemployed	2.3	2.3	0.47 (0.06–3.54)	0.462
Number of comorbidities	1–3	19.8	10.5	1	–
	≥ 4	18.6	51.2	5.19 (1.93–13.98)	0.001
Polypharmacy (more than 4 medications)	No	17.4	3.5	1	–
	Yes	20.9	58.1	13.89 (3.59–53.66)	0.000
Hospitalization in previous year	No	34.9	3.5	1	–
	Yes	47.7	14.0	2.93 (0.76–11.29)	0.107
Emergency department visit in previous year	No	29.1	53.5	1	–
	Yes	9.3	8.1	0.48 (0.15–1.46)	0.190
Hypertension	No	8.1	30.0	1	–
	Yes	30.2	65.8	4.49 (1.07–18.81)	0.029
Type 2 diabetes	No	31.4	33.7	1	–
	Yes	7.0	27.9	3.70 (1.32–10.50)	0.010
Dyslipidaemia	No	26.7	20.9	1	–
	Yes	11.6	40.7	4.47 (1.76–11.39)	0.001

[a] OR – odds ratio; [b] CI – confidence interval

across various clinical settings, patient types and practitioners, delivery of CMM services still appears to be inconsistent and its implementation process relatively poorly documented (34). Therefore, this manuscript innovates as it provides an in-depth description of the process of the initial implementation of CMM services at a primary care practice site, thus adding important knowledge about both the process of implementation of pharmacist-led care delivery models and the most prevalent drug-therapy problems experienced by Croatian patients in the real world.

To the best of authors' knowledge, this is the first study providing an exhaustive research--based depiction of the process of the initial implementation of CMM in Croatia and Europe. The narrative provided here presents the footsteps and strategies to assist willing practitioners to successfully introduce this new service in health care systems. Even more, this study describes some of the topics that need to be reflected upon to prepare a 'new pharmacist', a professional with a completely different set of competencies required for the assimilation of a new professional practice, pharmaceutical care practice, and the provision of patient-centred services (1, 9, 44). Namely, the traditional education provided at most universities worldwide does not prepare pharmacists to work as patient-centred health-care providers, neither professionals with competencies to work as a part of a multidisciplinary team. Although graduate curricula highlight the importance of inter-disciplinarity, the science-practice gap still remains unabridged (44, 45).

As the project unfolded, it became clear that the responsibilities and functions of pharmaceutical care practitioners are very different from those of community pharmacists. Action

Table IV. Multivariate analysis of factors associated with the DTP occurrence among patients with chronic diseases receiving CMM services

Variable		OR[a] (95 % CI[b])	*p*-value
Age	< 65	1	–
	≥ 65	2.75 (0.32–23.75)	0.359
Employment status	Retired	1	–
	Employed	0.65 (0.05–8.46)	0.738
	Unemployed	0.68 (0.03–17.70)	0.819
Number of comorbidities	1–3	1	–
	≥ 4	1.14 (0.26–4.95)	0.865
Polypharmacy (more than 4 medications)	No	1	–
	Yes	8.86 (1.66–47.37)	0.011
Hospitalization in previous year	No	1	–
	Yes	2.41 (0.46–12.79)	0.301
Hypertension	No	1	–
	Yes	0.71 (0.10–5.03)	0.735
Type 2 diabetes	No	1	–
	Yes	4.76 (1.21–18.66)	0.025
Dyslipidaemia	No	1	–
	Yes	2.06 (0.58–7.35)	0.267

[a] OR – odds ratio
[b] CI – confidence interval

research became a valuable mechanism that instigated the team or pharmacists/researchers to think about its responsibilities within the context of primary care outside the community pharmacy setting. To provide CMM services, pharmacists had to accept co-responsibility for patients' clinical outcomes, thus becoming like the other members of the health care team, and finally to recreate their identity as patient-centred healthcare professionals. As already confirmed in previous research (16), pharmacists can feel fearful and insecure to assume new roles that imply being held accountable for patients' clinical outcomes. As stressed by Rosenthal *et al.* (46), staying in one's own familiar environment and avoiding leaving one's comfort zone is ingrained in pharmacist's culture. In addition, as revealed in other studies (16, 47–49), action research encouraged individual and group reflections on new circumstances and allowed for the conception of the most fitting organizational model for an efficient implementation of CMM services.

This study showed how challenging it is to introduce a new service into a rigid and already established health care system. As the project progressed, several challenges were encountered: a) resistance of GPs to embrace the new service available at their premises; b) lack of experience of both practising pharmacists in establishing collaboration with GPs and working in a multidisciplinary team; and c) defining the new work process necessary to provide a standardized and reproducible service. The latter two were mastered throughout the course of the project, while the first one still remains a challenge for researchers/practitioners. Finally, the initial implementation of the pharmacy service demanded major work as new collaborative channels with GPs were initiated and, consequently profound transformation in pharmacists' role. Again, the utilized research methodology became an excellent approach that allowed change to occur.

Moreover, this is the first Croatian study that evaluated the incidence and type of DTPs in ambulatory patients, thus providing insights regarding the types of medication problems patients experience at the primary care level in Croatia. The high number of patients with one or more identified DTPs was similar to the rates noted in previous research (9, 17, 18, 24), demonstrating how CMM services add value to the current standard of care patients are receiving in Croatian health care system. Moreover, consistent with previous evaluations of CMM practices, the two most common DTPs were "Needs additional therapy" and "Dosage too low" (17, 18, 23), suggesting that the major DTP in present population is the underutilization of effective medications. This finding is quite contrary to the assumption that pharmacists' major role is to reduce the number of medications and medication costs for patients. As showed by Isetts *et al.* (23), the economic impact of CMM services is mainly due to a significant decrease in the total costs of health care, instead of a decrease in medication costs. By helping patients to reach their therapeutic goals, CMM pharmacists can enhance health outcomes, and thus impacting the overwhelming costs associated with bad outcomes. In addition, "Adherence" was one of the least commonly presented DTPs. Although pharmacy practice tends to focus on patients' adherence, low prevalence of non-adherence problems in the current and previous studies (9, 18) point to the importance of following the rational decision-making process proposed by pharmaceutical care practice, which means firstly ensuring that every medication is appropriate, effective and safe for a specific patient, and only in the end guaranteeing that the patient is willing and able to take their medications (50).

This study is one of the first research to have determined the factors associated with the occurrence of DTPs at the primary care level (24), by employing the theoretical framework proposed by Cipolle *et al.* Moreover, it appears to be the first study to have established

DTP-associated factors among general ambulatory patients, by using the aforementioned methodology. In line with published evidence (24, 28, 29), polymedicated patients were more likely to have a higher number of DTPs. The second characteristic most strongly associated with the occurrence of three or more DTPs was type 2 diabetes. Both of the above-mentioned factors associated with the DTP occurrence could be used as screening criteria for patients' referral to CMM services, since those types of patients potentially have higher drug-related needs and therefore, could benefit more from the service. Consistently, results of this study provide information to better tailor the training of practitioners, so that encountered DTPs could be more efficiently identified, resolved and prevented.

CONCLUSIONS

The action research methodology enabled an effective approach to introducing a new pharmacist-led service in the Croatian primary health care, as well as detecting the challenges encountered throughout the process of the initial implementation of CMM services. The challenges encountered should be tackled for full implementation of CMM services and need to be taken into consideration in the future implementation of this service in other health care settings. Additionally, a deeper understanding of work processes and resources needed for the initial implementation of CMM were of paramount importance for a successful introduction of CMM within a primary care setting.

The high incidence of DTPs identified among patients with chronic conditions at the primary care level indicates the need for pharmaceutical care services in this population. Type 2 diabetic patients and patients using five or more medications should be prioritized for CMM services as potentially they could have a higher number of drug therapy problems and could, therefore, have a greater benefit from the service. The analysis provided in this study refers to the need for tailoring a targeted education for practitioners, so that encountered DTPs could be more efficiently identified, resolved and prevented. Further research is needed to establish the impact of provided care on clinical outcomes in the Croatian health care setting.

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Appendix

List of drug therapy problems with the most common examples

Drug therapy problem category and cause	Number of drug therapy problems; *n* (%)	Examples of the most common drug therapy problems	Number of drug therapy problems; *N* (%)
I. INDICATION			
1. Unnecessary drug therapy	30 (12.4)		
1.1. No medical indication at this time	13 (5.4)	Pantoprazole use without indication (no long-term prescribed medication that indicates PPI use)	5 (2.1)
		Omega 3 fatty acids for secondary prevention of cardiovascular diseases	3 (1.2)
		Antihistamine use without allergy indication (loratadine *N* = 1. fexofenadine *N* = 1)	2 (0.8)
		Potassium use with unnecessary furosemide therapy	2 (0.8)
1.2. Addiction/recreational drug use	7 (2.9)	Addiction to benzodiazepines developed after long term use (diazepam *N* = 3. alprazolam *N* = 3. lorazepam *N* = 1)	7 (2.9)
1.3. Nondrug therapy more appropriate	2 (0.8)	Patients with hyperuricemia. without gout symptoms. taking allopurinol	2 (0.8)
1.4. Duplicate therapy	8 (3.3)	Patients taking two benzodiazepines	3 (1.2)
2. Needs additional therapy	64 (26.6)		
2.1. Untreated condition	30 (12.4)	Statin therapy required to treat hyperlipidaemia	7 (2.9)
		ACEI or ARB required for untreated hypertension (ramipril *N* = 1. perindopril *N* = 1. valsartan *N* = 1)	3 (1.2)
		Amlodipine required for untreated hypertension	3 (1.2)
		Duloxetine required for diabetic neuropathy treatment	4 (1.7)
		Phytotherapy for menopause symptoms required (cimicifuga extract *N* = 1. sage tea *N* = 1)	2 (0.8)
		An antidepressant required for untreated depression (escitalopram *N* = 1. duloxetine *N* = 1. vortioxetine *N* = 1)	3 (1.2)

Drug therapy problem category and cause	Number of drug therapy problems; *n* (%)	Examples of the most common drug therapy problems	Number of drug therapy problems; *N* (%)
		Patients with HF require eplerenone (stepping up)	3 (0.8)
2.2. Synergistic therapy	21 (8.7)	ACEI/ARB required in patients with unregulated hypertension (perindopril *N* = 2. ramipril *N* = 1. valsartan *N* = 2). CCB (amlodipine *N* = 1). BB (nebivolol *N* = 1). diuretic (hydrochlorothiazide *N* = 1) or moxonidine (*N* = 2)	10(3.7)
		Additional oral antidiabetic (metformin *N* = 1. empagliflozin *N* = 1) or insulin (*N* = 1) required for hyperglycaemia	3 (1.2)
2.3. Preventive therapy	4 (1.7)	ASA for primary prevention in patients with AP and T2DM (75 mg *N* = 1. 100 mg *N* = 1)	2 (0.8)
2.4. Need for diet change	9 (3.7)	Healthy eating habits introduced to T2DM patients	9 (3.7)
II. EFFECTIVENESS			
3. Ineffective drug	22 (9.1)		
3.1. Contraindication present	2 (0.8)	Indapamide contraindicated in patients with urinary incontinency and eGFR<30 ml/min	2 (0.8)
3.2. Condition refractory to drug	3 (1.2)	Patients with long history of T2DM unresponsive to sulfonylureas treatment due to their burned-out pancreas	2 (0.8)
3.3. Drug not indicated for condition	1 (0.4)	Theophylline is not indicated for COPD treatment (GOLD 3 grade)	1 (0.4)
3.4. More effective drug available	16 (6.6)	Switching from human insulin (*N* = 1) or detemir (*N* = 1) to glargine	2 (0.8)
		Budesonide ineffective in COPD patients (GOLD 2 and 3)	2 (0.8)
		Switching from one CCB (lacidipine *N* = 1. lercanidipine *N* = 1) to the other (amlodipine) in patients with unregulated hypertension due to its pleiotropic effects	2 (0.8)

Drug therapy problem category and cause	Number of drug therapy problems; *n* (%)	Examples of the most common drug therapy problems	Number of drug therapy problems; *N* (%)
4. Dosage too low	59 (24.5)		
		Patients taking statin for hyperlipidaemia are unresponsive to prescribed dose	2 (0.8)
		Starting dose of furosemide in HF (up-titration needed)	2 (0.8)
		Patients on ACEI or ARB (ramipril *N* = 2. perindopril *N* = 1. valsartan *N* = 1) for unregulated hypertension are unresponsive to prescribed dose	4 (1.7)
		Starting dose of BB in HF (up-titration needed)	6 (2.5)
4.1. Ineffective dose	42 (17.4)	Patients on BB (bisoprolol *N* = 3. metoprolol *N* = 1) for unregulated hypertension are unresponsive to prescribed dose	4 (1.7)
		Dose of calcium needs to be increased in patients with osteoporosis or osteopenia	3 (1.2)
		Higher dose of moxonidine needed for unregulated hypertension	2 (0.8)
		Higher dose of metformin needed for unregulated T2DM	2 (0.8)
		Higher doses of vitamin D needed for osteoporosis prevention or treatment	3 (1.2)
4.2. Needs additional monitoring	5 (2.1)	Statin use required liver enzymes monitoring	2 (0.8)
4.3. Frequency inappropriate	6 (2.5)	Antihypertensive drugs used occasionally (ramipril *N* = 1. bisoprolol *N* = 1)	2 (0.8)
4.4. Incorrect administration	7 (2.9)	Pantoprazole use for gastritis administered during lunch	2 (0.8)
		Education on proper inhaler technique (aclidinium)	2 (0.8)
III. SAFETY			
5. Adverse drug reaction	26 (10.8)		
5.1. Undesirable effect	16 (6.6)	Urinary infection acquired on empagliflozin	2 (0.8)
5.2. Unsafe drug for the patient	9 (3.7)	Indapamide with an unfavourable effect on glycemia in T2DM patients	2 (0.8)
5.3. Incorrect administration	1 (0.4)	Insulin aspart improperly administered	1 (0.4)

Drug therapy problem category and cause	Number of drug therapy problems; *n* (%)	Examples of the most common drug therapy problems	Number of drug therapy problems; *N* (%)
6. Dosage too high	28 (11.6)		
6.1. Dose too high	12 (5.0)	Due to renal impairment dose reduction needed (moxonidine (*N* = 1). alogliptine (*N* = 1). perindopril (*N* = 1)	3 (1.2)
6.2. Needs additional monitoring	1 (0.4)	Elevated liver enzymes (3 fold) on atorvastatin	1 (0.4)
6.3. Frequency too short	9 (3.7)	Slow release urapidil three times instead of twice daily for hypertension	2 (0.8)
		Trimetazidine use twice daily in patients with eGFR<60ml/min	3 (1.2)
6.4. Duration too long	6 (2.5)	Patients with chronic gastritis in remission continuously taking pantoprazole	1 (0.4)
IV. ADHERENCE			
7. Nonadherence or noncompliance	12 (5.0)		
7.1. Cannot afford drug product	1 (0.4)	Patients cannot afford sitagliptine	1 (0.4)
7.2. Patient forgets to take	1 (0.4)	Patient forgets taking metformin	1 (0.4)
7.3. Does not understand instructions	2 (0.8)	Patient with permanent AF does not understand the importance of methyldigoxin use	1 (0.4)
		Patient administering one instead of a half a tablet of mirtazapine before going to sleep	1 (0.4)
7.4. Patient prefers not to take	4 (1.7)	Furosemide is not taken due to the fear of potential side effects	2 (0.8)
7.5. Simplifying drug administration	4 (1.7)	Daily use of vitamin D drops switched for once per month vitamin D ampules for osteoporosis treatment	1 (0.4)

ACEI – angiotensin-converting enzyme inhibitor; AF – atrial fibrillation; AP – angina pectoris; ARB – angiotensin receptor blocker; ASA – acetylsalicylic acid; BB – beta blocker; BMI – body mass index; BPH – benign prostatic hyperplasia; CCB – calcium channel blocker; COPD – chronic obstructive pulmonary disease; CVI – cerebrovascular insult; DM2 – type 2 diabetes mellitus; ECG – electrocardiogram; eGFR – estimated glomerular filtration rate; GERD – gastroesophageal reflux disease; HbA1c – glycated haemoglobin A1c; HF – heart failure; INR – international ratio; ISH – isolated systolic hypertension; ISMN – isosorbide mononitrate; IM – myocardial infarction; NSAIDs – nonsteroidal anti-inflammatory drugs; PPIs – proton pump inhibitors.

3. Healthcare utilisation and clinical outcomes in older cardiovascular patients receiving comprehensive medication management services: a nonrandomised clinical study

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Healthcare Utilisation and Clinical Outcomes in Older Cardiovascular Patients Receiving Comprehensive Medication Management Services: A Nonrandomised Clinical Study

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Abstract: The objective of this study was to evaluate the impact of comprehensive medication management (CMM) services on healthcare utilisation and cardiovascular risk factors among older patients with established cardiovascular diseases (CVDs). This quasi-experimental study that was performed at the Croatian primary care ambulatory clinic included patients aged 65 to 80 years. Patients were divided into intervention (65 patients) and control groups (68 patients) and were followed-up for one year. Pharmacists provided face-to-face consultations to patients from the intervention group. Groups were compared with regards to the clinical parameters (blood pressure, HbA1c, LDL, TC) and healthcare utilisation (hospital admission, emergency visits, unplanned GP visits). The CMM intervention significantly improved systolic blood pressure ($p = 0.038$), diastolic blood pressure ($p = 0.001$), total cholesterol ($p = 0.014$), low-density lipoprotein cholesterol ($p = 0.005$), and glycosylated haemoglobin ($p = 0.045$) in comparison with the control group. Patients included in CMM services had statistically and clinically lower systolic (−9.02 mmHg, $p < 0.001$) and diastolic blood pressure (−4.99 mmHg, $p < 0.001$) at the end of the study. The number of hospital admissions and unplanned GPs visits were 3.35 (95% CI 1.16–10.00) and 2.34 (95% CI 1.52–3.57) times higher in the control group compared to the intervention group, respectively. This study demonstrated that pharmacists providing CMM services can significantly contribute to better clinical outcomes and lower healthcare utilisation, thus potentially contributing to total healthcare savings.

Keywords: medication management services; nonrandomised; primary care; cardiovascular; older patients

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1. Introduction

Cardiovascular diseases (CVDs) are the number one cause of global mortality, responsible for an estimated 17.9 million deaths each year [1]. Likewise, CVDs are the leading cause of death in Croatia, which, compared to other European countries, has a much higher death rate from diseases of the circulatory system than the European Union averages [2,3]. Furthermore, an ample worldwide evidence base suggests that patients with established CVDs are often inadequately treated or not offered therapies that are likely to bring them benefits [4,5]. Treatment of CVDs and their modifiable risk factors requires the use of multiple medications, thus predisposing patients to a higher risk of experiencing drug therapy problems (DTP) [6–8]. Therefore, in order for the effective and safe use of medications to

be ensured, there is a call for actions aimed at strengthening primary healthcare services focused on medication management.

In the last few decades, pharmacists have played a crucial role in the medication management through the provision of various pharmaceutical services. However, comprehensive medication management (CMM) services are the only patient-centred pharmaceutical services supported by a vast amount of evidence-based literature in the scientific and clinical area [9,10] and are promoted by several organisations such as the American College of Clinical Pharmacy [11,12], Get the Medications Right Institute [13], and the Patient-Centered Primary Care Collaborative [14]. In this service, the fundamental purpose of the pharmacist's work is to address all of a patient's medication-related needs, optimise their medication use, and improve their health outcomes. In addition, pharmacists' patient care process in CMM is made specific by a unique assessment process and a taxonomy that the professional applies to define the patient's medication-related needs, both of which are embedded in the Medication Therapy Problem Framework adopted and promoted as a standard of practice by the Pharmacy Quality Alliance organisation [15].

Although the service has been established and reproduced in many countries worldwide, mainly the Anglo-Saxon countries [11,16,17], limited published data on CMM service implementation [18] confirms that the service has not been developed nor recognised in Europe. Croatia is one of the first European countries where the implementation of CMM services started, and this has occurred only recently through the pilot project at the primary healthcare site [18].

The benefits of CMM services are numerous and include better care [9,10,19–26], cost reduction [10,27,28], and improved patient and provider experience [10,29,30]. Thus far, various studies have demonstrated the positive impact of pharmacists' interventions on the management of chronic diseases by improving individual cardiovascular (CV) risk factors such as blood pressure [22,24,31–33], glycated haemoglobin (HbA1c) [19,20,23,24,26,34], and LDL cholesterol [10,19,20,23,31], as well as on the reduction of patients' utilisation of healthcare services [10,28,31,32]. However, to the best of our knowledge, the effect of the CMM services on healthcare utilisation and clinical parameters has not yet been evaluated among older patients with established CVDs at the primary care level. Hence, the aim of our study was to evaluate the clinical impact of CMM services on healthcare utilisation (unplanned office visits, emergency department visits, and hospitalisations) and CV risk factors (hypertension, glycated haemoglobin, lipid profile) among older patients with established CVDs in a primary public healthcare system.

2. Materials and Methods

2.1. Study Design and Setting

A prospective, open controlled pre- and post-intervention study was carried out from January 2018 to December 2020 at the primary care ambulatory clinic, Health Care Centre Zagreb–Centre (HCZC). HCZC is the largest county healthcare centre in Croatia, with 101 active general practitioner (GP) teams, and is the only healthcare centre providing CMM services in Croatia thus far. The HCZC's CMM services, developed in partnership with the University of Zagreb (UoZ) Faculty of Pharmacy and Biochemistry, are provided by two pharmacists from the UoZ Faculty of Pharmacy and Biochemistry who facilitated the implementation of the CMM services at the health centre. The full implementation process of this new practice management system of CMM services was described elsewhere [18].

All Croatian citizens and residents have the right to healthcare through the compulsory mandatory health insurance scheme that provides universal health insurance coverage to the whole population. In Croatia, primary care physicians (GPs, paediatricians, and gynaecologists) are usually patients' first point of contact with the health system, and each insured citizen is required to register with a GP (adults) or a paediatrician (children), whom they can choose freely [35]. There are not many group practices and interdisciplinary teams in primary healthcare in Croatia, and thus the inclusion of pharmacists as health-

care providers at the primary care level was an innovative and unique endeavour in the studied setting.

2.2. The Patient Care Process

Pharmacist practitioners providing CMM services followed the philosophy and the standardised patient care process, as proposed by Cipolle et al. [36]. Since all patient care providers need a structured, rational thought process for sound clinical decision retrieval, the Pharmacotherapy Workup developed as a systematic problem-solving process specific to the practice of pharmaceutical care was employed in this study. This validated standardised process is used to identify, resolve, and prevent DTPs; establish therapy goals; select interventions; and evaluate outcomes in order to achieve the better possible health results. Patients' DTPs identified and addressed by CMM pharmacists were grouped into seven categories and always assessed in the same systematic order—first, the appropriateness of the drug therapy; followed by the effectiveness of the drug regimen; safety; and, at the end, adherence [36].

2.3. Sample Definition and Data Collection

In quasi-experimental designs such as an open controlled pre- and post-intervention research employed in our study, at least two separate groups are evaluated: one which receives the intervention of interest (CMM services); and another one that serves as a control or comparison group (usual care provided by GPs). Thus, the non-random control group is similar in design to a randomised controlled trial, except that patients are assigned to treatment groups in a non-random fashion. It should be emphasised that this type of quasi-experimental design is strongly supported by the World Health Organisation, as it enables researchers to use real-world processes and data [37].

2.3.1. Study Subjects and Sample Size

The patients who were eligible for inclusion in our study (1) were aged 65 to 80 years, (2) had hypertension and at least one additional established CVD, and (3) were willing and able to sign an informed consent form. Patients with mental and behavioural disorders due to psychoactive substance use, with behavioural syndromes associated with physiological disturbances and physical factors, with cognitive impairment, or who were not able to decide independently on health-related aspects were excluded from the study. The sample size was calculated to detect a minimum difference of 7.5 mmHg between the groups, with a statistical power of 80% and a significance level of 0.05. A target sample size of 70 patients in each group was assumed to ensure statistical power and account for 20% dropouts during the study.

2.3.2. Control Group

Patients included in the control group received the usual care, which included GPs and other specialists' visits, on an "as-needed" basis. Their data were collected by the "control" GP, parallel with the collection of data for the intervention group. The control GP was not involved in the care of patients pertaining to the intervention group. Routine procedures administered to patients were recorded in the patient records and consisted of adjustments in prescribed therapy, requests for laboratory exams, general information about patient health, and specialist referrals.

2.3.3. Intervention Group

In addition to the usual care provided by GPs and other healthcare providers, patients from the intervention group also received pharmaceutical care intervention (CMM services). On the basis of the pre-defined inclusion criteria, GPs and/or medical specialists identified patients and referred them to pharmacists. Moreover, self-referral by the patients was enabled. CMM services were provided through face-to-face consultations at the private counselling area, namely a pharmacotherapy counselling service located at the HCZC, and,

when necessary by telephone, especially amidst the COVID-19 lockdown (a 4 month period in 2020).

The initial assessment was performed at the first consultation, followed by the provision of the care plan created in agreement with the patient and the GP. For the purposes of this study, "initial assessment" was defined as the first and second consultation to ensure that the pharmacist had been able to capture and evaluate all the health problems and medications used by the patient. On each following visit, follow-up consultations were conducted, and the frequency of follow-up consultations depended on the complexity of the drug therapy used by the patient and the number of DTPs identified by the pharmacist. The initial assessment lasted 60–90 min, and every follow-up encounter was 30–60 min. A minimum of 3 consultations were held for each patient. Communication with GPs took place in written form (electronic consultation system Health net. PRO; e-mail) and, if needed, by face-to-face or phone conversation. All the GPs included in the study had less than 10 years of professional experience in primary healthcare.

2.3.4. Data Collection

All of the patients' data, including sociodemographic data (gender, age, level of education and habits), anthropometric data (height, body weight, and body mass index), medical history (current and past medical conditions), utilised medications (prescription medications for chronic conditions, over-the-counter (OTC) medications, herbal remedies, supplements and medications used for a limited time), past medication use, allergies, and adverse drug events were collected during the initial assessment by a review of patients' medical records, as well as through the interview with the patients. The International Classification of Diseases (ICD-10 Version: 2019) and Anatomical Therapeutic Chemical (ATC) Classification codes were used to analyse the principal diagnosis and comorbidities, and the drug therapy, respectively.

Clinical parameters such as systolic blood pressure (SBP, in mmHg), diastolic blood pressure (DBP, in mmHg), heart rate (HR, in bpm), low-density lipoprotein cholesterol (LDL-C, in mmol/L), triglycerides (in mmol/L), high-density lipoprotein cholesterol (HDL-C, in mmol/L), total cholesterol (TC, in mmol/L), glycosylated haemoglobin (HbA1c, in percentage), fasting blood glucose (FBG, in mmol/L), number of hospital admissions, number of emergency department visits, and number of unplanned GP visits were assessed at the baseline and following a 12 month period, for both groups. Number and types of DTPs, types of interventions implemented to resolve them, and changes in patients' clinical status were collected during every follow-up consultation in the intervention group, along with the number of CMM consultations. During each encounter, patients' data were thoroughly documented in the CMM documentation system.

2.4. Clinical Outcomes

The primary outcome was the difference in healthcare utilisation events between the two studied groups (hospital admission, emergency department visits, and unplanned GPs visits). Furthermore, within- and between-treatment differences in SBP; DBP; and serum levels of HbA1c, TC, LDL-C, HDL-C, and triglycerides were also calculated as primary outcome measures.

2.5. Data Analysis

The impact of CMM services on clinical outcomes was determined by measuring the differences between the intervention and the control group, and the differences between serial measurements within the same group with regards to the evaluated parameters. The total number and type of identified and resolved DTPs and clinical outcomes status were established by comparing the baseline values collected during the initial assessment with the 12 month follow-up end-point values only for the intervention group. During the initial stage of care plan development, the following parameters were established for each of the patients' medical conditions and utilised in the evaluation of achieved therapy goals: SBP

130–139 mmHg, DBP 70–79 mmHg [38]; LDL-C < 1.8 (high CV risk); < 1.4 mmol/L (very high CV risk) [39]; improvement of clinical symptoms.

Quantitative variables were described according to their mean, standard deviation, median, and inter-quartile range, while categorical variables were shown as frequency and percentage. The Kolmogorov–Smirnov test was utilised to test the normality of the data distribution. Pearson's chi-squared test was used to test the difference in baseline characteristics, as well as to compare the number of healthcare utilisation events between the groups. To compare the differences between baseline and end-point values within one group, we used a paired *t*-test. Factorial two-way ANOVA and Fisher's LSD test were used to compare the differences between the baseline and end-point values between the intervention and the control group. The data were analysed with the STATISTICA, software, version 6.1 (StatSoft Inc, USA). A value of $p < 0.05$ was considered to be statistically significant.

3. Results

A total of 137 patients were included in the study, of which 69 patients pertained to the intervention group and 68 patients to the control group. Dropouts in the intervention group were four in number; one dropout was caused by death and three by loss of interest for further participation in the study. Analysis of baseline parameters revealed that the two groups were similar in all demographic and clinical parameters ($p > 0.05$). Overall, 133 participants (48 men and 85 women), aged 72.7 ± 4.7 years (mean ± SD), with essential hypertension and at least one established CVDs, and who met the eligibility criteria completed the study.

Cardiovascular medications were the most frequently prescribed group of medications (44.1%), followed by medications for alimentary tract and metabolism (18.0%), and nervous system medications (12.4%). Accordingly, diseases of the circulatory system were the most prevalent conditions (34.9%), followed by endocrine, nutritional, and metabolic diseases (15.3%) and diseases of the musculoskeletal system and connective tissue (12.2%). Detailed baseline characteristics of study participants are shown in Table 1.

Table 1. Baseline characteristics of study subjects.

Characteristic	Group		*p*
	Intervention	Control	
Sample size (*n*)	65	68	
Age (years) *	72.4 ± 4.6	73.0 ± 4.7	0.447
Gender female/male	43/22	42/26	0.598
BMI *	29.5 ± 4.9	29.0 ± 4.8	0.584
Alcohol consumption yes/no	15/50	13/55	0.576
Smoking status yes/no	2/63	9/59	0.033 **
Physical activity yes/no	28/37	48/20	0.001 **
Level of education primary/secondary/higher	3/31/29	21/40/7	<0.001 **
Polypharmacy (≥5 medications) yes/no	64/1	48/20	<0.001 **
Type 2 diabetes mellitus yes/no	26/39	17/51	0.064
Hyperlipidaemia yes/no	35/30	33/35	0.400
Medications used per patient at the initial visit *	10.8 ± 3.6	5.8 ± 2.5	<0.001 **
Medications used at the initial visit	699	394	
Diagnoses per patient at the initial visit *	7.9 ± 3.4	8.8 ± 2.5	0.071
Diagnosis at the initial visit	510	598	

BMI, body mass index. * Data expressed as mean ± SD. ** For smoking status, physical activity, level of education, polypharmacy, and number of medications, statistically significant differences between groups were found. Hence, the additional test was conducted to ensure that these parameters did not affect the end-point results. Factorial ANOVA and correlation test showed that the intervention and control group were compatible for comparison, regardless of initial differences ($p > 0.05$).

3.1. Healthcare Utilisation

The number of hospital admissions and unplanned GP visits were significantly higher in the control group in comparison with the intervention group ($p = 0.034$; $p < 0.001$, respectively). Participants in the control group had 3.35 (95% CI 1.16–10.00) times the risk of hospital admissions and 2.34 (95% CI 1.52–3.57) times the risk of unplanned GP visits compared to participants in the intervention group. No significant difference was found between the groups in the mean number of emergency department visits ($p = 0.545$).

3.2. Clinical Outcomes

Within- and between-treatment differences were assessed for the intervention and the control group in all clinical parameters. There was a significant dependent and independent effect of intervention and time on blood pressure, HbA1c, and lipid profile changes. According to the factorial two-way ANOVA, a significant reduction in SBP ($p = 0.038$), DBP ($p = 0.001$), TC ($p = 0.014$), LDL-C ($p = 0.005$), and HbA1c ($p = 0.045$) was observed in the intervention group at 1 year compared to the control group (Table 2).

Table 2. Between- and within-treatment change from baseline differences.

Parameter	Control Group Baseline vs. End-Point [a]	Intervention Group Baseline vs. End-Point [a]	Baseline Control Group vs. Intervention Group [a]	End-Point Control Group vs. Intervention Group [a]
SBP (mmHg)	0.103	0.002 [b]	0.630	*0.038* [c]
DBP (mmHg)	0.883	*0.007* [b]	0.576	*0.001* [c]
TC-C (mmol/L)	0.934	0.555	0.075	*0.014* [c]
LDL-C (mmol/L)	0.495	*0.021* [b]	0.015 [d]	*0.005* [c]
HDL-C (mmol/L)	0.347	0.786	0.632	0.471
Triglycerides (mmol/L)	0.113	0.580	0.998	0.325
HbA1c (%)	0.244	0.526	0.839	*0.045* [c]
FBG (mmol/L)	0.931	0.171	0.420	0.650

[a] Fisher's LSD. [b] The SBP, DBP, and LDL-C decreased significantly in the intervention group after 1 year. [c] A significant reduction in SBP, DBP, TC-C, LDL-C, and HbA1c was observed in the intervention group in comparison with the control group after 1 year. [d] A significant baseline difference between groups was found in LDL-C.

A significant within-treatment decrease was found in SBP ($p < 0.001$), DBP ($p < 0.001$), and LDL ($p = 0.021$) in patients who received CMM services (pharmacy intervention) (Table 3). SBP decreased by 6.5%, DBP by 6.3%, and LDL-C by 9.2% in the intervention group after 1 year of intervention. At the study baseline, only 50.8% of patients pertaining to the intervention group had controlled hypertension, whereas this figure significantly increased after the pharmacy intervention to 84.6% ($p < 0.001$). The mean absolute BP, heart rate, TC, HDL-C, triglycerides, HbA1c, and fasting blood glucose did not differ significantly between both patient groups at baseline. The LDL-C was the only parameter that differed significantly between both patient groups at baseline, being lower in the intervention group ($p = 0.015$).

Table 3. Change in clinical parameters within control and intervention groups.

Parameter	Control Group (N = 68)		Δ (%)	Intervention Group (N = 65)		Δ (%)
	Baseline	End-Point		Baseline	End-Point	
SBP (mmHg)	139.74	135.21	−4.53 (−3.24)	138.39	129.37	−9.02 (−6.52)
DBP (mmHg)	80.79	81.06	0.27 (0.33)	79.78	74.79	−4.99 (−6.25)
TC-C (mmol/L)	4.98	5.00	0.02 (0.40)	4.62 *	4.51 *	−0.11 (−2.38)

Table 3. *Cont.*

Parameter	Control Group (N = 68)		Δ (%)	Intervention Group (N = 65)		Δ (%)
	Baseline	End-Point		Baseline	End-Point	
LDL-C (mmol/L)	3.02	2.91	−0.11 (−3.64)	2.61 *	2.37 *	−0.24 (−9.20)
HDL-C (mmol/L)	1.37	1.42	0.05 (3.65)	1.39 *	1.38 *	−0.01 (−0.72)
Triglycerides (mmol/L)	1.40	1.76	0.36 (25.71)	1.40 *	1.49 *	0.08 (5.71)
HbA1c (%)	7.25 **	7.71 **	−0.46 (−6.34)	7.16 **	6.90 **	−0.21 (−3.63)
FBG (mmol/L)	8.48 **	8.72 **	−0.24 (−2.83)	8.40 **	7.72 **	−0.68 (−8.10)

Data expressed as mean ± SD. * Missing data for two patients in the intervention group (N = 63). ** Data for patients with type 2 diabetes mellitus (17 patients in the control group and 26 patients in the intervention group).

3.3. Drug Therapy Problems

A total of 317 consultations were carried out in the intervention group, with an average of 4.9 ± 2.6 consultations (mean ± SD) per patient. At the initial assessment, a total of 242 DTPs were identified with an average of 3.8 ± 1.9 (mean ± SD) DTPs per patient. Overall, across all consultations, 563 DTPs were identified. The most prevalent DTPs were "dosage too low" (35.5%), followed by "needs additional therapy" (25.6%) and "dosage too high" (11.9%). Table 4 lists the prevalence of DTP categories. The medications most frequently associated with DTPs were calcium channel blockers (8.3%), statins (7.2%), and beta blockers (6.7%).

Table 4. The frequency of DTPs by category in the intervention group across all consultations.

DTP Category	*n* (%)
1. Unnecessary drug therapy	32 (5.7)
2. Needs additional drug therapy	144 (25.6)
3. Ineffective drug	40 (7.1)
4. Dosage too low	200 (35.5)
5. Adverse drug reaction	47 (8.4)
6. Dosage too high	67 (11.9)
7. Nonadherence	33 (5.9)
Total	563 (100.0)

4. Discussion

To the best of our knowledge, this is the first prospective, open, controlled pre- and postintervention study assessing the clinical impact of the CMM services in older patients with hypertension and established CVDs in Europe and beyond. The obtained results indicate that provision of the pharmaceutical care practice in the primary healthcare setting in Croatia improves patients' clinical parameters such as blood pressure, TC, LDL-C, and HbA1c, and reduces healthcare utilisation. The results of this study are consistent with previous research, indicating improvements in clinical outcomes and avoidance of healthcare service utilisation in the CMM group [9] and interprofessional collaborative practices in general [40]. Furthermore, this is the first quasi-experimental study with the inclusion of a non-random control group that used the methodology of Cipolle et al. [36] in the provision of pharmaceutical care to older CV patients. A quasi-experimental type of study is widely supported by the WHO [37], as it allows researchers to examine a single question in a "real-world" scenario where true experiments cannot be used for ethical or practical reasons.

Of particular note is that the percentage of patients at blood pressure goal improved remarkably over the course of the study from 50.8% to 84.6%. In congruence with previously

published research [24,32,33,40,41], our study findings showed a clinically significant reduction both in SBP (9.0 mmHg) and DBP (4.9 mmHg). As reported by the European Society of Cardiology, meta-analyses of RCTs have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP has a strong clinical impact on all major CV events, all-cause mortality, stroke, coronary events, and heart failure, hence rendering our study findings highly relevant [38]. Similarly to our study, Zillich and co-workers found a significant SBP (7.1 mmHg) and DBP (3.2 mmHg) reduction in patients with hypertension over a 1 year period [33], while Prudencio et al. found a significant reduction in SPB (7.4 mmHg), albeit without any change in DBP [34]. However, unlike in the studies conducted in a patient-centred medical home model where pharmacists were able to prescribe and discontinue hypertension medications without direct oversight from the primary care physician [33,41], pharmacists providing direct patient care in our study could not change therapy without primary care physician's authorisation. A vast array of evidence, including the largest database published until now [36], demonstrated the improvement in the impact of CMM services on blood pressure, yet without including the control group as the limitation [9,19,20,31,42].

The results of this pre- and post-intervention study add to a rather scarce evidence base demonstrating the impact of CMM services on healthcare utilisation, and consequently financial savings [10,28,31,32]. In a study that tested the effectiveness of medication management program in 12 community and hospital pharmacy clinics in Asheville, patients were 50% less likely to have a CV-related ED visit and 55% less likely to have a CV-related hospitalisation at the end of the 6 year period, albeit without the comparison group [31]. Our study is one of the first that looked at the impact of CMM services on medical service avoidance in older CV patients, thus demonstrating significantly more unfavourable outcomes (hospital admissions and unplanned GPs visits) in participants receiving the usual care compared to participants attended by a pharmaceutical care practitioner. Taking into consideration the fact that CVDs are a leading cause of mortality in the world and consequently a major economic burden, by diminishing healthcare utilisation and improving CV risk factors in a general population of patients with hypertension and established CVDs, CMM services could potentially contribute to total healthcare costs savings and prove substantial benefit not only at the primary care level but also at the secondary and tertiary care levels. Further larger-scale research is needed to confirm these findings and to broaden the evidence base with regards to the impact of CMM on healthcare utilisation in older patients with CVDs. Although the economic value of clinical pharmacists in team-based settings is well documented [11], patient access to CMM services in Europe remains limited due to a lack of payer recognition of the value of clinical pharmacists in collaborative care settings and current healthcare payment policy.

The other clinical outcomes, LDL-C and HbA1c, also substantially improved, consistent with findings published elsewhere [19,20,23,24,26,31,34,40]. Moreover, although the LDL baseline values were lower in the intervention group, this study demonstrated a significant improvement in LDL-C compared to the control group. Since patients with diabetes and dyslipidaemia are at increased risk for cardiovascular disease, any improvement in HbA1c and LDL-C, even the slightest, is deemed clinically relevant proving the value of pharmacists' interventions, that is, CMM services [39,43]. Given the positive findings of the study, this proposed model of patient-centred pharmacist care may offer a viable solution for medication mismanagement in healthcare systems across the world.

In addition, we argue that significantly more prevalent polypharmacy detected in the intervention group could partly be explained by the data collection process. Namely, comprehensive data collection conducted in CMM services undoubtedly resulted in a more detailed medication record, thus contributing to a higher incidence of polypharmacy in patients receiving this service in comparison with the patients receiving usual care. Furthermore, in accordance with previously published work, a higher number of DTPs identified in polymedicated patients was found in the intervention group [10,18].

The most prevalent DTPs identified during CMM visits included "needs additional therapy" and "dosage too low", as reported elsewhere [10,18]. This emphasises the underutilisation of effective therapy in hypertensive patients with CVDs, adversely impacting both clinical and economic outcomes. The fact that patients are receiving inadequate dosages of medications to provide a therapeutic benefit is frequently encountered in the practice, thus pointing to the ever-greater need for enforcing the offering of CMM services, according to the comprehensiveness of pharmaceutical care practice, for populations with chronic medical conditions.

The current study has several limitations. First, the non-randomisation of the conducted study could have led to the underestimation of the obtained results. However, we argue that this study design was the only ethically acceptable approach, allowing a "control" GP to provide unbiased medical care, hence precluding the Hawthorne effect that could have possibly masked the effect of the intervention. Moreover, a small reduction in HbA1c (0.283%) in the intervention group could be explained by a smaller number of participants with diabetes mellitus. We strongly believe that this reduction could have been clinically more prominent had we included more diabetic patients for a longer study period. Despite all of the study limitations, it is important to emphasise that the results of this study showed the robust statistical and clinical impact of the provided service, even though the study started simultaneously with the process of the early-stage implementation of the service in the Croatian health system. Additionally, it should be noted that the data collection was hindered by the COVID-19 lockdown which reduced post-COVID healthcare accessibility.

5. Conclusions

In conclusion, the present study indicates that CMM services can strongly decrease the healthcare utilisation, and significantly improve blood pressure, LDL-C and HbA1c in patients with hypertension and established CVDs at the primary care level. The high prevalence of identified and resolved DTPs in this study confirms the appropriate provision of CMM services in the Croatian healthcare setting and demonstrates how this service can improve the effectiveness of patients' medications. However, for the service to be fully incorporated into the primary healthcare setting in Croatia, well-prepared and competent pharmacists need to be available in the system. Thus, teaching the practice of pharmaceutical care and CMM services should be made a priority in pharmacy schools. Moreover, further research of the impact of pharmacists' provision of CMM services on economic outcomes is needed.

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4. The impact of pharmacist-led medication management services on the quality of life and adverse drug reaction occurrence

pharmacy

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Article

The Impact of Pharmacist-Led Medication Management Services on the Quality of Life and Adverse Drug Reaction Occurrence

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Abstract: The aim of this research was to assess the impact of comprehensive medication management (CMM) services on patients' health-related quality of life (HRQoL) and frequency of adverse drug reactions (ADRs) in older patients with cardiovascular diseases (CVDs). A prospective, pre- and post-intervention study with a one-year follow-up was conducted at the Health Care Centre Zagreb—Centre (HCZC). The Euro-Quality of Life Questionnaire 5 Dimensions 5 Levels (EQ-5D-5L) was used to measure the HRQoL at baseline (initial visit at the HCZC) and 12 months following CMM services. The ADRs collected at the initial assessment of the CMM services and throughout follow-up consultations were analyzed according to the occurrence mechanism, seriousness, expectedness and distribution of the Preferred Term according to the System Organ Class. Following the CMM intervention, 65 patients reported significant improvement in dimensions "self-care" ($p = 0.011$) and "usual activities" ($p = 0.003$), whereas no significant change was found in the "mobility" ($p = 0.203$), "pain/discomfort" ($p = 0.173$) and "anxiety/depression" ($p = 0.083$) dimensions and the self-rated VAS scale ($p = 0.781$). A total of 596 suspected ADR reports were found, the majority at patients' initial assessment (67.3%), with a mean ± SD of 9.2 ± 16.9 per patient. The CMM services significantly reduced the rate of suspected ADRs, namely 2.7 ± 1.7 ADRs per patient at the initial assessment vs. 1.0 ± 1.5 ADRs per patient at the last consultation ($p < 0.001$). The obtained results indicate that CMM services may improve patients' HRQoL. Additionally, as CMM services diminished the proportion of ADRs following 1-year patient follow-up, they may serve as a viable solution for safety management.

Keywords: health-related quality of life; adverse drug reactions; comprehensive medication management; pharmacist; cardiovascular diseases; older patients

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1. Introduction

Since cardiovascular diseases (CVDs) present the leading comorbidity and cause of death in Croatia often requiring long-term and complex medication use, patients with CVDs are at a higher risk of having less effective treatment, a higher prevalence of adverse drug reactions (ADRs) and increased health care utilization [1]. Studies have shown that these patients have a reduced health-related quality of life (HRQoL), worse clinical outcomes and present a significant financial burden to the health care system [2–8]. Therefore, medication management is deemed crucial for the treatment of CVDs and their modifiable risk factors, and pharmaceutical care practice has emerged as a solution to the abovementioned predicaments [9,10].

Identifiable events in pharmaceutical care practice are termed comprehensive medication management services (CMM services), and they present an evidence-based and patient-centered service where a pharmacist is held responsible for patients' drug-related

needs and accountable for this commitment. Pharmacists use the theoretical framework proposed by Cipolle et al. to prevent, identify and resolve drug therapy problems, develop a care plan and provide continuous follow-up to achieve positive clinical outcomes, reduce unwanted adverse effects and improve patients' quality of life [9,11]. Along with the improvement of clinical and economic outcomes, HRQoL is considered a fundamental objective of the provision of pharmaceutical care practice.

HRQoL represents a multidimensional assessment of a patient's physical, functional, psychological and social health [12]. Insights into the patients' HRQoL provide new findings on the impact chronic diseases have on life, and in the past few years, HRQoL became an important indicator of therapeutic benefit and health outcomes in patients with CVDs [2,3]. Even more, since the COVID-19 pandemic started, the HRQoL has further been adversely affected by its detrimental effect [13,14]. Regardless of the growing body of evidence, disparate studies that have explored the influence of a multitude of pharmacy interventions on patients' HRQoL have found diverse results [15]. To the best of the authors' knowledge, no study to date has examined the impact of pharmaceutical care practice that follows the theoretical framework proposed by Cipolle et al., namely CMM services, on patients' HRQoL at the primary care level. Hence, the primary objective of this research was to assess the impact of CMM services on the HRQoL before and during the COVID-19 pandemic in older patients with CVDs at the county health center in Croatia.

Furthermore, it has been noticed that when drug therapies produce adverse effects, studies mainly focus on their clinical and physical impact (namely whether they resulted in death, life-threatening conditions, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, etc.) rather than on the evaluation of all the aspects of a patient's HRQoL. Despite the growing interest in HRQoL, there is not much information about the quality of life among patients with ADRs [16]. Previous studies have shown that ADRs have an unfavorable impact on patients' HRQoL [16–19], and it is the elderly patients with multiple chronic comorbidities and polypharmacy who are at a significantly increased risk of experiencing ADRs [20–23]. In addition, according to the authors, this is the first research with an in-depth analysis of ADRs in patients receiving CMM services. Therefore, the secondary aim of the present study was to evaluate the impact of CMM services on the frequency of ADRs in cardiovascular patients and to ascertain their extent and type.

2. Materials and Methods

2.1. Study Design and Setting

This prospective, pre- and post-intervention study with a one-year follow-up was conducted from January 2018 to December 2020 at the Health Care Centre Zagreb—Centre (HCZC). Presented data represent a secondary subset analysis of trial data evaluating the clinical impact produced by CMM services in patients with hypertension and at least one additional established CVD as a primary outcome measure [24]. The CMM services provided at the HCZC were developed in cooperation with the University of Zagreb (UoZ) Faculty of Pharmacy and Biochemistry whose staff was in charge of the implementation and provision of the CMM services. The detailed process of pre- and early implementation of this novel practice management system of CMM services was presented elsewhere [25].

2.2. Study Participants and Data Collection

Study participants aged 65 to 80 years, with diagnosed hypertension and at least one additional established CVD were enrolled in the study. Exclusion criteria included mental and behavioral disorders due to psychoactive substance use, behavioral syndromes, cognitive impairment and inability to decide independently on health-related aspects. Patients eligible for the study were identified based on the pre-defined inclusion criteria by their general practitioners and/or medical specialists and then referred to pharmacists. All the anthropometric, sociodemographic and clinical data were collected by a review of patients' medical records and the interview during the initial consultation at the HCZC.

Patients' HRQoL, the primary outcome of the study, was measured by the Euro-Quality of Life Questionnaire 5 Dimensions 5 Levels (EQ-5D-5L) at baseline (initial visit at the HCZC) and 12 months following pharmacists' intervention (CMM services).

2.3. Health-Related Quality of Life Assessment Tool

The EQ-5D-5L is a questionnaire that consists of an EQ-5D descriptive system with five dimensions measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression and an EQ visual analog scale (EQ VAS) measuring patients' overall current health. For the purposes of this study, the questionnaire translated into the Croatian language and validated in the Croatian version was used [26]. EQ-5D-5L health state was represented by a 5-digit code, which states a unique health state for each individual. There are 3125 possible health states defined. The impact of CMM services on HRQoL was assessed by the changes in the distribution of responses to the self-care and usual activities dimensions of the EQ-5D-5L. For the purpose of detecting change in health status over time, an EQ-5D health state was assumed to be "better" than another if it was better on at least one dimension and no worse in any other dimension [27]. The participants completed questionnaires with the assistance of pharmacists-researchers providing the service.

2.4. Pharmacy Intervention

Pharmacists providing CMM services followed the validated standardized process used to assess initial information, identify, resolve and prevent drug therapy problems (DTP), develop a patient care plan and reassess new information, which is followed up with the patients' health status [9]. In doing so, pharmacists also determined personalized therapy goals, chose interventions and evaluated outcomes, all to achieve the best feasible health status and reach the highest possible quality of life. The workflow included collaboration with both general practitioners and patients to implement suggested interventions and provide care at the highest possible level.

2.5. Adverse Drug Reactions

Case reports collected at the initial assessment of the CMM services and throughout follow-up consultations were stored in the CMM documentation system and used as the data source. Data concerning ADRs that were experienced prior to approaching and during CMM services and were possibly, probably or certainly related to the use of the suspected drug [28–30] were taken into account. Once identified, suspected ADRs were coded into the related Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) terminology [31] and further analyzed with respect to the total and average number of reports per patient, sequence number of consultation, baseline characteristics of patients (including age, sex, number of drugs used and number of comorbidities), distribution of PT according to the System Organ Class (according to MedDRA [31]), occurrence mechanism (according to Edwards and Aronson [28]), seriousness [32,33] and expectedness [32,33]. With regards to seriousness, ADRs were considered serious if they resulted in one of the following outcomes: death, life-threatening condition, inpatient hospitalization, or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect or another important medical event. Additionally, in respect of expectedness, ADRs were considered unexpected if their nature of severity was not consistent with the applicable summary of product characteristics.

2.6. Statistical Analysis

Statistical analyses were performed by using the statistical program IBM SPSS Statistics version 25 (IBM, Armonk, NY, USA) applying a significance level of 0.05. Descriptive statistics were used to present the general characteristics of the respondents, and the collected data were presented using frequency, percentage, mean and standard deviation, median and inter-quartile range. To test the normality of the data distribution, the Kolmogorov–Smirnov test was used. The Wilcoxon signed-rank test was used to analyze the change

from baseline to end-point values of the EQ-5D-5L and VAS scale. T-test was applied to determine the difference between baseline and end-point rates of suspected ADR reports, while the correlation between the rate of suspected ADR reports and number of drugs used, number of comorbidities and age was determined with Pearson's correlation.

3. Results

During the study period, a total of 69 patients were enrolled. Following a dropout rate of 5.8 % (one patient died and three patients dropped out of the study after losing interest in further participation), 65 participants (22 men and 43 women) aged 72.4 ± 4.6 years (mean ± SD) completed the study. Detailed participant characteristics that include sociodemographic and clinical data are depicted in Table 1.

Table 1. Patient population receiving comprehensive medication management services.

Patient Characteristic	Group
	Intervention
Sample size (*n*)	65
Age (years) *	72.4 ± 4.6
Sex female male	43 22
Body mass index	29.5 ± 4.9
Alcohol consumption yes/no	15/50
Cigarette consumption yes/no	2/63
Status of physical activity yes/no	28/37
Level of education primary/secondary/higher	3/31/29
≥5 medications used (polypharmacy) yes/no	64/1
Patients diagnosed with type 2 diabetes mellitus yes/no	26/39
Patients diagnosed with hyperlipidemia yes/no	35/30
Number of medications per patient at the initial visit *	10.8 ± 3.6
Number of medications used at the initial visit	699
Use of cardiovascular system medications, *n* (%)	267 (38.2)
Use of gastrointestinal system and endocrine system medications, *n* (%)	123 (17.6)
Use of nervous system medications, *n* (%)	78 (11.2)
Number of diagnoses per patient at the initial visit *	7.9 ± 3.4
Number of diagnoses	510
Diseases of the circulatory system, %	32.5
Endocrine, nutritional and metabolic diseases, %	21.6
Diseases of the musculoskeletal system and connective tissue, %	11.2

* Data expressed as mean ± SD.

3.1. Health-Related Quality of Life

The health profiles of patients based on their answers to the EQ-5D-5L questionnaire are depicted in Table 2. At the end of the study, none of the patients stated to have an extreme level in any EQ-5D dimension. Overall, following the intervention, patients reported a significant improvement in dimensions "self-care" ($p = 0.011$) and "usual activities" ($p = 0.003$), whereas in the "mobility" ($p = 0.203$), "pain/discomfort" ($p = 0.173$) and "anxiety/depression" ($p = 0.083$) dimensions, no significant change was found. Results obtained using the self-rated VAS scale demonstrate that the CMM services had no impact on the

self-assessed health (p = 0.781), with a mean value of 57.42 at the baseline and 57.67 at the end of the study.

Table 2. Health state profiles according to the EQ-5D-5L dimensions.

EQ-5D-5L Dimension		T0 * (%) n = 60	T1 * (%) n = 58	p Value
MOBILITY	No problems	38.3	37.9	0.203
	Slight problems	18.3	32.8	
	Moderate problems	28.3	19.0	
	Severe problems	15.0	10.3	
	Unable to walk	0.0	0.0	
SELF-CARE	No problems	78.3	89.7	0.011
	Slight problems	10.0	6.9	
	Moderate problems	6.7	1.7	
	Severe problems	3.3	1.7	
	Unable to do	1.7	0.0	
USUAL ACTIVITIES	No problems	50.0	63.8	0.003
	Slight problems	26.7	20.7	
	Moderate problems	16.7	12.1	
	Severe problems	3.3	3.4	
	Unable to do	3.3	0.0	
PAIN/ DISCOMFORT	No pain	16.7	20.7	0.173
	Slight pain	26.7	29.3	
	Moderate pain	31.7	34.5	
	Severe pain	23.3	15.5	
	Extreme pain	1.7	0.0	
ANXIETY/ DEPRESSION	Not anxious or depressed	51.7	39.7	0.083
	Slightly anxious or depressed	31.7	31.0	
	Moderately anxious or depressed	11.7	20.7	
	Severely anxious or depressed	5.0	8.6	
	Extremely anxious or depressed	0.0	0.0	

* T0, baseline; T1, after 12 months.

3.2. Adverse Drug Reactions

Altogether, a total of 596 suspected ADR reports were found, with a mean ± SD of 9.2 ± 16.9 per patient, out of which 67.3% were experienced by patients prior to undergoing CMM services and were reported at the initial assessment. Surprisingly, only one patient did not experience any ADR, whereas one patient experienced as many as 138 ADRs. The majority of reported ADRs concerned women (77.3%), with a mean value of ADRs being 10.6 +/− 20.7, as opposed to 6.8 +/− 4.5 in men. There was a strong, positive correlation between the number of drugs used and the rate of suspected ADRs (r = 0.823, p < 0.001). However, the correlation between the older age and the number of comorbidities and a higher rate of ADRs, previously reported in the literature, was not found in our study. The rate of suspected ADRs declined with the number of consultations patients attended (Figure 1). Therewithal, a positive and statistically significant impact of CMM services on the reduction in the rate of suspected ADRs was observed, namely 2.7 ± 1.7 ADRs per patient at the initial assessment vs. 1.0 ± 1.5 ADRs per patient at the last consultation (p < 0.001).

Reported suspected ADRs were further classified according to MedDRA SOC, occurrence mechanism (by Edwards and Aronson), seriousness and expectedness, as shown in Table 3.

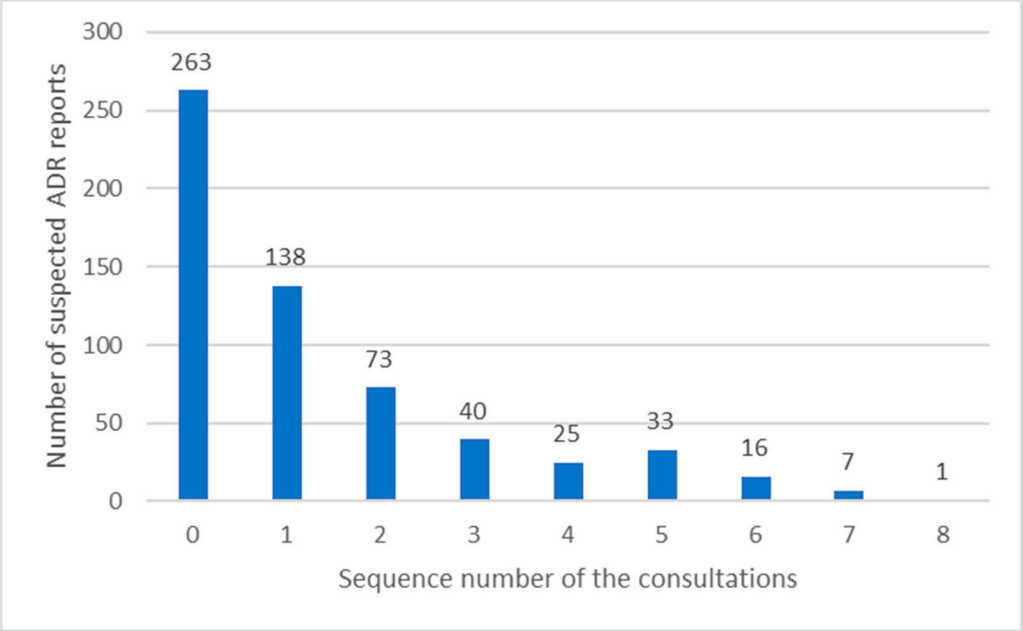

Figure 1. The prevalence of suspected ADRs reported according to the sequence number of consultations patients attended.

Table 3. Distribution of reported suspected ADRs classified by MedDRA SOC, occurrence mechanism (by Edwards and Aronson), seriousness and expectedness.

Classification	*n* (%) of Suspected ADRs
MedDRA SOC [31]	
General disorders and administration site conditions	103 (17.28%)
Vascular disorders	71 (11.91%)
Gastrointestinal disorders	68 (11.41%)
Musculoskeletal and connective tissue disorders	61 (10.23%)
Nervous system disorders	59 (9.90%)
Skin and subcutaneous tissue disorders	37 (6.21%)
Renal and urinary disorders	37 (6.21%)
Metabolism and nutrition disorders	32 (5.37%)
Cardiac disorders	26 (4.36%)
Respiratory, thoracic and mediastinal disorders	20 (3.36%)
Investigations	19 (3.19%)
Ear and labyrinth disorders	17 (2.85%)
Psychiatric disorders	11 (1.85%)
Immune system disorders	10 (1.68%)
Reproductive system and breast disorders	9 (1.51%)
Eye disorders	7 (1.17%)
Endocrine disorders	6 (1.01%)
Infections and infestations	2 (0.34%)
Injury, poisoning and procedural complications	1 (0.17%)

Table 3. *Cont.*

Classification	*n* (%) of Suspected ADRs
Occurrence mechanism (by Edwards and Aronson) *	
Type A	448 (75.17%)
Type B	110 (18.46%)
Type C	9 (1.51%)
Type D	29 (4.87%)
Seriousness	
Serious	73 (12.25%)
Non-serious	523 (87.75%)
Expectedness	
Expected	465 (81.44%)
Unexpected	106 (18.56%)

ADR, adverse drug reaction. MedDRA SOC, Medical Dictionary for Regulatory Activities System Organ Class. * **Occurrence mechanism (by Edwards and Aronson)**—ADRs classified into six types: dose-related (A), non-dose-related (B), dose-related and time-related (C), time-related (D), withdrawal (E) and failure of therapy (F).

4. Discussion

CMM, as found in our study, is a large-scale intervention shown to have a beneficial impact on patients' HRQoL. To our knowledge, this is the first prospective study evaluating the impact of CMM services on HRQoL, regardless of the patient sample, clinical setting or instrument used. Epidemiological data confirm that CVDs are the leading cause of death, taking yearly an estimated 17.9 million lives, with Croatia being no exception [1,10]. Hence, the CMM services employed in our study targeted patients with CVDs as these are among the most prevalent and costly chronic diseases worldwide.

Health-related quality of life, alongside clinical outcome measures, is a crucial outcome in patients with chronic diseases since, in some instances, the value of a particular intervention can only be described by the patient. The EQ-5D-5L instrument used to evaluate the HRQoL in our study is a generic patient-reported outcome measure (PROM) used to assess a patient's health status at a particular point in time. PROMs present an important part of the patient-centered approach as they are measured from the patient's viewpoint and are used to more fully evaluate the quality of care [34]. Clearly, HRQoL represents an important indicator of the benefit pharmaceuticals and pharmacy interventions offer, and although still underused, it is likely to increase over time as it can be employed by various stakeholders in the decision-making process.

The obtained results indicate that CMM services have a positive impact on two dimensions of patients' HRQoL, "self-care" and "usual activities", with no significant impact on the remaining three dimensions, hence rendering the overall EQ-5D-5L health status improved [26]. Namely, an EQ-5D health state was deemed to be "better" over time if it was better in at least one dimension and no worse in any other dimension [27]. Moreover, our study incorporated multiple in-person and online consultations over a one-year period and was partially conducted during the COVID-19 lockdown. Patients were at home most of the time, and therefore, their mobility was indeed limited to the in-house setting. In spite of that, we did not find any deterioration in the "mobility" dimension nor in the "anxiety/depression" dimension, both of which were seriously affected by the pandemic. The fact that patients neither reported nor perceived their physical and/or psychological status worsened, but rather comparable, is considered a favorable result, given that the COVID-19 pandemic did not leave any sphere of life or public health system intact. That said, CMM appears to be a good solution for addressing non-optimal medication management as it improved patients' HRQoL and as such should be considered for implementation in the healthcare system.

Moreover, analysis of the EQ-VAS scale, which represents patients' perspective, did not reveal any significant change between the two time points. This result is in accordance with other studies that have looked at the impact of various pharmaceutical care interventions on a specter of diseases and have not found any significant improvement in the EQ-VAS score [35–37]. It could be argued that the VAS score is not strictly defined as the abovementioned EQ-5D-5L dimensions, allowing every patient to perceive the scale differently. Interestingly, 26% of patients at baseline and 28% after the 12-month follow-up marked their health in the middle (at exactly 50), and this preference was also shown in other studies [37]. There is a possibility that patients with chronic diseases had already got used to their health conditions [38], and therefore, they chose a score exactly in-between the two extremes.

Various studies have investigated the influence of a multitude of pharmacy interventions on patients' HRQoL and have found diverse results [39]. Namely, in addition to the lack of pharmaceutical care particular measures for HRQoL, the lack of standardization in the reporting of pharmaceutical care interventions [40] and the heterogeneity of the services provided might be responsible for the variability in the pharmaceutical care impact on HRQoL outcomes. Moreover, majority of the studies that have used the EQ-5D-5L as an assessment tool [35,36,41–47] have not found any significant impact of the pharmacists' intervention on HRQoL, irrespective of the clinical setting or study design. Statistically significant HRQoL between-group differences were observed in a study that aimed to determine the impact of a community pharmacist's intervention on patients who had initiated antidepressant treatment, indicating that patients who received extra pharmaceutical care perceived improved HRQoL [48]. The authors challenged their results by stating that the effect size was small to moderate, making the clinical relevance of this difference questionable.

Additionally, to the best of our knowledge, this is the first study to have analyzed the impact of CMM services on the prevalence of adverse drug reactions. Despite ADRs being one of the main causes of morbidity and mortality worldwide [49,50], thus adversely influencing the clinical outcomes and quality of life as well as burdening limited health care budgets [51], only a small body of literature has thus far analyzed the epidemiology of ADRs in the primary care setting. The currently available body of literature unambiguously shows rather wide prevalence rates of reported ADRs, from only 6% to as much as 80% [23,52], largely due to the fact that as many as 95% of all ADRs are not even being reported [53]. Notably, the higher prevalence of suspected ADRs reported in this study can indubitably be explained by the comprehensive data collection process conducted within the CMM services as well as by the patients' characteristics and prospective study design. Every consultation begins with uncovering patients' medication experience followed by a detailed assessment of patients' medication history and current medical record. As such, CMM contributes unique data and valuable new knowledge on the effectiveness and safety of medications in practice [54] and, as found in our study, reduces the prevalence of ADRs.

In this study, based on the occurrence mechanism, type A ADRs made up the majority of the total number of reported ADRs. On account of being a result of an exaggeration of a drug's pharmacological effect, type A ADRs are predictable and as such potentially or definitely avoidable. Notwithstanding the relatively small patient sample included in this study for a limited period of time, 73 serious and 106 unexpected ADRs were reported (12.3% and 18.5%, respectively). These findings denote that there is plenty of room for improvement in the care of elderly cardiovascular patients. Taking into consideration the increasing number of medications patients take, the ever more complex therapy regimens and the increasing number of healthcare professionals that can prescribe medications, on the one hand, and the lack of control over the prescription and consumption of medications, on the other [9,55,56], CMM services could serve as a solution to the evergrowing clinical, financial and humanistic burden of ADRs through more careful selection and more frequent monitoring of patients' therapy. Furthermore, an extremely high prevalence of ADRs reported at patients' initial assessment in this study must have contributed to the poor

baseline patients' quality of life pointing to the fact that a greater emphasis should be put on measuring the quality of life in patients with ADRs.

This study had a number of limitations. First, it was conducted on a relatively small patient sample and in only one health center, thus limiting the generalizability of study results. Second, the lack of a control group could have led to the misinterpretation of the obtained results as it is harder to be certain that the outcome was caused by the experimental treatment or new service and not by other variables. Third, it was recently found that HRQoL measures used in pharmaceutical care studies provide very limited coverage of themes related to the burden of medicine on HRQoL and may have limited potential for use as a sole humanistic measure when evaluating pharmaceutical care interventions [15]. Fourth, patients did not fill out the questionnaire completely on their own but with a help of a pharmacist-researcher which could have inadvertently influenced the patients' responses, leading to the introduction of bias. On the other hand, this can be regarded as a strength of the study, especially since the patients were of older age and had some limitations in understanding and reading the questionnaire. Hence, they were assisted by a pharmacist-researcher who could have addressed patients' questions and clarified the meaning of particular dimensions of the EQ-5D-5L. Finally, it should be noted that one patient experienced a significant proportion of ADRs recorded by the study, potentially compromising the data analysis as an outlier.

5. Conclusions

In conclusion, the results of the present study indicate that comprehensive medication management services provided at the primary care level may improve health-related quality of life in older patients with CVDs. Furthermore, CMM services detected a large amount of ADRs and significantly diminished the proportion of ADRs following 1-year patient follow-up rendering this pharmacist-led intervention a viable solution for safety management. Considering the fact that CMM improved patients' HRQoL and patients' well-being along with patient safety, it should be considered for implementation in the healthcare system as an effective solution for addressing medication mismanagement and irrational drug use.

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Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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5. Budget impact analysis of pharmacist-led medication management in cardiovascular and type 2 diabetic patients

healthcare

MDPI

Article

Budget Impact Analysis of Pharmacist-Led Medication Management in Cardiovascular and Type 2 Diabetic Patients

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Abstract: The paper aims to identify and measure the costs and savings associated with the delivery of Comprehensive Medication Management (CMM) services in Croatia in patients diagnosed with hypertension accompanied by at least one additional established cardiovascular disease (CVD) and/or type 2 diabetes mellitus (DMT2) who use five or more medicines daily. The budget impact analysis (BIA) employed in this study compares the total costs of CMM to the cost reductions expected from CMM. The cost reductions (or savings) are based on the reduced incidence of unwanted clinical events and healthcare service utilisation rates due to CMM. The BIA model is populated by data on medication therapy costs, labour, and training from the pilot CMM intervention introduced in Zagreb's main Health Centre, while relevant international published sources were used to estimate the utilisation, incidence, and unwanted clinical events rates. Total direct costs, including pharmacists' labour and training (EUR 2,667,098) and the increase in the cost of prescribed medication (EUR 5,182,864) amounted to EUR 7,849,962 for 3 years, rendering the cost per treated patient per year EUR 57. CMM is expected to reduce the utilisation rates of healthcare services and the incidence of unwanted clinical events, leading to a total 3-year reduction in healthcare costs of EUR 7,787,765. Given the total CMM costs of EUR 7,849,962, CMM's 3-year budget impact equals EUR 92,869, rendering per treated patient an incremental cost of CMM EUR 0.67. Hence, CMM appears to be an affordable intervention for addressing medication mismanagement and irrational drug use.

Keywords: budget impact analysis; comprehensive medication management services; pharmacists' services; polypharmacy; medication therapy management; cardiovascular diseases; type 2 diabetes mellitus

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1. Introduction

With the increasing incidence and prevalence of chronic diseases, the demand for healthcare services is growing worldwide, exerting major funding pressures on constrained healthcare resources. Medicines are among the most common medical interventions for the treatment, prevention, and therapy of chronic diseases [1]. The demand for medicines and therefore the pharmaceutical spending is increasing worldwide, typically at rates higher than the growth rates of other health spending categories, driving the growth in total healthcare expenditure [2]. Croatia is no exception—between 2014 and 2018 the pharmaceutical spending increased on average 5% a year, while the growth of other health spending categories was slower [3]. Countries apply various pricing and reimbursement policies to curb the growth in pharmaceutical spending and contain costs (as well as

increase the overall cost-effectiveness of pharmaceutical spending). However, once the reimbursement process is finished, and the medicines are listed and available to patients (with or without copayments), the procedures which monitor different aspects of postlisting follow-up of medicines, including rational prescribing and rational use monitoring, are not always in place or are underdeveloped, as is the case in South-Eastern Europe [4].

In Croatia, primary care physicians prescribe all outpatient medicines. The Croatian health insurance fund (CHIF), the main healthcare payer, strictly controls physicians' prescribing behaviour, imposing fines if physicians do not comply with prescribing restrictions. To promote rational prescribing, CHIF's restrictions determine which medicines can be prescribed for which diagnosis (Due to reference pricing, there is little pressure to prescribe generics). However, other aspects of rational prescribing (such as duplication of therapies, potential adverse drug events (ADEs), subtherapeutic dosage, and variations between prescribers) typically remain under the radar. Like rational prescribing, the rational use of prescribed medicines (such as monitoring polypharmacy in elderly patients and nonadherence) is also not promoted, in spite of considerable costs of inappropriate prescribing, ADEs, and nonadherence [5–14].

Comprehensive Medication Management (CMM) services provided by trained pharmacists can bridge this gap by increasing rational drug use, improving the prescribing of medicines, and reducing the unnecessary and often harmful use of medications and the resulting complications [15–19]. Grounded in the practice of pharmaceutical care [20–22] and promoted by major professional organizations [19,23–25], the standardised and internationally recognised CMM protocol proposed by Cipolle at all [22] is an effective approach to resolving drug therapy problems (DTPs), improving clinical outcomes [16,17,26–33], reducing costs [16,34,35], and improving patient and provider experience [16,36,37], hence increasing the value of medicines used.

The CMM protocol of Cipolle et al. [22] targets patients with diabetes type 2 (DMT2) and/or cardiovascular diseases (CVD) because these are among the most prevalent and costly chronic diseases worldwide, with CVD being the leading cause of global mortality [38]. Croatia is no exception. Ischaemic heart disease and stroke are the two main causes of death in Croatia. The preventable mortality rates from ischaemic heart disease and stroke are twice the EU average [39]. Unlike most EU countries, the mortality rate from ischaemic heart disease decreased only slightly between 2000 and 2016, while mortality rates from diabetes have increased sharply since 2000. The rise in mortality from treatable conditions such as diabetes should be a cause for concern and an argument for introducing CMM services. The same can be said for polypharmacy, a common occurrence in the elderly and chronically ill, which increases the risk of medication errors and DTPs, namely omissions, duplicate prescriptions, and harmful interactions. In the era of aging populations, polypharmacy, multiple chronic conditions, and complex and decreasingly manageable therapy regimens, CMM programmes are especially important for chronic elderly patients taking five or more medicines, who are at an increased risk of experiencing medication errors, ADEs, duplications of therapy, and detrimental interactions and who often fail to reach therapy goals (Although other pharmacist interventions, besides CMM, also have a positive impact on patient therapy goals, various studies have demonstrated the positive impact of CMM on the management of chronic diseases, by improving individual cardiovascular risk factors such as blood pressure [30,32,33], glycosylated haemoglobin (HbA1c) [17,26,30–32], and LDL cholesterol [16,17,31,32]). In turn, CMMs' data could help payers to develop increasingly detailed prescribing guidelines and update their policies to monitor and enforce rational use, which would have a potential double benefit: fewer adverse events and lower overall prescribing costs.

In January 2018, a standardised CMM service was introduced as a pilot project in the largest county health centre in Croatia—Health Centre Zagreb Centre [40], making it the first health centre in Croatia and South-Eastern Europe to offer CMM. CMM was offered to eligible patients free of charge. The CMM patient care process followed Cipolle et al. [22] methodology, as described in Table 1. The same standardised CMM service

protocol was previously applied in the US [16,20,26,28] and elsewhere [27,29–31], in the same patient groups (i.e., patients with DMT2 and/or CVD, as explained later on). These CMM services have demonstrated their ability to improve clinical outcomes [16,17,26–33] and reduce costs [16,34,35]. However, it is unclear to what extent such standardised CMM interventions can be deemed affordable.

Table 1. Standardised CMM activities in the patient care process [22].

The Patient Care Process	
ASSESSMENT OF THE PATIENT'S DRUG-RELATED NEEDS	➢ Meet the patient and understand patient's medication experience (preferences, expectations, and beliefs). ➢ Collect patient-specific information: demographics, health-related behaviour (alcohol, tobacco, and caffeine intake) and clinical information (relevant medical history, medication history, current medication list including prescription and over-the-counter medications, herbal remedies, supplements and medications used for a limited period of time, and relevant laboratory values) including allergies, side effects, and immunizations. ➢ Prioritise patient's active medical conditions and medication-related needs.
IDENTIFICATION OF DRUG-RELATED PROBLEMS	➢ Determine that all the patient's medications are properly indicated, the most effective given the medical condition, the safest possible, and that the patient is able and willing to take the medication as intended. ➢ Analyse the assessment data to determine if any drug therapy problems are present.
CARE PLAN DEVELOPMENT	➢ Identify therapy goals for each indication managed with drug therapy. ➢ Develop a care plan that includes interventions to resolve current drug therapy problems, prevent potential drug therapy problems, and achieve therapy goals. ➢ Discuss and negotiate the care plan with the patient and his prescriber, ensure patient's and prescriber's understanding and agreement with the plan, and schedule follow-up evaluation. ➢ Document the care plan, which includes all the steps and clinical status determined for every patient's medical condition.
FOLLOW-UP EVALUATION	➢ Follow-up evaluation for each patient reassesses whether any new drug therapy problems have developed, monitors patient's progress toward the achievement of the goals of therapy, and refines the care plan to ensure therapy goals are achieved and medication therapy is optimised.

Budget impact analysis (BIA) assesses the affordability of interventions and helps policymakers decide whether the adoption of a new health intervention is within their

means, given the resource and budget constraints of the context. So far, quantitative cost analyses and evaluations of pharmacist interventions have been in short supply [9], and the question of CMM's affordability remains unanswered. This paper reports the results of the BIA of CMM in the Croatian context to show whether, from the payer's perspective (Croatia operates a single healthcare payer system, the Croatian health insurance fund (CHIF), which finances and contracts all public health services), introducing a nationwide CMM is affordable. Using data from various sources, the BIA identifies and models the costs, the savings, and the nonmonetary benefits [41–43] associated with introducing and rolling-out a standardised nationwide CMM service [22] in Croatia over a 3-year period (2022–2024) to predict CMM's financial impact on the CHIF's budget. Our study contributes to the literature by being the first budget impact analysis of CMM. As such, this study adds to the small body of literature by being among the few quantitative analyses and evaluations of pharmacist interventions more generally [9].

2. Materials and Methods

2.1. Data Formation

The pilot CMM intervention introduced in Zagreb's main Health Centre has provided a myriad of data [40], including the data on medication therapy costs, labour, and training. However, the data on health-related benefits of CMM from the pilot study are not mature or comprehensive enough to feed the entire BIA model. More generally, readily available data on, e.g., the rate of healthcare service utilisation or the incidence of particular clinical events does not exist in Croatia. Hence, conducting a quantitative assessment of CMM in Croatia, and other jurisdictions with similar data insufficiencies (such as South-Eastern Europe [4]), usually requires the transfer of data on incidence, health-related benefits, or outcomes from other (international) sources and studies conducted in other jurisdictions, as is also common in other economic assessments (e.g., HTA).

A large-scale US study by Ramalho de Oliveira et al. (2010) was used as a source of data on health care utilisation [16]. The study used the same CMM protocol as the one used in Croatia. Beyond the equivalent care protocols, both the CMM service in Croatia and in US were offered to patient populations diagnosed with hypertension and at least one additional established cardiovascular disease (CVD) and/or type 2 diabetes mellitus (DMT2) who used five or more medicines daily, similar in terms of sociodemographic and other clinical characteristics (Comparable in terms of number of medical conditions, number of medications at baseline, number and type of drug therapy problems, and gender) with the exception of beneficiary age. Unlike in Croatia where the mean beneficiary age was 72.4 $\pm$ 4.6 (range 65–80), the US patient population included a much broader age distribution (21 to 102 years) with 55.5% of patients younger than age 65 years. Regardless of the age disparities between the two patient samples, all the other relevant results, such as type and incidence of drug therapy problems and clinical outcomes (percentage of reduction of blood pressure, glycated haemoglobin, and lipid status) coincide, pointing to the conclusion that these data can be used in our calculations and that the age difference does not influence the study results in a prohibitive manner.

Leading international treatment guidelines for management of hypertension in the adult European population, the European Society of Cardiology and European Society of Hypertension's guidelines [44] were used as sources of benefits of achieving particular therapeutic goals. Finally, different empirical studies were used as the sources of the incidence rates of particular unwanted clinical events [45–62], as explained below. Once the studies reporting the incidence rates of particular unwanted clinical events were identified in the literature, these were discussed with key opinion leaders and experts to confirm their usefulness in the Croatian context and used in our BIA models when deemed relevant.

2.2. Budget Impact Model

The BIA model, developed in Microsoft Excel (Microsoft Corp., Redmond, WA, USA), is presented in Figure 1. In the status quo scenario (i.e., the current standard of care),

eligible patients receive usual primary care (i.e., medication prescribing and consultations in the outpatient setting) with no additional pharmacist-led services explaining why CMM is treated as an addition to the existing standard of care and the status quo is not modelled. The CMM scenario includes inputs and outputs. Model inputs include the eligible population size per year and the total yearly costs of implementing CMM in that population (labour and training costs as well as therapy modification costs). Based on our pilot CMM intervention, we knew beforehand that CMM in Croatia will likely lead to an increase in therapy costs instead of cost savings (as has been observed in other CMM programmes [34]), so we attributed those to the model input parameters (the particulars of the cost and population calculations are explained below). As an output of the model, the BIA compared these total costs of CMM (expressed as aggregate intervention cost per year as well as cost per treated patient per year) to the cost reductions expected from CMM to calculate the budget impact of CMM. These cost reductions (or savings) are based on the reduced incidence of unwanted clinical events and healthcare service utilisation rates due to CMM. As explained in more detail below, the reduced costs of unwanted clinical events and healthcare service utilisation were based on a costing catalogue of CHIF (diagnosis-related group or DRG costs for particular treatment and service) multiplied by the reduction rate of healthcare service utilisation and the reduction rate in the incidence of unwanted clinical events respectively, to obtain the incremental cost savings per patient participating in CMM. Further calculation details are provided in the following section.

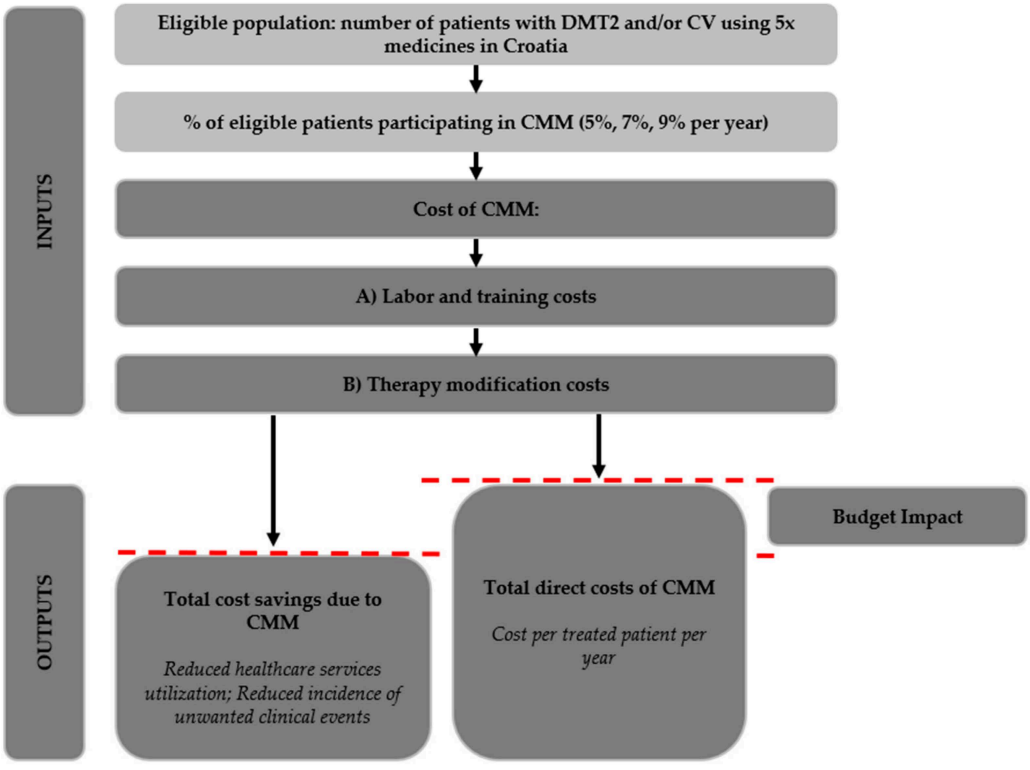

Figure 1. Model structure.

2.3. Eligible Patients

Eligible patients were those diagnosed with hypertension and at least one additional established cardiovascular disease (CVD) and/or type 2 diabetes mellitus (DMT2) and using five or more medicines daily (as is typically the case with CMM service [28]). To correct for the fact that some patients have both DMT2 and CVD, we used a simple assumption that all patients with diabetes have a CVD, while the remaining CVD patients do not have DMT2, thereby reducing the total number of prevalent DMT2 + CVD patients taking medication by the number of DMT2 patients (Table 2). Due to fiscal limitations

as well as a limited number of trained pharmacists available in the labour market, a nationwide CMM could not be rolled out and offered to all eligible patients in Croatia. Based on the estimated availability of pharmacists (A limited number of clinical pharmacists is currently available rendering it difficult to recruit the required number of professionals (or staff members) to provide the service, without installing additional education) and the maximum number of patient visits per pharmacist per day, as discussed below, we calculated a manageable proportion of eligible patients who could be enrolled in CMM in Croatia each year (Point: BIA does not account for geographical distribution of CMM, availability or cost—taken one national average) (5%, 7%, and 9% respectively each year; Table 2) and used those estimates in the BIA model.

Table 2. Eligible population and the number of patients in CMM.

Croatian Population	**4,087,934**			**Source**
	2022	2023	2024	
DMT2 prevalence (%)	7.74%	7.82%	7.89%	Prevalence growth is estimated at 1% yearly [62]
Of which on medication	76%	76%	76%	[38]
Number of DMT2 patients on medication	240,398	242,802	245,230	
CVD prevalence (%)	26.02%	26.28%	26.54%	Prevalence growth is estimated at 1% yearly [63].
Of which on medication	90%	90%	90%	Data based on expert opinion
Number of CVD patients on medication	765,687	773,344	781,077	Equal to the number of prevalent patients DMT2 + CVD on medication in Croatia *
Of which on 5+ medicines	85%	85%	85%	Data based on expert opinion and pilot results
Total number of CMM eligible patients in Croatia, of which:	650,834	657,342	663,916	
DMT2 + CVD	204,340	206,383	208,447	
CVD	446,494	450,959	455,469	
% of eligible patients included in CMM	5.0%	7.0%	9.0%	Calculated based on the number of eligible trained pharmacists in the labour market
Number of eligible patients included in CMM, of which:	32,542	46,014	59,752	
DMT2 + CVD	10,217	14,447	18,760	
CVD	22,325	31,567	40,992	

* Corrected for CVD/DMT2 overlap.

2.4. Estimating the Costs of CMM

The Direct Costs of CMM consist of:

(a) Labour and training costs: pharmacists need to be hired and trained to provide CMM (employed by local primary care Health Centres but funded by CHIF). The number of new pharmacists required for CMM was estimated based on the projected number of pharmacists available on the labour market in 2022–2024, the pace at which training can be provided within a single year, the number of working days per year, and the target number of patient visits per day/per pharmacist (To establish a financially viable practice, that is to build a stable revenue base, care needs to be provided to a minimum of 10 to 15 patients per day [64,65]) (Table 3).

(b) Therapy modification costs: based on the results of our pilot study [40] (confirmed by other studies [16,20,34]), the main drug therapy problems typically identified and addressed by CMM pharmacists are the need for additional drug therapy and

subtherapeutic dosage [64]. Introducing new medicines and/or increasing dosages creates additional costs for the healthcare system. Based on the findings from our pilot study, we estimated the additional cost per defined daily dose (DDD) at EUR 0.10 per patient in CMM; the total costs of additional medication therapy are presented in the Results section. For each patient involved in our pilot study, the additional medication costs were calculated by subtracting the costs of medication per day (i.e., the sum of costs per prescribed and used daily dose for each drug, obtained from the CHIF) at the last visit from the costs of medication per day at the initial visit. The average was then used to determine the approximate average additional cost of EUR 0.10 per defined daily dose per patient (EUR 37.47 per patient per year in DDD).

Table 3. Eligible population and the number of patients in CMM.

Cost Per Pharmacist			2022	2023	2024
Number of patient visits per day	11	Number of pharmacists in CMM	22	32	41
Working days per month/year	22/264	Total cost of labour/year	EUR 632,008.13	EUR 889,177.20	EUR1,154,142.67
Number of visits month/year	264/2904	Total cost of training/year *	EUR 4482.27	EUR 1855.73	EUR 1892.40
Before tax salary pharmacist + administrative personnel */year	EUR 28,000.00				
Average cost per visit	EUR 9.60				

Note: Half of the administrative personnel's salary was attributed to each pharmacist (one administrative person was assumed to serve two pharmacists). Because the budget impact analysis uses a short-term time horizon and overhead costs are fixed in the short term, these overhead costs are ordinarily excluded from BIA. * Estimated at EUR 200 per pharmacists.

2.5. Estimating the Cost Savings of CMM

Research has shown that CMM reduces the use of healthcare services and the incidence of unwanted clinical events [16,32,35,65]. However, as already noted, our pilot CMM data are not comprehensive or mature enough to calculate the rates of reductions in the use of healthcare services and the incidence of unwanted clinical events. Hence, we relied on published sources to proxy CMM's cost-saving effects, as follows:

(a) The rates of reduction in healthcare service utilisation were approximated by dividing the number of avoided healthcare services by the number of patients visits reported in a large-scale study of the effects of CMM in the US (Table 4) [16]. The estimated rates of services avoided per visit obtained from the study of Ramalho de Oliveira et al. were then applied to patient visits within CMM in Croatia to approximate the expected number of avoided healthcare services per visit due to CMM in Croatia. Next, the number of avoided services due to CMM were multiplied by the respective DRG-based prices of service in Croatia to calculate the cost off-setting impact of CMM (Table 4). The BIA also accounted for the cost of employee work days saved because in Croatia, the costs of employment health-related benefits are funded from the CHIF's budget and hence are relevant from the payer's perspective.

(b) The rates of reduction in the incidence of unwanted clinical events per patient (Table 5) (While the rates of healthcare service utilisation were calculated per visit (because that is how Ramalho de Oliveira et al. [16] reported their results), the reduction in the incidence rates was calculated per patient (not per visit) since incidence rates are usually reported in such a manner) were based on (1) incidence rates of unwanted clinical events per 1000 inhabitants in two disease groups (CV and CV + DMT2), converted to per patient rates, and reported in various published studies (final column in Table 5) and (2) well-documented target of medication management [44] for all eligible patients participating in CMM, that is, the reduction in blood pressure (SBP for 10 mmHg or DBP for 5 mmHg), since all the patients had at least hypertension as

a CVD indication. If patients achieve this target in CMM, we assumed it will lead to a certain percentage reduction in the individual risk of an unwanted clinical effect, as it has been shown in the literature [44].

Table 4. Rates of avoided healthcare service utilisation and their respective costs in Croatia.

Data from Ramalho de Oliveira et al. (2010) [16]				
Healthcare services	Total number of encounters in CMM	Total number of healthcare services avoided	Rate of services avoided, per visit	DRG-based price of services in Croatia **
Clinic outpatient visit avoided	33,706	7219.1 *	0.214	EUR 10.40
Specialty office visit avoided	33,706	1346	0.040	EUR 18.93
Employee work days saved	33,706	277	0.008	EUR 47.19
Laboratory service avoided	33,706	240	0.007	EUR 8.10
Urgent care visit avoided	33,706	355	0.011	EUR 54.13
Hospital admission avoided	33,706	41	0.001	EUR 120.13
Nursing home admissions	33,706	3	0.000	EUR 20.00
Home health visit	33,706	1	0.000	EUR 16.02

Note: * The rate of clinic outpatient visit avoided was reduced by 30% relative to the original study (which reported 10,313 services avoided) to account for the fact that pharmacists in Croatia, unlike in the US, cannot prescribe medicines and hence patients still need to visit the primary care physician to obtain prescriptions. A total of 30% is an estimate based on an assumption that in some instances (at least one third of GP encounters) patients will still need to visit their GP to have their therapy modified, whereas in the rest of the occurrences where GPs have established direct rapport with practising pharmacists, GPs would adopt pharmacist recommendations and alter patient therapies without seeing the patient ** available at https://hzzo.hr/hzzo-za-partnere/sifrarnici-hzzo-0 (access date 4 February 2022).

We estimated the incidence rates of unwanted clinical events per patient and per disease group (DMT2 and CVD) from the published literature (Croatian data were not available so international references were used, Table 5, column 1). From these multisource incidence rates per 1000 inhabitants for a particular event per disease group, we recalculated individual risks of each unwanted event by disease group (column 2). As suggested by the Guidelines for the management of arterial hypertension [44], we assumed these individual risks would be reduced by a certain percentage when the target reduction in blood pressure was reached with CMM (SBP for 10 mmHg or DBP for 5 mmHg, column 3). That is, we assumed that the risk reductions can be achieved once the target reduction in SBP or DBP has been achieved. Based on the results of our pilot study, however, we evaluated that the target reduction in blood pressure (SBP for 10 mmHg or DBP for 5 mmHg) will not be reached in all CMM patients. Instead, we used a more conservative target (lowering SBP by 9 mmHg or DBP by 5 mmHg, based on average reduction actually observed in our pilot study (Ongoing study; to be published). We assumed that this 10% decrease in efficiency of CMM in Croatia (i.e., SBP reduced by 9 mmHg instead of 10 mmHg) will consequently reflect linearly in the 10% reduction in the individual risk reduction (column 4) and incidence rates converted to individual risk rates (column 5 and 6) in all patients participating in CMM.

The cost savings stemming from the reduced incidence rate of unwanted clinical events are DRG-based (Table 6). The costs of treating unwanted clinical events consist of a

DRG-based inpatient treatment cost and the cost of rehabilitation following the event (plus the cost of electro stimulator implantation following heart failure). Based on expert opinion, the cost of rehabilitation was assigned to each event to proxy a multitude of possible additional inpatient and outpatient costs surrounding each of the unwanted clinical events of interest, to avoid underestimating the costs of treatments if those were based only on inpatient DRG costs. Due to the lack of more detailed healthcare cost data in Croatia, it was impossible to obtain an average total cost per event (which would include, among other costs, the DRG-based inpatient cost of treatment). Hence, we use the cost of 21-day rehabilitation (which would typically be prescribed to patients in those conditions, based on expert opinion) as a proxy for all the additional costs surrounding each event. To avoid overestimating the costs, on the other hand, we used a conservative cost of rehabilitation at EUR 56.00/day (EUR 1,176,00/21 days, which is an underestimation of the real cost of rehabilitation since under the costing regimen of CHIF, this amount covers only the accommodation in a rehabilitation facility, without physical or any other form of therapy).

Table 5. Risk reduction and incidence rates of unwanted clinical events.

Event	Patient Group	Incidence Rate (Per 1000 Inhabitants)	Individual Risk	Individual Risk Reduction *	Individual Risk Reduction (−10%) *	Incidence Rate (Per 1000 Inhabitants)	Individual Risk	Reduction in Individual Risk Due to CMM	Ref
		1	2	3	4	5	6	6–2	
		before intervention	before intervention			after intervention	after intervention		
Heart failure	DMT2 + CVD	23.86	0.02386	40%	36%	15.27	0.01527	0.00859	[45–48]
	CVD	9.70	0.00970	40%	36%	6.21	0.00621	0.00349	[47–51]
Stroke	DMT2 + CVD	14.60	0.01460	35%	32%	10.00	0.01000	0.00460	[47–49,52,53]
	CVD	7.70	0.00770	35%	32%	5.27	0.00527	0.00243	[47,49]
Myocardial infarction—fatal	DMT2 + CVD	18.00	0.01800	20%	18%	14.76	0.01476	0.00324	[47,54]
	CVD	8.70	0.00870	20%	18%	7.13	0.00713	0.00157	[47,55]
Myocardial infarction—nonfatal	DMT2 + CVD	27.8	0.02780	20%	18%	22.80	0.02280	0.00500	[56]
	CVD	13.00	0.01300	20%	18%	10.66	0.01066	0.00234	[57,58]
Angina	DMT2 + CVD	21.60	0.02160	20%	18%	17.71	0.01771	0.00389	[59]
	CVD	14.60	0.01460	20%	18%	11.97	0.01197	0.00263	[60]
Revascularization—stenotic coronary arteries	DMT2 + CVD	3.85	0.00385	20%	18%	3.16	0.00316	0.00069	[59,61]
	CVD	3.85	0.00385	20%	18%	3.16	0.00316	0.00069	[60,61]

* Note: The incidence rates (columns 1 and 5) were divided by 1000 to obtain individual risk rates (columns 2 and 6). As suggested by the Guidelines for the management of arterial hypertension [44], achieving target reduction in blood pressure (lowering SBP by 9 mmHg or DBP by 5 mmHg) will lead to a reduction in the individual risk (by percentage outlined in column 4) and consequently to lower incidence rates converted to individual risk rates (columns 5 and 6) in all patients participating in CMM.

Table 6. DRG prices for the treatment of unwanted clinical events (costing catalogue of CHIF).

Event	DRG-Based Price (InPatient Treatment)	DRG-Based Price of the Follow-Up Treatment and/or Rehabilitation	Total Cost of Event Treatment
Heart failure	EUR 1182.24	EUR 1176.00 + EUR 2473.95 (pacemaker)	EUR 4832.19
Stroke	EUR 1959.45	EUR 1176.00	EUR 3135.45
Myocardial infarction—fatal	EUR 864.79	EUR 1176.00	EUR 864.79
Myocardial infarction—nonfatal	EUR 1806.20	EUR 1176.00	EUR 2982.20
Angina	EUR 1127.51	EUR 1176.00	EUR 2303.51
Revascularization—stenotic coronary arteries	EUR 1061.83	EUR 1176.00	EUR 2237.83

Note: DRG prices from the costing catalogue of CHIF available at https://hzzo.hr/hzzo-za-partnere/sifrarnici-hzzo-0 (access date 14 February 2022).

2.6. Sensitivity Analysis

Two-way deterministic sensitivity analysis was used to evaluate the impact of overestimating and underestimating the main variable inputs on CMM's budget impact. Not all input parameters can be considered variable, i.e., some costs are set by CHIF (e.g., DRG costs), some are defined by the availability of the pharmacists in the labour market in Croatia, and some are based on the available Croatian epidemiological data (e.g., prevalence of CVD or DMT2), which means those inputs are predefined and exogenically set. The more interesting variability to investigate concerns the remaining two main parameters: the rates of healthcare services avoided (Table 7) as well as the risk reduction of unwanted clinical events (Table 8). The baseline sensitivity analysis scenario involves 5% over- and underestimation of the rates of healthcare services avoided and the risk reduction of unwanted clinical events. Beyond the baseline scenario, we also explored the impact of a much larger overestimation of the risk reductions and utilisation rates (by 20% and 40%) reported in the original studies [16] used to populate the BIA model (Table 7 and 8). If those rates are overly optimistic and could not be—for whatever reason—achieved in the Croatian context, we used the one-way sensitivity analysis scenario to estimate the budget impact of such a large overestimation of CMM's benefits, using arbitrary albeit considerably lower reductions in utilisation and risk rates.

Table 7. Sensitivity analysis—rates of avoided healthcare services.

Healthcare Services	Baseline Rate of Services Avoided, Per Visit	+5%	−5%	−20%	−40%
Clinic outpatient visit avoided	0.214	0.042	0.203	0.171	0.129
Specialty office visit avoided	0.040	0.009	0.038	0.032	0.024
Employee work days saved	0.008	0.007	0.008	0.007	0.005
Laboratory service avoided	0.007	0.011	0.007	0.006	0.004
Urgent care visit avoided	0.011	0.001	0.010	0.008	0.006
Hospital admission avoided	0.001	0.000	0.001	0.001	0.001
Nursing home admissions	0.000	0.000	0.000	0.000	0.000
Home health visit	0.000	0.042	0.000	0.000	0.000

Table 8. Sensitivity analysis—risk reduction of unwanted clinical events.

Event	Patient Group	Baseline Individual Risk Reduction Due to CMM	+5%	−5%	−20%	−40%
Heart failure	DMT2 + CVD	0.00859	0.00902	0.00816	0.00687	0.00515
	CVD	0.00349	0.00367	0.00332	0.00279	0.00210
Stroke	DMT2 + CVD	0.00460	0.00483	0.00437	0.00368	0.00276
	CVD	0.00243	0.00255	0.00230	0.00194	0.00146
Myocardial infarction—fatal	DMT2 + CVD	0.00324	0.00340	0.00308	0.00259	0.00194
	CVD	0.00157	0.00164	0.00149	0.00125	0.00094
Myocardial infarction—nonfatal	DMT2 + CVD	0.00500	0.00525	0.00475	0.00400	0.00300
	CVD	0.00234	0.00246	0.00222	0.00187	0.00140
Angina	DMT2 + CVD	0.00389	0.00408	0.00369	0.00311	0.00233
	CVD	0.00263	0.00276	0.00250	0.00210	0.00158
Revascularization—stenotic coronary arteries	DMT2 + CVD	0.00069	0.00073	0.00066	0.00055	0.00042
	CVD	0.00069	0.00073	0.00066	0.00055	0.00042

3. Results

Total direct costs (Table 9) of labour and training amount to EUR 2,667,098 for 3 years. CMM is expected to increase the cost of medication prescribed to patients by EUR 5,182,864 in 3 years, amounting to the total CMM costs of EUR 7,849,962 for 138,308 patients over 3 years. CMM's cost per treated patient per year is therefore EUR 57. The annual cost increase is driven by the increase in the patient population covered by CMM (5% in year 1; 7% in year 2; and 9% in year 3) as well as the predicted 1% rise in the prevalence of CVD and DMT2 (Table 2).

Table 9. Total costs of CMM in Croatia.

Total Direct Costs	2022	2023	2024	Total 2022–2024
Labour costs + education/training costs	EUR 627,526 (22 pharmacists)	EUR 887,321 (32 pharmacists)	EUR 1,152,250 (41 pharmacists)	EUR 2,667,098
Additional medication therapy cost	EUR 1,219,446	EUR 1,724,296	EUR 2,239,122	EUR 5,182,864
Total	EUR 1,846,972	EUR 2,611,618	EUR 3,391,372	EUR 7,849,962

CMM is expected to reduce the utilisation rates and costs of healthcare service utilisation (Table 10) and the incidence of unwanted clinical events (Table 11), leading to a total 3-year reduction in healthcare costs of EUR 7,787,765.60. Given the total CMM costs of EUR 7,849,962, CMM's 3-year budget impact equals EUR 92,869. Per treated patient incremental cost of CMM is therefore EUR 0.67.

Table 10. Cost savings: reduced healthcare service utilisation.

Cost Savings: Reduced Healthcare Service Utilisation	2022	2023	2024	Total 2022–2024
Clinic outpatient visits avoided	EUR 144,970	EUR 204,988	EUR 266,192	EUR 616,150
Specialty office visit avoided	EUR 49,204	EUR 69,575	EUR 90,348	EUR 209,128
Employee work days saved	EUR 25,241	EUR 35,691	EUR 46,348	EUR 107,280
Laboratory service avoided	EUR 3753	EUR 5307	EUR 6891	EUR 15,951
Urgent care visit avoided	EUR 37,107	EUR 52,469	EUR 68,135	EUR 157,712
Hospital admission avoided	EUR 9511	EUR 13,448	EUR 17,463	EUR 40,422
Nursing home admissions	EUR 116	EUR 164	EUR 213	EUR 492
Home health visit	EUR 31	EUR 44	EUR 57	EUR 131
Total	EUR 269,934	EUR 381,686	EUR 495,647	EUR 1,147,267

Note: Data not available per disease group.

Table 11. Cost savings: reduced incidence of unwanted clinical events.

	Patient Group	2022	2023	2024	Total 2022–2024
Heart failure	DMT2 + CVD	EUR 424,072	EUR 599,637	EUR 778,672	EUR 1,802,380
	CVD	EUR 376,707	EUR 532,664	EUR 691,702	EUR 1,601,073
Stroke	DMT2 + CVD	EUR 147,328	EUR 208,322	EUR 270,521	EUR 626,172
	CVD	EUR 321,921	EUR 455,197	EUR 591,105	EUR 1,368,224
Myocardial infarction—fatal	DMT2 + CVD	EUR 28,627	EUR 40,479	EUR 52,564	EUR 121,670
	CVD	EUR 62,552	EUR 88,448	EUR 114,856	EUR 265,857
Myocardial infarction—nonfatal	DMT2 + CVD	EUR 44,213	EUR 62,517	EUR 81,183	EUR 187,913
	CVD	EUR 45,176	EUR 63,879	EUR 82,952	EUR 192,007
Angina	DMT2 + CVD	EUR 34,352	EUR 48,574	EUR 63,077	EUR 146,004
	CVD	EUR 50,736	EUR 71,741	EUR 93,161	EUR 215,639
Revascularization—stenotic coronary arteries	DMT2 + CVD	EUR 6123	EUR 8658	EUR 11,243	EUR 26,024
	CVD	EUR 13,379	EUR 18,918	EUR 24,567	EUR 56,864
Total		EUR 1,555,187	EUR 2,199,035	EUR 2,855,604	EUR 6,609,827

Based on the incidence rates and the reduced individual risk rates due to CMM for a given event per disease group (Table 5), CMM's benefits can also be expressed in terms of the number of avoided unwanted clinical events. The number of avoided events per year in the group of patients participating in CMM are presented in Table 12, totalling 2742 cases over 3 years (Some double counting may arise. The number of avoided events was calculated as an individual risk rate for any and all individuals in the sample but some individuals probably face a risk of developing two or more conditions simultaneously. The risk rates of combined conditions are not known). In preventing other severe conditions (stroke, nonfatal myocardial infarction, and others), CMM can contribute to saving and prolonging lives as well as increasing the quality of life and productivity of patients and their caregivers.

Table 12. Number of avoided unwanted events in the eligible population (n = 138,308).

		2022	2023	2024	Total 2022–2024
Heart failure	DMT2 + CVD	88	124	161	373
	CVD	78	110	143	331
Stroke	DMT2 + CVD	47	66	86	200
	CVD	103	145	189	436
Myocardial infarction—fatal	DMT2 + CVD	33	47	61	141
	CVD	72	102	133	307
Myocardial infarction—nonfatal	DMT2 + CVD	51	72	94	217
	CVD	52	74	96	222
Angina	DMT2 + CVD	40	56	73	169
	CVD	59	83	108	249
Revascularization—stenotic coronary arteries	DMT2 + CVD	7	10	13	30
	CVD	15	22	28	66
Total		645	912	1185	2742

In the sensitivity analysis, we investigated CMM's budget impact of the rates of avoided healthcare services as well as the risk reduction of unwanted events in case these were 5% under- or overestimated as well as 20% and 40% overestimated (Table 13). Relative to the baseline budget impact estimates, the combined effect of 40% overestimation of both rates yields a budget impact of EUR 3.2 million and the incremental cost per patient of EUR 23. Alternatively, if the benefits of CMM are underestimated by mere 5%, the budget impact would be negative, making CMM the dominant intervention.

Table 13. Sensitivity analysis—risk reduction of unwanted clinical events and the rates of avoided healthcare services.

	Baseline	+5%	−5%	−20%	−40%
Total budget impact for 3 years	EUR 92,869	− EUR 294,986	EUR 480,723	EUR 1,644,287	EUR 3,195,706
Incremental cost per treated patient per year	EUR 0.67	− EUR 2	EUR 3	EUR 12	EUR 23

4. Discussion

CMM—as modelled in our budget impact analysis—is a large-scale intervention that would encompass over 138,000 patients over 3 years and employ 41 new pharmacists. CMM's net budget impact—at just over EUR 92,000 for 3 years and EUR 0.67 incremental cost per patient—can be considered modest. That said, CMM appears to be a good investment also because of Croatia's health and healthcare system profile. As already mentioned, ischaemic heart disease and stroke are the two main causes of death in Croatia, with preventable mortality rates from ischaemic heart disease and stroke twice the EU average [39]. Mortality rates from diabetes have increased sharply since 2000. The rise in mortality from treatable conditions such as diabetes should be a cause for concern and an argument for introducing CMM services, which can help patients and physicians achieve desired health outcomes more efficiently.

There are various arguments for introducing CMM services into our healthcare systems. CMM is an intersectoral programme, requiring the coordination of GPs and pharmacists. As such, CMM could contribute to strengthening otherwise weak intersectoral policies and contribute to addressing key determinants of ill health, which in turn contribute to high rates of death from preventable and treatable causes. Moreover, CMM can help healthcare payers throughout Europe improve the postlisting value-for-money of

prescription medicines. The fact that prescription medicine volumes are rising throughout Europe is not necessarily surprising given our aging populations, but this fact emphasises the need to further promote rational use. Greater efforts need to be made to ensure that medications are appropriately prescribed and coordinated to avoid DTPs, namely omissions, duplicate prescriptions, and harmful interactions, and CMM can be a great asset. As mentioned before, CMM can be used as a basis for developing increasingly detailed prescribing guidelines to monitor and enforce rational medicine use, which would have a double effect: fewer adverse events and lower overall prescribing costs.According to the results of our BIA model, the pilot CMM study could be transformed into a nationwide CMM service in Croatia, at a relatively modest price tag. CMM is not necessarily a dominant intervention in the sense that it reduces costs and generates incremental benefits, but these incremental benefits are generated at a modest cost. However, for CMM to become a reality in Croatia and elsewhere, both the policymakers and the payers need to support the development and implementation of CMM by reimbursing it and making it reproducible and sustainable over time. There need to be governments and health plans willing to support clinical pharmacists, namely professionals eager and capable to provide this service, as CMM will only live its full potential when we have well trained and experienced practitioners. The service is currently being piloted in Croatia although the pharmacists providing it are not being remunerated for their efforts. Considering the fact that CMM seems economically viable, both through this and previous analyses [34], CMM is a highly recommended solution for addressing medication mismanagement and irrational drug use and as such should be a top priority for implementation in the healthcare system.

Limitations

The first point we wish to address is the realistic representation of healthcare costs. As explained in the methods section, the cost savings of reduced incidence of treating unwanted events are DRG-based. In Croatia, the price of DRGs is considerably lower than in neighbouring EU member states, and their price fluctuates often, depending on the financial situation in the healthcare system [66,67]. Moreover, the DRGs contain only inpatient costs, while the treatment of conditions such as stroke requires additional medications, rehabilitation, and many other (direct and indirect) follow-up costs, which are not considered in the hospital-based DRG. There is no national costing catalogue. To correct (at least partly) for the underestimation of the total DRG-based inpatient cost of the treatment of unwanted clinical events, we added the cost of one-time rehabilitation lasting 21 days to all events although at a fraction of its price. Hence, it is reasonable to expect that the inclusion of all costs of treatments would lead to higher cost savings related to CMM and consequently lower its budget impact. However, even our conservative estimate of the cost-saving impact of CMM shows that CMM can be affordable, even at unrealistically low costs for treating expensive conditions.

The second point we wish to address is the issue of using data from published sources. One may argue that the risk rates and the utilisation rates employed in our analysis—although taken from published sources—may not necessarily be the best representation of the Croatian epidemiological, clinical, and utilisation data. Ideally, we would calculate the actual and detailed costs of treating unwanted clinical events and the costs of particular healthcare services in the Croatian population and multiply those by the actual rates of healthcare services used and the incidence rates of unwanted clinical events per patient group receiving CMM and a group not receiving CMM (and subtract the difference). However, the rate of healthcare service utilisation and incidence rates of unwanted clinical events relevant for our study are not available in Croatia (let alone, for the target patient group). To reduce the risk associated with using published results in our BIA model, several measures were taken. With regard to the utilisation and clinical event rates, we used the study, which was methodologically and results-wise comparable to our CMM study, using the same CMM protocol as the one used in Croatia and a comparable patient population [16]. With respect to the incidence rates of unwanted clinical events [45–62], these were discussed with key opinion

leaders to confirm their applicability in the Croatian context. Finally, the sensitivity analysis was developed precisely to test the effect of overestimating the individual risk and rates of utilisation, to obtain a sense of the effect of over- or underestimation of these parameters as possible consequences of using data from different sources. Under the unfavourable assumption of 40% overestimation of the risk and utilisation rate reductions due to CMM, the budget impact reaches around EUR 3.2 mil for 3 years. Nevertheless, even with this relatively high budget impact, when we take into account the large number of patients included in CMM, the incremental cost per patient remains relatively low.

Third, the usefulness of data from the US and its transferability to the Croatian context may be hampered by the differences in healthcare payments and health insurance coverage (and the related accessibility of CMM). The United States has Medicare, a government-provided insurance for older individuals compared to more private insurance options for younger individuals. The coverage differences result in varying use of health care services. Unlike the US, Croatia operates a generous universal health insurance covering all citizens, funded from income-based contributions. Healthcare is free at the point of entry, except for certain medicines which require copayments. Hence, there is little variability in age-related access and use of healthcare, which would be determined by insurance coverage since healthcare is accessible and free at the point of entry for all (including CMM). In that sense, the US data may offer a conservative outlook on CMM's benefits relative to its potential in Croatia.

The fourth point we wish to address is the scope of the BIA model. CMM is an intervention that could be intended for all patient groups irrespective of the condition they suffer from. The BIA conducted in this study included CVD and DMT2 patients only, rendering the budget impact relevant exclusively for this patient group. Future research should be focused on evaluating the impact of CMM on a broader range of health conditions.

Finally, the implementation of CMM initially leads to medication cost increase, as the main drug therapy problems typically identified and addressed by CMM service are the need for additional drug therapy and subtherapeutic dosage requiring increasing the doses and introducing new therapies. However, in the course of time, most often within the first year of CMM introduction, the related cost savings resulting from the reduction in the use of healthcare services and the incidence of unwanted clinical events balance and exceed this initial cost increase.

5. Conclusions

CMM provided by trained pharmacists reduces the unnecessary and often harmful use of medications and can help patients and physicians achieve desired health outcomes more efficiently. The budget impact analysis performed in our study shows that CMM services for high-risk patients led to a budget impact at just over EUR 92,000 within a 3-year horizon, rendering CMM an affordable intervention. Studies quantifying the costs and the effects of pharmacist interventions are lacking and lag behind other public health interventions and technologies. In the era of increasing and irrational medicine use, medication errors, inappropriate prescribing, duplicate therapy, and detrimental interactions on the one hand and tight healthcare budgets on the other, we cannot afford to ignore the costs and benefits of pharmacist interventions nor their potential to increase the value of money spent on medicines.

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6. DISCUSSION

Patients with CVDs, especially older ones, are at a higher risk of irrational drug use and experiencing DTPs. Those patients can often be seen with uncontrolled disease parameters, high prevalence of ADRs and hospital admissions, and reduced quality of life. Hence, to properly address those problems, there was an urgent need to introduce a controlled and comprehensive medication management carried out by a health care professional devoted to the rational medication use, in collaboration with GPs and other health care providers. The introduction of the pharmacist-led care delivery model started in 2018 when CMM services were piloted at the Health Centre Zagreb - Centar (HCZC) in an independent counselling unit, Pharmacotherapy counselling service. The HCZC's CMM services, developed in partnership with the University of Zagreb Faculty of Pharmacy and Biochemistry as a part of the joint research project, was established to help patients manage their chronic health conditions and optimize the therapeutic value of medicines. The results of this dissertation add significant value to the existing evidence base and corroborate with the concept of quadruple aim. Namely, the quadruple aim was suggested as a framework to optimize healthcare system performance and it includes improvement of patients' health, enhancement of patients' experience of care, reduction of the per capita cost of health care, and health care providers' work-life improvement (88).

This dissertation is the first one providing an in-depth insight into the initial implementation of CMM services in the primary care setting. Using a mixed-method methodology that combined the action research method and a quantitative approach, pharmacist-practitioners/researchers fully described the newly implemented practice management system of CMM services at the county health centre in Croatia with an aim of broadening general understanding regarding the process of CMM services implementation. Additionally, patients' factors associated with DTP occurrence among general ambulatory patients were determined informing thus the patient sample that would benefit most from the service. The action research methodology, defined by Kurt Lewin in 1976 (89), was used as a tool while introducing the pharmaceutical care practice into various health care systems (34,90–92). Our results proved that this approach was suitable for the process of early-stage implementation since starting a new patient care service in this rigid, existent healthcare system was quite complex. One of the most crucial issues defined by the practice philosophy (7) and confirmed by our study was the importance of taking a responsibility for patients' clinical outcomes, thus becoming a full and equal member of the health care team. Pharmacists' role directed mainly at providing patient-centred care should already start at the graduate level following which

pharmacy students should be equipped with knowledge and skills necessary for patient-centred medication management. Unfortunately, traditional education still takes a major part of the curriculum, contributing to a lack of both knowledge and skills in patient-centred approach, precluding thus later integration into inter-disciplinary teams and pharmacists' functioning within them (93,94). Hence, pharmacist-practitioners who started with the pre- and early implementation of CMM in the ambulatory setting needed to prepare and educate themselves additionally to be able to start with the process of assimilation of this new professional practice. This was conducted through a 3-year Specialization in Clinical Pharmacy assigned from the Ministry of Health, internship (3-month observational visits) established to offer pharmacists willing to provide CMM services with a structured learning experience intended to provide a comprehensive exposure to health system pharmaceutical care practice, self-directed learning and online meetings and discussions. Furthermore, our findings emphasized the importance of a close collaboration between pharmaceutical care practitioners and GPs and other team members to ensure patient inflow, improved patient care and sustainability of the practice.

The profound process of pre- and early implementation brought up the challenges researchers faced at the outset of CMM services introduction. These hurdles were related to resistance of GPs to embrace the new service available at their premises and lack of practising pharmacists' experience in establishing collaboration with GPs and working in a multidisciplinary team. An additional challenge was associated with defining the new work process necessary to provide a standardized and reproducible service. As time passed by and the project unfolded, a close collaboration with several GPs was set up, but the resistance and indifference encountered by the majority of GPs remained and still remains a big challenge and a future research question. Prior to starting with CMM implementation, the main idea for patients' inflow was through GP referrals. During the study, due to a low number of GPs acknowledging the service, pharmacists started providing the service to self-referred patients or patients referred by their medical specialists. In addition, for any success of a practice and its full integration into the healthcare system, a standardized and reproducible service has to be provided. Thus, throughout the initial implementation phase, this study defined the fundamental new work process specific to the Croatian healthcare system and set the foundation for the practice outset in any other health care setting in Croatia.

Concurrently with the provision of CMM services, patients' data were collected and the most prevalent DTPs, including the DTP-associated factors were determined for the first time in Croatia. In accordance with previous published data from the retrospective analysis of a larger patient database (18,22), the two most prevalent DTPs determined in a majority of patients were the need for introducing a new medication (26.1%) and a need for increasing the dose (24.5%). By repeating the results from the studies conducted elsewhere, we confirmed that pharmacist-practitioners followed the standardised, rational decision-making process proposed by Cipolle et al. By employing a multivariate analysis, polypharmacy and type 2 diabetes were found as two most significantly associated factors with a higher number of DTPs. Studies have already shown that polymedicated patients more often experience medication-related problems, however this is the first study that determined DTP-associated factors among chronic patients at the primary care level. These results gave an insight into the type of patients that benefit most from the service, thus describing the study population that the health providers and educators should reach out to and focus on to assure the most efficient health care.

Our study is the first one that adopted a quasi-experimental design to evaluate the clinical impact of the new cognitive pharmacist-led service based on the methodology of Cipolle et al. in older patients with hypertension and established CVDs in the primary care setting. Although randomised controlled trials still represent the golden standard for establishing the efficacy of pharmaceutical interventions, the non-randomised designs i.e., quasi-experimental studies are starting to be widely accepted as they allow determining outcomes of a new practice in a real-world scenario. When a new pharmacy intervention is being provided and tested at the same time, a practitioner (in this instance a GP) learns the new practice through his and patient’s active participation, namely through applying pharmacists’ recommendations. Hence, it might be difficult and non-ethical for a GP to withhold provision of the service to the control group patients knowing that the new intervention (such as medication management services) could bring them tremendous benefits (95). Furthermore, this type of the study, supported by WHO (96), prevents the occurrence of the Hawthorne effect (a type of reactivity in which individuals modify an aspect of their behaviour in response to their awareness of being observed) and enables the “control” GPs to provide unbiased medical care.

All of the patients included in the intervention group were using 5 or more medications, being a predisposing factor for the identification of a higher number of DTPs. At the initial assessment an average of 3.8 DTPs per patient was identified. During the CMM visits, the most prevalent DTPs were “Dosage too low” (35.5%), followed by “Needs additional therapy” (25.6%), consistent with previously published evaluations of CMM services (18,22,36). These findings point to the underutilisation of effective medications leading to worse disease control and increased health care utilization. Hence, due to the scarce scientific literature in this field (22,36–38,45,49), the main goal of this pre- and post-intervention open controlled study was to determine the impact of GP-pharmacist collaboration on health care utilization that can consequently have potential financial savings. Our study demonstrated that patients receiving CMM services had significantly fewer hospital admissions and unplanned GPs visits compared to control participants, albeit insignificantly less emergency department visits. In comparison, Obreli-Neto et al. (45) found a significantly higher mean number of emergency room visits in the control group, although through the longer study period and on a larger patient sample.

Heretofore reported studies demonstrated the positive impact of CMM services on CV-related hospitalisations (38) and medication-related hospitalisations (37). But yet, our study is the first to have tested the effectiveness of pharmacist-led medication management on medical avoidance in older CV patients by employing a comparison group. Being the most prevalent health conditions in the world and the leading cause of global mortality, CVDs can adversely impact health care costs. Hence, this study demonstrated how CMM services delivered in the ambulatory setting could potentially contribute to total health care savings and prove their benefit. As our study included a relatively small number of patients, it may be beneficial to repeat it and confirm the findings on a larger sample size. Even though the evidence of cost-savings due to CMM services has already been shown in other published articles (22,36–38), the awareness of the benefits CMM provider-GP collaboration could bring to patients and health care systems across Europe stays unrecognised.

Improvement of the CVD-associated risk factors (blood pressure, lipid profile, fasting glucose and HbA1c) can contribute to CVD prevention and disease management, and consequently affect medical utilisation and health budget. A change in the evaluated parameters was observed within and between groups following a one-year period. A statistically significant decrease in blood pressure (SBP and DBP), LDL-C, TC and HbA1c was found in the

intervention group compared to the control group. Even more, both clinically and statistically significant decrease in SBP and DBP (9/5 mmHg) was observed in the intervention group following a 1-year period. Hence, the new pharmacist-led interprofessional collaborative practice improved SBP, DBP, LDL-C, TC and HbA1c in older patients with hypertension and established CVDs in the primary care setting. So far, several studies demonstrated the positive impact of CMM services on the control of blood pressure, yet in different study populations, diverse settings, and with different study designs (26,38–40,42–45,47,97). This study showed SBP reduction of 9.0 mmHg and DBP of 4.9 mmHg, a highly relevant one according to the European Society of Cardiology (98). Meta-analyses of RCTs (99,100) showed that a 10 mmHg and 5 mmHg reductions in SBP and DBP, respectively have a strong clinical impact on all major CV events, heart failure, stroke, coronary events and all-cause mortality.

A lipid panel consisting of LDL-C, TC, HDL-C and triglycerides is another major factor in the prevention and control of CVDs (50), and studies showed that these parameters can be improved when the pharmaceutical care practice is provided alongside standard care (26,38,39,42,46). Our findings demonstrated that LDL-C, together with the TC can be significantly improved when CMM services are provided to older patients with CVDs. Clinical trials have pointed out that the lower the achieved LDL-C values, the lower the risk of future CV events (101). Thus, even the slightest reduction in LDL-C, as our findings demonstrated (-0.23 mmol/L in the intervention group), can reaffirm the value of CMM services. Conversely to other studies (26,38,39,42), a significant change in HDL-C and triglycerides was not found when comparing within- and between-treatment differences.

The glycated haemoglobin represents a reliable risk factor of all-cause and CV mortality in both diabetics and nondiabetics (102,103). A meta-analysis of three important studies suggested that an HbA1c reduction of 1% in patients with type 2 diabetes is related to a 15% relative risk reduction of non-fatal MI (103). Many published studies testing CMM services found a clinically significant HbA1c reduction, varying between 0.54% to 0.8% (26,39,41,42). Although statistically significant, our study failed to show a clinically significant reduction in HbA1c in the intervention group what could be explained by the small patient sample and relatively short study period. According to the results of our study, it might be beneficial to target diabetic patients since they could benefit most from the patient-centred pharmaceutical care practice.

In the light of rapid worldwide growth of old population and the incidence of CVDs leading to higher expenses (57,60), ensuring healthy aging and satisfying life quality are of special interest (75). To determine CMM's impact on CVD-older patients' quality of life, the EQ-5D-5L questionnaire was administered to intervention group participants at the beginning and following one year assessment. The findings of our pre- and post—intervention study add to a rather scarce evidence base with regards to the impact of pharmacy interventions on HRQoL (104). Despite the growing interest in this field of research, notably since the COVID-19 pandemic has started (72,73), very few researchers have yielded consistent results. The CMM services were introduced to improve patients' clinical outcomes, reduce undesirable ADRs and enhance their quality of life. Until now, the majority of the studies focused on clinical and economic outcomes, and only a few assessed the impact on humanistic outcomes (22,83). Our research is the first that has evaluated the impact of CMM services on HRQoL in CV older patients at the primary care level, showing thus that CMM services can have a valuable influence on the patients' HRQoL. Out of five dimensions EQ-5D-5L questionnaire consists of, significant improvement was found in two dimensions, "self-care" and "usual acitivites", while in the remaining three no significant change was observed. Authors of the used tool stated that the EQ-5D-5L health state is considered to be "better" over time if it is improved in a minimum of one dimension and no worse in any other (105). Furthemore, the COVID-19 lockdown during the study period had an enormous effect on patients' mobility and psychological status, yet our patients did not report nor perceive any worsening in those dimensions, what was seen as a positive result. Based on the given findings, it can be concluded that the overall EQ-5D-5L health status improved following CMM services. Taking into account that those patients had significant improvement in clinical outcomes while they were attended by the pharmacist-practitioners, the improvement of their overall HRQoL was no surprise.

Moreover, we found no difference at the beginning and the end of the study in the EQ visual analogue scale (VAS), possibly because the VAS score is less specific in comparison with the EQ-5D-5L dimensions, leading to the fact that every participant comprehends the scale in his/her own way. As previously observed, the mean VAS value was similar at the baseline and at the end of the study (57.43 and 57.67, respectively) (106). Older patients with CVDs tend to get used to their long-lasting health problems (107), hence they are likely to choose the middle value on the VAS scale (between 0 and 100) to express their overall current health.

A major feature of the EQ-5D-5L instrument is index value, a single summary number derived from EQ-5D-5L health states, reflecting how bad or good a health state is according to the preferences of the population of a country or a region. Index values facilitate the calculation of quality-adjusted life years (QALYs), used in economic analyses of health care interventions (105), and this factor can assist various stakeholders in their decision-making process. Thus, it would be specially interesting to increase the patient sample, include the control group as to allow for QALY calculation.

One of the prominent causes of lower life quality and adverse clinical outcomes, including hospital admissions, in older patients with chronic diseases are ADRs (108–110). Despite these facts, to the best of the author's knowledge, the prevalence of ADRs at the primary care level has not been widely studied. Our study showed a high prevalence of reported, suspected ADRs in older CV patients in the ambulatory care setting at the initial assessment with 98.5% of patients experiencing a minimum of one ADR, before or during the study. Furthermore, according to the authors, the high prevalence of suspected ADRs, as the result of a comprehensive data collection process, could have influenced relatively low HRQoL reported at the beginning of the study. In congruence with other studies (111–113), a strong positive association between the number of medications and the rate of suspected ADRs was found. Furthermore, as previously found, correlation with the older age and the number of comorbidities was not revealed by our study (110,112,113). Therewithal, our results demonstrated a significant reduction in the rate of suspected ADRs per patient during the study. Knowing that ADRs can strongly impact patients' clinical and humanistic outcomes and further restrict health care budget (114), the presented positive impact of CMM on ADR prevalence in older CV patients made evident that CMM services can serve as a solution for abovementioned problems by ensuring safe and effective medication use.

To the best of our knowledge, this is the first study that used the BIA model to predict the CMM's financial impact on a national health insurance fund budget over a 3-year period. Although CMM represents a large-scale intervention, intended for all patient groups regardless of their health condition, BIA analysis was conducted on a patient sample with CVDs and type 2 diabetes (T2DM). Namely, T2DM and CVD patients using five or more medicines daily were eligible for inclusion in the BIA model as these are among the most prevalent and costly chronic diseases worldwide (52,115), with Croatia being no exception. Our analysis resulted in CMM's 3-year budget impact of around EUR 90,000 and EUR 0.67

incremental cost per patient, rendering CMM an affordable intervention. With some study limitations, such as conservative estimation of CMM's cost-saving impact and data from published sources, we successfully demonstrated how full implementation of cost-effective and viable CMM services into the Croatian health care system could be carried out at approximately moderate cost by bringing benefits to patients, medical caregivers, policymakers, payers and health care system. Finally, it was concluded that CMM provided by trained pharmacists reduces the unnecessary and often harmful use of medications and can help patients and GPs to achieve desired health outcomes more efficiently.

This dissertation has several limitations. First, the study was conducted in only one primary health care setting and included a relatively small number of patients, hence limiting the generalizability of research findings. Second, the non-randomisation of the groups could have led to an undervaluation of given results, yet this approach allowed the authors to assess the study in the "real world" scenario, without ethical or practical concerns. Given the constraints of the study related to the HRQoL, it was not possible to measure HRQoL in the comparison group and therefore, authors are aware that the clinical relevance of the CMM's impact on HRQoL is questionable. Namely, it is hard to claim with certainty that the outcome was due to the new intervention and that it was not biased by some other variable.

It is important to emphasize that this dissertation simultaneously employed the quasi-experimental study, budget impact analysis and qualitative research to perform and describe the initial implementation of an entirely new medical service provided by two practitioner-researchers in Croatia. Despite the process complexity, demands and challenges met throughout the study period, the results succeeded to demonstrate statistically and clinically relevant impact of CMM services on clinical outcomes in older CV patients, and a successful introduction of CMM within a primary care setting.

However, for the service to be fully embraced by health care policy makers and other stakeholders, further pharmacoeconomic analysis as well as qualitative research have to be conducted. Qualitative research could be of outstanding importance by giving an in-depth insight into the obstacles that stand in the way of completing CMM services adoption by GPs, health centres, and the health care system in general.

7. CONCLUSIONS

The results of this dissertation demonstrated how team-based, patient-centred CMM services, when being piloted and introduced in the Croatian ambulatory care setting at the primary care level, can enhance the care of older patients with hypertension and established CVDs by improving their clinical and humanistic outcomes, preventing and resolving DTPs and achieving therapy goals.

By using the action-research methodology in the early-stage implementation, this study identified an array of challenges met throughout the process of implementation that pharmacist-practitioners and other health care providers should deal with to allow for full implementation of the service at the primary care level. Moreover, it enabled deeper insight into the work processes and resources, namely components of the practice management system, needed for pre- and early CMM implementation, crucial for the successful incorporation of CMM within a primary care setting.

The central part of pharmaceutical care provision are drug therapy problems, presenting an outcome of patients' medication-related needs that have gone unmet. This study showed a high prevalence of DTPs among patients with chronic conditions, especially patients with CVDs, thus pointing to the pivotal need for introducing CMM services to address them. The results underscored the diabetic patients and patients with polypharmacy (using 5 or more medications) as the ones that could have greater benefit from CMM services and should thus be prioritised.

Improvement of patients' clinical parameters and reduction of health care utilisation is of paramount importance for patients’ well-being and health care budget. This study indicated that CMM services can reduce the number of hospital admissions and unplanned GPs visits in patients with hypertension and established CVDs, suggesting that patients receiving CMM care alongside the standard care have lower health care utilization, hence potentially leading to a reduced economic burden. The significant improvement in CV risk factors such as blood pressure, LDL-C, TC, and HbA1c found in this study confirms the multiple benefits of pharmacist-general practitioner collaboration and likely contributes to the beneficial budget impact.

The present study indicates that CMM services may improve patients' HRQoL, one of the PROMs/extremely valuable indicators of successful service implementation. Moreover, CMM services provided in this study allowed for an identification of a rather high prevalence rate of

suspected ADRs, implying that the comprehensive data collection process employed in CMM is a valuable pharmacists' endowment contributing to patient safety.

The conducted budget impact analysis is the first one used to assess the affordability of CMM services. The results suggest that the budget impact on Croatian health insurance fund over a 3-year period renders CMM an economical intervention, and contributes to a rather scarce evidence base with regards to the economic outcomes of a new pharmacist-led intervention.

The results of this dissertation highlight the need for well-trained, educated, and competent practitioners by defining the fundamental knowledge and skills required to position the pharmacist as a patient-centred health care provider and a member of a multidisciplinary healthcare team. Furthermore, the components of the newly introduced practice in the primary setting were determined and the foundations for the new workplace laid, thus enabling CMM to become an equal part of the Croatian health care system and live its full potential. Additionally, the presented results contribute to the development of scientific, research and teaching area of pharmaceutical care and clinical pharmacy in Croatia and Europe.

This doctoral dissertation demonstrates how CMM services at the primary care level can bring several health benefits to older patients with hypertension and established CVDs, and consequently to the health care system. The successful pharmacist-general practitioner collaboration provided in this research proved to be an effective solution for irrational drug use and medication mismanagement and adds significant input to the existing evidence–based literature supporting CMM's full implementation in the Croatian health care system.

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9. LIST OF ABBREVIATIONS

ADR	adverse drug reaction
BIA	budget-impact analysis
CMM	comprehensive medication management
DBP	diastolic blood pressure
DTPs	drug therapy problems
CHD	coronary heart disease
CV	cardiovascular
CVDs	cardiovascular disease
GPs	general practitioner
HbA1c	glycated haemoglobin
HDL-C	high-density lipoprotein cholesterol
HRQoL	health-related quality of life
LDL-C	low-density lipoprotein cholesterol
PROM	patient reported outcome measure
QALYs	quality-adjusted life years
SBP	systolic blood pressure
TC	total cholesterol
T2DM	type 2 diabetes
VAS	visual analogue scale
WHO	World Health Organization

10. BIOGRAPHY

Andrea Brajković was born on 30th November 1990 in Rijeka, Croatia. After completing her primary and secondary school (Classical Gymnasium), she graduated as MPharm in 2014 at the Faculty of Pharmacy and Biochemistry, University of Zagreb. Following the pre-registration period (registered pharmacist since 2016) she became a research and teaching assistant at the Centre for Applied Pharmacy at the Faculty of Pharmacy and Biochemistry where she currently teaches Pharmaceutical care, Clinical pharmacy and Pharmacotherapy, Consultation skills, Personalized Healthcare and participates in organisation of the Professional Training for Pharmacists. In 2016 she enrolled PhD programme in "Pharmaceutical-Biochemical Sciences" at the Faculty of Pharmacy and Biochemistry with her PhD thesis titled 'The impact of Comprehensive Medication Management services on clinical outcomes in patients with cardiovascular diseases at primary care level'. During her study she was awarded the Dean's Prize for the project "Case Study Competition goes regional 2013". In 2014 she received the Erasmus+ study programme scholarship for a 4-month study period in the Food Science Lab, University of Algarve (Faro, Portugal) where she conducted her Master thesis titled "Antioxidant activity of the ethanol extract of plant species traditionally used in Croatian ethnomedicine in treatment of diabetes". Following graduation she was awarded Erasmus+ traineeship programme in the Hospital de Poniente (El Ejido, Spain).

In 2016 she visited the Department of Practice and Policy, School of Pharmacy, University College London for a two-week period where she gained experience in post-registration pharmacist-practitioner training development and the workplace-based teaching design in clinical environments. In 2017 she conducted a three-month doctoral internship at the Centre for Pharmaceutical Care Studies, College of Pharmacy, Federal University of Minas Gerais (Belo Horizonte, Brazil) where she mastered the philosophy of pharmaceutical care practice and the core elements of comprehensive medication management services. Her main field of interest is pharmaceutical care focused on patients' medication management and clinical outcomes improvement. Andrea is a member of the Croatian Chamber of Pharmacists and the Croatian Pharmaceutical Society. She co-authored 9 peer-reviewed papers and participated with posters and oral communications at several Croatian and international scientific conferences.

List of Publications

1. **Brajković A**, Bićanić LA, Strgačić M, Orehovački H, Ramalho de Oliveira D, Mucalo I. The Impact of Pharmacist-Led Medication Management Services on the Quality of Life and Adverse Drug Reaction Occurrence. Pharmacy (Basel). 2022 Aug 25;10(5):102.
2. Mucalo I, **Brajković A**, Strgačić M, Ramalho de Oliveira D, Ribarić E, Bobinac A. Budget Impact Analysis of Pharmacist-Led Medication Management in Cardiovascular and Type 2 Diabetic Patients. Healthcare (Basel). 2022;10(4):722.
3. **Brajković A**, Bosnar L, Nascimento MMGD, Prkačin I, Balenović A, Ramalho de Oliveira D, Mucalo I. Healthcare Utilisation and Clinical Outcomes in Older Cardiovascular Patients Receiving Comprehensive Medication Management Services: A Nonrandomised Clinical Study. Int J Environ Res Public Health. 2022;19(5):2781.
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6. Mucalo I, **Brajković A**, Jukić I, Jonjić D, Radin D, Balenović A i sur. Comprehensive Medication Management Services as a Solution to Medication Mismanagement:A European Perspective. RAD CASA - Medicinske znanosti. 2019;540(48-49):33-40.
7. **Brajković A**, Mucalo I, Vidović T, Gonzaga MM, Nascimento D, Balenović A, Protrka I, De Oliveira DR. Implementation of medication management services at the primary healthcare level - a pilot study. Acta Pharm. 2019 Dec 1;69(4):585-606.
8. Mucalo I, Hadžiabdić MO, **Brajković A**, Lukić S, Marić P, Marinović I, Bačić-Vrca V. Potentially inappropriate medicines in elderly hospitalised patients according to the EU(7)-PIM list, STOPP version 2 criteria and comprehensive protocol. Eur J Clin Pharmacol. 2017 Aug;73(8):991-9.
9. Bljajić K, Šoštarić N, Petlevski R, Vujić L, **Brajković A**, Fumić B, de Carvalho IS, Končić MZ. Effect of Betula pendula Leaf Extract on α-Glucosidase and Glutathione Level in Glucose-Induced Oxidative Stress. Evid Based Complement Alternat Med. 2016;2016:8429398.

BASIC DOCUMENTATION CARD

University of Zagreb **Doctoral Thesis**
Faculty of Pharmacy and Biochemistry
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THE IMPACT OF COMPREHENSIVE MEDICATION MANAGEMENT SERVICES ON CLINICAL OUTCOMES IN PATIENTS WITH CARDIOVASCULAR DISEASES AT PRIMARY CARE LEVEL

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SUMMARY

Patients with established cardiovascular diseases (CVDs) often use multiple medications that increase the risk of irrational drug use, subsequently leading to unfavourable clinical and health outcomes. New pharmacist's intervention named Comprehensive Medication Management (CMM) services provided at the primary care level could address the abovementioned problem by optimizing patients' therapy and improving their outcomes. Hence, the main aim of this dissertation was to evaluate the impact of CMM services on healthcare utilisation, cardiovascular risk factors and health-related quality of life (HRQoL) among older patients with established CVDs. Moreover, the study aimed to describe the newly implemented practice management system of CMM services at the primary care level and to predict CMM's budget impact on Croatian health insurance fund. Results showed that the intervention group patients receiving CMM services had significantly lower systolic ($p = 0.038$) and diastolic blood pressure ($p = 0.001$), total cholesterol ($p = 0.014$), low-density lipoprotein cholesterol ($p = 0.005$), and glycosylated haemoglobin ($p = 0.045$) in comparison to the control group. Moreover, patients in the control group had 3.35 (95% CI 1.16–10.00) and 2.34 (95% CI 1.52–3.57) times higher number of hospital admissions and unplanned GPs visits compared to the intervention group, respectively. The HRQoL was measured in the intervention group by using the EQ-5D-5L questionnaire. A significant improvement in dimensions "self-care" ($p = 0.011$) and "usual activities" ($p = 0.003$) was found. The implementation process included two stages: a pre-implementation stage that set the groundwork for the early implementation stage. The budget impact analysis employed in this research led to a CMM's net budget impact of EUR 92,869 and EUR 0.67 incremental cost per patient within a 3-year horizon, rendering CMM an affordable intervention for the Croatian healthcare system. The results of this dissertation add to the evidence base supporting the CMM's full implementation in the Croatian health care system by demonstrating that CMM interventions can significantly contribute to better clinical outcomes and lower healthcare utilisation, may improve patients' HRQoL, thus serving as a viable solution for safety management in older patients with hypertension and established CVDs at the primary care level.

The thesis is deposited in the Central library of the Faculty of Pharmacy and Biochemistry, University of Zagreb.

Thesis includes: 110 pages, 5 figures, 26 tables and 115 references. Original is in English language.

Keywords: comprehensive medication management services; pharmaceutical care; nonrandomised; primary health care; cardiovascular diseases; older patients; clinical outcomes; health-related quality of life; implementation stage; budget impact analysis

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UTJECAJ USLUGE UPRAVLJANJA FARMAKOTERAPIJOM NA KLINIČKE ISHODE U PACIJENATA S KARDIOVASKULARNIM BOLESTIMA NA RAZINI PRIMARNE ZDRAVSTVENE ZAŠTITE

Andrea Brajković

SAŽETAK

Pacijenti s postojećim kardiovaskularnim bolestima (KVB) često koriste veći broj lijekova što vodi k neracionalnoj uporabi lijekova te posljedično doprinosi nepovoljnim kliničkim i zdravstvenim ishodima. Kao posljedica spomenutog pojavila se potreba za uvođenjem nove ljekarničke intervencije usmjerene optimizaciji terapije pacijenata i poboljšanju ishoda - usluge upravljanja farmakoterapijom (UFT). Glavni cilj ovog doktorskog rada bio je utvrditi utjecaj usluge UFT na utilizaciju zdravstvene skrbi, kardiovaskularne rizične čimbenike, i kvalitetu života povezanu sa zdravljem u pacijenata starije životne dobi s KVB. Dodatno, cilj ovog istraživanja bio je opisati cjelokupni proces rane implementacije usluge UFT u Dom zdravlja Zagreb – Centar te procijeniti utjecaj usluge UFT na hrvatski zdravstveni proračun. Ovo je istraživanje pokazalo da su pacijenti u intervencijskoj skupini koji su primali uslugu UFT imali statistički značajno niži sistolički ($p = 0,038$) i dijastolički krvni tlak ($p = 0,001$), LDL-kolesterol ($p = 0,005$), ukupni kolesterol ($p = 0,014$) i glikirani hemoglobin ($p = 0,045$) u odnosu na pacijente iz kontrolne skupine. Vjerojatnost hospitalizacije i nenadanih posjeta LOM-u bili su 3,35 (95% CI 1,16-10,00) i 2,34 (95% CI 1,52-3,57) puta veći u kontrolnoj skupini u odnosu na intervencijsku skupinu. Kvaliteta života vezane uz zdravlje pacijenata mjerena je pomoću EQ-5D-5L upitnika u intervencijskoj grupi. Do statistički značajnog poboljšanja došlo je u dvije dimenzije: „skrb o sebi“ ($p = 0,011$) i „uobičajene aktivnosti“ ($p = 0,003$). Proces inicijalne implementacije uključivao je dvije faze: pred-implementacijsku fazu (pripremna faza) koja je postavila temelje za fazu rane implementacije. Rezultati studije utjecaja usluge UFT na proračun pokazali su da bi uvođenje usluge UFT u zdravstveni sustav opteretilo proračun u iznosu od 92.869 EUR (po liječenom pacijentu 0,67 EUR) tijekom tri godine što se smatra cjenovno pristupačnom intervencijom. Rezultati ovog doktorskog rada predstavljaju značajan doprinos postojećim dokazima koji podržavaju potpunu implementaciju usluge UFT u hrvatski zdravstveni sustav pokazujući da ova ljekarnička intervencija značajno doprinosi poboljšanju kliničkih ishoda, smanjenju utilizacije zdravstvene skrbi te da može poboljšati kvalitetu života vezanu uz zdravlje, predstavljajući tako održivo rješenje za osiguravanje sigurne terapije pacijenata starije životne dobi s hipertenzijom i KVB na razini primarne zdravstvene zaštite.

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