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Barriers and facilitators to deprescribing of cardiovascular medications: a systematic review

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ABSTRACT

Objective: To synthesize the current knowledge on barriers and facilitators to deprescribing cardiovascular medications (CVMs) at the levels of patients, informal caregivers, and healthcare providers (HCPs).

Design/Setting: We conducted a systematic review of studies exploring/assessing patient, informal caregiver and/or HCP barriers and/or facilitators to deprescribing CVMs.

Data sources: Ovid/MEDLINE and Embase from January 2003 to November 2021.

Data extraction and synthesis: We performed a deductive thematic analysis based on the framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.

Results: Important deprescribing barriers for patients, informal caregivers and HCPs included uncertainty due to lack of evidence regarding CVM deprescribing, fear of negative consequences following deprescribing, and time constraints. An important facilitator to deprescribing for patients and HCPs was the occurrence of ADEs. Other facilitators for patients were dislike of CVMs or establishment of a deprescribing plan. Necessity and benefit of CVMs were seen as barriers or facilitators similarly by patients and HCPs. Social influences and patient ambivalence acted both as barriers and facilitators to deprescribing.

Conclusion: The differences in patient, informal caregiver and HCP regarding barriers and facilitators to deprescribing CVMs stress the need for ground discussions about beliefs and preferences of each stakeholder implicated in deprescribing decisions.

Review registration on Prospero: CRD42020221973

Strengths and limitations of this study:

- Systematic review process with publication review; data extraction, analysis and synthesis; and quality assessment independently conducted by two independent reviewers.
- Assessment of both quantitative and qualitative studies, providing complementary information on barriers and facilitators to deprescribing.
- In some studies, cardiovascular medications were part of, but not the focus of the medications evaluated.
- We did not assess specific classes of cardiovascular medications.

Key words: cardiovascular medication, deprescribing, barriers, facilitators, older people

1. Introduction

In recent years, a less-is-more attitude regarding medication use has pushed to reevaluate the balance between medication risks and benefits[1]. In this context, the notion of *deprescribing* emerged, which is defined as the "systematic process of identifying and discontinuing [medications] in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values and preferences"[2].

Cardiovascular medications (CVMs) belong to the most prescribed medications worldwide[3]. Although their use is beneficial in many cases, CVMs can also cause significant adverse drug events (ADEs), drug-drug, and drug-disease interactions [4-6]. However, the lack of evidence regarding benefits and risks of some CVMs in primary prevention in older people or in those with limited life expectancy, may lead to insecurity of patients and prescribers regarding CVM use and deprescribing[1, 7-12].

In this context, the decision to deprescribe a CVM often becomes a preference-sensitive decision[13, 14]. A better understanding of barriers and facilitators experienced by all stakeholders involved in decision-making regarding CVM deprescribing may help to take informed decisions in line with individual values and preferences, and increase confidence in the decision made[15, 16]. While literature exists on deprescribing general medications, we do not know if barriers and facilitators differ for deprescribing CVMs.

With this systematic review, we aimed at synthetizing the current knowledge on barriers and facilitators to deprescribing CVMs at the levels of patients, informal caregivers, and healthcare providers (HCPs).

2. Methods

We conducted a systematic review of studies assessing barriers and/or facilitators to deprescribing CVMs in adults. The review was registered on Prospero (CRD42020221973).

2.1. Ethics approval

An ethics approval was not needed for this study, since it was a review of the literature.

2.2. Types of studies and inclusion criteria

We included any type of publication – except editorials, conference abstracts and study protocols – discussing stakeholder barriers and/or facilitators regarding the process of deprescribing CVMs. Studies on prescribing, use, or adherence were not included. Studies reporting patients stopping CVMs without previous discussion with HCPs were considered as non-adherence studies and excluded.

2.3. Search strategy

We searched Ovid/MEDLINE and Embase from January 2003 to November 2021. We started the search in 2003 because it corresponds to the first mention of the term *deprescribing* in the literature[17]. We included studies published in English language and focusing on patients taking or having taken CVMs previously, and/or informal caregivers, and/or HCPs of such patients. We developed the 3 following concepts for our search strategy: 1) CVMs; 2) deprescribing; 3) barriers and facilitators. All three concepts were combined with the operator "and". The detailed search strategy is provided in **Supplemental Text S1**.

LB and CEA independently reviewed all publications identified through the search strategy after removing duplicates. First, ineligible articles were excluded based on title/abstract. Second, full text of the remaining articles was reviewed to identify eligible studies. Reference lists of included publications were also searched for additional relevant articles (hand

searching). Reviews and meta-analyses were kept in the first selection, but only original studies identified in the reference lists were included. For each step, LB and CEA resolved discrepancies by discussion.

2.4. Data extraction and analysis

Eligible articles were imported in MAXQDA 2020 data analysis software (VERBI Software, Berlin, Germany). Extracted data included author(s), year of publication, country, study design, setting, and population, and details on barriers and/or facilitators. Given the topic of this systematic review, we conducted a qualitative rather than a quantitative synthesis of the results. We performed a deductive thematic analysis to identify common and discrepant themes within and between stakeholder categories[18, 19]. The thematic analysis was based on the framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.[4]. This framework, based on Reeve's framework of patient barriers and facilitators to deprescribing medications[20], includes the following categories: appropriateness of cessation, process of cessation, dislike of medications, fear, uncertainty, and conflicting attitudes. We analyzed patient and informal caregiver outputs together and HCP outputs separately, since we expected to identify different barriers and facilitators. In an iterative process, we created themes within the predefined categories.

2.5. Risk of bias and quality assessment

LB and CA conducted the quality and risk of bias assessment separately using the Mixed Methods Appraisal Tool (MMAT) 2018[21, 22]. The MMAT allows assessing the methodological quality of studies included in a systematic review encompassing both qualitative and quantitative data. Discussions were held until a consensus on quality of each study was reached.

2.6. Patient and Public Involvement:

Patients and Public were not involved in the design, conduct or reporting of this review, but in a follow-up project based on this review.

3. Results

3.1. Study selection and characteristics

Among the 4,164 unique studies identified, 71 were included for full-text assessment (**Figure 1**). Among those, 16 fulfilled inclusion criteria. Through hand-searching, six additional studies were included, leading to a total of 22 publications. Study characteristics are presented in **Tables 1-3** and detailed in **Supplemental Table S1**.

Table 1: Principal characteristics of studies including patients and/or informal caregivers

First author, publication year	N population	Age	Studied CVM(s)	Prevention type
Benson, 2005 (UK[25]	38 patients	Any	Antihypertensives	Unknown
Brinton, 2018 (USA)[42]	5,014 patients	Mean age: 64 years	Statin	Primary & secondary
Crutzen, 2020 (Netherlands)[26]	17 patients 1 informal caregiver	Median age: 78 years	Cardiometabolic medication	Primary & secondary
Goyal, 2020 (USA)[4]	10 patients	Median age: 80 years	β-blockers	Primary & secondary
Jansen, 2019 (Australia)[28]	30 patients	≥75 years	Preventive cardiovascular medication	Primary & secondary
Luymes, 2017 (Netherlands)[43]	33 patients	Mean age: 57 years	Lipid-lowering drugs Antihypertensives	Primary

Pickering, 2020 (USA)[31]	16 patients 17 informal caregivers	Patients ≥ 65 years Caregivers 22-69 years	Unspecified (identified: statins, antihypertensives, antiplatelets, antidiabetics)	Primary & secondary
Qi, 2015 (Australia)[39]	180 patients	Median age: 78 years	Regular medications Statins	Primary & secondary
Tija, 2017 (USA)[40]	297 patients	Mean age: 72 years	Statin	Primary & secondary
Van Bussel, 2019 (Netherlands)[34]	15 patients	Mean age: 81 years	Antihypertensives	Primary

Abbreviations: CVM, cardiovascular medication.

Table 2: Main characteristics of studies including HCPs

First author	N population	Characteristics of patients cared by study HCPs		
		Age	Studied CVM(s)	Prevention type
Ailabouni, 2016 (New Zealand)[36]	10 GPs	83 years	Antiplatelets, statin, antidiabetics, diuretics, β-blocker, ACE inhibitor	Secondary
Ailabouni, 2016 (New Zealand)[23]	10 GPs	Unspecified (older patients)	Unspecified (identified: statin and aspirin)	Unknown

Anderson, 2017 (Australia)[24]	32 GPs 15 CPs	Unknown	Unspecified (identified: statin)	Unknown
Geijteman, 2018 (Netherlands)[38]	174 GPs 147 clinical specialists	88 years	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary
Goyal, 2020 (USA)[37]	184 geriatricians 182 general internists 87 cardiologists	79 years	4 cardiovascular medications	Unknown
Green, 2019 (USA)[29]	19 physicians 2 nurse practitioners	Unspecified (older patients)	Unspecified (identified: statins, oral anticoagulants, antidiabetics)	Unknown
Jansen, 2017 (Australia)[27]	25 GPs	≥75 years	Preventive CV medication	Primary
Thompson, 2020 (Denmark)[32]	11 GPs	≥ 80 years	Statin	Unknown
Van Middelaar, 2020 (Netherlands)[35]	15 GPs	Unspecified (older patients)	Antihypertensives	Unknown
Van der Ploeg, 2018 (30 countries)[41]	2250 GPs	≥ 80 years	Statin	Primary and secondary

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; CVM, cardiovascular medication; GP, general practitioner.

Table 3: Main characteristics of studies including HCPs and patients and/or informal caregivers

First author	N population	Patients' characteristics		
		Age	Studied CVM(s)	Prevention type
Luymes, 2016 (Netherlands)[30]	10 GPs 49 patients	Median age: 55 years	Antihypertensives, lipid-lowering drugs	Primary
Todd, 2016 (UK)[33]	12 patients 12 informal caregivers 3 palliative consultants 3 nurse practitioners 6 GPs	Any	Unspecified (preventive medications, including statins, antihypertensives)	Unknown

Abbreviations: CVM, cardiovascular medication; GP, general practitioner.

3.2. Quality assessment

Details of each study quality assessment can be found in **Supplemental Table S2**. Of the 15 qualitative studies included in this systematic review, 14 were deemed of good quality[4, 23-35], while one lacked data to support interpretation of the results[36]. Five of the six included quantitative studies did not provide sample representative of the target population, as nonresponse was high, increasing the risk of nonresponse bias[37-41]. The sixth quantitative study provided few details on the method used for data analysis[42]. The only mixed methods study included failed to address divergences between quantitative and qualitative results[43]. We did not exclude any study based on the quality assessment, as our aim was to describe all available data regarding barriers and facilitators to deprescribing CVMs.

3.3. Thematic analysis

Following the framework of Goyal et al.[4], seven categories were created to describe patient and HCP main barriers and facilitators to deprescribing CVMs. Categories one and four were divided into three and two themes respectively. Differences between patients, informal caregivers and HCPs, as well as across HCP categories, are highlighted when relevant. HCPs other than general practitioners (GPs, including general internists and family medicine clinicians) are regrouped under the term "specialists". Differences across specialties are highlighted when relevant. Barriers and facilitators did not appear to differ significantly between studies assessing different CVMs.

3.3.1. Appropriateness

Patient and HCP agreement or disagreement with appropriateness of CVM deprescribing were based on three main themes: CVM necessity, CVM benefit, and ADE occurrence. All barriers and facilitators according to categories, themes and stakeholders, are displayed in **Table 4** and detailed in **Supplementary Table S3**.

Table 4: Summary of categories, themes and codes of barriers and facilitators to deprescribing CVMs

	Patients /informal caregivers	HCPs	All

Appropriateness	CVM linked to survival, ADEs foster deprescribing discussion with HCP *Low CV risk, disease under control, robustness, ADEs balanced against reasons to take CVMs*	Unhealthy lifestyle, many CVRFs *Primary prevention, age as single CVRF, short life expectancy, cognitive impairment, nursing home / palliative care, ADEs*	Past CV event, family history of CVD, CVM should be taken until end of life, no ADE *No improvement under CVM, no symptom from disease*, *reduction in QOL through ADEs*
Fear	Fear of CV event & becoming a burden *Fear of ADEs, of becoming dependent on CVMs*	Feeling of giving up on patients	Fear of CV event, return of previous condition, health deterioration, shorter lifespan
Dislike	*Medication dislike, costs, living a long life without using CVMs, pride in not taking medications, CVMs = poison / bad for health, therapeutic competition*		
Influences	**HCP (especially GP) advice**	**Patient's preferences** Patient's lack of understanding; patient's family wants CVMs; specialist prescription; interference with other HCPs' treatment plan	**Previous experience with deprescribing** (*QOL improvement, no stroke*, restart medication, stroke)
Process	*Deprescribing trial with possibility of restarting*	Lack of remuneration for close monitoring	*Dose-lowering scheme; close monitoring* Time constraints

Uncertainty	Lack of understanding of CVDs and risk reduction with CVMs; uncertainty about risks and benefits; conflicting treatment targets	Lack of evidence on deprescribing, uncertainty about when to deprescribe / risk-benefit ratio. Limited training on deprescribing	Unknown consequences of deprescribing *Uncertainty about possible consequences of taking CVMs*
Ambivalence	Concern about CVM effect on health vs consequences of not taking CVMs Aversion towards CVMs vs obligation to take CVMs		

Abbreviations: ADE, adverse drug event; CV, cardiovascular; CVD, cardiovascular disease; CVM, cardiovascular medication; CVRF, cardiovascular risk factor; GP, general practitioner; HCP, healthcare provider; QOL, quality of life.

Legend: Categories are displayed in the first column. Barriers are displayed in normal character, facilitators in italics, and items that can act both as barrier or facilitator in bold.

3.3.1.1 Necessity

Some patients considered taking CVMs as a necessity, even an obligation, especially in case of past cardiovascular (CV) event or family history of cardiovascular disease (CVD)[28, 30, 43]. This view was shared by GPs, who also deemed necessary to treat patients with unhealthy lifestyle, or presenting many cardiovascular risk factors (CVRF)[30, 35]. Many patients and one GP even stated that CVMs should not be stopped until the end of life[28, 32, 33, 40], while some patients considered CVMs linked to their survival[4]. Contrastively, patients at low CV risk and GPs treating patients in primary prevention or patients without any CVRF other than age, considered CVMs less necessary[27, 30, 41, 43]. Some patients questioned the continuous necessity of their CVM, as they felt that their disease was well-controlled[30, 34].

3.3.1.2 Benefit

GPs were more inclined to continue treating patients with good physical and cognitive function or few comorbidities, especially if they presented no CVM-related ADEs, expecting them to derive a higher benefit from CVMs[24, 27, 32, 35, 36]. In contrast, GPs and specialists considered patients with a short life expectancy, cognitive impairment, or living in palliative/nursing homes less likely to benefit from CVMs[24, 27, 29, 32, 37, 38, 41]. They felt that, in these cases, prolonging life or avoiding a CV event should not be the main objective of care[27]. However, frail patients were less willing to stop their statin than robust ones[39].

Some patients and informal caregivers also considered CVMs to be beneficial when they saw an objective (e.g., cholesterol levels) or subjective (e.g., less dizziness) improvement under treatment[4, 25, 26, 31]. Some patients also considered that taking CVMs enabled them to make an active contribution to their health, and to have control over themselves and the future[44].

3.3.1.3 ADEs

Patients, informal caregivers and HCPs reported ADEs as one of the main reasons to consider stopping CVMs, especially if ADEs were associated with a reduction in quality of life[4, 24-26, 28, 31, 34-38, 42]. Patients usually compliant with medications considered ADEs as a reason to discuss deprescribing with their GP[28, 34]. Patients considering taking CVMs as a routine to stay healthy were still willing to discontinue their CVMs in case of ADEs[28, 34]. Contrastively, some patients continued taking their CVMs after balancing ADEs against reasons to take CVMs (i.e., CVM perceived benefit, minor ADEs[25]. When patients were asymptomatic and had no ADE, patients and GPs were unwilling to deprescribe CVMs[34, 35]. When ADEs occurred in patients with CVD, GPs were also unwilling to deprescribe[41].

3.2. Fear

Fear of consequences following CVM deprescribing was an important barrier to deprescribing. Many patients stated their fear of a return of the previous condition, health deterioration,

becoming a burden, or a shorter lifespan following deprescribing[4, 28, 30, 31, 34, 43]. Some linked this fear with the perceived severity of their disease[26, 31]. These concerns were shared by informal caregivers.

GPs and specialists feared harming patients by deprescribing (e.g., occurrence of CV event with functional limitation, death)[23, 24, 29, 30, 35-37], and giving patients the feeling that they were giving up on them, especially by deprescribing towards the end of life, a feeling not shared by patients[23, 29, 35, 38, 40]. Furthermore, patients fearing ADEs or becoming "dependent" on their CVMs were more willing to deprescribe[26, 39].

3.3. Dislike

CVM dislike was an important facilitator to deprescribing for patients and informal caregivers, but not for HCPs. Some patients stated a general dislike of medications or explained feeling burdened by the number of medications (CVMs and others), or medication-associated costs[4, 26, 28, 30, 31, 33, 34, 42]. Others were aiming at living a long life without using medications, or derived a personal pride of not taking medications[28, 43]. Some patients and informal caregivers considered CVMs as "not good for health"[26] or despised CVMs that created therapeutic competition (i.e., helping one condition while worsening another one) or which administration was complicated or disrupted daily routine (e.g., glycaemia before insulin injections)[4, 31].

3.4. Influences

Patient and HCP opinions towards deprescribing were largely shaped by their previous experiences in deprescribing CVMs, and social influences.

3.4.1 Previous experiences

Patients and HCPs with a positive previous experience with CVM deprescribing were more amenable to deprescribe again, as opposed to those with a negative previous experience [4, 23, 24,

[26, 29, 30, 35]. GPs considered patients feeling better or with improved quality of life after deprescribing as positive experiences[23, 35], and having to restart medications after deprescribing as a negative experience[35]. For statins, occurrence or absence of stroke after deprescribing influenced GPs' and specialists' further actions[24, 29].

3.4.2 Social influences

HCPs highly influenced patients' and informal caregivers' opinion on deprescribing [31, 39]. Patients were willing to stop one or more CVM if this was proposed by a trusting physician[26]. Patients especially trusted their GP because of their knowledge and the fact that they knew them well[28, 30, 34, 43]. Some patients also recognized their dependency towards their GP and highlighted their authority, feeling that it would be inappropriate to discuss their evaluation[34]. Many were waiting for their GP to start discussions about preferences, or were happy to follow their recommendations[28, 34].

GPs accounted for patient preferences [24, 27, 32, 35, 41]. They considered deprescribing in patients wanting to take less medications[27, 32]. They continued CVMs in patients expecting longevity or whose family was urging for medication continuation[27]. GPs were also unwilling to deprescribe CVMs prescribed by specialists, even if they questioned the indication[23, 24, 27, 30, 36]. Specialists were concerned by interfering with other HCPs' treatment plan[29, 37]. They were also unwilling to deprescribe when communication with other HCPs was suboptimal or when patients were reluctant or could not understand the concept of deprescribing[33, 37].

3.5. Process

HCPs and patients reported time constraint, such as lacking time to review medication lists or to discuss CVMs, as an important barrier to CVM deprescribing[26, 29, 35, 37, 38].

For patients, a dose-lowering scheme, a close monitoring after deprescribing and a temporary stopping trial with possibility of medication resumption facilitated the deprescribing process[4,

[26, 28, 30]. GPs also viewed gradual CVM discontinuation as a facilitator to deprescribing, especially when they were unsure about CVM risk/benefit ratio [24, 36]. However, they considered the lack of remuneration for the close follow-up needed during gradual discontinuation as a barrier[24].

3.6. Uncertainty

HCPs formulated the lack of evidence about CVM deprescribing as a barrier, especially in older patients or those with dementia[23, 29, 37]. GPs found complicated to know when to deprescribe preventive medications – especially in patients neither frail nor robust[23, 35] – and how to balance CVM harms and benefits when approaching deprescribing[27]. One clinical pharmacist explained having difficulties making professional recommendations about statin deprescribing in older patients[24]. Specialists regretted the limited training on deprescribing[37].

Patients expressed a lack of understanding of CVDs and risk reduction with CVMs, as well as uncertainty regarding potential risks and benefits of CVMs, thus feeling uncertain about the value of deprescribing[4, 26, 34]. They were also confused by conflicting treatment targets mentioned by HCPs[26].

Some HCPs and patients also felt uneasy about the uncertainty surrounding possible consequences of CVM deprescribing[24, 38]. This led to "therapeutic inertia", even in case of unclear benefits of pursuing CVMs[29]. On the contrary, GPs and clinical pharmacists feeling uneasy about possible long-term consequences of taking CVMs were more willing to deprescribe[24].

3.7. Ambivalence

Patients expressed ambivalence about CVM use, prompting them to wish CVM continuation and deprescribing concurrently. They were concerned about the effects of CVMs on their

health, but also about what could happen if they did not take them[4]. They also showed aversion towards CVMs coupled with a feeling of obligation to take them[4, 34].

4. Discussion

In this systematic review, we provided an overview of barriers and facilitators to deprescribing CVMs, from the point of view of patients, informal caregivers and HCPs. Barriers and facilitators could be classified in the following categories: appropriateness, fear, dislike, influences, process, uncertainty, ambivalence. Appropriateness was divided into three themes (necessity, benefit, ADEs), and influences into two themes (previous experiences, social influences). Important deprescribing barriers for HCPs and patients included uncertainty due to lack of evidence regarding CVM deprescribing, fear of negative consequences following deprescribing, and time constraints. An important facilitator to deprescribing for patients and HCPs was the occurrence of ADEs. Other facilitators for patients were dislike of CVMs or establishment of a deprescribing plan. Necessity and benefit of CVMs were seen as barriers or facilitators similarly by patients and HCPs. However, patients and HCPs disagreed on the necessity and benefit of taking CVMs in case of frailty or robustness. Social influences and patient ambivalence acted both as barriers and facilitators to deprescribing.

Barriers and facilitators to deprescribing CVMs did not differ significantly from those of deprescribing general medications[20, 45]. A systematic review on patients' barriers and facilitators to deprescribing displayed the same structure as ours, reporting agreement with appropriateness of cessation, fear, influences, dislike and process as barriers and/or facilitators to deprescribing[20]. However, this review that included mainly nervous system medications, did not report uncertainty and ambivalence towards deprescribing, suggesting that these two factors were more specific to CVM deprescribing. Another systematic review on prescribers' barriers and facilitators to deprescribing potentially inappropriate medications reported four

main categories: awareness, inertia, self-efficacy and feasibility[45]. Although studies included in our review did not really reflect on HCPs' level of awareness of the appropriateness of their CVM prescribing, we also found that some HCPs experienced deprescribing inertia, continuing CVMs even if they might be inappropriate, partly because of fear of bad/unknown consequences of deprescribing.

We found that patient and HCP points of view towards CVM deprescribing were largely similar. One main difference was the necessity/benefit of CVMs in robust versus frail patients. As shown in a study evaluating frail patient beliefs about prescribed medications, most patients saw their medications as highly necessary[46]. However, over one-third of patients included in this study stated that their medications were a mystery to them[46]. This stresses the fact that patients might see a medication as necessary without being able to understand its potential (lack of) benefit. HCPs, on the other hand, seemed to place importance on their patients deriving benefits from their CVMs. Thus, they endorsed deprescribing in frail patients due to a lack of time to benefit, but renounced deprescribing in robust patients. This view is concordant with other studies on treating frail and/or robust patients[9, 47].

Lack of evidence on the risk/benefit profile of CVMs and potential consequences of deprescribing in certain populations made patients and HCPs uncertain towards CVM deprescribing. Such uncertainty was also reported in studies focusing on deprescribing general medications in older, multimorbid adults, likely because of the complexity of interactions between diseases and the single-disease focused guidelines that might not apply to patients with multimorbidity[48-50]. However, one of these studies stated that balancing benefits and harms was particularly complicated for preventive medications[48]. As shown in our review and in previous studies, HCP and patient uncertainty might lead to fear of bad or unknown consequences and prevent deprescribing[51, 52]. HCPs were also afraid of patients feeling that

they were giving up on them, especially towards the end of life, a point of view that was nevertheless not shared by patients. These divergent views emphasize the need for discussion between HCPs and patients about representations and beliefs, and how these might influence decision-making in the context of uncertainty about deprescribing. This is especially important for HCPs to consider, given that patients might assume that they do not have to discuss their preferences and beliefs as these are already clear for their HCPs[53].

This systematic review highlights the uncertainty that can arise when approaching CVM deprescribing, and the inertia that can result from it. In this context, discussions between HCPs and patients and/or informal caregivers about representations, beliefs and preferences have the potential to mitigate such uncertainty, and enable shared decision-making. Finding ways to make deprescribing as safe as possible in the current context of uncertainty is also central. To achieve this, some studies included in this review provided keys to enable patients to feel safe about deprescribing: gradual deprescribing and close monitoring of medical parameters, as well as deprescribing trials and possibility of medication resumption.

5. Strengths and limitations

This study has several strengths. First, data extraction, analysis and synthesis, as well as quality assessment were conducted by two independent reviewers on all available data based on a systematic review. Second, we included both quantitative and qualitative studies, providing complementary information on barriers and facilitators to deprescribing.

However, this study also has limitations. First, in some studies, CVMs were part of the evaluated medications but not the focus. However, this enabled inclusion of more studies and thus exploration of more barriers and facilitators to deprescribing CVMs. Second, as this review focused on CVMs in general, no conclusion can be made on individual CVMs. However, barriers and facilitators did not appear to differ significantly between studies

assessing/exploring different CVMs, which leads to thinking that most barriers and facilitators might be common across CVMs.

6. Conclusion

In this systematic review, we provided an overview of barriers and facilitators to deprescribing CVMs, from the point of view of patients, informal caregivers and HCPs. We could see that patient, informal caregiver and HCP expressed barriers and facilitators to deprescribing did not differ significantly. However, we could highlight certain differences in opinions between patients and HCPs that stress the need for ground discussions about beliefs and preferences about deprescribing of each stakeholder implicated in the deprescribing decision. As uncertainty prevails when it comes to deprescribing CVMs, strategies to enable the safest deprescribing, such as gradual deprescribing or close monitoring following deprescribing, can be established in everyday practice.

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7.1. Financial and personal conflicts of interest:

The authors declare no conflict of interest.

7.2. Author contributions:

CEA, LB and NR designed the study protocol. CEA and LB extracted and analyzed the data. CEA, LB and NR drafted the article. All authors gave final approval to submit the article.

7.3. Sponsors' role:

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7.4. Data sharing statement:

The coding of the articles is available by the authors on reasonable request.

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7.6. Competing interests statement:

Nothing to disclose.

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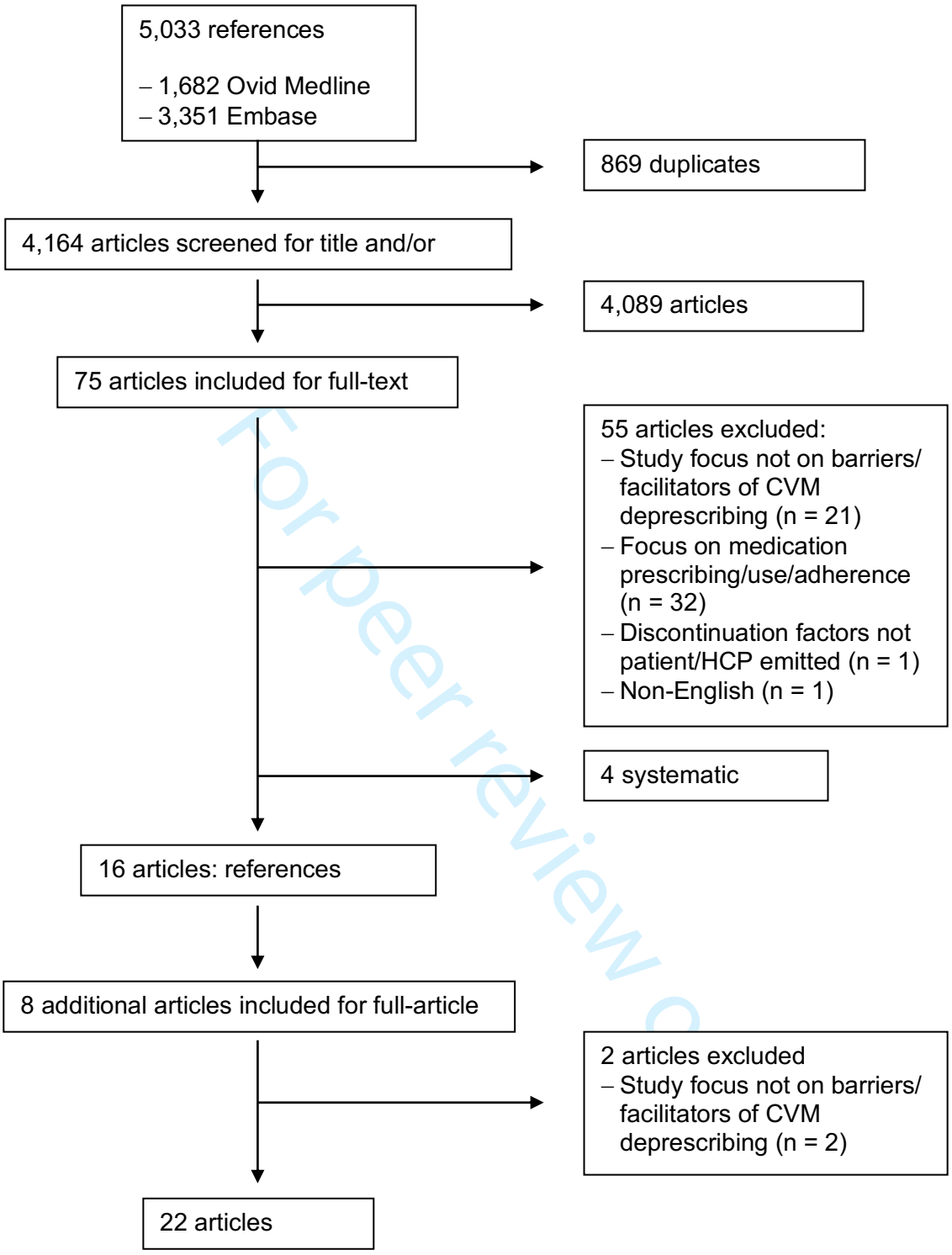
FIGURE LEGEND:

Figure 1: Study selection results

Abbreviations: CVM: cardiovascular medication; HCP: healthcare providers

9. Supplemental material

The detailed search strategy, the detailed study characteristics, and the study quality appraisal are presented in the supplemental material section.



Supplemental text S1: Search strategy of barriers and facilitators of deprescribing CVMs

OVID/MEDLINE 2021.11.15: 1,682 results

Concept 1: cardiovascular medications
1. exp cardiovascular agents/
2. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors, hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors, hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or "Cardiovascular medic*" or "cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or "cardiometabolic prescrib*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering treat*" or " lipid-lowering medic*" or " lipid-lowering drug*" or " lipid-lowering agent*" or " lipid-lowering preparation*" or " lipid-lowering prescrib*" or "lipid-lowering therapeutic*").ab,ti.
4. "cardiovascular disease".ab,ti.
5. *cardiovascular diseases/
6. prevention.ab,ti.
7. *primary prevention/
8. *secondary prevention/
9. 4 or 5
10. 6 or 7 or 8
11. 9 and 10

Concept 2: prescribing / deprescribing
12. exp Deprescriptions/
13. exp Withholding Treatment/
14. exp Potentially Inappropriate Medication List/
15. exp Inappropriate Prescribing/
16. (reduce or reducing or reduction or reduced or withdraw* or withhold* or stop or stopped or stopping or elimin* or tapering or taper or cease or ceasing or ceased or cessation* or de-intensif* or deintensif* or deprescribing or deprescrib* or "de-prescribing" or "de-prescrib*" or "de-implementation*" or "de-implement*" or deimplement* or discontinue* or discontinuation* or curb or curbing or curbed).ab,ti.

Concept 3: barriers and facilitators
17. *patient acceptance of health care/
18. *patient preference/
19. *attitude to health/
20. *physician-patient relations/
21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or deciding or motivation or conversation or acceptance or acceptability).ti.

22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or discuss* or discussion*).ti.
23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or relative* or caregiver*).ti.
24. 22 and 23
25. 1 or 2 or 3 or 11
26. 12 or 13 or 14 or 15 or 16
27. 17 or 18 or 19 or 20 or 21 or 24
28. 25 and 26 and 27
29. limit 28 to (English language and yr="2003-Current")
30. (child or kid or kids or childhood or children or pediatric or paediatric or pediatrics or paediatrics or mouse or mice or animals or animal).ab,ti.
31. 29 not 30

EMBASE 2021.11.15: 3,351 results

Concept 1: cardiovascular medications
1. 'cardiovascular agent'/exp
2. 'hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp
3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors, hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors, hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or "Cardiovascular medic*” or “cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or "cardiometabolic prescrib*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering treat*" or " lipid-lowering medic*" or " lipid-lowering drug*" or " lipid-lowering agent*" or " lipid-lowering preparation*" or " lipid-lowering prescrib*" or "lipid-lowering therapeutic*"):ab,ti
4. "cardiovascular disease":ab,ti
5. 'cardiovascular diseases'/mj
6. prevention:ab,ti
7. 'primary prevention'/mj
8. 'secondary prevention'/mj
9. 4 or 5
10. 6 or 7 or 8
11. 9 and 10

Concept 2: prescribing / deprescribing
12. 'deprescription'/mj
13. 'treatment withdrawal'/mj
14. 'potentially inappropriate medication'/mj
15. 'inappropriate prescribing'/mj

16. (reduce or reducing or reduction or reduced or withdraw* or withhold* or stop or stopped or stopping or elimin* or tapering or taper or cease or ceasing or ceased or cessation* or de-intensif* or deintensif* or deprescribing or deprescrib* or "de-prescribing" or "de-prescrib*" or "de-implementation*" or "de-implement*" or deimplement* or discontinue* or discontinuation* or curb or curbing or curbed):ab,ti

Concept 3: barriers and facilitators
17. 'patient attitude'/mj
18. 'patient preference'/mj
19. 'attitude to health'/mj
20. 'doctor patient relationship'/mj
21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or deciding or motivation or conversation or acceptance or acceptability):ti
22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or discuss* or discussion*):ti
23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or relative* or caregiver*):ti
24. #22 AND #23
25. #1 OR #2 OR #3 OR #11
26. #12 OR #13 OR #14 OR #15 OR #16
27. #17 OR #18 OR #19 OR #20 OR #21 OR #24
28. #25 AND #26 AND #27
29. (child or kid or kids or childhood or children or pediatric or paediatric or pediatrics or paediatrics or mouse or mice or animals or animal):ti,ab
30. #25 AND #26 AND #27 NOT #29 AND ([article]/lim OR [review]/lim) AND [english]/lim AND ([embase]/lim OR [embase classic]/lim OR [pubmed-not-medline]/lim) AND [2003-2020]/py

Supplemental table S1: Study characteristics

	First author, publication year	Setting	Design	Data collection mean	N population	Age	No of medication taken	Studied CVM(s)	Prevention type	Life-limiting disease
PATIENTS AND INFORMAL CAREGIVERS	Benson, 2005 (UK[25])	Primary care	Qualitative	Interviews	38 patients	18% <50 years 16% 50-59 years 29% 60-69 years 24% 70-79 years 13% ≥80 years	Antihypertensives: 50%: 1; 39%: 2; 11%: ≥3 Non-antihypertensives: 34%: 0; 18%: 2, 13%: 3; 11%: 4; 8%: ≥5	Antihypertensives	Unknown	No
	Brinton, 2018 (USA)[42]	Online panels	Quantitative descriptive	Survey	5014 patients	Mean age: 64	99% of current statin users taking a mean of 7.7 meds	Statin	Primary & secondary	No
	Crutzen, 2020 (Netherlands)[26]	Primary care	Qualitative	FGs	17 patients 1 informal caregiver	Median age: FG1: 78 FG2: 77.5	FG1: 6: 5-10; 2: >10 FG2: 4: 5-10; 5: >10	Cardiometabolic medication	Primary & secondary	No
	Goyal, 2020 (USA)[4]	Quaternary care	Qualitative	Interviews	10 patients	Median age: 80	Median of 12	β-blockers	Primary & secondary	No
	Jansen, 2019 (Australia)[28]	Primary care	Qualitative	Interviews	30 patients	20: 75-79 years 4: 80-84 years 5: 85-89 years 1: ≥90 years	Unknown	Preventive cardiovascular medication	Primary & secondary	No
	Luymes, 2017 (Netherlands)[43]	Primary care	Mixed methods	Q-sorts Group discussions	33 patients	Mean age: - Q-Sort: 57.1 - Discussion: 57.7	Unknown	Lipid-lowering drugs Antihypertensives	Primary	No

	Pickering, 2020 (USA)[31]	Claude D. Pepper Older Americans Independence Center Research Registry; Pitt+Me registry	Qualitative	FGs	16 patients 17 informal caregivers	Patients ≥ 65 Caregivers 22-69	≥ 5 prescribed	Unspecified (identified: antihypertensives, statins, antiplatelets, antidiabetics)	Primary & secondary	No
	Qi, 2015 (Australia)[39]	Tertiary care	Quantitative descriptive	Survey	180 patients	Median age: 78	Median of 8	Regular medications Statins	Primary & secondary	No
	Tija, 2017 (USA)[40]	PCRC member sites	Quantitative descriptive	Survey	297 patients	Mean age: 71.8	Mean of 11.5	Statin	Primary & secondary	Yes
	Van Bussel, 2019 (Netherlands)[34]	Primary care	Qualitative	Interviews	15 patients	Mean age: 81	Median of 4 with median of 2 antihypertensives	Antihypertensives	Primary	No

	First author	**Setting**	**Design**	**Data collection mean**	**N population**	**Years of experiences**	**Characteristics of patients cared by study HCPs**				
							Age	**No of medication taken**	**Studied CVM(s)**	**Prevention type**	**Life-limiting disease**
HCPs	Ailabouni, 2016 (New Zealand)[36]	Primary care	Qualitative	Interviews	10 GPs	Unknown	83	17	Antiplatelets, statin, antidiabetics, diuretics, β-blocker, ACE inhibitor	Secondary	No
	Ailabouni, 2016 (New Zealand)[23]	Primary care	Qualitative	Interviews	10 GPs	2-32	Unspecified (older patients)	Unknown	Unspecified (statin and aspirin mentioned)	Unknown	No
	Anderson, 2017 (Australia)[24]	Primary care	Qualitative	FGs	32 GPs 15 CPs	GPs: median of 18 CP: median of 9	Unknown	Unknown	Unspecified (statin mentioned)	Unknown	No

Geijteman, 2018 (Netherlands)[38]	Primary & secondary care	Quantitative descriptive	Survey	174 GPs 147 clinical specialists (medical oncologists, geriatricians, cardiologists, pulmonologists, neurologists	203: 0-9 years 56: 10-19 years 40: 20-29 years 18: ≥ 30 years	88	10	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary	Yes
Goyal, 2020 (USA)[37]	Secondary and tertiary care	Quantitative descriptive	Survey	184 geriatricians 182 general internists 87 cardiologists	86: 1-10 years 99: 11-20 years 138: 21-30 years 130: > 30 years	79	Unspecified (several)	4 cardiovascular medications	Unknown	Yes and no
Green, 2019 (USA)[29]	Primary & secondary care	Qualitative	Interviews	19 physicians 2 nurse practitioners (family, internal & geriatric medicine, urogynecology, endocrinology, cardiology)	Mean of 14	Unspecified (older patients)	Unknown	Unspecified (oral anticoagulants, antidiabetics, statins mentioned)	Unknown	Yes
Jansen, 2017 (Australia)[27]	Primary care	Qualitative	Interviews	25 GPs	2: < 10 years 4: 10-19 years 7: 20-29 years 12: ≥ 30 years	≥75	Unknown	Preventive cardiovascular medication	Primary	No
Thompson, 2020 (Denmark)[32]	Primary care	Qualitative	Interviews	11 GPs	Mean of 9	≥ 80	Unknown	Statin	Unknown	Yes and no
Van Middelaar, 2020 (Netherlands)[35]	Primary care	Qualitative	Interviews	15 GPs	4: 0-5 years 3: 5-10 years 3: 10-15 years 5: > 15 years	Unspecified (older patients)	Unknown	Antihypertensives	Unknown	Yes and no
Van der Ploeg, 2018 (30 countries)[41]	Primary care	Quantitative descriptive	Survey	2250 GPs	358: < 5 years 1024: 5-20 years 865: > 20 years	≥ 80	Unknown	Statin	Primary and secondary	Yes and no

PATIENTS, INFORMAL CAREGIVERS AND HCPs	First author	Setting	Design	Data collection mean	N population	Years of experiences	Patients' characteristics				
							Age	No of medication taken	Studied CVM(s)	Prevention type	Life-limiting disease
	Luymes, 2016 (Netherlands)[30]	Primary care	Qualitative	Audiotaped deprescribing consultations	10 GPs 49 patients	Unknown	Median of 55.4	27: < 2 kinds 22: ≥ 2 kinds	Antihypertensives, lipid-lowering drugs	Primary	No
	Todd, 2016 (UK)[33]	Specialist palliative care unit at a daycare centre	Qualitative	Interviews	12 patients 12 informal caregivers 3 palliative consultants 3 nurse practitioners 6 GPs	Unknown	1: < 50 3: 51-60 3: 61-70 3: 71-79 2: ≥ 80	Unknown	Unspecified (preventive medications, including statins, antihypertensives)	Unknown	Yes

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; CP, clinical pharmacist; CVM, cardiovascular medication; FG, focus group; GP, general practitioner; PCRC: Palliative Care Research Cooperation Group.

Supplemental table S2: Study quality appraisal

	First author, publication year	Is the qualitative approach appropriate to answer the research question?	Are the qualitative data collection methods adequate to address the research question?	Are the findings adequately derived from the data?	Is the interpretation of results sufficiently substantiated by data?	Is there coherence between qualitative data sources, collection, analysis and interpretation?
QUALITATIVE	Ailabouni, 2016	Can't tell	Yes	Yes	Can't tell	Yes
	Ailabouni, 2016	Yes	Yes	Yes	Yes	Yes
	Anderson, 2017	Yes	Yes	Yes	Yes	Yes
	Benson, 2005	Yes	Yes	Yes	Yes	Yes
	Crutzen, 2020	Yes	Yes	Yes	Yes	Yes
	Goyal, 2020	Yes	Yes	Yes	Yes	Yes
	Green, 2019	Yes	Yes	Yes	Yes	Yes
	Jansen, 2017	Yes	Yes	Yes	Yes	Yes
	Jansen, 2019	Yes	Yes	Yes	Yes	Yes
	Luymes, 2016	Yes	Yes	Yes	Yes	Yes
	Pickering, 2020	Yes	Yes	Yes	Yes	Yes
	Thompson 2019	Yes	Yes	Yes	Yes	Yes
	Todd, 2016	Yes	Yes	Yes	Yes	Yes
	Van Bussel, 2019	Yes	Yes	Yes	Yes	Yes
	Van Middelaar, 2018	Yes	Yes	Yes	Yes	Yes
QUANTITATIVE DESCRIPTIVE		Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low?	Is the statistical analysis appropriate to answer the research question?
	Brinton, 2018	Yes	Yes	Can't tell	No	Can't tell
	Geijteman, 2018	Yes	No	Yes	No	Yes
	Goyal, 2020	Yes	No	Yes	No	Yes
	Qi, 2015	Yes	No	Yes	Yes	Yes
	Tija, 2017	Yes	No	Yes	Yes	Yes

	Van der Ploeg, 2019	Yes	No	Yes	No	Yes
MIXED METHODS		**Is there an adequate rationale for using a mixed methods design to address the research question?**	**Are the different components of the study effectively integrated to answer the research question?**	**Are the outputs of the integration of qualitative and quantitative components adequately interpreted?**	**Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?**	**Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?**
	Luymes, 2017	Yes	Yes	Yes	No	Yes

Supplemental Table S3: Summary of categories, themes and codes of barriers and facilitators to deprescribing CVMs

Categories	Themes	Barriers or facilitators	Patients and/or informal caregivers	HCPs	Patients and/or informal caregivers and HCPs
APPROPRIATENESS	Necessity	Facilitators	Low CV risk Disease under control Trigger disappearance	Primary prevention Age as single CVRF	
		Barriers	CVM linked to survival	Unhealthy lifestyle Many CVRFs	Past CV event Family history of CVD CVM should be taken until end of life
	Benefit	Facilitators	Robustness	Short life expectancy Cognitive impairment Nursing home patients Palliative patients	No objective improvement under CVM No subjective improvement under CVM
		Barriers	Frailty CVM use = active contribution to health CVM use = having control over one's self	Good physical & cognitive function Few comorbidities	Objective improvement under CVM Subjective improvement under CVM
	ADEs	Facilitators	ADEs foster deprescribing discussion with HCP		Reduction in QOL through ADEs
		Barriers	ADEs balanced against reasons to take CVMs	ADEs in patients with CVD	No ADE, no symptom from disease
FEAR		Facilitators	Fear of ADEs Fear of becoming dependent on CVMs		
		Barriers	Fear of deprescribing due to severity of underlying disease Fear of experiencing a CV event after deprescribing & becoming a burden	Feeling of giving up on patients	Fear of CV event, return of previous condition, health deterioration following deprescribing Fear of shorter lifespan without CVM

DISLIKE		Facilitators	General dislike of medications Medication-associated costs Living a long life without using CVMs Pride in not taking medications CVMs = poison CVMs = bad for health Therapeutic competition		
INFLUENCES	**Previous experiences**	Facilitators			Positive previous experience with deprescribing (QOL improvement, no stroke)
		Barriers			Negative previous experience with deprescribing (restart medication, stroke)
	Social influences	Facilitators	HCPs (especially GP) advising deprescribing	Patient's preferences	
		Barriers	HCPs (especially GP) advising against deprescribing	Patient's preferences (reluctance) Patient's lack of understanding Patient's family wants CVMs Specialist prescription Interference with other HCPs' treatment plan	
PROCESS		Facilitators	Temporary deprescribing trial Possibility of CVM resumption		Dose-lowering scheme Close monitoring
		Barriers		Lack of remuneration for close monitoring	Time constraints
UNCERTAINTY		Facilitators			Uncertainty about possible consequences of taking CVMs
		Barriers	Lack of understanding of CVDs and risk reduction with CVMs Uncertainty about risks and benefits Conflicting treatment targets	Lack of evidence on deprescribing Uncertainty about when to deprescribe Uncertainty about risk-benefit balance Limited training on deprescribing	Unknown consequences of deprescribing

AMBIVALENCE		Facilitators and/or barriers	Concern about CVM effect on health vs consequences of not taking CVMs Aversion towards CVMs vs obligation to take CVMs		

Abbreviations: ADE, adverse drug event; CV, cardiovascular; CVD, cardiovascular disease; CVM, cardiovascular medication; CVRF, cardiovascular risk factor; GP, general practitioner; HCP, healthcare provider; QOL, quality of life.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl. material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.8 (and Figure 1)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 (and suppl. Table S1)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p.8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.17
	23b	Discuss any limitations of the evidence included in the review.	p.17-18
	23c	Discuss any limitations of the review processes used.	p.17-18
	23d	Discuss implications of the results for practice, policy, and future research.	p.17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Registration on PROSPERO (CRD42020221973)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Adaptation of the framework used to analyze the data to better suit cardiovascular medications deprescribing
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Swiss National

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			Science Foundation Grant IICT 33IC30-193052; grant from the College of General Internal Medicine (Fribourg, Switzerland)
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Available on demand

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Barriers and facilitators to deprescribing of cardiovascular medications: a systematic review

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Running title: Deprescribing cardiovascular medications

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ABSTRACT

Objective: To synthesize the current knowledge on barriers and facilitators to deprescribing cardiovascular medications (CVMs) at the levels of patients, informal caregivers, and healthcare providers (HCPs).

Design/Setting: We conducted a systematic review of studies exploring/assessing patient, informal caregiver and/or HCP barriers and/or facilitators to deprescribing CVMs.

Data sources: Ovid/MEDLINE and Embase from January 2003 to November 2021.

Data extraction and synthesis: We performed a deductive thematic analysis based on the framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al. We added a quantification of the occurrence of categories and themes in the selected articles to identify the resounding themes that indicate the greater impetus to address in future research.

Results: Most frequent deprescribing barriers for patients, informal caregivers and HCPs included uncertainty due to lack of evidence regarding CVM deprescribing, fear of negative consequences following deprescribing, and social influences. A frequently reported facilitator to deprescribing, especially for patients and informal caregivers, was the occurrence of ADEs. Another frequently reported facilitator for patients were dislike of CVMs. Necessity and benefit of CVMs were seen as barriers or facilitators similarly by patients and HCPs.

Conclusion: The differences in patient, informal caregiver and HCP regarding barriers and facilitators to deprescribing CVMs stress the need for ground discussions about beliefs and preferences of each stakeholder implicated in deprescribing decisions. Furthermore, HCP uncertainty regarding CVM deprescribing highlights the need to provide HCPs with tools that enable sharing the risks and benefits of deprescribing with patients and ensure a safe deprescribing process.

Review registration on Prospero: CRD42020221973

Strengths and limitations of this study:

- Systematic review process with publication review; data extraction, analysis and synthesis; and quality assessment independently conducted by two independent reviewers.
- Assessment of both quantitative and qualitative studies, providing complementary information on barriers and facilitators to deprescribing.
- In some studies, cardiovascular medications were part of, but not the focus of the medications evaluated.
- We did not assess specific classes of cardiovascular medications.

Key words: cardiovascular medication, deprescribing, barriers, facilitators, older people

1. Introduction

In recent years, a less-is-more attitude regarding medication use has pushed to reevaluate the balance between medication risks and benefits.[1] In this context, the notion of *deprescribing* emerged, which is defined as the "systematic process of identifying and discontinuing [medications] in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values and preferences".[2]

Cardiovascular medications (CVMs) belong to the most prescribed medications worldwide.[3] Although their use is beneficial in many cases, CVMs can also cause significant adverse drug events (ADEs), drug-drug, and drug-disease interactions.[4-6] However, the lack of evidence regarding benefits and risks of some CVMs in primary prevention in older people or in those with limited life expectancy, may lead to insecurity of patients and prescribers regarding CVM use and deprescribing.[1, 7-11]

In this context, the decision to deprescribe a CVM often becomes a preference-sensitive decision.[12, 13] A better understanding of barriers and facilitators experienced by all stakeholders involved in decision-making regarding CVM deprescribing may help to take informed decisions in line with individual values and preferences, and increase confidence in the decision made.[14, 15] While literature exists on deprescribing general medications, we do not know if barriers and facilitators differ for deprescribing CVMs.

With this systematic review, we aimed at synthetizing the current knowledge on barriers and facilitators to deprescribing CVMs at the levels of patients, informal caregivers, and healthcare providers (HCPs).

2. Methods

We conducted a systematic review of studies assessing barriers and/or facilitators to deprescribing CVMs in adults. The review was registered on Prospero (CRD42020221973).

2.1. Ethics approval

An ethics approval was not needed for this study, since it was a review of the literature.

2.2. Types of studies and inclusion criteria

We included any type of publication – except editorials, conference abstracts and study protocols – discussing stakeholder barriers and/or facilitators regarding the process of deprescribing CVMs. Studies on prescribing, use, or adherence were not included. Studies reporting patients stopping CVMs without previous discussion with HCPs were considered as non-adherence studies and excluded.

2.3. Search strategy

We searched Ovid/MEDLINE and Embase from January 2003 to November 2021. We started the search in 2003 because it corresponds to the first mention of the term *deprescribing* in the literature.[16] We included studies published in English language and focusing on patients taking or having taken CVMs previously, and/or informal caregivers, and/or HCPs of such patients. We developed the 3 following concepts for our search strategy: 1) CVMs; 2) deprescribing; 3) barriers and facilitators. All three concepts were combined with the operator "and". The detailed search strategy is provided in **Supplemental Material S1**.

LB and CEA independently reviewed all publications identified through the search strategy after removing duplicates. First, ineligible articles were excluded based on title/abstract. Second, full text of the remaining articles was reviewed to identify eligible studies. Reference lists of included publications were also searched for additional relevant articles (hand

searching). Reviews and meta-analyses were kept in the first selection, but only original studies identified in the reference lists were included. For each step, LB and CEA resolved discrepancies by discussion.

2.4. Data extraction and analysis

Eligible articles were imported in MAXQDA 2020 data analysis software (VERBI Software, Berlin, Germany). Extracted data included author(s), year of publication, country, study design, setting, and population, and details on barriers and/or facilitators. Given the topic of this systematic review, we conducted a qualitative rather than a quantitative synthesis of the results. We performed a deductive thematic analysis to identify common and discrepant themes within and between stakeholder categories.[17, 18] The thematic analysis was based on the framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.[4] This framework, based on Reeve's framework of patient barriers and facilitators to deprescribing medications,[19] includes the following categories: appropriateness of cessation, process of cessation, dislike of medications, fear, uncertainty, and conflicting attitudes. We analyzed patient and informal caregiver outputs together and HCP outputs separately, since we expected to identify different barriers and facilitators. In an iterative process, we created themes within the predefined categories. To identify the resounding themes that indicate the greater impetus to address in future research, we added a quantitative aspect to our thematic analysis, in which we identified the number of times each category and theme appeared in the selected studies.

2.5. Risk of bias and quality assessment

LB and CA conducted the quality and risk of bias assessment separately using the Mixed Methods Appraisal Tool (MMAT) 2018.[20, 21] The MMAT allows assessing the methodological quality of studies included in a systematic review encompassing both qualitative and quantitative data. Discussions were held until a consensus on quality of each study was reached.

2.6. Patient and Public Involvement:

Patients and Public were not involved in the design, conduct or reporting of this review, but in a follow-up project based on this review.

3. Results

3.1. Study selection and characteristics

Among the 4,164 unique studies identified, 71 were included for full-text assessment (**Figure 1**). Among those, 16 fulfilled inclusion criteria. Through hand-searching, six additional studies were included, leading to a total of 22 publications. Study characteristics are presented in **Tables 1** and detailed in **Supplemental Material S2**.

158 **Table 1: main characteristics of studies reporting patient, informal caregiver and HCP barriers and facilitators to deprescribing CVMs**

	First author, publication year	N population	Age	Studied CVM(s)	Prevention type
Patients and informal caregivers	Benson, 2005 (UK)[22]	38 patients	Any	Antihypertensives	Unknown
	Brinton, 2018 (USA)[23]	5,014 patients	Mean age: 64 years	Statins	Primary & secondary
	Crutzen, 2020 (Netherlands)[24]	17 patients, 1 informal caregiver	Median age: 78 years	Cardiometabolic medication	Primary & secondary
	Goyal, 2020 (USA)[4]	10 patients	Median age: 80 years	β-blockers	Primary & secondary
	Jansen, 2019 (Australia)[25]	30 patients	≥75 years	Preventive CV medication	Primary & secondary
	Luymes, 2017 (Netherlands)[26]	33 patients	Mean age: 57 years	Lipid-lowering drugs Antihypertensives	Primary
	Pickering, 2020 (USA)[27]	16 patients, 17 informal caregivers	Patients ≥ 65 years Caregivers 22-69 years	Unspecified (identified: statins, antihypertensives, antiplatelets, antidiabetics)	Primary & secondary
	Qi, 2015 (Australia)[28]	180 patients	Median age: 78 years	Regular medications, statins	Primary & secondary
	Tija, 2017 (USA)[29]	297 patients	Mean age: 72 years	Statins	Primary & secondary
	Van Bussel, 2019 (Netherlands)[30]	15 patients	Mean age: 81 years	Antihypertensives	Primary
	First author, publication year	**N population**	**Characteristics of patients cared for by study HCPs**		
			Age	**Studies CVM(s)**	**Prevention type**
HCPs	Ailabouni, 2016 (New Zealand)[31]	10 GPs	83 years	Antiplatelets, statin, antidiabetics, diuretics, β-blocker, ACE inhibitor	Secondary
	Ailabouni, 2016 (New Zealand)[32]	10 GPs	Unspecified (older pts)	Unspecified (identified: statin and aspirin)	Unknown
	Anderson, 2017 (Australia)[33]	32 GPs, 15 CPs	Unknown	Unspecified (identified: statin)	Unknown

	Geijteman, 2018 (Netherlands)[34]	174 GPs, 147 clinical specialists	88 years	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary
	Goyal, 2020 (USA)[35]	184 geriatricians, 182 general internists, 87 cardiologists	79 years	4 CV medications	Unknown
	Green, 2019 (USA)[36]	19 physicians, 2 nurse practitioners	Unspecified (older pts)	Unspecified (identified: statins, oral anticoagulants, antidiabetics)	Unknown
	Jansen, 2017 (Australia)[37]	25 GPs	≥75 years	Preventive CV medication	Primary
	Thompson, 2020 (Denmark)[38]	11 GPs	≥ 80 years	Statins	Unknown
	Van Middelaar, 2020 (Netherlands)[39]	15 GPs	Unspecified (older pts)	Antihypertensives	Unknown
	Van der Ploeg, 2018 (30 countries)[40]	2250 GPs	≥ 80 years	Statins	Primary & secondary
Patients & informal caregivers & HCPs	**First author, publication year**	**N population**	**Characteristics of patients**		
			Age	**Studied CVM(s)**	**Prevention type**
	Luymes, 2016 (Netherlands)[41]	10 GPs, 49 patients	Median age: 55 years	Antihypertensives, lipid-lowering drugs	Primary
	Todd, 2016 (UK)[42]	12 patients, 12 informal caregivers, 3 palliative consultants, 3 nurse practitioners, 6 GPs	Any	Unspecified (preventive medications, including statins, antihypertensives)	Unknown

Abbreviations: ACE inhibitors: angiotensin-converting enzyme inhibitors; CPs: community pharmacists; CV: cardiovascular; CVM(s): cardiovascular medication(s); GPs: general practitioners; pts: patients

3.2. Quality assessment

Details of each study quality assessment can be found in **Supplemental Material S3**. Of the 15 qualitative studies included in this systematic review, 14 were deemed of good quality,[4, 22, 24, 25, 27, 30, 31, 33, 36-39, 41, 42] while one lacked data to support interpretation of the results.[32] Five of the six included quantitative studies did not provide sample representative of the target population, as nonresponse was high, increasing the risk of nonresponse bias.[28, 29, 34, 35, 40] The sixth quantitative study provided few details on the method used for data analysis.[23] The only mixed methods study included failed to address divergences between quantitative and qualitative results.[26] We did not exclude any study based on the quality assessment, as our aim was to describe all available data regarding barriers and facilitators to deprescribing CVMs.

3.3. Thematic analysis

Following the framework of Goyal et al.,[4] seven categories were created to describe patient and HCP main barriers and facilitators to deprescribing CVMs. Categories one and four were divided into three and two themes respectively. Differences between patients, informal caregivers and HCPs, as well as across HCP categories, are highlighted when relevant. HCPs other than general practitioners (GPs, including general internists and family medicine clinicians) are regrouped under the term "specialists". Differences across specialties are highlighted when relevant. Of the 22 articles, all encompassed barriers and facilitators to deprescribing CVMs, except for one (Brinton et al. reported only facilitators).[23] Barriers and facilitators did not appear to differ significantly between studies assessing different CVMs. All barriers and facilitators according to categories, themes and stakeholders, are displayed in **Table 2**. The facilitators most frequently mentioned by patients were ADE occurrence and dislike, respectively reported in seven and nine of the 12 articles studying patient and informal caregiver barriers and facilitators, as shown in **Table 3**. The facilitator most commonly reported by HCPs was the lack of benefit (reported in seven of the 12 articles studying HCP barriers and

facilitators). One of the barriers most frequently cited by patients/informal caregivers and HCPs was fear, reported in seven of the 12 articles on patients, informal caregivers and HCPs. Social influences were another barrier frequently mentioned by HCPs (reported in 10 of the 12 articles). Additional frequent barriers were uncertainty for HCPs (in seven of the 12 articles), and perceived benefit and social influences for patients and informal caregivers (in six of the 12 articles).

197 **Table 2: Summary of categories, themes and codes of barriers and facilitators to deprescribing CVMs**

Categories	Themes	Barriers or facilitators	Patients and/or informal caregivers	HCPs	HCPs and patients and/or informal caregivers
Appropriateness	**Necessity**	Facilitators	Low CV risk Disease under control Trigger disappearance	Primary prevention Age as single CVRF	
		Barriers	CVM linked to survival	Unhealthy lifestyle Many CVRFs	Past CV event Family history of CVD CVM should be taken until end of life
	Benefit	Facilitators	Robustness	Short life expectancy Cognitive impairment Nursing home patients Palliative patients	No objective improvement under CVM No subjective improvement under CVM
		Barriers	Frailty CVM use = active contribution to health CVM use = having control over one's self	Good physical & cognitive function Few comorbidities	Objective improvement under CVM Subjective improvement under CVM
	ADEs	Facilitators	ADEs foster deprescribing discussion with HCP		Reduction in QOL through ADEs
		Barriers	ADEs balanced against reasons to take CVMs	ADEs in patients with CVD	No ADE, no symptom from disease
Fear		Facilitators	Fear of ADEs Fear of becoming dependent on CVMs		
		Barriers	Fear of deprescribing due to severity of underlying disease Fear of experiencing a CV event after deprescribing & becoming a burden	Feeling of giving up on patients	Fear of CV event, return of previous condition, health deterioration following deprescribing Fear of shorter lifespan without CVM
Dislike		Facilitators	General dislike of medications Medication-associated costs Living a long life without using CVMs Pride in not taking medications CVMs = poison CVMs = bad for health Therapeutic competition		

Influences	**Previous experiences**	Facilitators			Positive previous experience with deprescribing (QOL improvement, no stroke)
		Barriers			Negative previous experience with deprescribing (restart medication, stroke)
	Social influences	Facilitators	HCPs (especially GP) advising deprescribing	Patient's preferences	
		Barriers	HCPs (especially GP) advising against deprescribing	Patient's preferences (reluctance) Patient's lack of understanding Patient's family wants CVMs Specialist prescription Interference with other HCPs' treatment plan	
Process		Facilitators	Temporary deprescribing trial Possibility of CVM resumption		Dose-lowering scheme Close monitoring
		Barriers		Lack of remuneration for close monitoring	Time constraints
Uncertainty		Facilitators			Uncertainty about possible consequences of taking CVMs
		Barriers	Lack of understanding of CVDs and risk reduction with CVMs Uncertainty about risks and benefits Conflicting treatment targets	Lack of evidence on deprescribing Uncertainty about when to deprescribe Uncertainty about risk-benefit balance Limited training on deprescribing	Unknown consequences of deprescribing
Ambivalence		Facilitators and/or barriers	Concern about CVM effect on health vs consequences of not taking CVMs Aversion towards CVMs vs obligation to take CVMs		

Abbreviations: ADEs: adverse drug events; CV: cardiovascular; CVD: cardiovascular disease; CVM: cardiovascular medication; CVRF: cardiovascular risk factor; GP: general practitioner; HCPs: healthcare providers; QOL: quality of life

Table 3: Occurrence of categories and themes in the included studies

Author	Facilitators									Barriers								Facilitators & barriers
	Appropriateness			Fear	Dislike	Influences		Process	Uncertainty	Appropriateness			Fear	Influences		Process	Uncertainty	Ambivalence
	Necessity	Benefit	ADEs			Social	Exp			Necessity	Benefit	ADEs		Social	Exp			
Patients and informal caregivers																		
Benson[22]			x				x				x	x						
Brinton[23]		x	x		x													
Crutzen[24]			x	x	x	x	x	x			x		x		x	x	x	
Goyal[4]		x	x		x			x		x	x		x				x	x
Jansen[25]			x		x	x		x		x	x		x	x				
Luymes[26]	x				x	x				x			x	x				
Pickering[27]			x		x	x					x		x	x				
Qi[28]		x		x		x					x							
Tija[29]				x						x								
Van Bussel[30]			x		x							x	x	x			x	x
Healthcare providers																		
Ailabouni[31]							x						x	x			x	
Ailabouni[32]			x					x			x		x	x				
Anderson[33]		x	x			x	x	x	x		x		x	x	x	x	x	
Geijteman[34]		x	x													x	x	
Goyal[35]		x	x										x	x		x	x	
Green[36]		x											x	x	x	x	x	
Jansen[37]	x	x				x					x			x			x	
Thompson[38]		x				x				x	x							
Van Middelaar[39]			x			x	x			x	x	x	x	x	x	x	x	
Van der Ploeg[40]	x	x				x						x		x				
Patients, informal caregivers and healthcare providers																		
Luyme[41]	x				x	x		x		x			x	x	x	x		
Todd[42]					x					x				x				

Legend: "x" means that the category/theme was mentioned in the article.

Abbreviations: exp: previous experiences; social: social influences

3.3.1. Appropriateness

Patient and HCP agreement or disagreement with appropriateness of CVM deprescribing were based on three main themes: CVM necessity, CVM benefit, and ADE occurrence. While CVM necessity and benefit were almost as frequently mentioned as facilitators than as barriers, ADE occurrence was clearly reported as a facilitator to deprescribing (in 12 of the 22 articles).

3.3.1.1 Necessity

Patients in three studies considered taking CVMs as a necessity, even an obligation, especially in case of past cardiovascular (CV) event or family history of cardiovascular disease (CVD).[25, 26, 41] This view was shared by GPs in two studies, who also deemed necessary to treat patients with unhealthy lifestyle, or presenting many cardiovascular risk factors (CVRF).[39, 41] Patients and one GP even stated that CVMs should not be stopped until the end of life,[25, 29, 38, 42] while other patients considered CVMs linked to their survival.[4] Contrastively, patients at low CV risk and GPs treating patients in primary prevention or patients without any CVRF other than age, considered CVMs less necessary.[26, 37, 40, 41] Some patients questioned the continuous necessity of their CVM, as they felt that their disease was well-controlled.[30, 41]

3.3.1.2 Benefit

GPs were more inclined to continue treating patients with good physical and cognitive function or few comorbidities, especially if they presented no CVM-related ADEs, expecting them to derive a higher benefit from CVMs.[32, 33, 37-39] In contrast, GPs and specialists considered patients with a short life expectancy, cognitive impairment, or living in palliative/nursing homes less likely to benefit from CVMs.[33-38, 40] They felt that, in these cases, prolonging life or avoiding a CV event should not be the main objective of care.[37] However, frail patients were less willing to stop their statin than robust ones.[28]

Some patients and informal caregivers also considered CVMs to be beneficial when they saw an objective (e.g., cholesterol levels) or subjective (e.g., less dizziness) improvement under treatment.[4, 22, 24, 27] Some patients also considered that taking CVMs enabled them to make an active contribution to their health, and to have control over themselves and the future.[25]

3.3.1.3 ADEs

Patients, informal caregivers and HCPs reported ADEs as one of the main reasons to consider stopping CVMs, especially if ADEs were associated with a reduction in quality of life.[4, 22-25, 27, 30, 32-35, 39] Patients usually compliant with medications considered ADEs as a reason to discuss deprescribing with their GP.[25, 30] Patients considering taking CVMs as a routine to stay healthy were still willing to discontinue their CVMs in case of ADEs.[25, 30] Contrastively, some patients continued taking their CVMs after balancing ADEs against reasons to take CVMs (i.e., CVM perceived benefit, minor ADEs.[22] When patients were asymptomatic and had no ADE, patients and GPs were unwilling to deprescribe CVMs.[30, 39] When ADEs occurred in patients with CVD, GPs were also unwilling to deprescribe.[40]

3.2. Fear

Fear of consequences following CVM deprescribing was reported in 13 studies as a barrier to deprescribing. In multiple studies, patients stated their fear of a return of the previous condition, health deterioration, becoming a burden, or a shorter lifespan following deprescribing.[4, 25-27, 30, 41] Some linked this fear with the perceived severity of their disease.[24, 27] These concerns were shared by informal caregivers. GPs and specialists feared harming patients by deprescribing (e.g., occurrence of CV event with functional limitation, death),[31-33, 35, 36, 39, 41] and giving patients the feeling that they were giving up on them, especially by deprescribing towards the end of life, a feeling not shared by patients.[29, 31, 34, 36, 39]

Conversely, patients fearing ADEs or becoming "dependent" on their CVMs were more willing to deprescribe.[24, 28] HCPs did not report fear as a facilitator.

3.3. Dislike

CVM dislike was one of the most common facilitators to deprescribing for patients and informal caregivers, but not for HCPs. Patients stated a general dislike of medications or explained feeling burdened by the number of medications (CVMs and others), or medication-associated costs.[4, 23-25, 27, 30, 41, 42] Other patients were aiming at living a long life without using medications, or derived a personal pride of not taking medications.[25, 26] Some patients and informal caregivers considered CVMs as "not good for health"[24] or despised CVMs that created therapeutic competition (i.e., helping one condition while worsening another one) or which administration was complicated or disrupted daily routine (e.g., glycaemia before insulin injections).[4, 27]

3.4. Influences

Patient and HCP opinions towards deprescribing were shaped by their previous experiences in deprescribing CVMs, and by social influences. While social influences were reported as a facilitator as frequently than as a barrier by patients and informal caregivers, they were more frequently reported as a barrier to deprescribing by HCPs.

3.4.1 Previous experiences

Patients and HCPs with a positive previous experience with CVM deprescribing were more amenable to deprescribe again, as opposed to those with a negative previous experience.[4, 24, 31, 33, 36, 39, 41] GPs considered patients feeling better or with improved quality of life after deprescribing as positive experiences,[31, 39] and having to restart medications after

deprescribing as a negative experience.[39] For statins, occurrence or absence of stroke after deprescribing influenced GPs' and specialists' further actions.[33, 36]

3.4.2 Social influences

HCPs influenced patients' and informal caregivers' opinion on deprescribing.[27, 28] Patients were willing to stop one or more CVM if this was proposed by a trusting physician.[24] Patients especially trusted their GP because of their knowledge and the fact that they knew them well.[25, 26, 30, 41] Some patients also recognized their dependency towards their GP and highlighted their authority, feeling that it would be inappropriate to discuss their evaluation.[30] Others were waiting for their GP to start discussions about preferences, or were happy to follow their recommendations.[25, 30]

GPs accounted for patient preferences.[33, 37-40] They considered deprescribing in patients wanting to take less medications.[37, 38] They continued CVMs in patients expecting longevity or whose family was urging for medication continuation.[37] GPs were also unwilling to deprescribe CVMs prescribed by specialists, even if they questioned the indication.[31-33, 37, 41] Specialists were concerned by interfering with other HCPs' treatment plan.[35, 36] They were also unwilling to deprescribe when communication with other HCPs was suboptimal or when patients were reluctant or could not understand the concept of deprescribing.[35, 42]

3.5. Process

The process required to deprescribe CVMs was more frequently reported as a barrier than as a facilitator by HCPs.

HCPs and patients reported time constraint, such as lacking time to review medication lists or to discuss CVMs, as a barrier to CVM deprescribing.[24, 34-36, 39]

For patients, a dose-lowering scheme, a close monitoring after deprescribing and a temporary stopping trial with possibility of medication resumption facilitated the deprescribing process.[4,

[24, 25, 41] GPs also viewed gradual CVM discontinuation as a facilitator to deprescribing, especially when they were unsure about CVM risk/benefit ratio.[32, 33] However, they considered the lack of remuneration for the close follow-up needed during gradual discontinuation as a barrier.[33]

3.6. Uncertainty

As shown in **Table 3**, uncertainty was cited more often in HCP than patient/informal caregiver articles, acting almost exclusively as a barrier to deprescribing. HCPs formulated the lack of evidence about CVM deprescribing as a barrier, especially in older patients or those with dementia.[31, 35, 36] GPs found complicated to know when to deprescribe preventive medications – especially in patients neither frail nor robust[31, 39] – and how to balance CVM harms and benefits when approaching deprescribing.[37] One clinical pharmacist explained having difficulties making professional recommendations about statin deprescribing in older patients.[33] Specialists regretted the limited training on deprescribing.[35]

Patients expressed a lack of understanding of CVDs and risk reduction with CVMs, as well as uncertainty regarding potential risks and benefits of CVMs, thus feeling uncertain about the value of deprescribing.[4, 24, 30] They were also confused by conflicting treatment targets mentioned by HCPs.[24]

Some HCPs and patients also felt uneasy about the uncertainty surrounding possible consequences of CVM deprescribing.[33, 34, 41] This led to "therapeutic inertia", even in case of unclear benefits of pursuing CVMs.[36] On the contrary, GPs and clinical pharmacists feeling uneasy about possible long-term consequences of taking CVMs were more willing to deprescribe.[33]

3.7. Ambivalence

Patients expressed ambivalence about CVM use, prompting them to wish CVM continuation and deprescribing concurrently. They were concerned about the effects of CVMs on their health, but also about what could happen if they did not take them.[4] They also showed aversion towards CVMs coupled with a feeling of obligation to take them.[4, 30] HCPs did not express ambivalence.

4. Discussion

In this systematic review, we provided an overview of barriers and facilitators to deprescribing CVMs, from the point of view of patients, informal caregivers and HCPs. Barriers and facilitators could be classified in the following categories: appropriateness, fear, dislike, influences, process, uncertainty, and ambivalence. Appropriateness was divided into three themes (necessity, benefit, ADEs), and influences into two (previous experiences, social influences). Frequent deprescribing barriers for both HCPs and patients/informal caregivers included influences of others on the decision, and fear of negative consequences following CVM deprescribing. Another barrier frequently mentioned by HCPs was the uncertainty to deprescribe due to the lack of evidence regarding CVM deprescribing. The occurrence of ADEs was frequently reported as a facilitator to deprescribing, especially by patients and informal caregivers. Another facilitator for patients was dislike of CVMs. Necessity and benefit of CVMs were seen as barriers or facilitators similarly by patients and HCPs. However, patients and HCPs disagreed on the necessity and benefit of taking CVMs in case of frailty or robustness. The process required to deprescribe CVMs acted both as barrier and facilitator for patients and was more often reported as a barrier than as a facilitator by HCPs.

Barriers and facilitators to deprescribing CVMs did not differ significantly from those of deprescribing general medications.[19, 43] A systematic review on patients' barriers and facilitators to deprescribing displaying the same structure as ours, reported agreement with appropriateness of cessation, fear, influences, dislike and process as barriers and/or facilitators to deprescribing.[19] However, this review that included mainly nervous system medications, did not report uncertainty and ambivalence towards deprescribing, suggesting that these two factors were more specific to CVM deprescribing. Another systematic review on prescribers' barriers and facilitators to deprescribing potentially inappropriate medications reported inertia as importantly influencing deprescribing.[43] In our review, we also found that some HCPs experienced deprescribing inertia, continuing CVMs even if they might be inappropriate, partly because of fear of bad/unknown consequences of deprescribing.

Fear of and uncertainty about deprescribing due to unknown/possible negative consequences was indeed frequently mentioned as a barrier to deprescribing in the articles included in this systematic review. Interestingly, while fear was as frequently reported as a barrier by patients/informal caregivers than by HCPs, uncertainty was more frequently reported as a barrier by HCPs, suggesting a different level of knowledge and feeling of responsibility between HCPs and patients/informal caregivers. Such uncertainty was also reported in studies focusing on deprescribing general medications in older, multimorbid adults, potentially because of the complexity of interactions between diseases and the single-disease focused guidelines that might not apply to patients with multimorbidity.[44-46] However, one of these studies stated that balancing benefits and harms was particularly complicated for preventive medications.[44] Tools to facilitate the deprescribing process and ensure safe CVM deprescribing could help to do so, especially since HCPs in our review frequently reported the deprescribing process as a barrier.

While patient/informal caregiver and HCP points of view towards CVM deprescribing were largely similar, we could highlight differences in the perceived benefit of CVMs in robust versus frail patients. As shown in a study evaluating frail patient beliefs about prescribed medications, most patients saw their medications as highly necessary.[47] However, over one-third of patients included in this study stated that their medications were a mystery to them.[47] This stresses the fact that patients might see a medication as necessary without being able to understand its potential (lack of) benefit. HCPs, on the other hand, seemed to place importance on their patients deriving benefits from their CVMs. Thus, they endorsed deprescribing in frail patients due to a lack of time to benefit, but renounced deprescribing in robust patients. This view is concordant with other studies on treating frail and/or robust patients.[9, 48] Other differences between patients/informal caregivers and HCPs regarded ADE occurrence, that was slightly more frequently cited as a facilitator in studies on patients/informal caregivers than on HCPs, and dislike, which was a facilitator to deprescribing only mentioned by patients. These divergent views emphasize the need for discussion between HCPs and patients/informal caregivers about representations and beliefs, and how these might influence decision-making about deprescribing. This is especially important for HCPs to consider, given how patients rely on them for decision-making and might assume that they do not have to discuss their preferences and beliefs as these are already clear for their HCPs.[49-51]

5. Strengths and limitations

This study has several strengths. First, data extraction, analysis and synthesis, as well as quality assessment were conducted by two independent reviewers on all available data based on a systematic review. Second, we included both quantitative and qualitative studies, providing complementary information on barriers and facilitators to deprescribing.

However, this study also has limitations. First, in some studies, CVMs were part of the evaluated medications but not the focus. However, this enabled inclusion of more studies and

thus exploration of more barriers and facilitators to deprescribing CVMs. Second, as this review focused on CVMs in general, no conclusion can be made on individual CVMs. However, barriers and facilitators did not appear to differ significantly between studies assessing/exploring different CVMs, which leads to thinking that most barriers and facilitators might be common across CVMs.

6. Implications

The identification of barriers and facilitators to deprescribing CVMs and the quantification of the reporting frequency at the patient, informal caregiver and HCP levels, have several implications and call for future actions to address the current lack of evidence regarding potential benefits and risks of CVM deprescribing. First, differences in opinions between patients and HCPs, such as CVM benefits and CVM dislike, stress the need for ground discussions about beliefs and preferences about deprescribing of each stakeholder implicated in the deprescribing decision. Second, the uncertainty about deprescribing CVMs that HCPs frequently mentioned, HCP wish to account for patient preferences when approaching deprescribing, and patients relying on HCPs for decision-making highlight the need to translate a part of HCP responsibility in deprescribing to patients, so that decision-making can be shared and jointly carried. To enable this, HCPs must be provided with tools that enable sharing the risks and benefits of deprescribing with patients and ensure a safe deprescribing process. Furthermore, HCPs should be trained on deprescribing processes and changes at the policy making level should provide HCPs with sufficient time and adequate remuneration to approach deprescribing with patients. Less time pressure would also enable patients to feel more comfortable to address deprescribing with their HCPs.

7. Conclusion

In this systematic review, we provided an overview of barriers and facilitators to deprescribing CVMs, from the point of view of patients, informal caregivers and HCPs. The identification and quantification of barriers and facilitators most frequently cited by patients, informal caregivers and/or HCPs can help to develop future actions needed to improve evidence in CVM deprescribing and reduce the burden of medications for the patients.

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The authors declare no conflict of interest.

8.2. Author contributions:

CEA, LB and NR designed the study protocol. CEA and LB extracted and analyzed the data. CEA, LB and NR drafted the article. All authors gave final approval to submit the article.

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The coding of the articles is available by the authors on reasonable request.

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8.6. Competing interests statement:

Nothing to disclose.

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FIGURE LEGEND:

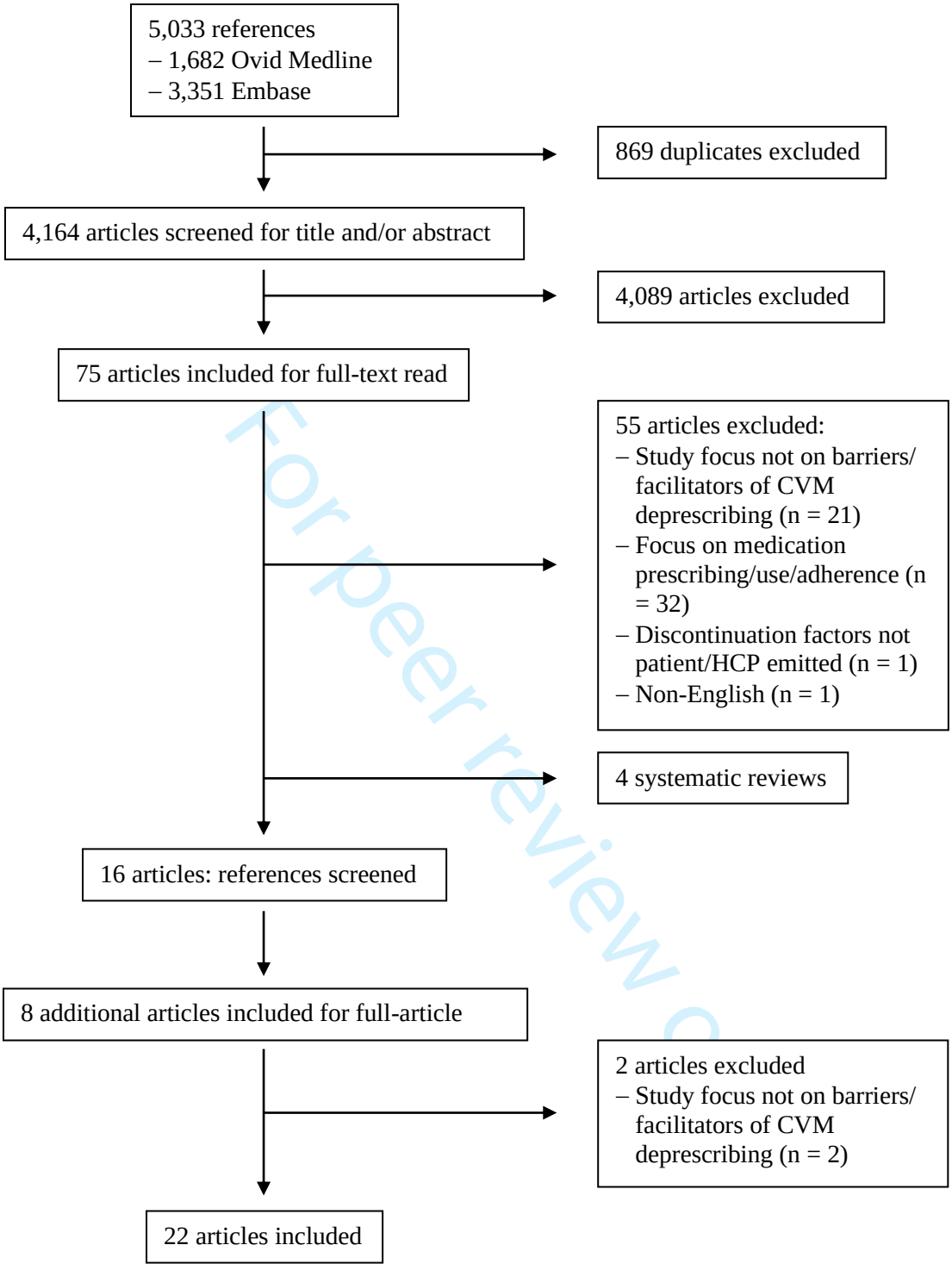
Figure 1: Study selection results

Abbreviations: CVM: cardiovascular medication; HCP: healthcare providers

10. Supplemental material

The detailed search strategy, the detailed study characteristics, and the study quality appraisal are presented in the supplemental material section.

Figure 1: Study selection results



Legend: CVM: cardiovascular medication; HCP: healthcare providers

Supplemental Material S1: Search strategy barriers and facilitators to deprescribing cardiovascular medications

OVID/MEDLINE 2021.11.15: 1,682 results

Concept 1: cardiovascular medications
1. exp cardiovascular agents/
2. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors, hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors, hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or "Cardiovascular medic*" or "cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or "cardiometabolic prescrib*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering treat*" or " lipid-lowering medic*" or " lipid-lowering drug*" or " lipid-lowering agent*" or " lipid-lowering preparation*" or " lipid-lowering prescrib*" or "lipid-lowering therapeutic*").ab,ti.
4. "cardiovascular disease".ab,ti.
5. *cardiovascular diseases/
6. prevention.ab,ti.
7. *primary prevention/
8. *secondary prevention/
9. 4 or 5
10. 6 or 7 or 8
11. 9 and 10

Concept 2: prescribing / deprescribing
12. exp Deprescriptions/
13. exp Withholding Treatment/
14. exp Potentially Inappropriate Medication List/
15. exp Inappropriate Prescribing/
16. (reduce or reducing or reduction or reduced or withdraw* or withhold* or stop or stopped or stopping or elimin* or tapering or taper or cease or ceasing or ceased or cessation* or de-intensif* or deintensif* or deprescribing or deprescrib* or "de-prescribing" or "de-prescrib*" or "de-implementation*" or "de-implement*" or deimplement* or discontinue* or discontinuation* or curb or curbing or curbed).ab,ti.

Concept 3: barriers and facilitators
17. *patient acceptance of health care/
18. *patient preference/
19. *attitude to health/
20. *physician-patient relations/
21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or deciding or motivation or conversation or acceptance or acceptability).ti.
22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or discuss* or discussion*).ti.
23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or relative* or caregiver*).ti.
24. 22 and 23
25. 1 or 2 or 3 or 11
26. 12 or 13 or 14 or 15 or 16
27. 17 or 18 or 19 or 20 or 21 or 24
28. 25 and 26 and 27
29. limit 28 to (English language and yr="2003-Current")
30. (child or kid or kids or childhood or children or pediatric or paediatric or pediatrics or paediatrics or mouse or mice or animals or animal).ab,ti.
31. 29 not 30

EMBASE 2021.11.15: 3,351 results

Concept 1: cardiovascular medications
1. 'cardiovascular agent'/exp
2. 'hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp
3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors, hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors, hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or "Cardiovascular medic*" or "cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or "cardiometabolic prescrib*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering treat*" or " lipid-lowering medic*" or " lipid-lowering drug*" or " lipid-lowering agent*" or " lipid-lowering preparation*" or " lipid-lowering prescrib*" or "lipid-lowering therapeutic*"):ab,ti
4. "cardiovascular disease":ab,ti
5. 'cardiovascular diseases'/mj
6. prevention:ab,ti
7. 'primary prevention'/mj
8. 'secondary prevention'/mj
9. 4 or 5
10. 6 or 7 or 8
11. 9 and 10

Concept 2: prescribing / deprescribing
12. 'deprescription'/mj
13. 'treatment withdrawal'/mj
14. 'potentially inappropriate medication'/mj
15. 'inappropriate prescribing'/mj
16. (reduce or reducing or reduction or reduced or withdraw* or withhold* or stop or stopped or stopping or elimin* or tapering or taper or cease or ceasing or ceased or cessation* or de-intensif* or deintensif* or deprescribing or deprescrib* or "de-prescribing" or "de-prescrib*" or "de-implementation*" or "de-implement*" or deimplement* or discontinue* or discontinuation* or curb or curbing or curbed):ab,ti

Concept 3: barriers and facilitators
17. 'patient attitude'/mj
18. 'patient preference'/mj
19. 'attitude to health'/mj
20. 'doctor patient relationship'/mj
21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or deciding or motivation or conversation or acceptance or acceptability):ti
22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or discuss* or discussion*):ti
23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or relative* or caregiver*):ti
24. #22 AND #23
25. #1 OR #2 OR #3 OR #11
26. #12 OR #13 OR #14 OR #15 OR #16
27. #17 OR #18 OR #19 OR #20 OR #21 OR #24
28. #25 AND #26 AND #27
29. (child or kid or kids or childhood or children or pediatric or paediatric or pediatrics or paediatrics or mouse or mice or animals or animal):ti,ab
30. #25 AND #26 AND #27 NOT #29 AND ([article]/lim OR [review]/lim) AND [english]/lim AND ([embase]/lim OR [embase classic]/lim OR [pubmed-not-medline]/lim) AND [2003-2020]/py

Supplemental Material S2: study characteristics

First author	Setting	Design	Data collection mean	N population	Age	No of medication taken	Studied CVM(s)	Prevention type	Life-limiting disease
Benson, 2005 (UK)	Primary care	Qualitative	Interviews	38 patients	18% <50 years 16% 50-59 years 29% 60-69 years 24% 70-79 years 13% ≥80 years	Antihypertensives: 50%: 1; 39%: 2; 11%: ≥3 Non-antihypertensives: 34%: 0; 18%: 2, 13%: 3; 11%: 4; 8%: ≥5	Antihypertensives	Unknown	No
Brinton, 2018 (USA)	Online panels	Quantitative descriptive	Survey	5014 patients	Mean age: 64	99% of current statin users taking a mean of 7.7 meds	Statin	Primary & secondary	No
Crutzen, 2020 (Netherlands)	Primary care	Qualitative	FGs	17 patients 1 caregiver	Median age: FG1: 78 FG2: 77.5	FG1: 6: 5-10; 2: >10 FG2: 4: 5-10; 5: >10	Cardiometabolic medication	Primary & secondary	No
Goyal, 2020 (USA)	Quaternary care	Qualitative	Interviews	10 patients	Median age: 80	Median of 12	β-blockers	Primary & secondary	No
Jansen, 2019 (Australia)	Primary care	Qualitative	Interviews	30 patients	20: 75-79 years 4: 80-84 years 5: 85-89 years 1: ≥90 years	Unknown	Preventive CV medication	Primary & secondary	No
Luymes, 2017 (Netherlands)	Primary care	Mixed methods	Q-sorts Group discussions	33 patients	Mean age: - Q-Sort: 57.1 - Discussion: 57.7	Unknown	LLTs Antihypertensives	Primary	No
Pickering, 2020 (USA)	Claude D. Pepper Older Americans Independence Center Research Registry; Pitt+Me registry	Qualitative	FGs	16 patients 17 caregivers	Patients ≥ 65 Caregivers 22-69	≥ 5 prescribed	Unspecified (identified: antihypertensives, statins, antiplatelets, antidiabetics)	Primary & secondary	No
Qi, 2015 (Australia)	Tertiary care	Quantitative descriptive	Survey	180 patients	Median age: 78	Median of 8	Regular medications Statins	Primary & secondary	No
Tija, 2017 (USA)	PCRC member sites	Quantitative descriptive	Survey	297 patients	Mean age: 71.8	Mean of 11.5	Statin	Primary & secondary	Yes

Van Bussel, 2019 (Netherlands)	Primary care	Qualitative	Interviews	15 patients	Mean age: 81	Median of 4 with median of 2 antihypertensives	Antihypertensives	Primary	No	

First author	**Setting**	**Design**	**Data collection mean**	**N population**	**Years of experiences**	**HCPs' patients' characteristics**				
						Age	**No of medication taken**	**Studied CVM(s)**	**Prevention type**	**Life-limiting disease**
Ailabouni, 2016 (New Zealand)	Primary care	Qualitative	Interviews	10 GPs	Unknown	83	17	Antiplatelets, statin, antidiabetics, diuretics, β-blocker, ACE inhibitor	Secondary	No
Ailabouni, 2016 (New Zealand)	Primary care	Qualitative	Interviews	10 GPs	2-32	Unspecified (older patients)	Unknown	Unspecified (statin and aspirin mentioned)	Unknown	No
Anderson, 2017 (Australia)	Primary care	Qualitative	FGs	32 GPs 15 CPs	GPs: median of 18 CP: median of 9	Unknown	Unknown	Unspecified (statin mentioned)	Unknown	No
Geijteman, 2018 (Netherlands)	Primary & secondary care	Quantitative descriptive	Survey	174 GPs 147 clinical specialists (medical oncologists, geriatricians, cardiologists, pulmonologists, neurologists	203: 0-9 years 56: 10-19 years 40: 20-29 years 18: ≥ 30 years	88	10	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary	Yes
Goyal, 2020 (USA)	Secondary and tertiary care	Quantitative descriptive	Survey	184 geriatricians 182 general internists 87 cardiologists	86: 1-10 years 99: 11-20 years 138: 21-30 years 130: > 30 years	79	Unspecified (several)	4 CV medications	Unknown	Yes and no

	Green, 2019 (USA)	Primary & secondary care	Qualitative	Interviews	19 physicians 2 nurse practitioners (family, internal & geriatric medicine, urogynecology, endocrinology, cardiology)	Mean of 14	Unspecified (older patients)	Unknown	Unspecified (oral anticoagulants, antidiabetics, statins mentioned)	Unknown	Yes
	Jansen, 2017 (Australia)	Primary care	Qualitative	Interviews	25 GPs	2: < 10 years 4: 10-19 years 7: 20-29 years 12: ≥ 30 years	≥75	Unknown	Preventive CV medication	Primary	No
	Thompson, 2020 (Denmark)	Primary care	Qualitative	Interviews	11 GPs	Mean of 9	≥ 80	Unknown	Statin	Unknown	Yes and no
	Van Middelaar, 2020 (Netherlands)	Primary care	Qualitative	Interviews	15 GPs	4: 0-5 years 3: 5-10 years 3: 10-15 years 5: > 15 years	Unspecified (older patients)	Unknown	Antihypertensives	Unknown	Yes and no
	Van der Ploeg, 2018 (30 countries)	Primary care	Quantitative descriptive	Survey	2250 GPs	358: < 5 years 1024: 5-20 years 865: > 20 years	≥ 80	Unknown	Statin	Primary and secondary	Yes and no
PATIENTS, INFORMAL CARERS	**First author**	**Setting**	**Design**	**Data collection mean**	**N population**	**Years of experiences**	**HCPs' patients' characteristics**				
							Age	**No of medication taken**	**Studied CVM(s)**	**Prevention type**	**Life-limiting disease**
	Luymes, 2016 (Netherlands)	Primary care	Qualitative	Audiotaped deprescribing consultations	10 GPs 49 patients	Unknown	Median of 55.4	27: < 2 kinds 22: ≥ 2 kinds	Antihypertensives, LLTs	Primary	No

	Todd, 2016 (UK)	Specialist palliative care unit at a daycare centre	Qualitative	Interviews	12 patients 12 informal caregivers 3 palliative consultants 3 nurse practitioners 6 GPs	Unknown	1: < 50 3: 51-60 3: 61-70 3: 71-79 2: ≥ 80	Unknown	Unspecified (preventive medications, including statins, antihypertensives)	Unknown	Yes

Legend: CPs: community pharmacists; CV: cardiovascular; CVM: cardiovascular medications; FGs: focus groups; GPs: general practitioners; HCPs: healthcare providers; LLTs: lipid-lowering therapies; PCRC: Palliative Care Research Cooperation Group

Supplemental Material S3: Details of study quality appraisal

	Authors	Is the qualitative approach appropriate to answer the research question?	Are the qualitative data collection methods adequate to address the research question?	Are the findings adequately derived from the data?	Is the interpretation of results sufficiently substantiated by data?	Is there coherence between qualitative data sources, collection, analysis and interpretation?
QUALITATIVE	Ailabouni, 2016	Can't tell	Yes	Yes	Can't tell	Yes
	Ailabouni, 2016	Yes	Yes	Yes	Yes	Yes
	Anderson, 2017	Yes	Yes	Yes	Yes	Yes
	Benson, 2005	Yes	Yes	Yes	Yes	Yes
	Crutzen, 2020	Yes	Yes	Yes	Yes	Yes
	Goyal, 2020	Yes	Yes	Yes	Yes	Yes
	Green, 2019	Yes	Yes	Yes	Yes	Yes
	Jansen, 2017	Yes	Yes	Yes	Yes	Yes
	Jansen, 2019	Yes	Yes	Yes	Yes	Yes
	Luymes, 2016	Yes	Yes	Yes	Yes	Yes
	Pickering, 2020	Yes	Yes	Yes	Yes	Yes
	Thompson 2019	Yes	Yes	Yes	Yes	Yes
	Todd, 2016	Yes	Yes	Yes	Yes	Yes
	Van Bussel, 2019	Yes	Yes	Yes	Yes	Yes
	Van Middelaar, 2018	Yes	Yes	Yes	Yes	Yes
QUANTITATIVE DESCRRIPTIVE		**Is the sampling strategy relevant to address the research question?**	**Is the sample representative of the target population?**	**Are the measurements appropriate?**	**Is the risk of nonresponse bias low?**	**Is the statistical analysis appropriate to answer the research question?**
	Brinton, 2018	Yes	Yes	Can't tell	No	Can't tell
	Geijteman, 2018	Yes	No	Yes	No	Yes
	Goyal, 2020	Yes	No	Yes	No	Yes
	Qi, 2015	Yes	No	Yes	Yes	Yes
	Tija, 2017	Yes	No	Yes	Yes	Yes
	Van der Ploeg, 2019	Yes	No	Yes	No	Yes

MIXED METHODS		**Is there an adequate rationale for using a mixed methods design to address the research question?**	**Are the different components of the study effectively integrated to answer the research question?**	**Are the outputs of the integration of qualitative and quantitative components adequately interpreted?**	**Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?**	**Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?**
	Luymes, 2017	Yes	Yes	Yes	No	Yes

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl. Material 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.7 (and Figure 1)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 (and suppl. Table S1)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p.10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.20-22
	23b	Discuss any limitations of the evidence included in the review.	p.22-23
	23c	Discuss any limitations of the review processes used.	p.22-23
	23d	Discuss implications of the results for practice, policy, and future research.	p.23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Registration on PROSPERO (CRD42020221973)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Adaptation of the framework used to analyze the data to better suit cardiovascular medications deprescribing
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Swiss National

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			Science Foundation Grant IICT 33IC30-193052; grant from the College of General Internal Medicine (Fribourg, Switzerland)
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Available on demand

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

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Barriers and facilitators to deprescribing of cardiovascular medications: a systematic review

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Barriers and facilitators to deprescribing of cardiovascular medications: a systematic review

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Running title: Deprescribing cardiovascular medications

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Number of tables and figures: 4

Abstract word count: 264

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ABSTRACT

Objective: To synthesize the current knowledge on barriers and facilitators to deprescribing cardiovascular medications (CVMs) at the levels of patients, informal caregivers, and healthcare providers (HCPs).

Design/Setting: We conducted a systematic review of studies exploring/assessing patient, informal caregiver and/or HCP barriers and/or facilitators to deprescribing CVMs.

Data sources: Ovid/MEDLINE and Embase from January 2003 to November 2021.

Data extraction and synthesis: We performed a deductive thematic analysis based on the framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al. We added a quantification of the occurrence of categories and themes in the selected articles to identify the resounding themes that indicate the greater impetus to address in future research.

Results: Most frequent deprescribing barriers for patients, informal caregivers and HCPs included uncertainty due to lack of evidence regarding CVM deprescribing (in n=10 studies), fear of negative consequences following deprescribing (n=13), and social influences (n=14). A frequently reported facilitator to deprescribing, especially for patients and informal caregivers, was the occurrence of ADEs (n=7). Another frequently reported facilitator for patients were dislike of CVMs (n=9). Necessity and benefit of CVMs were seen as barriers or facilitators similarly by patients and HCPs.

Conclusion: The differences in patient, informal caregiver and HCP regarding barriers and facilitators to deprescribing CVMs stress the need for ground discussions about beliefs and preferences of each stakeholder implicated in deprescribing decisions. Furthermore, HCP uncertainty regarding CVM deprescribing highlights the need to provide HCPs with tools that enable sharing the risks and benefits of deprescribing with patients and ensure a safe deprescribing process.

Review registration on Prospero: CRD42020221973

Strengths and limitations of this study:

- Systematic review process with publication review; data extraction, analysis and synthesis; and quality assessment independently conducted by two independent reviewers.
- Assessment of both quantitative and qualitative studies, providing complementary information on barriers and facilitators to deprescribing.
- In some studies, cardiovascular medications were part of, but not the focus of the medications evaluated.
- We did not assess specific classes of cardiovascular medications.
- The majority of healthcare providers were general practitioners, whose perspectives might differ from those of other healthcare providers.

Key words: cardiovascular medication, deprescribing, barriers, facilitators, older people

1. Introduction

In recent years, a less-is-more attitude regarding medication use has pushed to reevaluate the balance between medication risks and benefits.[1] In this context, the notion of *deprescribing* emerged, which is defined as the "systematic process of identifying and discontinuing [medications] in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values and preferences".[2]

Cardiovascular medications (CVMs) belong to the most prescribed medications worldwide.[3] Although their use is beneficial in many cases, CVMs can also cause significant adverse drug events (ADEs), drug-drug, and drug-disease interactions.[4-6] However, the lack of evidence regarding benefits and risks of some CVMs in primary prevention in older people or in those with limited life expectancy, may lead to insecurity of patients and prescribers regarding CVM use and deprescribing.[1, 7-11]

In this context, the decision to deprescribe a CVM often becomes a preference-sensitive decision.[12, 13] A better understanding of barriers and facilitators experienced by all stakeholders involved in decision-making regarding CVM deprescribing may help to take informed decisions in line with individual values and preferences, and increase confidence in the decision made.[14, 15] While literature exists on deprescribing general medications, we do not know if barriers and facilitators differ for deprescribing CVMs.

With this systematic review, we aimed at synthetizing the current knowledge on barriers and facilitators to deprescribing CVMs at the levels of patients, informal caregivers, and healthcare providers (HCPs).

2. Methods

We conducted a systematic review of studies assessing barriers and/or facilitators to deprescribing CVMs in adults. The review was registered on Prospero (CRD42020221973).

2.1. Types of studies and inclusion criteria

We included any type of publication – except editorials, conference abstracts and study protocols – discussing stakeholder barriers and/or facilitators regarding the process of deprescribing CVMs. Studies on prescribing, use, or adherence were not included. Studies reporting patients stopping CVMs without previous discussion with HCPs were considered as non-adherence studies and excluded.

2.2. Search strategy

We searched Ovid/MEDLINE and Embase from January 2003 to November 2021. We started the search in 2003 because it corresponds to the first mention of the term *deprescribing* in the literature.[16] We included studies published in English language and focusing on patients taking or having taken CVMs previously, and/or informal caregivers, and/or HCPs of such patients. We developed the 3 following concepts for our search strategy: 1) CVMs; 2) deprescribing; 3) barriers and facilitators. All three concepts were combined with the operator "and". The detailed search strategy is provided in **Supplemental Material S1**.

LB and CEA independently reviewed all publications identified through the search strategy after removing duplicates. First, ineligible articles were excluded based on title/abstract. Second, full text of the remaining articles was reviewed to identify eligible studies. Reference lists of included publications were also searched for additional relevant articles (hand searching). Reviews and meta-analyses were kept in the first selection, but only original studies identified in the reference lists were included. For each step, LB and CEA resolved discrepancies by discussion.

2.3. Data extraction and analysis

Eligible articles were imported in MAXQDA 2020 data analysis software (VERBI Software, Berlin, Germany). Extracted data included author(s), year of publication, country, study design, setting, and population, and details on barriers and/or facilitators. Given the topic of this systematic review, we conducted a qualitative rather than a quantitative synthesis of the results. We performed a deductive thematic analysis to identify common and discrepant themes within and between stakeholder categories.[17, 18] The thematic analysis was based on the framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.[4] This framework, based on Reeve's framework of patient barriers and facilitators to deprescribing medications,[19] includes the following categories: appropriateness of cessation, process of cessation, dislike of medications, fear, uncertainty, and conflicting attitudes. We analyzed patient and informal caregiver outputs together and HCP outputs separately, since we expected to identify different barriers and facilitators. In an iterative process, we created themes within the predefined categories. To identify the resounding themes that indicate the greater impetus to address in future research, we added a quantitative aspect to our thematic analysis, in which we identified the number of times each category and theme appeared in the selected studies.

2.4. Risk of bias and quality assessment

LB and CA conducted the quality and risk of bias assessment separately using the Mixed Methods Appraisal Tool (MMAT) 2018.[20, 21] The MMAT allows assessing the methodological quality of studies included in a systematic review encompassing both qualitative and quantitative data. Discussions were held until a consensus on quality of each study was reached.

2.5. Patient and Public Involvement:

Patients and Public were not involved in the design, conduct or reporting of this review, but in a follow-up project based on this review.

3. Results

3.1. Study selection and characteristics

Among the 4,164 unique studies identified, 71 were included for full-text assessment (**Figure 1**). Among those, 16 fulfilled inclusion criteria. Through hand-searching, six additional studies were included, leading to a total of 22 publications that were included for data extraction and analysis. Ten studies focused on patients and/or informal caregivers, ten studies on HCPs and two studies on patients and/or informal caregivers and HCPs. Overall, the CVMs most frequently discussed were lipid lowering therapies, especially statins (mentioned in 12 studies). Eleven studies focused on older patients (median or mean patient age of 74 years) Among HCP studies, the most represented HCPs were general practitioners (in 10 studies). Study characteristics are presented in **Tables 1** and detailed in **Supplemental Material S2**.

Table 1: main characteristics of studies reporting patient, informal caregiver and HCP barriers and facilitators to deprescribing CVMs

	First author, publication year	N population	Age	Studied CVM(s)	Prevention type
Patients and informal caregivers	Benson, 2005 (UK)[22]	38 patients	Any	Antihypertensives	Unknown
	Brinton, 2018 (USA)[23]	5,014 patients	Mean age: 64 years	Statins	Primary & secondary
	Crutzen, 2020 (Netherlands)[24]	17 patients, 1 informal caregiver	Median age: 78 years	Cardiometabolic medication	Primary & secondary
	Goyal, 2020 (USA)[4]	10 patients	Median age: 80 years	β-blockers	Primary & secondary
	Jansen, 2019 (Australia)[25]	30 patients	≥75 years	Preventive CV medication	Primary & secondary
	Luymes, 2017 (Netherlands)[26]	33 patients	Mean age: 57 years	Lipid-lowering drugs Antihypertensives	Primary
	Pickering, 2020 (USA)[27]	16 patients, 17 informal caregivers	Patients ≥ 65 years Caregivers 22-69 years	Unspecified (identified: statins, antihypertensives, antiplatelets, antidiabetics)	Primary & secondary
	Qi, 2015 (Australia)[28]	180 patients	Median age: 78 years	Regular medications, statins	Primary & secondary
	Tija, 2017 (USA)[29]	297 patients	Mean age: 72 years	Statins	Primary & secondary
	Van Bussel, 2019 (Netherlands)[30]	15 patients	Mean age: 81 years	Antihypertensives	Primary
	First author, publication year	**N population**	**Characteristics of patients cared for by study HCPs**		
			Age	**Studies CVM(s)**	**Prevention type**
HCPs	Ailabouni, 2016 (New Zealand)[31]	10 GPs	83 years	Antiplatelets, statin, antidiabetics, diuretics, β-blocker, ACE inhibitor	Secondary
	Ailabouni, 2016 (New Zealand)[32]	10 GPs	Unspecified (older pts)	Unspecified (identified: statin and aspirin)	Unknown
	Anderson, 2017 (Australia)[33]	32 GPs, 15 CPs	Unknown	Unspecified (identified: statin)	Unknown

	Geijteman, 2018 (Netherlands)[34]	174 GPs, 147 clinical specialists	88 years	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary
	Goyal, 2020 (USA)[35]	184 geriatricians, 182 general internists, 87 cardiologists	79 years	4 CV medications	Unknown
	Green, 2019 (USA)[36]	19 physicians, 2 nurse practitioners	Unspecified (older pts)	Unspecified (identified: statins, oral anticoagulants, antidiabetics)	Unknown
	Jansen, 2017 (Australia)[37]	25 GPs	≥75 years	Preventive CV medication	Primary
	Thompson, 2020 (Denmark)[38]	11 GPs	≥ 80 years	Statins	Unknown
	Van Middelaar, 2020 (Netherlands)[39]	15 GPs	Unspecified (older pts)	Antihypertensives	Unknown
	Van der Ploeg, 2018 (30 countries)[40]	2250 GPs	≥ 80 years	Statins	Primary & secondary
Patients & informal caregivers & HCPs	**First author, publication year**	**N population**	**Characteristics of patients**		
			Age	**Studied CVM(s)**	**Prevention type**
	Luymes, 2016 (Netherlands)[41]	10 GPs, 49 patients	Median age: 55 years	Antihypertensives, lipid-lowering drugs	Primary
	Todd, 2016 (UK)[42]	12 patients, 12 informal caregivers, 3 palliative consultants, 3 nurse practitioners, 6 GPs	Any	Unspecified (preventive medications, including statins, antihypertensives)	Unknown

Abbreviations: ACE inhibitors: angiotensin-converting enzyme inhibitors; CPs: community pharmacists; CV: cardiovascular; CVM(s): cardiovascular medication(s); GPs: general practitioners; pts: patients

3.2. Quality assessment

Details of each study quality assessment can be found in **Supplemental Material S3**. Of the 15 qualitative studies included in this systematic review, 14 were deemed of good quality,[4, 22, 24, 25, 27, 30, 31, 33, 36-39, 41, 42] while one lacked data to support interpretation of the results.[32] Five of the six included quantitative studies did not provide sample representative of the target population, as nonresponse was high, increasing the risk of nonresponse bias.[28, 29, 34, 35, 40] The sixth quantitative study provided few details on the method used for data analysis.[23] The only mixed methods study included failed to address divergences between quantitative and qualitative results.[26] We did not exclude any study based on the quality assessment, as our aim was to describe all available data regarding barriers and facilitators to deprescribing CVMs.

3.3. Thematic analysis

Following the framework of Goyal et al.,[4] seven categories were created to describe patient and HCP main barriers and facilitators to deprescribing CVMs. Categories one and four were divided into three and two themes respectively. Differences between patients, informal caregivers and HCPs, as well as across HCP categories, are highlighted when relevant. HCPs other than general practitioners (GPs, including general internists and family medicine clinicians) are regrouped under the term "specialists". Differences across specialties are highlighted when relevant. Of the 22 articles, all encompassed barriers and facilitators to deprescribing CVMs, except for one (Brinton et al. reported only facilitators)[23]. Barriers and facilitators did not appear to differ significantly between studies assessing different CVMs. All barriers and facilitators according to categories, themes and stakeholders, are displayed in **Table 2**. The facilitators most frequently mentioned by patients were ADE occurrence and dislike, respectively reported in seven and nine studies (n=7 and n=9), as shown in **Table 3**. The facilitator most commonly reported by HCPs was the lack of benefit (reported in n=7). One of the barriers most frequently cited by patients/informal caregivers and HCPs was fear,

reported in n=7. Social influences were another barrier frequently mentioned by HCPs (reported in n=10). Additional frequent barriers were uncertainty for HCPs (reported in n=7), and perceived benefit and social influences for patients and informal caregivers (reported in n=6).

197 **Table 2: Summary of categories, themes and codes of barriers and facilitators to deprescribing CVMs**

Categories	Themes	Barriers or facilitators	Patients and/or informal caregivers	HCPs	HCPs and patients and/or informal caregivers
Appropriateness	**Necessity**	Facilitators	Low CV risk Disease under control Trigger disappearance	Primary prevention Age as single CVRF	
		Barriers	CVM linked to survival	Unhealthy lifestyle Many CVRFs	Past CV event Family history of CVD CVM should be taken until end of life
	Benefit	Facilitators	Robustness	Short life expectancy Cognitive impairment Nursing home patients Palliative patients	No objective improvement under CVM No subjective improvement under CVM
		Barriers	Frailty CVM use = active contribution to health CVM use = having control over one's self	Good physical & cognitive function Few comorbidities	Objective improvement under CVM Subjective improvement under CVM
	ADEs	Facilitators	ADEs foster deprescribing discussion with HCP		Reduction in QOL through ADEs
		Barriers	ADEs balanced against reasons to take CVMs	ADEs in patients with CVD	No ADE, no symptom from disease
Fear		Facilitators	Fear of ADEs Fear of becoming dependent on CVMs		
		Barriers	Fear of deprescribing due to severity of underlying disease Fear of experiencing a CV event after deprescribing & becoming a burden	Feeling of giving up on patients	Fear of CV event, return of previous condition, health deterioration following deprescribing Fear of shorter lifespan without CVM
Dislike		Facilitators	General dislike of medications Medication-associated costs Living a long life without using CVMs Pride in not taking medications CVMs = poison CVMs = bad for health Therapeutic competition		

Influences	**Previous experiences**	Facilitators			Positive previous experience with deprescribing (QOL improvement, no stroke)
		Barriers			Negative previous experience with deprescribing (restart medication, stroke)
	Social influences	Facilitators	HCPs (especially GP) advising deprescribing	Patient's preferences	
		Barriers	HCPs (especially GP) advising against deprescribing	Patient's preferences (reluctance) Patient's lack of understanding Patient's family wants CVMs Specialist prescription Interference with other HCPs' treatment plan	
Process		Facilitators	Temporary deprescribing trial Possibility of CVM resumption		Dose-lowering scheme Close monitoring
		Barriers		Lack of remuneration for close monitoring	Time constraints
Uncertainty		Facilitators			Uncertainty about possible consequences of taking CVMs
		Barriers	Lack of understanding of CVDs and risk reduction with CVMs Uncertainty about risks and benefits Conflicting treatment targets	Lack of evidence on deprescribing Uncertainty about when to deprescribe Uncertainty about risk-benefit balance Limited training on deprescribing	Unknown consequences of deprescribing
Ambivalence		Facilitators and/or barriers	Concern about CVM effect on health vs consequences of not taking CVMs Aversion towards CVMs vs obligation to take CVMs		

Abbreviations: ADEs: adverse drug events; CV: cardiovascular; CVD: cardiovascular disease; CVM: cardiovascular medication; CVRF: cardiovascular risk factor; GP: general practitioner; HCPs: healthcare providers; QOL: quality of life

Table 3: Occurrence of categories and themes in the included studies

Author	Facilitators									Barriers								Facilitators & barriers
	Appropriateness			Fear	Dislike	Influences		Process	Uncertainty	Appropriateness			Fear	Influences		Process	Uncertainty	Ambivalence
	Necessity	Benefit	ADEs			Social	Exp			Necessity	Benefit	ADEs		Social	Exp			
Patients and informal caregivers																		
Benson[22]			x				x				x	x						
Brinton[23]		x	x		x													
Crutzen[24]			x	x	x	x	x	x			x		x		x	x	x	
Goyal[4]		x	x		x			x		x	x		x				x	x
Jansen[25]			x		x	x		x		x	x		x	x				
Luymes[26]	x				x	x				x			x	x				
Pickering[27]			x		x	x					x		x	x				
Qi[28]		x		x		x					x							
Tija[29]				x						x								
Van Bussel[30]	x		x		x							x	x	x			x	x
Healthcare providers																		
Ailabouni[31]							x						x	x			x	
Ailabouni[32]			x					x			x		x	x				
Anderson[33]		x	x			x	x	x	x		x		x	x	x	x	x	
Geijteman[34]		x	x													x	x	
Goyal[35]		x	x										x	x		x	x	
Green[36]		x											x	x	x	x	x	
Jansen[37]	x	x				x					x			x			x	
Thompson[38]		x				x				x	x							
Van Middelaar[39]			x			x	x			x	x	x	x	x	x	x	x	
Van der Ploeg[40]	x	x				x						x		x				
Patients, informal caregivers and healthcare providers																		
Luyme[41]	x				x	x		x		x			x	x	x	x		
Todd[42]					x					x				x				

Legend: "x" means that the category/theme was mentioned in the article.

Abbreviations: exp: previous experiences; social: social influences

3.3.1. Appropriateness

Patient and HCP agreement or disagreement with appropriateness of CVM deprescribing were based on three main themes: CVM necessity, CVM benefit, and ADE occurrence. While CVM necessity and benefit were almost as frequently mentioned as facilitators than as barriers, ADE occurrence was clearly reported as a facilitator to deprescribing (n=12).

3.3.1.1 Necessity

Patients more often reported their necessity of the CVMs (n=5 for necessity as a barrier to deprescribing)[4, 25, 26, 29, 42] than their non-necessity (n=3)[26, 30, 41]. Necessity was a theme less reported by HCPs (n=3 for necessity as a barrier to deprescribing,[38, 39, 41] and n=2 for non-necessity as a facilitator)[37, 40]. Patients in three studies considered taking CVMs as a necessity, even an obligation, especially in case of past cardiovascular (CV) event or family history of cardiovascular disease (CVD).[25, 26, 41] This view was shared by GPs in two studies, who also deemed necessary to treat patients with unhealthy lifestyle, or presenting many cardiovascular risk factors (CVRF).[39, 41] Patients and one GP even stated that CVMs should not be stopped until the end of life,[25, 29, 38, 42] while other patients considered CVMs linked to their survival.[4] Contrastively, patients at low CV risk and GPs treating patients in primary prevention or patients without any CVRF other than age, considered CVMs less necessary.[26, 37, 40, 41] Some patients questioned the continuous necessity of their CVM, as they felt that their disease was well-controlled.[30, 41]

3.3.1.2 Benefit

CVM benefit was a frequently reported theme by patients/informal caregivers (n=7)[4, 22-25, 27, 28] – more often as a barrier (i.e., perception of benefit in n=6)[4, 22, 24, 25, 27, 28]. CVM benefit was also frequently reported by HCPs (n=9)[32-40], however more often as a facilitator (i.e., lack of benefit of CVMs in n=7)[33-38, 40]. GPs were more inclined to continue treating patients with

good physical and cognitive function or few comorbidities, especially if they presented no CVM-related ADEs, expecting them to derive a higher benefit from CVMs.[32, 33, 37-39] In contrast, GPs and specialists considered patients with a short life expectancy, cognitive impairment, or living in palliative/nursing homes less likely to benefit from CVMs.[33-38, 40] They felt that, in these cases, prolonging life or avoiding a CV event should not be the main objective of care.[37] However, frail patients were less willing to stop their statin than robust ones.[28]

Some patients and informal caregivers also considered CVMs to be beneficial when they saw an objective (e.g., cholesterol levels) or subjective (e.g., less dizziness) improvement under treatment.[4, 22, 24, 27] Some patients also considered that taking CVMs enabled them to make an active contribution to their health, and to have control over themselves and the future.[25]

3.3.1.3 ADEs

Patients, informal caregivers and HCPs reported ADEs as one of the main facilitators to stopping CVMs, especially if ADEs were associated with a reduction in quality of life (n=7 for patients and n=5 for HCPs).[4, 22-25, 27, 30, 32-35, 39] Patients usually compliant with medications considered ADEs as a reason to discuss deprescribing with their GP.[25, 30] Patients considering taking CVMs as a routine to stay healthy were still willing to discontinue their CVMs in case of ADEs.[25, 30] ADEs were not formally reported as barriers to deprescribing, but were put in perspective by patients/informal caregivers (n=2)[22, 30] and HCPs (n=2).[39, 40] Some patients continued taking their CVMs after balancing ADEs against reasons to take CVMs (i.e., CVM perceived benefit, minor ADEs).[22] When patients were asymptomatic and had no ADE, patients and GPs were unwilling to deprescribe CVMs.[30, 39] When ADEs occurred in patients with CVD, GPs were also unwilling to deprescribe.[40]

3.2. Fear

Fear of consequences following CVM deprescribing was reported as a barrier to deprescribing by patients/informal caregivers (n=7)[4, 24-27, 30, 41] and HCPs (n=7).[31-33, 35, 36, 39, 41] In multiple studies, patients stated their fear of a return of the previous condition, health deterioration, becoming a burden, or a shorter lifespan following deprescribing.[4, 25-27, 30, 41] Some linked this fear with the perceived severity of their disease.[24, 27] These concerns were shared by informal caregivers. GPs and specialists feared harming patients by deprescribing (e.g., occurrence of CV event with functional limitation, death),[31-33, 35, 36, 39, 41] and giving patients the feeling that they were giving up on them, especially by deprescribing towards the end of life, a feeling not shared by patients.[29, 31, 34, 36, 39]

Conversely, patients fearing ADEs or becoming "dependent" on their CVMs were more willing to deprescribe (n=3).[24, 28, 29] HCPs did not report fear as a facilitator (n=0).

3.3. Dislike

CVM dislike was a facilitator to deprescribing for patients and informal caregivers (n=9),[4, 23-27, 30, 41, 42] but not for HCPs (n=0). Dislike was never reported as a barrier by patients/informal caregivers (n=0) or by HCPs (n=0). Patients stated a general dislike of medications or explained feeling burdened by the number of medications (CVMs and others), or medication-associated costs.[4, 23-25, 27, 30, 41, 42] Other patients were aiming at living a long life without using medications, or derived a personal pride of not taking medications.[25, 26] Some patients and informal caregivers considered CVMs as "not good for health"[24] or despised CVMs that created therapeutic competition (i.e., helping one condition while worsening another one) or which administration was complicated or disrupted daily routine (e.g., glycaemia before insulin injections).[4, 27]

3.4. Influences

Patient and HCP opinions towards deprescribing were shaped by their previous experiences in deprescribing CVMs, and by social influences. While social influences were reported as a barrier (n=4)[25-27, 30] almost as frequently as a facilitator (n=6)[24-28, 41] by patients and informal caregivers, they were more frequently reported as a barrier (n=10)[31-33, 35-37, 39-42] to deprescribing by HCPs. Previous experiences were less reported than social influences and almost as often by patients and informal caregivers (reported both as a facilitator and a barrier in n=2)[22, 24, 41] as by HCPs (reported as a facilitator in n=3[31, 33, 39] and as a barrier in n=4).[33, 36, 39, 41]

3.4.1 Previous experiences

Patients and HCPs with a positive previous experience with CVM deprescribing were more amenable to deprescribe again, as opposed to those with a negative previous experience.[4, 24, 31, 33, 36, 39, 41] GPs considered patients feeling better or with improved quality of life after deprescribing as positive experiences,[31, 39] and having to restart medications after deprescribing as a negative experience.[39] For statins, occurrence or absence of stroke after deprescribing influenced GPs' and specialists' further actions.[33, 36]

3.4.2 Social influences

HCPs influenced patients' and informal caregivers' opinion on deprescribing.[27, 28] Patients were willing to stop one or more CVM if this was proposed by a trusting physician.[24] Patients especially trusted their GP because of their knowledge and the fact that they knew them well.[25, 26, 30, 41] Some patients also recognized their dependency towards their GP and highlighted their authority, feeling that it would be inappropriate to discuss their evaluation.[30] Others were waiting for their GP to start discussions about preferences, or were happy to follow their recommendations.[25, 30]

GPs accounted for patient preferences.[33, 37-40] They considered deprescribing in patients wanting to take less medications.[37, 38] They continued CVMs in patients expecting longevity or whose family was urging for medication continuation.[37] GPs were also unwilling to deprescribe CVMs prescribed by specialists, even if they questioned the indication.[31-33, 37, 41] Specialists were concerned by interfering with other HCPs' treatment plan.[35, 36] They were also unwilling to deprescribe when communication with other HCPs was suboptimal or when patients were reluctant or could not understand the concept of deprescribing.[35, 42]

3.5. Process

The process required to deprescribe CVMs was more frequently reported as a barrier (n=6)[33-36, 39, 41] than as a facilitator (n=2)[32, 33] by HCPs. For patients and informal caregivers, this process was more frequently reported as a facilitator (n=4)[4, 24, 25, 41] than a barrier (n=2).[24, 41] HCPs and patients reported time constraint, such as lacking time to review medication lists or to discuss CVMs, as a barrier to CVM deprescribing.[24, 34-36, 39]

For patients, a dose-lowering scheme, a close monitoring after deprescribing and a temporary stopping trial with possibility of medication resumption facilitated the deprescribing process.[4, 24, 25, 41] GPs also viewed gradual CVM discontinuation as a facilitator to deprescribing, especially when they were unsure about CVM risk/benefit ratio.[32, 33] However, they considered the lack of remuneration for the close follow-up needed during gradual discontinuation as a barrier.[33]

3.6. Uncertainty

Uncertainty was reported more often by HCPs (n=7)[31, 33-37, 39] than patient and informal caregiver (n=3),[4, 24, 30] and acted almost exclusively as a barrier to deprescribing for both groups. HCPs formulated the lack of evidence about CVM deprescribing as a barrier, especially in older patients or those with dementia.[31, 35, 36] GPs found complicated to know when to

deprescribe preventive medications – especially in patients neither frail nor robust[31, 39] – and how to balance CVM harms and benefits when approaching deprescribing.[37] One clinical pharmacist explained having difficulties making professional recommendations about statin deprescribing in older patients.[33] Specialists regretted the limited training on deprescribing.[35] Patients expressed a lack of understanding of CVDs and risk reduction with CVMs, as well as uncertainty regarding potential risks and benefits of CVMs, thus feeling uncertain about the value of deprescribing.[4, 24, 30] They were also confused by conflicting treatment targets mentioned by HCPs.[24]

Some HCPs and patients also felt uneasy about the uncertainty surrounding possible consequences of CVM deprescribing.[33, 34, 41] This led to "therapeutic inertia", even in case of unclear benefits of pursuing CVMs.[36] On the contrary, GPs and clinical pharmacists feeling uneasy about possible long-term consequences of taking CVMs were more willing to deprescribe.[33]

3.7. Ambivalence

Patients expressed ambivalence about CVM use, prompting them to wish CVM continuation and deprescribing concurrently (n=2).[4, 30] They were concerned about the effects of CVMs on their health, but also about what could happen if they did not take them.[4] They also showed aversion towards CVMs coupled with a feeling of obligation to take them.[4, 30] HCPs did not express ambivalence (n=0).

4. Discussion

In this systematic review, we provided an overview of barriers and facilitators to deprescribing CVMs, from the point of view of patients, informal caregivers and HCPs. Barriers and facilitators could be classified in the following categories: appropriateness, fear, dislike, influences, process, uncertainty, and ambivalence. Appropriateness was divided into three themes (necessity, benefit, ADEs), and influences into two (previous experiences, social influences). Frequent deprescribing barriers for both HCPs and patients/informal caregivers included influences of others on the decision, and fear of negative consequences following CVM deprescribing. Another barrier frequently mentioned by HCPs was the uncertainty to deprescribe due to the lack of evidence regarding CVM deprescribing. The occurrence of ADEs was frequently reported as a facilitator to deprescribing, especially by patients and informal caregivers. Another facilitator for patients was dislike of CVMs. Necessity and benefit of CVMs were seen as barriers or facilitators similarly by patients and HCPs. However, patients and HCPs disagreed on the necessity and benefit of taking CVMs in case of frailty or robustness. The process required to deprescribe CVMs acted both as barrier and facilitator for patients and was more often reported as a barrier than as a facilitator by HCPs.

While there is increasing literature on barriers and facilitators to deprescribing, there is little literature focusing specifically on barriers and facilitators to deprescribing CVMs. Our review provides readers with a current state of the knowledge on the perspectives of different stakeholders (i.e., patients, informal caregivers and HCPs) regarding deprescribing of such medications and its specific challenges. Other studies focusing on deprescribing of other medication types or potentially inappropriate medications showed barriers and facilitators that were similar to some found in our review[43-47]. On the patient level, these studies reported experiencing ADEs or feeling burdened by the medications as facilitators,[46, 47] and seeing the medications as necessary or beneficial as a barrier.[45] On the HCP level, these studies reported

gradual deprescribing as a facilitator,[46] and fear of unknown or negative consequences following deprescribing, or like of time to approach deprescribing as barriers.[43, 44, 46] Furthermore, a systematic review on patient barriers and facilitators to deprescribing also reported agreement with appropriateness of cessation, fear, influences, dislike and process as barriers and/or facilitators to deprescribing.[19] However, this review that included mainly nervous system medications, did not report uncertainty and ambivalence towards deprescribing. This suggests that these two factors are more specific to CVM deprescribing and might reflect the remaining controversy surrounding deprescribing of some of these medications (e.g., statins).

Fear of and uncertainty about deprescribing due to unknown/possible negative consequences was frequently mentioned as a barrier to deprescribing in the articles included in this systematic review. Interestingly, while fear was as frequently reported as a barrier by patients/informal caregivers than by HCPs, uncertainty was more frequently reported as a barrier by HCPs, suggesting a different level of knowledge and feeling of responsibility between HCPs and patients/informal caregivers. Such uncertainty was also reported in studies focusing on deprescribing general medications in older, multimorbid adults, potentially because of the complexity of interactions between diseases and the single-disease focused guidelines that might not apply to patients with multimorbidity.[48-50] However, one of these studies stated that balancing benefits and harms was particularly complicated for preventive medications.[48] Tools to facilitate the deprescribing process and ensure safe CVM deprescribing could help to do so, especially since HCPs in our review frequently reported the deprescribing process as a barrier.

While patient/informal caregiver and HCP points of view towards CVM deprescribing were largely similar, we could highlight differences in the perceived benefit of CVMs in robust versus frail patients. As shown in a study evaluating frail patient beliefs about prescribed

medications, most patients saw their medications as highly necessary.[51] However, over one-third of patients included in this study stated that their medications were a mystery to them.[51] This stresses the fact that patients might see a medication as necessary without being able to understand its potential (lack of) benefit. HCPs, on the other hand, seemed to place importance on their patients deriving benefits from their CVMs. Thus, they endorsed deprescribing in frail patients due to a lack of time to benefit, but renounced deprescribing in robust patients. This view is concordant with other studies on treating frail and/or robust patients.[9, 52] Other differences between patients/informal caregivers and HCPs regarded ADE occurrence, that was slightly more frequently cited as a facilitator in studies on patients/informal caregivers than on HCPs, and dislike, which was a facilitator to deprescribing only mentioned by patients. These divergent views emphasize the need for discussion between HCPs and patients/informal caregivers about representations and beliefs, and how these might influence decision-making about deprescribing. This is especially important for HCPs to consider, given how patients rely on them for decision-making and might assume that they do not have to discuss their preferences and beliefs as these are already clear for their HCPs.[53-55]

5. Strengths and limitations

This study has several strengths. First, data extraction, analysis and synthesis, as well as quality assessment were conducted by two independent reviewers on all available data based on a systematic review. Second, we included both quantitative and qualitative studies, providing complementary information on barriers and facilitators to deprescribing.

However, this study also has limitations. First, in some studies, CVMs were part of the evaluated medications but not the focus. However, this enabled inclusion of more studies and thus exploration of more barriers and facilitators to deprescribing CVMs. Second, as this review focused on CVMs in general, no conclusion can be made on individual CVMs. However, barriers and facilitators did not appear to differ significantly between studies

assessing/exploring different CVMs, which leads to thinking that most barriers and facilitators might be common across CVMs. Third, the studies reporting HCP barriers and facilitators to deprescribing CVMs encompass mostly GP barrier and facilitators, which may differ from those of other healthcare providers.

6. Implications

The identification of barriers and facilitators to deprescribing CVMs, and the quantification of the reporting frequency at the patient, informal caregiver and HCP levels, have several implications and call for future actions to address the current lack of evidence regarding potential benefits and risks of some CVM deprescribing. First, differences in opinions between patients and HCPs, such as CVM benefits and CVM dislike, stress the need for ground discussions about beliefs and preferences about deprescribing of each stakeholder implicated in the deprescribing decision. Second, the uncertainty about deprescribing CVMs that HCPs frequently mentioned, HCP wish to account for patient preferences when approaching deprescribing, and patients relying on HCPs for decision-making highlight the need to translate a part of HCP responsibility in deprescribing to patients, so that decision-making can be shared and jointly carried. To enable this, HCPs must be provided with tools that enable sharing the risks and benefits of deprescribing with patients and ensure a safe deprescribing process. Furthermore, HCPs should be trained on deprescribing processes and changes at the policy making level should provide HCPs with sufficient time and adequate remuneration to approach deprescribing with patients. Less time pressure would also enable patients to feel more comfortable to address deprescribing with their HCPs.

7. Conclusion

In this systematic review, we provided an overview of barriers and facilitators to deprescribing CVMs, from the point of view of patients, informal caregivers and HCPs. The identification and quantification of barriers and facilitators most frequently cited by patients, informal caregivers and/or HCPs can help to develop future actions needed to improve evidence in CVM deprescribing and reduce the burden of medications for the patients.

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8.1. Financial and personal conflicts of interest:

The authors declare no conflict of interest.

8.2. Author contributions:

CEA, LB and NR designed the study protocol. CEA and LB extracted and analyzed the data. CEA, LB and NR drafted the article. All authors gave final approval to submit the article.

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The coding of the articles is available by the authors on reasonable request.

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8.6. Competing interests statement:

Nothing to disclose.

9. Ethics approval

An ethics approval was not needed for this study, since it was a review of the literature.

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FIGURE LEGEND:

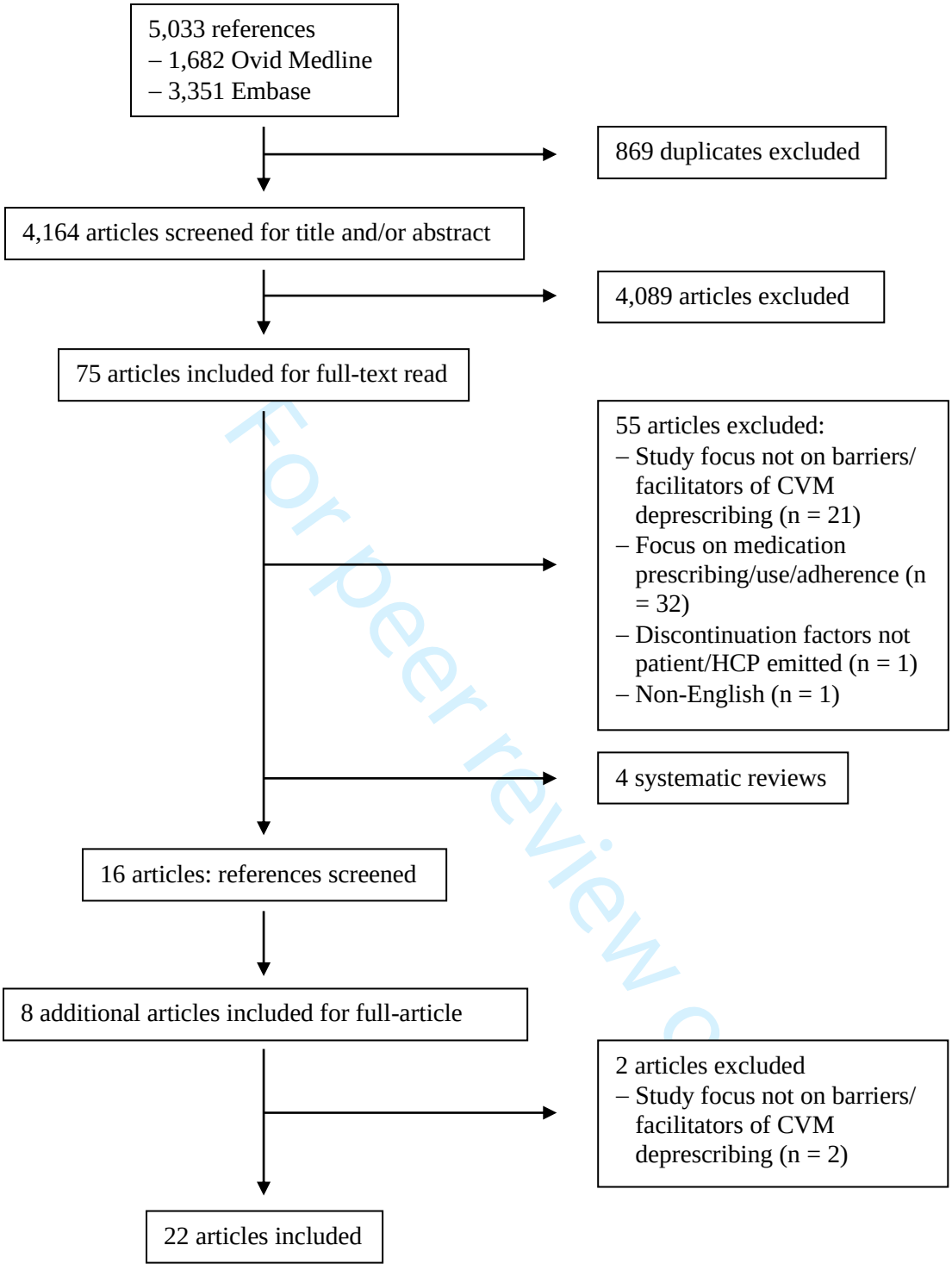
Figure 1: Study selection results

Abbreviations: CVM: cardiovascular medication; HCP: healthcare providers

11. Supplemental material

The detailed search strategy, the detailed study characteristics, and the study quality appraisal are presented in the supplemental material section.

Figure 1: Study selection results



Legend: CVM: cardiovascular medication; HCP: healthcare providers

Supplemental Material S1: Search strategy barriers and facilitators to deprescribing cardiovascular medications

OVID/MEDLINE 2021.11.15: 1,682 results

Concept 1: cardiovascular medications
1. exp cardiovascular agents/
2. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors, hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors, hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or "Cardiovascular medic*" or "cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or "cardiometabolic prescrib*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering treat*" or " lipid-lowering medic*" or " lipid-lowering drug*" or " lipid-lowering agent*" or " lipid-lowering preparation*" or " lipid-lowering prescrib*" or "lipid-lowering therapeutic*").ab,ti.
4. "cardiovascular disease".ab,ti.
5. *cardiovascular diseases/
6. prevention.ab,ti.
7. *primary prevention/
8. *secondary prevention/
9. 4 or 5
10. 6 or 7 or 8
11. 9 and 10

Concept 2: prescribing / deprescribing
12. exp Deprescriptions/
13. exp Withholding Treatment/
14. exp Potentially Inappropriate Medication List/
15. exp Inappropriate Prescribing/
16. (reduce or reducing or reduction or reduced or withdraw* or withhold* or stop or stopped or stopping or elimin* or tapering or taper or cease or ceasing or ceased or cessation* or de-intensif* or deintensif* or deprescribing or deprescrib* or "de-prescribing" or "de-prescrib*" or "de-implementation*" or "de-implement*" or deimplement* or discontinue* or discontinuation* or curb or curbing or curbed).ab,ti.

Concept 3: barriers and facilitators
17. *patient acceptance of health care/
18. *patient preference/
19. *attitude to health/
20. *physician-patient relations/
21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or deciding or motivation or conversation or acceptance or acceptability).ti.
22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or discuss* or discussion*).ti.
23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or relative* or caregiver*).ti.
24. 22 and 23
25. 1 or 2 or 3 or 11
26. 12 or 13 or 14 or 15 or 16
27. 17 or 18 or 19 or 20 or 21 or 24
28. 25 and 26 and 27
29. limit 28 to (English language and yr="2003-Current")
30. (child or kid or kids or childhood or children or pediatric or paediatric or pediatrics or paediatrics or mouse or mice or animals or animal).ab,ti.
31. 29 not 30

EMBASE 2021.11.15: 3,351 results

Concept 1: cardiovascular medications
1. 'cardiovascular agent'/exp
2. 'hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp
3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors, hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors, hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or "Cardiovascular medic*" or "cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or "cardiometabolic prescrib*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering treat*" or " lipid-lowering medic*" or " lipid-lowering drug*" or " lipid-lowering agent*" or " lipid-lowering preparation*" or " lipid-lowering prescrib*" or "lipid-lowering therapeutic*"):ab,ti
4. "cardiovascular disease":ab,ti
5. 'cardiovascular diseases'/mj
6. prevention:ab,ti
7. 'primary prevention'/mj
8. 'secondary prevention'/mj
9. 4 or 5
10. 6 or 7 or 8
11. 9 and 10

Concept 2: prescribing / deprescribing
12. 'deprescription'/mj
13. 'treatment withdrawal'/mj
14. 'potentially inappropriate medication'/mj
15. 'inappropriate prescribing'/mj
16. (reduce or reducing or reduction or reduced or withdraw* or withhold* or stop or stopped or stopping or elimin* or tapering or taper or cease or ceasing or ceased or cessation* or de-intensif* or deintensif* or deprescribing or deprescrib* or "de-prescribing" or "de-prescrib*" or "de-implementation*" or "de-implement*" or deimplement* or discontinue* or discontinuation* or curb or curbing or curbed):ab,ti

Concept 3: barriers and facilitators
17. 'patient attitude'/mj
18. 'patient preference'/mj
19. 'attitude to health'/mj
20. 'doctor patient relationship'/mj
21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or deciding or motivation or conversation or acceptance or acceptability):ti
22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or discuss* or discussion*):ti
23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or relative* or caregiver*):ti
24. #22 AND #23
25. #1 OR #2 OR #3 OR #11
26. #12 OR #13 OR #14 OR #15 OR #16
27. #17 OR #18 OR #19 OR #20 OR #21 OR #24
28. #25 AND #26 AND #27
29. (child or kid or kids or childhood or children or pediatric or paediatric or pediatrics or paediatrics or mouse or mice or animals or animal):ti,ab
30. #25 AND #26 AND #27 NOT #29 AND ([article]/lim OR [review]/lim) AND [english]/lim AND ([embase]/lim OR [embase classic]/lim OR [pubmed-not-medline]/lim) AND [2003-2020]/py

Supplemental Material S2: study characteristics

PATIENTS AND INFORMAL CAREGIVERS

First author	Setting	Design	Data collection mean	N population	Age	No of medication taken	Studied CVM(s)	Prevention type	Life-limiting disease
Benson, 2005 (UK)	Primary care	Qualitative	Interviews	38 patients	18% <50 years 16% 50-59 years 29% 60-69 years 24% 70-79 years 13% ≥80 years	Antihypertensives: 50%: 1; 39%: 2; 11%: ≥3 Non-antihypertensives: 34%: 0; 18%: 2, 13%: 3; 11%: 4; 8%: ≥5	Antihypertensives	Unknown	No
Brinton, 2018 (USA)	Online panels	Quantitative descriptive	Survey	5014 patients	Mean age: 64	99% of current statin users taking a mean of 7.7 meds	Statin	Primary & secondary	No
Crutzen, 2020 (Netherlands)	Primary care	Qualitative	FGs	17 patients 1 caregiver	Median age: FG1: 78 FG2: 77.5	FG1: 6: 5-10; 2: >10 FG2: 4: 5-10; 5: >10	Cardiometabolic medication	Primary & secondary	No
Goyal, 2020 (USA)	Quaternary care	Qualitative	Interviews	10 patients	Median age: 80	Median of 12	β-blockers	Primary & secondary	No
Jansen, 2019 (Australia)	Primary care	Qualitative	Interviews	30 patients	20: 75-79 years 4: 80-84 years 5: 85-89 years 1: ≥90 years	Unknown	Preventive CV medication	Primary & secondary	No
Luymes, 2017 (Netherlands)	Primary care	Mixed methods	Q-sorts Group discussions	33 patients	Mean age: - Q-Sort: 57.1 - Discussion: 57.7	Unknown	LLTs Antihypertensives	Primary	No
Pickering, 2020 (USA)	Claude D. Pepper Older Americans Independence Center Research Registry; Pitt+Me registry	Qualitative	FGs	16 patients 17 caregivers	Patients ≥ 65 Caregivers 22-69	≥ 5 prescribed	Unspecified (identified: antihypertensives, statins, antiplatelets, antidiabetics)	Primary & secondary	No
Qi, 2015 (Australia)	Tertiary care	Quantitative descriptive	Survey	180 patients	Median age: 78	Median of 8	Regular medications Statins	Primary & secondary	No
Tija, 2017 (USA)	PCRC member sites	Quantitative descriptive	Survey	297 patients	Mean age: 71.8	Mean of 11.5	Statin	Primary & secondary	Yes

	Van Bussel, 2019 (Netherlands)	Primary care	Qualitative	Interviews	15 patients	Mean age: 81	Median of 4 with median of 2 antihypertensives	Antihypertensives	Primary	No

HCPs

First author	Setting	Design	Data collection mean	N population	Years of experiences	HCPs' patients' characteristics				
						Age	No of medication taken	Studied CVM(s)	Prevention type	Life-limiting disease
Ailabouni, 2016 (New Zealand)	Primary care	Qualitative	Interviews	10 GPs	Unknown	83	17	Antiplatelets, statin, antidiabetics, diuretics, β-blocker, ACE inhibitor	Secondary	No
Ailabouni, 2016 (New Zealand)	Primary care	Qualitative	Interviews	10 GPs	2-32	Unspecified (older patients)	Unknown	Unspecified (statin and aspirin mentioned)	Unknown	No
Anderson, 2017 (Australia)	Primary care	Qualitative	FGs	32 GPs 15 CPs	GPs: median of 18 CP: median of 9	Unknown	Unknown	Unspecified (statin mentioned)	Unknown	No
Geijteman, 2018 (Netherlands)	Primary & secondary care	Quantitative descriptive	Survey	174 GPs 147 clinical specialists (medical oncologists, geriatricians, cardiologists, pulmonologists, neurologists	203: 0-9 years 56: 10-19 years 40: 20-29 years 18: ≥ 30 years	88	10	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary	Yes
Goyal, 2020 (USA)	Secondary and tertiary care	Quantitative descriptive	Survey	184 geriatricians 182 general internists 87 cardiologists	86: 1-10 years 99: 11-20 years 138: 21-30 years 130: > 30 years	79	Unspecified (several)	4 CV medications	Unknown	Yes and no

	Green, 2019 (USA)	Primary & secondary care	Qualitative	Interviews	19 physicians 2 nurse practitioners (family, internal & geriatric medicine, urogynecology, endocrinology, cardiology)	Mean of 14	Unspecified (older patients)	Unknown	Unspecified (oral anticoagulants, antidiabetics, statins mentioned)	Unknown	Yes
	Jansen, 2017 (Australia)	Primary care	Qualitative	Interviews	25 GPs	2: < 10 years 4: 10-19 years 7: 20-29 years 12: ≥ 30 years	≥75	Unknown	Preventive CV medication	Primary	No
	Thompson, 2020 (Denmark)	Primary care	Qualitative	Interviews	11 GPs	Mean of 9	≥ 80	Unknown	Statin	Unknown	Yes and no
	Van Middelaar, 2020 (Netherlands)	Primary care	Qualitative	Interviews	15 GPs	4: 0-5 years 3: 5-10 years 3: 10-15 years 5: > 15 years	Unspecified (older patients)	Unknown	Antihypertensives	Unknown	Yes and no
	Van der Ploeg, 2018 (30 countries)	Primary care	Quantitative descriptive	Survey	2250 GPs	358: < 5 years 1024: 5-20 years 865: > 20 years	≥ 80	Unknown	Statin	Primary and secondary	Yes and no
PATIENTS, INFORMAL	**First author**	**Setting**	**Design**	**Data collection mean**	**N population**	**Years of experiences**	**HCPs' patients' characteristics**				
							Age	**No of medication taken**	**Studied CVM(s)**	**Prevention type**	**Life-limiting disease**
	Luymes, 2016 (Netherlands)	Primary care	Qualitative	Audiotaped deprescribing consultations	10 GPs 49 patients	Unknown	Median of 55.4	27: < 2 kinds 22: ≥ 2 kinds	Antihypertensives, LLTs	Primary	No

	Todd, 2016 (UK)	Specialist palliative care unit at a daycare centre	Qualitative	Interviews	12 patients 12 informal caregivers 3 palliative consultants 3 nurse practitioners 6 GPs	Unknown	1: < 50 3: 51-60 3: 61-70 3: 71-79 2: ≥ 80	Unknown	Unspecified (preventive medications, including statins, antihypertensives)	Unknown	Yes

Legend: CPs: community pharmacists; CV: cardiovascular; CVM: cardiovascular medications; FGs: focus groups; GPs: general practitioners; HCPs: healthcare providers; LLTs: lipid-lowering therapies; PCRC: Palliative Care Research Cooperation Group

Supplemental Material S3: Details of study quality appraisal

	Authors	Is the qualitative approach appropriate to answer the research question?	Are the qualitative data collection methods adequate to address the research question?	Are the findings adequately derived from the data?	Is the interpretation of results sufficiently substantiated by data?	Is there coherence between qualitative data sources, collection, analysis and interpretation?
QUALITATIVE	Ailabouni, 2016	Can't tell	Yes	Yes	Can't tell	Yes
	Ailabouni, 2016	Yes	Yes	Yes	Yes	Yes
	Anderson, 2017	Yes	Yes	Yes	Yes	Yes
	Benson, 2005	Yes	Yes	Yes	Yes	Yes
	Crutzen, 2020	Yes	Yes	Yes	Yes	Yes
	Goyal, 2020	Yes	Yes	Yes	Yes	Yes
	Green, 2019	Yes	Yes	Yes	Yes	Yes
	Jansen, 2017	Yes	Yes	Yes	Yes	Yes
	Jansen, 2019	Yes	Yes	Yes	Yes	Yes
	Luymes, 2016	Yes	Yes	Yes	Yes	Yes
	Pickering, 2020	Yes	Yes	Yes	Yes	Yes
	Thompson 2019	Yes	Yes	Yes	Yes	Yes
	Todd, 2016	Yes	Yes	Yes	Yes	Yes
	Van Bussel, 2019	Yes	Yes	Yes	Yes	Yes
	Van Middelaar, 2018	Yes	Yes	Yes	Yes	Yes
QUANTITATIVE DESCRRIPTIVE		**Is the sampling strategy relevant to address the research question?**	**Is the sample representative of the target population?**	**Are the measurements appropriate?**	**Is the risk of nonresponse bias low?**	**Is the statistical analysis appropriate to answer the research question?**
	Brinton, 2018	Yes	Yes	Can't tell	No	Can't tell
	Geijteman, 2018	Yes	No	Yes	No	Yes
	Goyal, 2020	Yes	No	Yes	No	Yes
	Qi, 2015	Yes	No	Yes	Yes	Yes
	Tija, 2017	Yes	No	Yes	Yes	Yes
	Van der Ploeg, 2019	Yes	No	Yes	No	Yes

MIXED METHODS		**Is there an adequate rationale for using a mixed methods design to address the research question?**	**Are the different components of the study effectively integrated to answer the research question?**	**Are the outputs of the integration of qualitative and quantitative components adequately interpreted?**	**Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?**	**Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?**
	Luymes, 2017	Yes	Yes	Yes	No	Yes

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p.2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p.4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p.4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p.5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p.5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl. Material 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p.5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p.6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p.6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p.6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Not applicable
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p.7 (and Figure 1)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1 (and suppl. Table S1)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p.10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Not applicable
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p.20-22
	23b	Discuss any limitations of the evidence included in the review.	p.22-23
	23c	Discuss any limitations of the review processes used.	p.22-23
	23d	Discuss implications of the results for practice, policy, and future research.	p.23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Registration on PROSPERO (CRD42020221973)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Adaptation of the framework used to analyze the data to better suit cardiovascular medications deprescribing
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Swiss National

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			Science Foundation Grant IICT 33IC30-193052; grant from the College of General Internal Medicine (Fribourg, Switzerland)
Competing interests	26	Declare any competing interests of review authors.	None
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Available on demand

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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