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

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2
3 29 **ABSTRACT**
4

5 30 **Objective:** To synthesize the current knowledge on barriers and facilitators to deprescribing
6
7 31 cardiovascular medications (CVMs) at the levels of patients, informal caregivers, and
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9 32 healthcare providers (HCPs).
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12 33 **Design/Setting:** We conducted a systematic review of studies exploring/assessing patient,
13
14 34 informal caregiver and/or HCP barriers and/or facilitators to deprescribing CVMs.
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16
17 35 **Data sources:** Ovid/MEDLINE and Embase from January 2003 to November 2021.
18

19 36 **Data extraction and synthesis:** We performed a deductive thematic analysis based on the
20
21 37 framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.
22

23 38 **Results:** Important deprescribing barriers for patients, informal caregivers and HCPs included
24
25 39 uncertainty due to lack of evidence regarding CVM deprescribing, fear of negative
26
27 40 consequences following deprescribing, and time constraints. An important facilitator to
28
29 41 deprescribing for patients and HCPs was the occurrence of ADEs. Other facilitators for patients
30
31 42 were dislike of CVMs or establishment of a deprescribing plan. Necessity and benefit of CVMs
32
33 43 were seen as barriers or facilitators similarly by patients and HCPs. Social influences and
34
35 44 patient ambivalence acted both as barriers and facilitators to deprescribing.
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40 45 **Conclusion:** The differences in patient, informal caregiver and HCP regarding barriers and
41
42 46 facilitators to deprescribing CVMs stress the need for ground discussions about beliefs and
43
44 47 preferences of each stakeholder implicated in deprescribing decisions.
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47 48 **Review registration on Prospero:** CRD42020221973
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3 55 Strengths and limitations of this study:
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- 5 56 • Systematic review process with publication review; data extraction, analysis and
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8 57 synthesis; and quality assessment independently conducted by two independent
9
10 58 reviewers.
11
12 59 • Assessment of both quantitative and qualitative studies, providing complementary
13
14 60 information on barriers and facilitators to deprescribing.
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16
17 61 • In some studies, cardiovascular medications were part of, but not the focus of the
18
19 62 medications evaluated.
20
21
22 63 • We did not assess specific classes of cardiovascular medications.
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24 64

25
26 65 Key words: cardiovascular medication, deprescribing, barriers, facilitators, older people
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71 1. Introduction

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

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

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

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

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97 2. Methods

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

100

101 2.1. Ethics approval

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

103

104 2.2. Types of studies and inclusion criteria

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

110

111 2.3. Search strategy

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

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

1
2
3 123 searching). Reviews and meta-analyses were kept in the first selection, but only original studies
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5 124 identified in the reference lists were included. For each step, LB and CEA resolved
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8 125 discrepancies by discussion.
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11 12 127 2.4. Data extraction and analysis

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14 128 Eligible articles were imported in MAXQDA 2020 data analysis software (VERBI Software,
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16
17 129 Berlin, Germany). Extracted data included author(s), year of publication, country, study design,
18
19 130 setting, and population, and details on barriers and/or facilitators. Given the topic of this
20
21 131 systematic review, we conducted a qualitative rather than a quantitative synthesis of the results.
22
23 132 We performed a deductive thematic analysis to identify common and discrepant themes within
24
25 133 and between stakeholder categories^(18, 19). The thematic analysis was based on the framework
26
27 134 of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.⁽⁴⁾. This
28
29 135 framework, based on Reeve's framework of patient barriers and facilitators to deprescribing
30
31 136 medications⁽²⁰⁾, includes the following categories: appropriateness of cessation, process of
32
33 137 cessation, dislike of medications, fear, uncertainty, and conflicting attitudes. We analyzed
34
35 138 patient and informal caregiver outputs together and HCP outputs separately, since we expected
36
37 139 to identify different barriers and facilitators. In an iterative process, we created themes within
38
39
40 140 the predefined categories.
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47 142 2.5. Risk of bias and quality assessment

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49 143 LB and CA conducted the quality and risk of bias assessment separately using the Mixed
50
51 144 Methods Appraisal Tool (MMAT) 2018^(21, 22). The MMAT allows assessing the methodological
52
53 145 quality of studies included in a systematic review encompassing both qualitative and
54
55 146 quantitative data. Discussions were held until a consensus on quality of each study was reached.
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59 60 148 2.6. Patient and Public Involvement:

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3 149 Patients and Public were not involved in the design, conduct or reporting of this review, but in
4
5 150 a follow-up project based on this review.
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9
10 152 **3. Results**

11
12 153 3.1. Study selection and characteristics

13
14 154 Among the 4,164 unique studies identified, 71 were included for full-text assessment (**Figure**
15
16 155 **1**). Among those, 16 fulfilled inclusion criteria. Through hand-searching, six additional studies
17
18 156 were included, leading to a total of 22 publications. Study characteristics are presented in
19
20 157 **Tables 1-3** and detailed in **Supplemental Table S1**.

21
22
23
24 158 **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 \geq 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

159 **Abbreviations:** CVM, cardiovascular medication.

160 **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	Unspecifie d (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	Unspecifie d (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	Unspecifie d (older patients)	Antihypertensives	Unknown
Van der Ploeg, 2018 (30 countries) ⁽⁴¹⁾	2250 GPs	≥ 80 years	Statin	Primary and secondary

161

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

164

165 **Table 3: Main characteristics of studies including HCPs and patients and/or informal**
 166 **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

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

168

169 3.2. Quality assessment

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

179

180 3.3. Thematic analysis

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

190 **3.3.1. Appropriateness**

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

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

	Patients /informal caregivers	HCPs	All
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Appropriateness	CVM linked to survival, ADEs foster deprescribing discussion with HCP <i>Low CV risk, disease under control, robustness, ADEs balanced against reasons to take CVMs</i>	Unhealthy lifestyle, many CVRFs <i>Primary prevention, age as single CVRF, short life expectancy, cognitive impairment, nursing home / palliative care, ADEs</i>	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 <i>Fear of ADEs, of becoming dependent on CVMs</i>	Feeling of giving up on patients	Fear of CV event, return of previous condition, health deterioration, shorter lifespan
Dislike	<i>Medication dislike, costs, living a long life without using CVMs, pride in not taking medications, CVMs = poison / bad for health, therapeutic competition</i>		
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 <i>(QOL improvement, no stroke, restart medication, stroke)</i>
Process	<i>Deprescribing trial with possibility of restarting</i>	Lack of remuneration for close monitoring	<i>Dose-lowering scheme; close monitoring</i> 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 <i>Uncertainty about possible consequences of taking CVMs</i>
Ambivalence	Concern about CVM effect on health vs consequences of not taking CVMs Aversion towards CVMs vs obligation to take CVMs		

199 **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.

202 **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.

205 **3.3.1.1 Necessity**

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

216 **3.3.1.2 Benefit**

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3 217 GPs were more inclined to continue treating patients with good physical and cognitive function
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5 218 or few comorbidities, especially if they presented no CVM-related ADEs, expecting them to
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7 219 derive a higher benefit from CVMs^(24, 27, 32, 35, 36). In contrast, GPs and specialists considered
8
9 220 patients with a short life expectancy, cognitive impairment, or living in palliative/nursing homes
10
11 221 less likely to benefit from CVMs^(24, 27, 29, 32, 37, 38, 41). They felt that, in these cases, prolonging
12
13 222 life or avoiding a CV event should not be the main objective of care⁽²⁷⁾. However, frail patients
14
15 223 were less willing to stop their statin than robust ones⁽³⁹⁾.
16
17 224 Some patients and informal caregivers also considered CVMs to be beneficial when they saw
18
19 225 an objective (e.g., cholesterol levels) or subjective (e.g., less dizziness) improvement under
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21 226 treatment^(4, 25, 26, 31). Some patients also considered that taking CVMs enabled them to make an
22
23 227 active contribution to their health, and to have control over themselves and the future⁽⁴⁴⁾.
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30 229 **3.3.1.3 ADEs**

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33 230 Patients, informal caregivers and HCPs reported ADEs as one of the main reasons to consider
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35 231 stopping CVMs, especially if ADEs were associated with a reduction in quality of life^{(4, 24-26, 28,}
36
37 232 ^{31, 34-38, 42)}. Patients usually compliant with medications considered ADEs as a reason to discuss
38
39 233 deprescribing with their GP^(28, 34). Patients considering taking CVMs as a routine to stay healthy
40
41 234 were still willing to discontinue their CVMs in case of ADEs^(28, 34). Contrastively, some patients
42
43 235 continued taking their CVMs after balancing ADEs against reasons to take CVMs (i.e., CVM
44
45 236 perceived benefit, minor ADEs⁽²⁵⁾). When patients were asymptomatic and had no ADE, patients
46
47 237 and GPs were unwilling to deprescribe CVMs^(34, 35). When ADEs occurred in patients with
48
49 238 CVD, GPs were also unwilling to deprescribe⁽⁴¹⁾.
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54 239 55 240 **3.2. Fear**

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57 241 Fear of consequences following CVM deprescribing was an important barrier to deprescribing.
58
59 242 Many patients stated their fear of a return of the previous condition, health deterioration,
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3 243 becoming a burden, or a shorter lifespan following deprescribing^(4, 28, 30, 31, 34, 43). Some linked
4
5 244 this fear with the perceived severity of their disease^(26, 31). These concerns were shared by
6
7 245 informal caregivers.
8
9
10 246 GPs and specialists feared harming patients by deprescribing (e.g., occurrence of CV event with
11
12 247 functional limitation, death)^(23, 24, 29, 30, 35-37), and giving patients the feeling that they were giving
13
14 248 up on them, especially by deprescribing towards the end of life, a feeling not shared by
15
16 249 patients^(23, 29, 35, 38, 40). Furthermore, patients fearing ADEs or becoming “dependent” on their
17
18 250 CVMs were more willing to deprescribe^(26, 39).
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22 251

23 24 252 **3.3. Dislike**

25
26 253 CVM dislike was an important facilitator to deprescribing for patients and informal caregivers,
27
28 254 but not for HCPs. Some patients stated a general dislike of medications or explained feeling
29
30 255 burdened by the number of medications (CVMs and others), or medication-associated costs^{(4,}
31
32 256 ^{26, 28, 30, 31, 33, 34, 42)}. Others were aiming at living a long life without using medications, or derived
33
34 257 a personal pride of not taking medications^(28, 43). Some patients and informal caregivers
35
36 258 considered CVMs as “not good for health”⁽²⁶⁾ or despised CVMs that created therapeutic
37
38 259 competition (i.e., helping one condition while worsening another one) or which administration
39
40 260 was complicated or disrupted daily routine (e.g., glycaemia before insulin injections)^(4, 31).
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45 46 47 262 **3.4. Influences**

48
49 263 Patient and HCP opinions towards deprescribing were largely shaped by their previous
50
51 264 experiences in deprescribing CVMs, and social influences.
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54 265

55 56 266 **3.4.1 Previous experiences**

57
58 267 Patients and HCPs with a positive previous experience with CVM deprescribing were more
59
60 268 amenable to deprescribe again, as opposed to those with a negative previous experience ^{(4, 23, 24,}

269 26, 29, 30, 35). GPs considered patients feeling better or with improved quality of life after
270 deprescribing as positive experiences^(23, 35), and having to restart medications after
271 deprescribing as a negative experience⁽³⁵⁾. For statins, occurrence or absence of stroke after
272 deprescribing influenced GPs' and specialists' further actions^(24, 29).

273

274 3.4.2 Social influences

275 HCPs highly influenced patients' and informal caregivers' opinion on deprescribing ^(31, 39).
276 Patients were willing to stop one or more CVM if this was proposed by a trusting physician⁽²⁶⁾.
277 Patients especially trusted their GP because of their knowledge and the fact that they knew them
278 well^(28, 30, 34, 43). Some patients also recognized their dependency towards their GP and
279 highlighted their authority, feeling that it would be inappropriate to discuss their evaluation⁽³⁴⁾.
280 Many were waiting for their GP to start discussions about preferences, or were happy to follow
281 their recommendations^(28, 34).
282 GPs accounted for patient preferences ^(24, 27, 32, 35, 41). They considered deprescribing in patients
283 wanting to take less medications^(27, 32). They continued CVMs in patients expecting longevity
284 or whose family was urging for medication continuation⁽²⁷⁾. GPs were also unwilling to
285 deprescribe CVMs prescribed by specialists, even if they questioned the indication^{(23, 24, 27, 30,}
286 ³⁶⁾. Specialists were concerned by interfering with other HCPs' treatment plan^(29, 37). They were
287 also unwilling to deprescribe when communication with other HCPs was suboptimal or when
288 patients were reluctant or could not understand the concept of deprescribing^(33, 37).

289

290 3.5. Process

291 HCPs and patients reported time constraint, such as lacking time to review medication lists or
292 to discuss CVMs, as an important barrier to CVM deprescribing^(26, 29, 35, 37, 38).
293 For patients, a dose-lowering scheme, a close monitoring after deprescribing and a temporary
294 stopping trial with possibility of medication resumption facilitated the deprescribing process⁽⁴⁾.

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3 295 26, 28, 30). GPs also viewed gradual CVM discontinuation as a facilitator to deprescribing,
4
5 296 especially when they were unsure about CVM risk/benefit ratio (24, 36). However, they
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7 297 considered the lack of remuneration for the close follow-up needed during gradual
8
9 298 discontinuation as a barrier(24).

10
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13 14 300 **3.6. Uncertainty**

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16
17 301 HCPs formulated the lack of evidence about CVM deprescribing as a barrier, especially in older
18
19 302 patients or those with dementia(23, 29, 37). GPs found complicated to know when to deprescribe
20
21 303 preventive medications – especially in patients neither frail nor robust(23, 35) – and how to
22
23 304 balance CVM harms and benefits when approaching deprescribing(27). One clinical pharmacist
24
25 305 explained having difficulties making professional recommendations about statin deprescribing
26
27 306 in older patients(24). Specialists regretted the limited training on deprescribing(37).

28
29 307 Patients expressed a lack of understanding of CVDs and risk reduction with CVMs, as well as
30
31 308 uncertainty regarding potential risks and benefits of CVMs, thus feeling uncertain about the
32
33 309 value of deprescribing(4, 26, 34). They were also confused by conflicting treatment targets
34
35 310 mentioned by HCPs(26).

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38 311 Some HCPs and patients also felt uneasy about the uncertainty surrounding possible
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40 312 consequences of CVM deprescribing(24, 38). This led to “therapeutic inertia”, even in case of
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42 313 unclear benefits of pursuing CVMs(29). On the contrary, GPs and clinical pharmacists feeling
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44 314 uneasy about possible long-term consequences of taking CVMs were more willing to
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46 315 deprescribe(24).

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50 51 52 317 **3.7. Ambivalence**

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55 318 Patients expressed ambivalence about CVM use, prompting them to wish CVM continuation
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57 319 and deprescribing concurrently. They were concerned about the effects of CVMs on their
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3 320 health, but also about what could happen if they did not take them⁽⁴⁾. They also showed aversion
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5 321 towards CVMs coupled with a feeling of obligation to take them^(4, 34).
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10 323 **4. Discussion**

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12 324 In this systematic review, we provided an overview of barriers and facilitators to deprescribing
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14 325 CVMs, from the point of view of patients, informal caregivers and HCPs. Barriers and
15
16 326 facilitators could be classified in the following categories: appropriateness, fear, dislike,
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18 327 influences, process, uncertainty, ambivalence. Appropriateness was divided into three themes
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20 328 (necessity, benefit, ADEs), and influences into two themes (previous experiences, social
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22 329 influences). Important deprescribing barriers for HCPs and patients included uncertainty due to
23
24 330 lack of evidence regarding CVM deprescribing, fear of negative consequences following
25
26 331 deprescribing, and time constraints. An important facilitator to deprescribing for patients and
27
28 332 HCPs was the occurrence of ADEs. Other facilitators for patients were dislike of CVMs or
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30 333 establishment of a deprescribing plan. Necessity and benefit of CVMs were seen as barriers or
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32 334 facilitators similarly by patients and HCPs. However, patients and HCPs disagreed on the
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34 335 necessity and benefit of taking CVMs in case of frailty or robustness. Social influences and
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36 336 patient ambivalence acted both as barriers and facilitators to deprescribing.
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44 338 Barriers and facilitators to deprescribing CVMs did not differ significantly from those of
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46 339 deprescribing general medications^(20, 45). A systematic review on patients' barriers and
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48 340 facilitators to deprescribing displayed the same structure as ours, reporting agreement with
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50 341 appropriateness of cessation, fear, influences, dislike and process as barriers and/or facilitators
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52 342 to deprescribing⁽²⁰⁾. However, this review that included mainly nervous system medications,
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54 343 did not report uncertainty and ambivalence towards deprescribing, suggesting that these two
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56 344 factors were more specific to CVM deprescribing. Another systematic review on prescribers'
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58 345 barriers and facilitators to deprescribing potentially inappropriate medications reported four
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3 346 main categories: awareness, inertia, self-efficacy and feasibility⁽⁴⁵⁾. Although studies included
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5 347 in our review did not really reflect on HCPs' level of awareness of the appropriateness of their
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7 348 CVM prescribing, we also found that some HCPs experienced deprescribing inertia, continuing
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9 349 CVMs even if they might be inappropriate, partly because of fear of bad/unknown
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11 350 consequences of deprescribing.
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16
17 352 We found that patient and HCP points of view towards CVM deprescribing were largely
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19 353 similar. One main difference was the necessity/benefit of CVMs in robust versus frail patients.
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21 354 As shown in a study evaluating frail patient beliefs about prescribed medications, most patients
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23 355 saw their medications as highly necessary⁽⁴⁶⁾. However, over one-third of patients included in
24
25 356 this study stated that their medications were a mystery to them⁽⁴⁶⁾. This stresses the fact that
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27 357 patients might see a medication as necessary without being able to understand its potential (lack
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29 358 of) benefit. HCPs, on the other hand, seemed to place importance on their patients deriving
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31 359 benefits from their CVMs. Thus, they endorsed deprescribing in frail patients due to a lack of
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33 360 time to benefit, but renounced deprescribing in robust patients. This view is concordant with
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35 361 other studies on treating frail and/or robust patients^(9, 47).
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42 363 Lack of evidence on the risk/benefit profile of CVMs and potential consequences of
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44 364 deprescribing in certain populations made patients and HCPs uncertain towards CVM
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46 365 deprescribing. Such uncertainty was also reported in studies focusing on deprescribing general
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48 366 medications in older, multimorbid adults, likely because of the complexity of interactions
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50 367 between diseases and the single-disease focused guidelines that might not apply to patients with
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52 368 multimorbidity⁽⁴⁸⁻⁵⁰⁾. However, one of these studies stated that balancing benefits and harms
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54 369 was particularly complicated for preventive medications⁽⁴⁸⁾. As shown in our review and in
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56 370 previous studies, HCP and patient uncertainty might lead to fear of bad or unknown
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58 371 consequences and prevent deprescribing^(51, 52). HCPs were also afraid of patients feeling that
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3 372 they were giving up on them, especially towards the end of life, a point of view that was
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5 373 nevertheless not shared by patients. These divergent views emphasize the need for discussion
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7 374 between HCPs and patients about representations and beliefs, and how these might influence
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9 375 decision-making in the context of uncertainty about deprescribing. This is especially important
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11 376 for HCPs to consider, given that patients might assume that they do not have to discuss their
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13 377 preferences and beliefs as these are already clear for their HCPs⁽⁵³⁾.
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19 379 This systematic review highlights the uncertainty that can arise when approaching CVM
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21 380 deprescribing, and the inertia that can result from it. In this context, discussions between HCPs
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23 381 and patients and/or informal caregivers about representations, beliefs and preferences have the
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25 382 potential to mitigate such uncertainty, and enable shared decision-making. Finding ways to
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27 383 make deprescribing as safe as possible in the current context of uncertainty is also central. To
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29 384 achieve this, some studies included in this review provided keys to enable patients to feel safe
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31 385 about deprescribing: gradual deprescribing and close monitoring of medical parameters, as well
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33 386 as deprescribing trials and possibility of medication resumption.
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38 388 **5. Strengths and limitations**

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40 389 This study has several strengths. First, data extraction, analysis and synthesis, as well as quality
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42 390 assessment were conducted by two independent reviewers on all available data based on a
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44 391 systematic review. Second, we included both quantitative and qualitative studies, providing
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46 392 complementary information on barriers and facilitators to deprescribing.
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49 393 However, this study also has limitations. First, in some studies, CVMs were part of the
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51 394 evaluated medications but not the focus. However, this enabled inclusion of more studies and
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53 395 thus exploration of more barriers and facilitators to deprescribing CVMs. Second, as this review
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55 396 focused on CVMs in general, no conclusion can be made on individual CVMs. However,
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57 397 barriers and facilitators did not appear to differ significantly between studies
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3 398 assessing/exploring different CVMs, which leads to thinking that most barriers and facilitators
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5 399 might be common across CVMs.
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10 401 **6. Conclusion**

12 402 In this systematic review, we provided an overview of barriers and facilitators to deprescribing
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14 403 CVMs, from the point of view of patients, informal caregivers and HCPs. We could see that
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16
17 404 patient, informal caregiver and HCP expressed barriers and facilitators to deprescribing did not
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19 405 differ significantly. However, we could highlight certain differences in opinions between
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21 406 patients and HCPs that stress the need for ground discussions about beliefs and preferences
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23
24 407 about deprescribing of each stakeholder implicated in the deprescribing decision. As
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26 408 uncertainty prevails when it comes to deprescribing CVMs, strategies to enable the safest
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28 409 deprescribing, such as gradual deprescribing or close monitoring following deprescribing, can
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30 410 be established in everyday practice.
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33 411

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44
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49 418

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53
54 420 The authors declare no conflict of interest.
55

56 421

58 422 7.2. Author contributions:

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2
3 423 CEA, LB and NR designed the study protocol. CEA and LB extracted and analyzed the data.
4

5 424 CEA, LB and NR drafted the article. All authors gave final approval to submit the article.
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9

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15

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23 432 The coding of the articles is available by the authors on reasonable request.
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41 440 Nothing to disclose.
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21 607 **FIGURE LEGEND:**

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23 608 **Figure 1: Study selection results**

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25 609 **Abbreviations:** CVM: cardiovascular medication; HCP: healthcare providers
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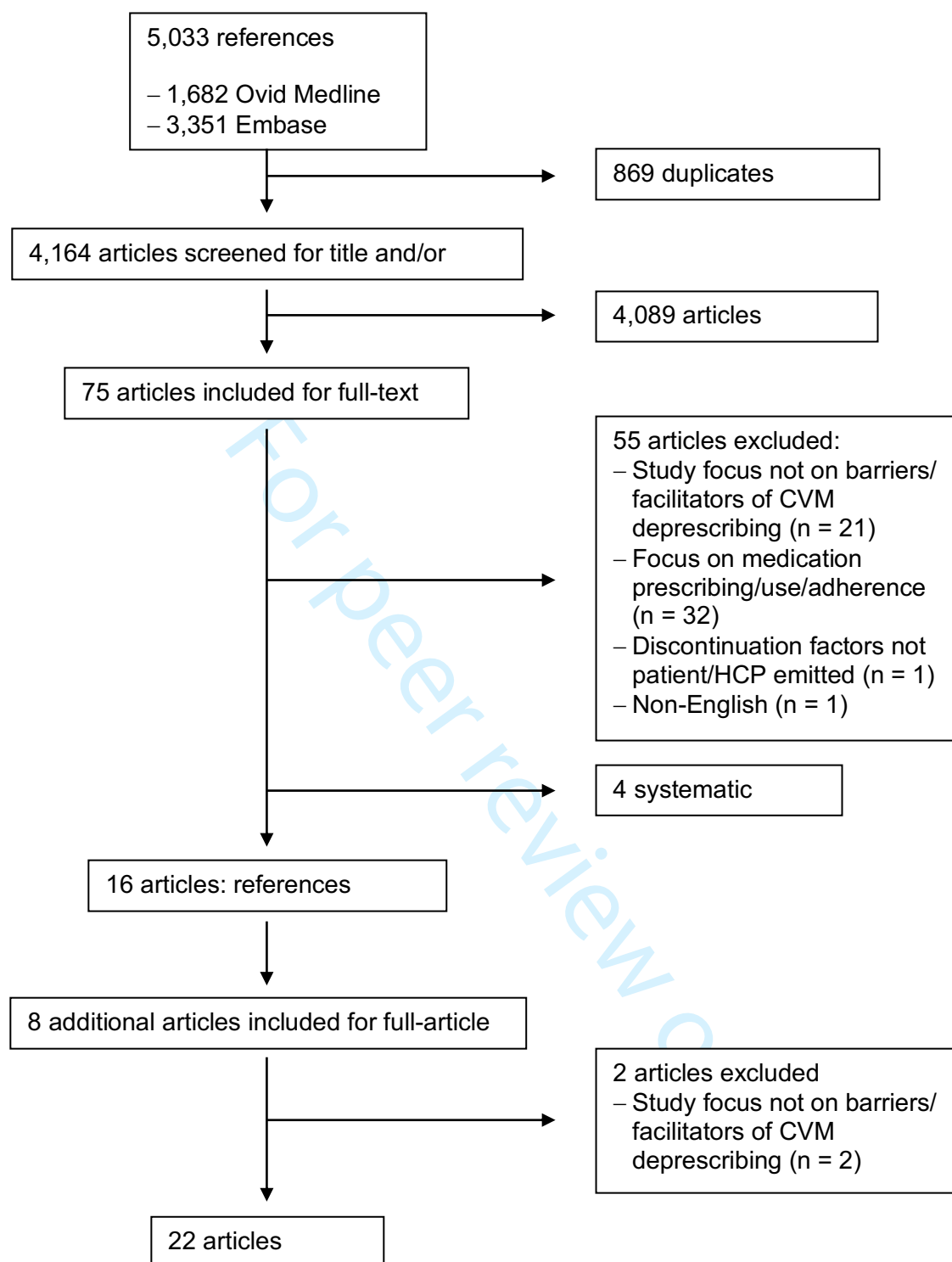
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For peer review only

9. Supplemental material

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

For peer review only



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

OID/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 "cardiomatabolic medic*" or "cardiomatabolic drug*" or "cardiomatabolic agent*" or "cardiomatabolic preparation*" or "cardiomatabolic prescrib*" or "cardiomatabolic therapeutic*" or "cardiomatabolic 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 "cardiomatabolic medic*" or "cardiomatabolic drug*" or "cardiomatabolic agent*" or "cardiomatabolic preparation*" or "cardiomatabolic prescri*" or "cardiomatabolic therapeutic*" or "cardiomatabolic treat*" or "lipid-lowering treat*" or "lipid-lowering medic*" or "lipid-lowering drug*" or "lipid-lowering agent*" or "lipid-lowering preparation*" or "lipid-lowering prescri*" 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

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3 16. (reduce or reducing or reduction or reduced or withdraw* or withhold* or stop or stopped or
4 stopping or elimin* or tapering or taper or cease or ceasing or ceased or cessation* or de-intensif* or
5 deintensif* or deprescribing or deprescrib* or "de-prescribing" or "de-prescrib*" or "de-
6 implementation*" or "de-implement*" or deimplement* or discontinue* or discontinuation* or curb
7 or curbing or curbed):ab,ti
8
9

10 Concept 3: barriers and facilitators

11 17. 'patient attitude'/mj

12 18. 'patient preference'/mj

13 19. 'attitude to health'/mj

14 20. 'doctor patient relationship'/mj

15 21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or
16 facilitate or facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or
17 difficulty or willingness or belief or believe* or preference* or willing or dialog* or conversation* or
18 decision or decide* or deciding or motivation or conversation or acceptance or acceptability):ti

19 22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or
20 attitude or input or inputs or experience or experiences or value or values or perspective* or
21 expectation* or choice or choices or empower* or choose* or choosing or acceptance or acceptability
22 or knowledge* or preference* or motivation* or intention* or involv* or engag* or consult* or
23 interact* or involv* or satisfaction or satisfied or discuss* or discussion*):ti

24 23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient*
25 or adult* or relative* or caregiver*):ti

26 24. #22 AND #23

27 25. #1 OR #2 OR #3 OR #11

28 26. #12 OR #13 OR #14 OR #15 OR #16

29 27. #17 OR #18 OR #19 OR #20 OR #21 OR #24

30 28. #25 AND #26 AND #27

31 29. (child or kid or kids or childhood or children or pediatric or paediatric or pediatrics or paediatrics
32 or mouse or mice or animals or animal):ti,ab

33 30. #25 AND #26 AND #27 NOT #29 AND ([article]/lim OR [review]/lim) AND [english]/lim AND
34 ([embase]/lim OR [embase classic]/lim OR [pubmed-not-medline]/lim) AND [2003-2020]/py
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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

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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

HCPs	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
	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

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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

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

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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

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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

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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		
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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.

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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

For more information, visit: <http://www.prisma-statement.org/>

BMJ Open

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1 1 **Barriers and facilitators to deprescribing of cardiovascular** 2 3 4 2 **medications: a systematic review** 5 6 3 7

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3 29 **ABSTRACT**
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5 30 **Objective:** To synthesize the current knowledge on barriers and facilitators to deprescribing
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7 31 cardiovascular medications (CVMs) at the levels of patients, informal caregivers, and
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9 32 healthcare providers (HCPs).
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12 33 **Design/Setting:** We conducted a systematic review of studies exploring/assessing patient,
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14 34 informal caregiver and/or HCP barriers and/or facilitators to deprescribing CVMs.
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17 35 **Data sources:** Ovid/MEDLINE and Embase from January 2003 to November 2021.
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19 36 **Data extraction and synthesis:** We performed a deductive thematic analysis based on the
20
21 37 framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.
22
23 38 We added a quantification of the occurrence of categories and themes in the selected articles to
24
25 39 identify the resounding themes that indicate the greater impetus to address in future research.
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27

28 40 **Results:** Most frequent deprescribing barriers for patients, informal caregivers and HCPs
29
30 41 included uncertainty due to lack of evidence regarding CVM deprescribing, fear of negative
31
32 42 consequences following deprescribing, and social influences. A frequently reported facilitator
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34 43 to deprescribing, especially for patients and informal caregivers, was the occurrence of ADEs.
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36 44 Another frequently reported facilitator for patients were dislike of CVMs. Necessity and benefit
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38 45 of CVMs were seen as barriers or facilitators similarly by patients and HCPs.
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42 46 **Conclusion:** The differences in patient, informal caregiver and HCP regarding barriers and
43
44 47 facilitators to deprescribing CVMs stress the need for ground discussions about beliefs and
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46 48 preferences of each stakeholder implicated in deprescribing decisions. Furthermore, HCP
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48 49 uncertainty regarding CVM deprescribing highlights the need to provide HCPs with tools that
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50 50 enable sharing the risks and benefits of deprescribing with patients and ensure a safe
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52 51 deprescribing process.
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56 52 **Review registration on Prospero:** CRD42020221973
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3 55 Strengths and limitations of this study:
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- 5 56 • Systematic review process with publication review; data extraction, analysis and
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8 57 synthesis; and quality assessment independently conducted by two independent
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10 58 reviewers.
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12 59 • Assessment of both quantitative and qualitative studies, providing complementary
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14 60 information on barriers and facilitators to deprescribing.
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17 61 • In some studies, cardiovascular medications were part of, but not the focus of the
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19 62 medications evaluated.
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22 63 • We did not assess specific classes of cardiovascular medications.
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24 64

25
26 65 Key words: cardiovascular medication, deprescribing, barriers, facilitators, older people
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69 1. Introduction

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

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

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

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

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95 2. Methods

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

99 2.1. Ethics approval

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

102 2.2. Types of studies and inclusion criteria

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

109 2.3. Search strategy

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

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

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3 121 searching). Reviews and meta-analyses were kept in the first selection, but only original studies
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5 122 identified in the reference lists were included. For each step, LB and CEA resolved
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8 123 discrepancies by discussion.
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11 12 125 2.4. Data extraction and analysis

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14 126 Eligible articles were imported in MAXQDA 2020 data analysis software (VERBI Software,
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17 127 Berlin, Germany). Extracted data included author(s), year of publication, country, study design,
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19 128 setting, and population, and details on barriers and/or facilitators. Given the topic of this
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21 129 systematic review, we conducted a qualitative rather than a quantitative synthesis of the results.
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23 130 We performed a deductive thematic analysis to identify common and discrepant themes within
24
25 131 and between stakeholder categories.^(17, 18) The thematic analysis was based on the framework
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27 132 of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.⁽⁴⁾ This
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29 133 framework, based on Reeve's framework of patient barriers and facilitators to deprescribing
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31 134 medications,⁽¹⁹⁾ includes the following categories: appropriateness of cessation, process of
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33 135 cessation, dislike of medications, fear, uncertainty, and conflicting attitudes. We analyzed
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35 136 patient and informal caregiver outputs together and HCP outputs separately, since we expected
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37 137 to identify different barriers and facilitators. In an iterative process, we created themes within
38
39 138 the predefined categories. To identify the resounding themes that indicate the greater impetus
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41 139 to address in future research, we added a quantitative aspect to our thematic analysis, in which
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43 140 we identified the number of times each category and theme appeared in the selected studies.
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50 51 142 2.5. Risk of bias and quality assessment

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53 143 LB and CA conducted the quality and risk of bias assessment separately using the Mixed
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55 144 Methods Appraisal Tool (MMAT) 2018.^(20, 21) The MMAT allows assessing the methodological
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57 145 quality of studies included in a systematic review encompassing both qualitative and
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59 146 quantitative data. Discussions were held until a consensus on quality of each study was reached.
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3 147 2.6. Patient and Public Involvement:
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5 148 Patients and Public were not involved in the design, conduct or reporting of this review, but in
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8 149 a follow-up project based on this review.
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12 151 **3. Results**
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14 152 3.1. Study selection and characteristics
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17 153 Among the 4,164 unique studies identified, 71 were included for full-text assessment (**Figure**
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19 154 **1**). Among those, 16 fulfilled inclusion criteria. Through hand-searching, six additional studies
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21 155 were included, leading to a total of 22 publications. Study characteristics are presented in
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23 156 **Tables 1** and detailed in **Supplemental Material S2**.
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158 **Table 1: main characteristics of studies reporting patient, informal caregiver and HCP barriers and facilitators to deprescribing CVMs**

Patients and informal caregivers	First author, publication year	N population	Age	Studied CVM(s)	Prevention type
	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	
HCPs	First author, publication year	N population	Characteristics of patients cared for by study HCPs		
			Age	Studies CVM(s)	Prevention type
	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	

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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
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

165 3.2. Quality assessment

166 Details of each study quality assessment can be found in **Supplemental Material S3**. Of the
167 15 qualitative studies included in this systematic review, 14 were deemed of good quality,^{(4, 22,}
168 24, 25, 27, 30, 31, 33, 36-39, 41, 42) while one lacked data to support interpretation of the results.⁽³²⁾ Five
169 of the six included quantitative studies did not provide sample representative of the target
170 population, as nonresponse was high, increasing the risk of nonresponse bias.^(28, 29, 34, 35, 40) The
171 sixth quantitative study provided few details on the method used for data analysis.⁽²³⁾ The only
172 mixed methods study included failed to address divergences between quantitative and
173 qualitative results.⁽²⁶⁾ We did not exclude any study based on the quality assessment, as our aim
174 was to describe all available data regarding barriers and facilitators to deprescribing CVMs.

176 3.3. Thematic analysis

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

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3 191 facilitators). One of the barriers most frequently cited by patients/informal caregivers and HCPs
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5 192 was fear, reported in seven of the 12 articles on patients, informal caregivers and HCPs. Social
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7 193 influences were another barrier frequently mentioned by HCPs (reported in 10 of the 12
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9 194 articles). Additional frequent barriers were uncertainty for HCPs (in seven of the 12 articles),
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11 195 and perceived benefit and social influences for patients and informal caregivers (in six of the
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13 196 12 articles).
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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

202 **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			
Goyal ⁽⁴⁾		x	x		x			x		x	x					x		x	
Jansen ⁽²⁵⁾			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 Busse ⁽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					

203

204 **Legend:** “x” means that the category/theme was mentioned in the article.

205 **Abbreviations:** exp: previous experiences; social: social influences

206 **3.3.1. Appropriateness**

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

212 **3.3.1.1 Necessity**

213 Patients in three studies considered taking CVMs as a necessity, even an obligation, especially
214 in case of past cardiovascular (CV) event or family history of cardiovascular disease (CVD).^{(25,}
215 ^{26, 41)} This view was shared by GPs in two studies, who also deemed necessary to treat patients
216 with unhealthy lifestyle, or presenting many cardiovascular risk factors (CVRF).^(39, 41) Patients
217 and one GP even stated that CVMs should not be stopped until the end of life,^(25, 29, 38, 42) while
218 other patients considered CVMs linked to their survival.⁽⁴⁾ Contrastively, patients at low CV
219 risk and GPs treating patients in primary prevention or patients without any CVRF other than
220 age, considered CVMs less necessary.^(26, 37, 40, 41) Some patients questioned the continuous
221 necessity of their CVM, as they felt that their disease was well-controlled.^(30, 41)

223 **3.3.1.2 Benefit**

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

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3 231 Some patients and informal caregivers also considered CVMs to be beneficial when they saw
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5 232 an objective (e.g., cholesterol levels) or subjective (e.g., less dizziness) improvement under
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7 233 treatment.^(4, 22, 24, 27) Some patients also considered that taking CVMs enabled them to make an
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9 234 active contribution to their health, and to have control over themselves and the future.⁽²⁵⁾

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236 3.3.1.3 ADEs

237 Patients, informal caregivers and HCPs reported ADEs as one of the main reasons to consider
238 stopping CVMs, especially if ADEs were associated with a reduction in quality of life.^{(4, 22-25,}
239 ^{27, 30, 32-35, 39)} Patients usually compliant with medications considered ADEs as a reason to
240 discuss deprescribing with their GP.^(25, 30) Patients considering taking CVMs as a routine to stay
241 healthy were still willing to discontinue their CVMs in case of ADEs.^(25, 30) Contrastively, some
242 patients continued taking their CVMs after balancing ADEs against reasons to take CVMs (i.e.,
243 CVM perceived benefit, minor ADEs.⁽²²⁾ When patients were asymptomatic and had no ADE,
244 patients and GPs were unwilling to deprescribe CVMs.^(30, 39) When ADEs occurred in patients
245 with CVD, GPs were also unwilling to deprescribe.⁽⁴⁰⁾

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247 3.2. Fear

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

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3 256 Conversely, patients fearing ADEs or becoming “dependent” on their CVMs were more willing
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5 257 to deprescribe.^(24, 28) HCPs did not report fear as a facilitator.
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9 10 259 **3.3. Dislike**

11
12 260 CVM dislike was one of the most common facilitators to deprescribing for patients and informal
13
14 261 caregivers, but not for HCPs. Patients stated a general dislike of medications or explained
15
16 262 feeling burdened by the number of medications (CVMs and others), or medication-associated
17
18 263 costs.^(4, 23-25, 27, 30, 41, 42) Other patients were aiming at living a long life without using
19
20 264 medications, or derived a personal pride of not taking medications.^(25, 26) Some patients and
21
22 265 informal caregivers considered CVMs as “not good for health”⁽²⁴⁾ or despised CVMs that
23
24 266 created therapeutic competition (i.e., helping one condition while worsening another one) or
25
26 267 which administration was complicated or disrupted daily routine (e.g., glycaemia before insulin
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28 268 injections).^(4, 27)
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34 35 270 **3.4. Influences**

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37 271 Patient and HCP opinions towards deprescribing were shaped by their previous experiences in
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39 272 deprescribing CVMs, and by social influences. While social influences were reported as a
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41 273 facilitator as frequently than as a barrier by patients and informal caregivers, they were more
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43 274 frequently reported as a barrier to deprescribing by HCPs.
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48 49 276 **3.4.1 Previous experiences**

50
51 277 Patients and HCPs with a positive previous experience with CVM deprescribing were more
52
53 278 amenable to deprescribe again, as opposed to those with a negative previous experience.^{(4, 24, 31,}
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55 279 ^{33, 36, 39, 41)} GPs considered patients feeling better or with improved quality of life after
56
57 280 deprescribing as positive experiences,^(31, 39) and having to restart medications after
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3 281 deprescribing as a negative experience.⁽³⁹⁾ For statins, occurrence or absence of stroke after
4
5 282 deprescribing influenced GPs' and specialists' further actions.^(33, 36)
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10 284 **3.4.2 Social influences**

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12 285 HCPs influenced patients' and informal caregivers' opinion on deprescribing.^(27, 28) Patients
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14 286 were willing to stop one or more CVM if this was proposed by a trusting physician.⁽²⁴⁾ Patients
15
16 287 especially trusted their GP because of their knowledge and the fact that they knew them well.^{(25,}
17
18 288 ^{26, 30, 41)} Some patients also recognized their dependency towards their GP and highlighted their
19
20 289 authority, feeling that it would be inappropriate to discuss their evaluation.⁽³⁰⁾ Others were
21
22 290 waiting for their GP to start discussions about preferences, or were happy to follow their
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24 291 recommendations.^(25, 30)
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28 292 GPs accounted for patient preferences.^(33, 37-40) They considered deprescribing in patients
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30 293 wanting to take less medications.^(37, 38) They continued CVMs in patients expecting longevity
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32 294 or whose family was urging for medication continuation.⁽³⁷⁾ GPs were also unwilling to
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34 295 deprescribe CVMs prescribed by specialists, even if they questioned the indication.^(31-33, 37, 41)
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36 296 Specialists were concerned by interfering with other HCPs' treatment plan.^(35, 36) They were
37
38 297 also unwilling to deprescribe when communication with other HCPs was suboptimal or when
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40 298 patients were reluctant or could not understand the concept of deprescribing.^(35, 42)
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46 300 **3.5. Process**

47
48 301 The process required to deprescribe CVMs was more frequently reported as a barrier than as a
49
50 302 facilitator by HCPs.
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53 303 HCPs and patients reported time constraint, such as lacking time to review medication lists or
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55 304 to discuss CVMs, as a barrier to CVM deprescribing.^(24, 34-36, 39)
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58 305 For patients, a dose-lowering scheme, a close monitoring after deprescribing and a temporary
59
60 306 stopping trial with possibility of medication resumption facilitated the deprescribing process.^{(4,}

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3 307 24, 25, 41) GPs also viewed gradual CVM discontinuation as a facilitator to deprescribing,
4
5 308 especially when they were unsure about CVM risk/benefit ratio.^(32,33) However, they considered
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7 309 the lack of remuneration for the close follow-up needed during gradual discontinuation as a
8
9 310 barrier.⁽³³⁾

311

312 3.6. Uncertainty

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

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

325 Some HCPs and patients also felt uneasy about the uncertainty surrounding possible
326 consequences of CVM deprescribing.^(33, 34, 41) This led to “therapeutic inertia”, even in case of
327 unclear benefits of pursuing CVMs.⁽³⁶⁾ On the contrary, GPs and clinical pharmacists feeling
328 uneasy about possible long-term consequences of taking CVMs were more willing to
329 deprescribe.⁽³³⁾

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333 **3.7. Ambivalence**

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

340 **4. Discussion**

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

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3 358 Barriers and facilitators to deprescribing CVMs did not differ significantly from those of
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5 359 deprescribing general medications.^(19, 43) A systematic review on patients' barriers and
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7 360 facilitators to deprescribing displaying the same structure as ours, reported agreement with
8
9 361 appropriateness of cessation, fear, influences, dislike and process as barriers and/or facilitators
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11 362 to deprescribing.⁽¹⁹⁾ However, this review that included mainly nervous system medications,
12
13 363 did not report uncertainty and ambivalence towards deprescribing, suggesting that these two
14
15 364 factors were more specific to CVM deprescribing. Another systematic review on prescribers'
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17 365 barriers and facilitators to deprescribing potentially inappropriate medications reported inertia
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19 366 as importantly influencing deprescribing.⁽⁴³⁾ In our review, we also found that some HCPs
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21 367 experienced deprescribing inertia, continuing CVMs even if they might be inappropriate, partly
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23 368 because of fear of bad/unknown consequences of deprescribing.
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31 370 Fear of and uncertainty about deprescribing due to unknown/possible negative consequences
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33 371 was indeed frequently mentioned as a barrier to deprescribing in the articles included in this
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35 372 systematic review. Interestingly, while fear was as frequently reported as a barrier by
36
37 373 patients/informal caregivers than by HCPs, uncertainty was more frequently reported as a
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39 374 barrier by HCPs, suggesting a different level of knowledge and feeling of responsibility
40
41 375 between HCPs and patients/informal caregivers. Such uncertainty was also reported in studies
42
43 376 focusing on deprescribing general medications in older, multimorbid adults, potentially because
44
45 377 of the complexity of interactions between diseases and the single-disease focused guidelines
46
47 378 that might not apply to patients with multimorbidity.⁽⁴⁴⁻⁴⁶⁾ However, one of these studies stated
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49 379 that balancing benefits and harms was particularly complicated for preventive medications.⁽⁴⁴⁾
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51 380 Tools to facilitate the deprescribing process and ensure safe CVM deprescribing could help to
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53 381 do so, especially since HCPs in our review frequently reported the deprescribing process as a
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55 382 barrier.
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3 384 While patient/informal caregiver and HCP points of view towards CVM deprescribing were
4
5 385 largely similar, we could highlight differences in the perceived benefit of CVMs in robust
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7 386 versus frail patients. As shown in a study evaluating frail patient beliefs about prescribed
8
9 387 medications, most patients saw their medications as highly necessary.⁽⁴⁷⁾ However, over one-
10
11 388 third of patients included in this study stated that their medications were a mystery to them.⁽⁴⁷⁾
12
13 389 This stresses the fact that patients might see a medication as necessary without being able to
14
15 390 understand its potential (lack of) benefit. HCPs, on the other hand, seemed to place importance
16
17 391 on their patients deriving benefits from their CVMs. Thus, they endorsed deprescribing in frail
18
19 392 patients due to a lack of time to benefit, but renounced deprescribing in robust patients. This
20
21 393 view is concordant with other studies on treating frail and/or robust patients.^(9, 48) Other
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23 394 differences between patients/informal caregivers and HCPs regarded ADE occurrence, that was
24
25 395 slightly more frequently cited as a facilitator in studies on patients/informal caregivers than on
26
27 396 HCPs, and dislike, which was a facilitator to deprescribing only mentioned by patients. These
28
29 397 divergent views emphasize the need for discussion between HCPs and patients/informal
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31 398 caregivers about representations and beliefs, and how these might influence decision-making
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33 399 about deprescribing. This is especially important for HCPs to consider, given how patients rely
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35 400 on them for decision-making and might assume that they do not have to discuss their
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37 401 preferences and beliefs as these are already clear for their HCPs.⁽⁴⁹⁻⁵¹⁾
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47 403 **5. Strengths and limitations**

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49 404 This study has several strengths. First, data extraction, analysis and synthesis, as well as quality
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51 405 assessment were conducted by two independent reviewers on all available data based on a
52
53 406 systematic review. Second, we included both quantitative and qualitative studies, providing
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55 407 complementary information on barriers and facilitators to deprescribing.
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58 408 However, this study also has limitations. First, in some studies, CVMs were part of the
59
60 409 evaluated medications but not the focus. However, this enabled inclusion of more studies and

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3 410 thus exploration of more barriers and facilitators to deprescribing CVMs. Second, as this review
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5 411 focused on CVMs in general, no conclusion can be made on individual CVMs. However,
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7 412 barriers and facilitators did not appear to differ significantly between studies
8
9 413 assessing/exploring different CVMs, which leads to thinking that most barriers and facilitators
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11 414 might be common across CVMs.
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16 416 **6. Implications**

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19 417 The identification of barriers and facilitators to deprescribing CVMs and the quantification of
20
21 418 the reporting frequency at the patient, informal caregiver and HCP levels, have several
22
23 419 implications and call for future actions to address the current lack of evidence regarding
24
25 420 potential benefits and risks of CVM deprescribing. First, differences in opinions between
26
27 421 patients and HCPs, such as CVM benefits and CVM dislike, stress the need for ground
28
29 422 discussions about beliefs and preferences about deprescribing of each stakeholder implicated
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31 423 in the deprescribing decision. Second, the uncertainty about deprescribing CVMs that HCPs
32
33 424 frequently mentioned, HCP wish to account for patient preferences when approaching
34
35 425 deprescribing, and patients relying on HCPs for decision-making highlight the need to translate
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37 426 a part of HCP responsibility in deprescribing to patients, so that decision-making can be shared
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39 427 and jointly carried. To enable this, HCPs must be provided with tools that enable sharing the
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41 428 risks and benefits of deprescribing with patients and ensure a safe deprescribing process.
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43 429 Furthermore, HCPs should be trained on deprescribing processes and changes at the policy
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45 430 making level should provide HCPs with sufficient time and adequate remuneration to approach
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47 431 deprescribing with patients. Less time pressure would also enable patients to feel more
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49 432 comfortable to address deprescribing with their HCPs.
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436 7. Conclusion

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

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23
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3 628 **FIGURE LEGEND:**
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5 629 **Figure 1: Study selection results**
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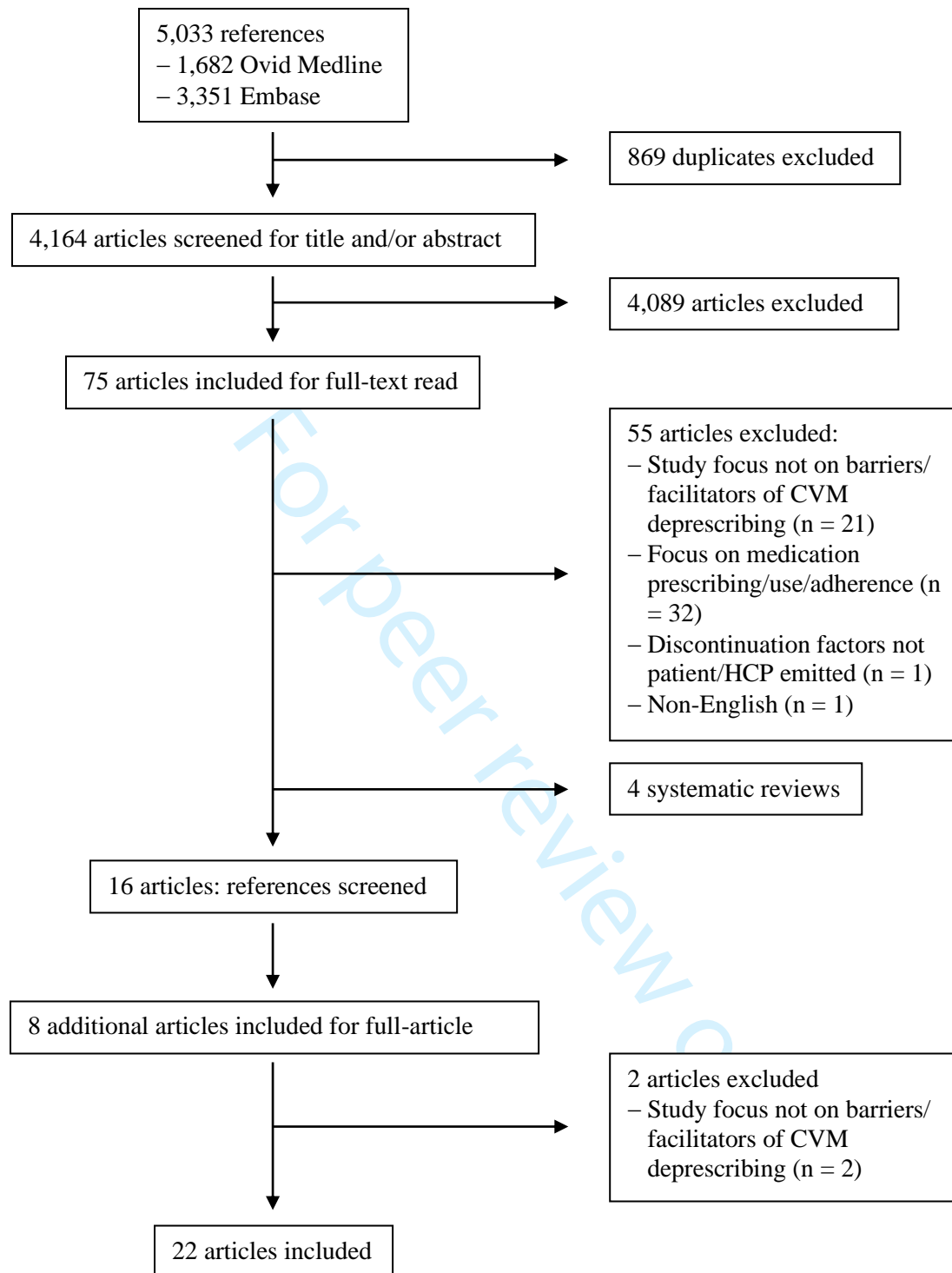
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8 630 **Abbreviations:** CVM: cardiovascular medication; HCP: healthcare providers
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10. Supplemental material

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

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Figure 1: Study selection results

Legend: CVM: cardiovascular medication; HCP: healthcare providers

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

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 4 **COVID/MEDLINE 2021.11.15: 1,682 results**

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 6 Concept 1: cardiovascular medications

- 7 1. exp cardiovascular agents/
 8 2. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
 9 3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase
 10 inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or
 11 "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa
 12 reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or
 13 "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors,
 14 hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors,
 15 hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or
 16 "Cardiovascular medic*" or "cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR
 17 "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic
 18 medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or
 19 "cardiometabolic prescri*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering
 20 treat*" or "lipid-lowering medic*" or "lipid-lowering drug*" or "lipid-lowering agent*" or "lipid-lowering
 21 preparation*" or "lipid-lowering prescri*" or "lipid-lowering therapeutic*").ab,ti.
 22 4. "cardiovascular disease".ab,ti.
 23 5. *cardiovascular diseases/
 24 6. prevention.ab,ti.
 25 7. *primary prevention/
 26 8. *secondary prevention/
 27 9. 4 or 5
 28 10. 6 or 7 or 8
 29 11. 9 and 10

30 Concept 2: prescribing / deprescribing

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

39 Concept 3: barriers and facilitators

- 40 17. *patient acceptance of health care/
 41 18. *patient preference/
 42 19. *attitude to health/
 43 20. *physician-patient relations/
 44 21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or
 45 facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or
 46 willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or
 47 deciding or motivation or conversation or acceptance or acceptability).ti.
 48 22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or
 49 input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or
 50 choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or
 51 motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or
 52 discuss* or discussion*).ti.
 53 23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or
 54 relative* or caregiver*).ti.
 55 24. 22 and 23
 56 25. 1 or 2 or 3 or 11
 57 26. 12 or 13 or 14 or 15 or 16
 58 27. 17 or 18 or 19 or 20 or 21 or 24
 59 28. 25 and 26 and 27
 60 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 "cardiomatabolic medic*" or "cardiomatabolic drug*" or "cardiomatabolic agent*" or "cardiomatabolic preparation*" or "cardiomatabolic prescri*" or "cardiomatabolic therapeutic*" or "cardiomatabolic treat*" or "lipid-lowering treat*" or "lipid-lowering medic*" or "lipid-lowering drug*" or "lipid-lowering agent*" or "lipid-lowering preparation*" or "lipid-lowering prescri*" 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 deprescri* 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 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-medicine]/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

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3	Van Bussel, 2019 (Netherlands)	Primary care	Qualitative	Interviews	15 patients	Mean age: 81	Median of 4 with median of 2 antihypertensives	Antihypertensives	Primary	No	
6	First author	Setting	Design	Data collection mean	N population	Years of experiences	HCPs' patients' characteristics				
9							Age	No of medication taken	Studied CVM(s)	Prevention type	Life- limiting disease
12	Ailabouni, 2016 (New Zealand)	Primary care	Qualitative	Interviews	10 GPs	Unknown	83	17	Antiplatelets, statin, antidiabetics, diuretics, β -blocker, ACE inhibitor	Secondary	No
16	Ailabouni, 2016 (New Zealand)	Primary care	Qualitative	Interviews	10 GPs	2-32	Unspecified (older patients)	Unknown	Unspecified (statin and aspirin mentioned)	Unknown	No
16	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
22	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: \geq 30 years	88	10	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary	Yes
30	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

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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
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

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3	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
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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

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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 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
	Tijja, 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

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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

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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/>

Pre-review only

BMJ Open

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

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Keywords:	Adult cardiology < CARDIOLOGY, GERIATRIC MEDICINE, PRIMARY CARE, QUALITATIVE RESEARCH, VASCULAR MEDICINE

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

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3 **29 ABSTRACT**
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5 **30 Objective:** To synthesize the current knowledge on barriers and facilitators to deprescribing
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8 **31 cardiovascular medications (CVMs) at the levels of patients, informal caregivers, and**
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10 **32 healthcare providers (HCPs).**

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12 **33 Design/Setting:** We conducted a systematic review of studies exploring/assessing patient,
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14 **34 informal caregiver and/or HCP barriers and/or facilitators to deprescribing CVMs.**

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16 **35 Data sources:** Ovid/MEDLINE and Embase from January 2003 to November 2021.

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18 **36 Data extraction and synthesis:** We performed a deductive thematic analysis based on the
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20 **37 framework of specific barriers and facilitators to deprescribing CVMs created by Goyal et al.**
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22 **38 We added a quantification of the occurrence of categories and themes in the selected articles to**
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24 **39 identify the resounding themes that indicate the greater impetus to address in future research.**

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26 **40 Results:** Most frequent deprescribing barriers for patients, informal caregivers and HCPs
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28 **41 included uncertainty due to lack of evidence regarding CVM deprescribing (in n=10 studies),**
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30 **42 fear of negative consequences following deprescribing (n=13), and social influences (n=14). A**
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32 **43 frequently reported facilitator to deprescribing, especially for patients and informal caregivers,**
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34 **44 was the occurrence of ADEs (n=7). Another frequently reported facilitator for patients were**
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36 **45 dislike of CVMs (n=9). Necessity and benefit of CVMs were seen as barriers or facilitators**
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38 **46 similarly by patients and HCPs.**

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40 **47 Conclusion:** The differences in patient, informal caregiver and HCP regarding barriers and
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42 **48 facilitators to deprescribing CVMs stress the need for ground discussions about beliefs and**
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44 **49 preferences of each stakeholder implicated in deprescribing decisions. Furthermore, HCP**
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46 **50 uncertainty regarding CVM deprescribing highlights the need to provide HCPs with tools that**
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48 **51 enable sharing the risks and benefits of deprescribing with patients and ensure a safe**
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50 **52 deprescribing process.**

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52 **53 Review registration on Prospero: CRD42020221973**
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3 55 Strengths and limitations of this study:
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- 5 56 • Systematic review process with publication review; data extraction, analysis and
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7 synthesis; and quality assessment independently conducted by two independent
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9 reviewers.
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12 59 • Assessment of both quantitative and qualitative studies, providing complementary
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14 information on barriers and facilitators to deprescribing.
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17 61 • In some studies, cardiovascular medications were part of, but not the focus of the
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19 medications evaluated.
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22 63 • We did not assess specific classes of cardiovascular medications.
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24 64 • The majority of healthcare providers were general practitioners, whose perspectives
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26 might differ from those of other healthcare providers.
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31 67 Key words: cardiovascular medication, deprescribing, barriers, facilitators, older people
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71 1. Introduction

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

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

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

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

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97 2. Methods

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

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101 2.1. Types of studies and inclusion criteria

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

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108 2.2. Search strategy

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

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

123 2.3. Data extraction and analysis

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

140 2.4. Risk of bias and quality assessment

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

146 2.5. Patient and Public Involvement:

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

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3 149 **3. Results**
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5 150 3.1. Study selection and characteristics
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8 151 Among the 4,164 unique studies identified, 71 were included for full-text assessment (**Figure**
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10 152 **1**). Among those, 16 fulfilled inclusion criteria. Through hand-searching, six additional studies
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12 153 were included, leading to a total of 22 publications that were included for data extraction and
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14 154 analysis. Ten studies focused on patients and/or informal caregivers, ten studies on HCPs and
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17 155 two studies on patients and/or informal caregivers and HCPs. Overall, the CVMs most
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19 156 frequently discussed were lipid lowering therapies, especially statins (mentioned in 12 studies).
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21 157 Eleven studies focused on older patients (median or mean patient age of 74 years) Among HCP
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24 158 studies, the most represented HCPs were general practitioners (in 10 studies). Study
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26 159 characteristics are presented in **Tables 1** and detailed in **Supplemental Material S2**.
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3 161 **Table 1: main characteristics of studies reporting patient, informal caregiver and HCP barriers and facilitators to deprescribing CVMs**

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Patients and informal caregivers	First author, publication year	N population	Age	Studied CVM(s)	Prevention type
	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	
HCPs	First author, publication year	N population	Characteristics of patients cared for by study HCPs		
			Age	Studies CVM(s)	Prevention type
	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	

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3	Geijteman, 2018 (Netherlands) ⁽³⁴⁾	174 GPs, 147 clinical specialists	88 years	ACE inhibitor, statin, anticoagulant, diuretic, antidiabetic	Secondary
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7	Goyal, 2020 (USA) ⁽³⁵⁾	184 geriatricians, 182 general internists, 87 cardiologists	79 years	4 CV medications	Unknown
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10	Green, 2019 (USA) ⁽³⁶⁾	19 physicians, 2 nurse practitioners	Unspecified (older pts)	Unspecified (identified: statins, oral anticoagulants, antidiabetics)	Unknown
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12					
13	Jansen, 2017 (Australia) ⁽³⁷⁾	25 GPs	≥75 years	Preventive CV medication	Primary
14					
15	Thompson, 2020 (Denmark) ⁽³⁸⁾	11 GPs	≥ 80 years	Statins	Unknown
16					
17	Van Middelaar, 2020 (Netherlands) ⁽³⁹⁾	15 GPs	Unspecified (older pts)	Antihypertensives	Unknown
18					
19	Van der Ploeg, 2018 (30 countries) ⁽⁴⁰⁾	2250 GPs	≥ 80 years	Statins	Primary & secondary
20	First author, publication year	N population	Characteristics of patients		
21			Age	Studied CVM(s)	Prevention type
22					
23	Luymes, 2016 (Netherlands) ⁽⁴¹⁾	10 GPs, 49 patients	Median age: 55 years	Antihypertensives, lipid-lowering drugs	Primary
24					
25					
26	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
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Patients & informal caregivers & HCPS

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

168 3.2. Quality assessment

169 Details of each study quality assessment can be found in **Supplemental Material S3**. Of the
170 15 qualitative studies included in this systematic review, 14 were deemed of good quality,^{(4, 22,}
171 24, 25, 27, 30, 31, 33, 36-39, 41, 42) while one lacked data to support interpretation of the results.⁽³²⁾ Five
172 of the six included quantitative studies did not provide sample representative of the target
173 population, as nonresponse was high, increasing the risk of nonresponse bias.^(28, 29, 34, 35, 40) The
174 sixth quantitative study provided few details on the method used for data analysis.⁽²³⁾ The only
175 mixed methods study included failed to address divergences between quantitative and
176 qualitative results.⁽²⁶⁾ We did not exclude any study based on the quality assessment, as our aim
177 was to describe all available data regarding barriers and facilitators to deprescribing CVMs.

179 3.3. Thematic analysis

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

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3 194 reported in n=7. Social influences were another barrier frequently mentioned by HCPs (reported
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5 195 in n=10). Additional frequent barriers were uncertainty for HCPs (reported in n=7), and
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7 196 perceived benefit and social influences for patients and informal caregivers (reported in n=6).
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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

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202 **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	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 Busse ⁽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	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	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					

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204 **Legend:** “x” means that the category/theme was mentioned in the article.

205 **Abbreviations:** exp: previous experiences; social: social influences

206 3.3.1. Appropriateness

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

212 3.3.1.1 Necessity

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

227 3.3.1.2 Benefit

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

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3 232 good physical and cognitive function or few comorbidities, especially if they presented no
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5 233 CVM-related ADEs, expecting them to derive a higher benefit from CVMs.^(32, 33, 37-39) In
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7 234 contrast, GPs and specialists considered patients with a short life expectancy, cognitive
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9 235 impairment, or living in palliative/nursing homes less likely to benefit from CVMs.^(33-38, 40)
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11 236 They felt that, in these cases, prolonging life or avoiding a CV event should not be the main
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13 237 objective of care.⁽³⁷⁾ However, frail patients were less willing to stop their statin than robust
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15 238 ones.⁽²⁸⁾

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17 239 Some patients and informal caregivers also considered CVMs to be beneficial when they saw
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19 240 an objective (e.g., cholesterol levels) or subjective (e.g., less dizziness) improvement under
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21 241 treatment.^(4, 22, 24, 27) Some patients also considered that taking CVMs enabled them to make an
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23 242 active contribution to their health, and to have control over themselves and the future.⁽²⁵⁾

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30 244 **3.3.1.3 ADEs**

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32 245 Patients, informal caregivers and HCPs reported ADEs as one of the main facilitators to
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34 246 stopping CVMs, especially if ADEs were associated with a reduction in quality of life (n=7 for
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36 247 patients and n=5 for HCPs).^(4, 22-25, 27, 30, 32-35, 39) Patients usually compliant with medications
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38 248 considered ADEs as a reason to discuss deprescribing with their GP.^(25, 30) Patients considering
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40 249 taking CVMs as a routine to stay healthy were still willing to discontinue their CVMs in case
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42 250 of ADEs.^(25, 30) ADEs were not formally reported as barriers to deprescribing, but were put in
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44 251 perspective by patients/informal caregivers (n=2)^(22, 30) and HCPs (n=2).^(39, 40) Some patients
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46 252 continued taking their CVMs after balancing ADEs against reasons to take CVMs (i.e., CVM
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48 253 perceived benefit, minor ADEs).⁽²²⁾ When patients were asymptomatic and had no ADE,
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50 254 patients and GPs were unwilling to deprescribe CVMs.^(30, 39) When ADEs occurred in patients
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52 255 with CVD, GPs were also unwilling to deprescribe.⁽⁴⁰⁾

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258 3.2. Fear

259 Fear of consequences following CVM deprescribing was reported as a barrier to deprescribing
260 by patients/informal caregivers (n=7)^(4, 24-27, 30, 41) and HCPs (n=7).^(31-33, 35, 36, 39, 41) In multiple
261 studies, patients stated their fear of a return of the previous condition, health deterioration,
262 becoming a burden, or a shorter lifespan following deprescribing.^(4, 25-27, 30, 41) Some linked this
263 fear with the perceived severity of their disease.^(24, 27) These concerns were shared by informal
264 caregivers. GPs and specialists feared harming patients by deprescribing (e.g., occurrence of
265 CV event with functional limitation, death),^(31-33, 35, 36, 39, 41) and giving patients the feeling that
266 they were giving up on them, especially by deprescribing towards the end of life, a feeling not
267 shared by patients.^(29, 31, 34, 36, 39)
268 Conversely, patients fearing ADEs or becoming “dependent” on their CVMs were more willing
269 to deprescribe (n=3).^(24, 28, 29) HCPs did not report fear as a facilitator (n=0).

271 3.3. Dislike

272 CVM dislike was a facilitator to deprescribing for patients and informal caregivers (n=9),<sup>(4, 23-
273 27, 30, 41, 42)</sup> but not for HCPs (n=0). Dislike was never reported as a barrier by patients/informal
274 caregivers (n=0) or by HCPs (n=0). Patients stated a general dislike of medications or explained
275 feeling burdened by the number of medications (CVMs and others), or medication-associated
276 costs.^(4, 23-25, 27, 30, 41, 42) Other patients were aiming at living a long life without using
277 medications, or derived a personal pride of not taking medications.^(25, 26) Some patients and
278 informal caregivers considered CVMs as “not good for health”⁽²⁴⁾ or despised CVMs that
279 created therapeutic competition (i.e., helping one condition while worsening another one) or
280 which administration was complicated or disrupted daily routine (e.g., glycaemia before insulin
281 injections).^(4, 27)

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284 **3.4. Influences**

285 Patient and HCP opinions towards deprescribing were shaped by their previous experiences in
286 deprescribing CVMs, and by social influences. While social influences were reported as a
287 barrier (n=4)^(25-27, 30) almost as frequently as a facilitator (n=6)^(24-28, 41) by patients and informal
288 caregivers, they were more frequently reported as a barrier (n=10)^(31-33, 35-37, 39-42) to
289 deprescribing by HCPs. Previous experiences were less reported than social influences and
290 almost as often by patients and informal caregivers (reported both as a facilitator and a barrier
291 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,}
292 36, 39, 41)

294 **3.4.1 Previous experiences**

295 Patients and HCPs with a positive previous experience with CVM deprescribing were more
296 amenable to deprescribe again, as opposed to those with a negative previous experience.^{(4, 24, 31,}
297 33, 36, 39, 41) GPs considered patients feeling better or with improved quality of life after
298 deprescribing as positive experiences,^(31, 39) and having to restart medications after
299 deprescribing as a negative experience.⁽³⁹⁾ For statins, occurrence or absence of stroke after
300 deprescribing influenced GPs' and specialists' further actions.^(33, 36)

302 **3.4.2 Social influences**

303 HCPs influenced patients' and informal caregivers' opinion on deprescribing.^(27, 28) Patients
304 were willing to stop one or more CVM if this was proposed by a trusting physician.⁽²⁴⁾ Patients
305 especially trusted their GP because of their knowledge and the fact that they knew them well.^{(25,}
306 26, 30, 41) Some patients also recognized their dependency towards their GP and highlighted their
307 authority, feeling that it would be inappropriate to discuss their evaluation.⁽³⁰⁾ Others were
308 waiting for their GP to start discussions about preferences, or were happy to follow their
309 recommendations.^(25, 30)

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3 310 GPs accounted for patient preferences.^(33, 37-40) They considered deprescribing in patients
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5 311 wanting to take less medications.^(37, 38) They continued CVMs in patients expecting longevity
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7 312 or whose family was urging for medication continuation.⁽³⁷⁾ GPs were also unwilling to
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9 313 deprescribe CVMs prescribed by specialists, even if they questioned the indication.^(31-33, 37, 41)
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11 314 Specialists were concerned by interfering with other HCPs' treatment plan.^(35, 36) They were
12
13 315 also unwilling to deprescribe when communication with other HCPs was suboptimal or when
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15 316 patients were reluctant or could not understand the concept of deprescribing.^(35, 42)
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22 318 **3.5. Process**

23
24 319 The process required to deprescribe CVMs was more frequently reported as a barrier (n=6)⁽³³⁻
25
26 320 ^{36, 39, 41)} than as a facilitator (n=2)^(32, 33) by HCPs. For patients and informal caregivers, this
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28 321 process was more frequently reported as a facilitator (n=4)^(4, 24, 25, 41) than a barrier (n=2).^(24, 41)
29
30 322 HCPs and patients reported time constraint, such as lacking time to review medication lists or
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32 323 to discuss CVMs, as a barrier to CVM deprescribing.^(24, 34-36, 39)
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34 324 For patients, a dose-lowering scheme, a close monitoring after deprescribing and a temporary
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36 325 stopping trial with possibility of medication resumption facilitated the deprescribing process.^{(4,}
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38 326 ^{24, 25, 41)} GPs also viewed gradual CVM discontinuation as a facilitator to deprescribing,
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40 327 especially when they were unsure about CVM risk/benefit ratio.^(32, 33) However, they considered
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42 328 the lack of remuneration for the close follow-up needed during gradual discontinuation as a
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44 329 barrier.⁽³³⁾
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51 331 **3.6. Uncertainty**

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53 332 Uncertainty was reported more often by HCPs (n=7)^(31, 33-37, 39) than patient and informal
54
55 333 caregiver (n=3),^(4, 24, 30) and acted almost exclusively as a barrier to deprescribing for both
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57 334 groups. HCPs formulated the lack of evidence about CVM deprescribing as a barrier, especially
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59 335 in older patients or those with dementia.^(31, 35, 36) GPs found complicated to know when to
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3 336 deprescribe preventive medications – especially in patients neither frail nor robust^(31, 39) – and
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5 337 how to balance CVM harms and benefits when approaching deprescribing.⁽³⁷⁾ One clinical
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7 338 pharmacist explained having difficulties making professional recommendations about statin
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9 339 deprescribing in older patients.⁽³³⁾ Specialists regretted the limited training on deprescribing.⁽³⁵⁾
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11 340 Patients expressed a lack of understanding of CVDs and risk reduction with CVMs, as well as
12
13 341 uncertainty regarding potential risks and benefits of CVMs, thus feeling uncertain about the
14
15 342 value of deprescribing.^(4, 24, 30) They were also confused by conflicting treatment targets
16
17 343 mentioned by HCPs.⁽²⁴⁾
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19 344 Some HCPs and patients also felt uneasy about the uncertainty surrounding possible
20
21 345 consequences of CVM deprescribing.^(33, 34, 41) This led to “therapeutic inertia”, even in case of
22
23 346 unclear benefits of pursuing CVMs.⁽³⁶⁾ On the contrary, GPs and clinical pharmacists feeling
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25 347 uneasy about possible long-term consequences of taking CVMs were more willing to
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27 348 deprescribe.⁽³³⁾
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35 350 **3.7. Ambivalence**

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37 351 Patients expressed ambivalence about CVM use, prompting them to wish CVM continuation
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39 352 and deprescribing concurrently (n=2).^(4, 30) They were concerned about the effects of CVMs on
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41 353 their health, but also about what could happen if they did not take them.⁽⁴⁾ They also showed
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43 354 aversion towards CVMs coupled with a feeling of obligation to take them.^(4, 30) HCPs did not
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45 355 express ambivalence (n=0).
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362 4. Discussion

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

378
379 While there is increasing literature on barriers and facilitators to deprescribing, there is little
380 literature focusing specifically on barriers and facilitators to deprescribing CVMs. Our review
381 provides readers with a current state of the knowledge on the perspectives of different
382 stakeholders (i.e., patients, informal caregivers and HCPs) regarding deprescribing of such
383 medications and its specific challenges. Other studies focusing on deprescribing of other
384 medication types or potentially inappropriate medications showed barriers and facilitators that
385 were similar to some found in our review⁽⁴³⁻⁴⁷⁾. On the patient level, these studies reported
386 experiencing ADEs or feeling burdened by the medications as facilitators,^(46, 47) and seeing the
387 medications as necessary or beneficial as a barrier.⁽⁴⁵⁾ On the HCP level, these studies reported

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3 388 gradual deprescribing as a facilitator,⁽⁴⁶⁾ and fear of unknown or negative consequences
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5 389 following deprescribing, or like of time to approach deprescribing as barriers.^(43, 44, 46)
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8 390 Furthermore, a systematic review on patient barriers and facilitators to deprescribing also
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10 391 reported agreement with appropriateness of cessation, fear, influences, dislike and process as
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12 392 barriers and/or facilitators to deprescribing.⁽¹⁹⁾ However, this review that included mainly
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14 393 nervous system medications, did not report uncertainty and ambivalence towards deprescribing.
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17 394 This suggests that these two factors are more specific to CVM deprescribing and might reflect
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19 395 the remaining controversy surrounding deprescribing of some of these medications (e.g.,
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21 396 statins).
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26 398 Fear of and uncertainty about deprescribing due to unknown/possible negative consequences
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28 399 was frequently mentioned as a barrier to deprescribing in the articles included in this systematic
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30 400 review. Interestingly, while fear was as frequently reported as a barrier by patients/informal
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32 401 caregivers than by HCPs, uncertainty was more frequently reported as a barrier by HCPs,
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34 402 suggesting a different level of knowledge and feeling of responsibility between HCPs and
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36 403 patients/informal caregivers. Such uncertainty was also reported in studies focusing on
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38 404 deprescribing general medications in older, multimorbid adults, potentially because of the
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40 405 complexity of interactions between diseases and the single-disease focused guidelines that
41
42 406 might not apply to patients with multimorbidity.⁽⁴⁸⁻⁵⁰⁾ However, one of these studies stated that
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44 407 balancing benefits and harms was particularly complicated for preventive medications.⁽⁴⁸⁾ Tools
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46 408 to facilitate the deprescribing process and ensure safe CVM deprescribing could help to do so,
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48 409 especially since HCPs in our review frequently reported the deprescribing process as a barrier.
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54 411 While patient/informal caregiver and HCP points of view towards CVM deprescribing were
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56 412 largely similar, we could highlight differences in the perceived benefit of CVMs in robust
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58 413 versus frail patients. As shown in a study evaluating frail patient beliefs about prescribed
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3 414 medications, most patients saw their medications as highly necessary.⁽⁵¹⁾ However, over one-
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5 415 third of patients included in this study stated that their medications were a mystery to them.⁽⁵¹⁾
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7 416 This stresses the fact that patients might see a medication as necessary without being able to
8
9 417 understand its potential (lack of) benefit. HCPs, on the other hand, seemed to place importance
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11 418 on their patients deriving benefits from their CVMs. Thus, they endorsed deprescribing in frail
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13 419 patients due to a lack of time to benefit, but renounced deprescribing in robust patients. This
14
15 420 view is concordant with other studies on treating frail and/or robust patients.^(9, 52) Other
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17 421 differences between patients/informal caregivers and HCPs regarded ADE occurrence, that was
18
19 422 slightly more frequently cited as a facilitator in studies on patients/informal caregivers than on
20
21 423 HCPs, and dislike, which was a facilitator to deprescribing only mentioned by patients. These
22
23 424 divergent views emphasize the need for discussion between HCPs and patients/informal
24
25 425 caregivers about representations and beliefs, and how these might influence decision-making
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27 426 about deprescribing. This is especially important for HCPs to consider, given how patients rely
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29 427 on them for decision-making and might assume that they do not have to discuss their
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31 428 preferences and beliefs as these are already clear for their HCPs.⁽⁵³⁻⁵⁵⁾
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430 **5. Strengths and limitations**

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

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

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3 440 assessing/exploring different CVMs, which leads to thinking that most barriers and facilitators
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5 441 might be common across CVMs. Third, the studies reporting HCP barriers and facilitators to
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7 442 deprescribing CVMs encompass mostly GP barrier and facilitators, which may differ from
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9 443 those of other healthcare providers.
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14 445 **6. Implications**

16 446 The identification of barriers and facilitators to deprescribing CVMs, and the quantification of
17
18 447 the reporting frequency at the patient, informal caregiver and HCP levels, have several
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20 448 implications and call for future actions to address the current lack of evidence regarding
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22 449 potential benefits and risks of some CVM deprescribing. First, differences in opinions between
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24 450 patients and HCPs, such as CVM benefits and CVM dislike, stress the need for ground
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26 451 discussions about beliefs and preferences about deprescribing of each stakeholder implicated
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28 452 in the deprescribing decision. Second, the uncertainty about deprescribing CVMs that HCPs
29
30 453 frequently mentioned, HCP wish to account for patient preferences when approaching
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32 454 deprescribing, and patients relying on HCPs for decision-making highlight the need to translate
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34 455 a part of HCP responsibility in deprescribing to patients, so that decision-making can be shared
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36 456 and jointly carried. To enable this, HCPs must be provided with tools that enable sharing the
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38 457 risks and benefits of deprescribing with patients and ensure a safe deprescribing process.
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40 458 Furthermore, HCPs should be trained on deprescribing processes and changes at the policy
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42 459 making level should provide HCPs with sufficient time and adequate remuneration to approach
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44 460 deprescribing with patients. Less time pressure would also enable patients to feel more
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46 461 comfortable to address deprescribing with their HCPs.
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466 7. Conclusion

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

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484 CEA, LB and NR designed the study protocol. CEA and LB extracted and analyzed the data.

485 CEA, LB and NR drafted the article. All authors gave final approval to submit the article.

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24 501 8.6. Competing interests statement:
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26 502 Nothing to disclose.
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30 504 **9. Ethics approval**
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32 505 An ethics approval was not needed for this study, since it was a review of the literature.
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683 **FIGURE LEGEND:**

684 **Figure 1: Study selection results**

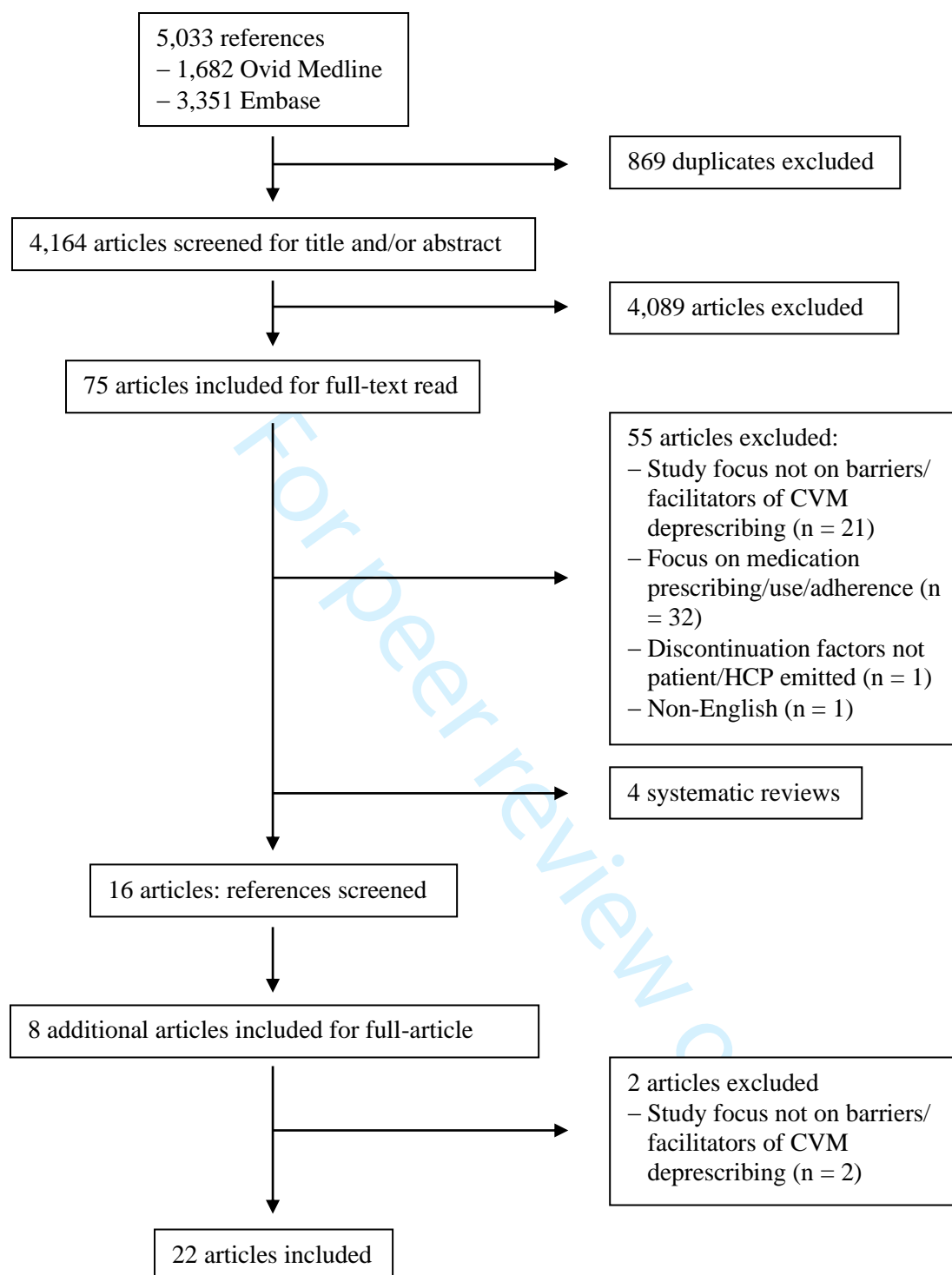
685 **Abbreviations:** CVM: cardiovascular medication; HCP: healthcare providers

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11. Supplemental material

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

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Figure 1: Study selection results

Legend: CVM: cardiovascular medication; HCP: healthcare providers

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

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 4 **OVID/MEDLINE 2021.11.15: 1,682 results**

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 6 Concept 1: cardiovascular medications

- 7 1. exp cardiovascular agents/
 8 2. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
 9 3. ("hmg coa reductase inhibitors" or "hmg-coa reductase inhibitors" or "hydroxymethylglutaryl coa reductase
 10 inhibitors" or "hydroxymethylglutaryl-coa inhibitors" or "hydroxymethylglutaryl-coa reductase inhibitors" or
 11 "hydroxymethylglutaryl-coenzyme a inhibitors" or "inhibitors, hmg coa reductase" or "inhibitors, hmg-coa
 12 reductase" or "inhibitors, hydroxymethylglutaryl coa" or "inhibitors, hydroxymethylglutaryl coenzyme a" or
 13 "inhibitors, hydroxymethylglutaryl-coa" or "inhibitors, hydroxymethylglutaryl-coa reductase" or "inhibitors,
 14 hydroxymethylglutaryl-coenzyme a" or "reductase inhibitors, hmg-coa" or "reductase inhibitors,
 15 hydroxymethylglutaryl-coa" or "hmg-coa statins" or statins or "statins, hmg coa" or "statins, hmg-coa" or
 16 "Cardiovascular medic*" or "cardiovascular drug*" or "cardiovascular preparation*" or "cardiovascular medic*" OR
 17 "cardiovascular prescri*" or "cardiovascular therapeutic*" or "cardiovascular treat*" or "cardiometabolic
 18 medic*" or "cardiometabolic drug*" or "cardiometabolic agent*" or "cardiometabolic preparation*" or
 19 "cardiometabolic prescri*" or "cardiometabolic therapeutic*" or "cardiometabolic treat*" or "lipid-lowering
 20 treat*" or "lipid-lowering medic*" or "lipid-lowering drug*" or "lipid-lowering agent*" or "lipid-lowering
 21 preparation*" or "lipid-lowering prescri*" or "lipid-lowering therapeutic*").ab,ti.
 22 4. "cardiovascular disease".ab,ti.
 23 5. *cardiovascular diseases/
 24 6. prevention.ab,ti.
 25 7. *primary prevention/
 26 8. *secondary prevention/
 27 9. 4 or 5
 28 10. 6 or 7 or 8
 29 11. 9 and 10

30 Concept 2: prescribing / deprescribing

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

39 Concept 3: barriers and facilitators

- 40 17. *patient acceptance of health care/
 41 18. *patient preference/
 42 19. *attitude to health/
 43 20. *physician-patient relations/
 44 21. (barriers or barrier or issues or issue or problems or problem or hinder or hindered or hinders or facilitate or
 45 facilitates or facilitated or facilitator or facilitators or ease or easy or easier or difficult or difficulty or
 46 willingness or belief or believe* or preference* or willing or dialog* or conversation* or decision or decide* or
 47 deciding or motivation or conversation or acceptance or acceptability).ti.
 48 22. (perceptions or perception or behaviors or behavior or behaviour or behaviours or attitudes or attitude or
 49 input or inputs or experience or experiences or value or values or perspective* or expectation* or choice or
 50 choices or empower* or choose* or choosing or acceptance or acceptability or knowledge* or preference* or
 51 motivation* or intention* or involv* or engag* or consult* or interact* or involv* or satisfaction or satisfied or
 52 discuss* or discussion*).ti.
 53 23. (GP* or pharmacist* or physician* or provider* or patient* or "general practitioner*" or patient* or adult* or
 54 relative* or caregiver*).ti.
 55 24. 22 and 23
 56 25. 1 or 2 or 3 or 11
 57 26. 12 or 13 or 14 or 15 or 16
 58 27. 17 or 18 or 19 or 20 or 21 or 24
 59 28. 25 and 26 and 27
 60 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 "cardiomatabolic medic*" or "cardiomatabolic drug*" or "cardiomatabolic agent*" or "cardiomatabolic preparation*" or "cardiomatabolic prescri*" or "cardiomatabolic therapeutic*" or "cardiomatabolic treat*" or "lipid-lowering treat*" or "lipid-lowering medic*" or "lipid-lowering drug*" or "lipid-lowering agent*" or "lipid-lowering preparation*" or "lipid-lowering prescri*" 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 deprescri* 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 problem 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-medicine]/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

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

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3	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
4	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
5	Thompson, 2020 (Denmark)	Primary care	Qualitative	Interviews	11 GPs	Mean of 9	≥ 80	Unknown	Statin	Unknown	Yes and no
6	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
7	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
8	First author	Setting	Design	Data collection mean	N population	Years of experiences	HCPs' patients' characteristics				
9							Age	No of medication taken	Studied CVM(s)	Prevention type	Life-limiting disease
10	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

PATIENTS, INFORMAL

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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
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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

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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 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	

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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

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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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