

1 **How to optimize the adherence to a guideline-directed medical therapy in the**
2 **secondary prevention of cardiovascular diseases: a clinical consensus statement from**
3 **the European Association of Preventive Cardiology (EAPC)**

4
5 ***Roberto F.E. Pedretti**, MD: Cardiovascular Department, IRCCS MultiMedica, Sesto San Giovanni, Milano, Italy

6 ***Dominique Hansen**, PhD: REVAL/BIOMED, Hasselt University, Belgium, Heart Centre Hasselt, Jessa Hospital,
7 Hasselt, Belgium

8 **Marco Ambrosetti** , MD: Cardiovascular Rehabilitation Unit, ASST Crema, Santa Marta Hospital, Rivolta D'
9 Adda, Italy.

10 **Maria Back**, PhD: Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy,
11 University of Gothenburg and Department of Health, Medicine and Caring Sciences, Linköping University,
12 Sweden.

13 **Thomas Berger**, MD: Cardiomed Linz, St.John of God Hospital Linz, Austria

14 **Mariana Cordeiro Ferreira**, Psychologist, Centro de Reabilitação Cardiovascular do Centro Universitário
15 Hospitalar Lisboa Norte, Portugal

16 **Véronique Cornelissen**, PhD: Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium

17 **Constantinos H Davos**, MD, PhD: Cardiovascular Research Laboratory, Biomedical Research Foundation,
18 Academy of Athens, Athens, Greece

19 **Wolfram Doehner**, MD, PhD: BIH Center for Regenerative Therapies (BCRT), Berlin Institute of Health at Charité
20 - Universitätsmedizin Berlin, Berlin, Germany, Department of Cardiology (Virchow Klinikum), Charité
21 Universitätsmedizin Berlin, and German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin,
22 Germany, Center for Stroke Research Berlin, Charité-Universitätsmedizin Berlin, Berlin, Germany.

23 **Carmen de Pablo y Zarzosa**, MD, PhD: Department of Cardiology. University Hospital Ramón y Cajal, Madrid,
24 Spain

25 **Ines Frederix**, MD, PhD: Heart Centre Hasselt, Jessa Hospital Hasselt Belgium, Hasselt University, Faculty of
26 Medicine and Life Sciences Diepenbeek Belgium, University of Antwerp, Faculty of Medicine and Health
27 Sciences Antwerp Belgium, Antwerp University Hospital Edegem Belgium.

28 **Andrea Greco**, PhD: Department of Human and Social Sciences, University of Bergamo, Bergamo, Italy

29 **Donata Kurpas**, MD, PhD: Department of Family Medicine, Wroclaw Medical University, Poland

1 **Matthias Michal**, MD: Department of Psychosomatic Medicine and Psychotherapy, University Medical Center
2 Mainz, Mainz, Germany; German Center for Cardiovascular Research (DZHK), Partner Site Rhine-Main, Mainz,
3 Germany

4 **Elena Osto** , MD, PhD: Institute of Clinical Chemistry & Department of Cardiology, Heart Center, University &
5 University Hospital Zurich, Zurich, Switzerland

6 **Susanne Pedersen**, PhD: Department of Psychology, University of Southern Denmark, Odense Denmark, and
7 Department of Cardiology, Odense University Hospital, Odense, Denmark

8 **Rita Esmeralda Salvador**, MD, PhD: Vienna, Austria

9 **Maria Simonenko**, MD, PhD: Heart Transplantation Outpatient Department, Cardiopulmonary Exercise Test
10 Research Department, Almazov National Medical Research Centre, St. Petersburg, Russia

11 **Patrizia Steca** , PhD: Department of Psychology, University of Milan-Bicocca, Italy

12 **David R. Thompson**, PhD: School of Nursing and Midwifery, Queen's University Belfast, Belfast, UK

13 ****Matthias Wilhelm**, MD: Department of Cardiology, Bern University Hospital, University of Bern, Bern,
14 Switzerland

15 **** Ana Abreu**, MD, PhD: Department of Cardiology of Hospital Santa Maria, Centro Hospitalar Universitário
16 Lisboa Norte, Institute of Preventive Medicine and Institute of Environmental Health of the Faculty of Medicine
17 of University of Lisbon, Centre of Cardiovascular Investigation of University of Lisbon (CCUL) and Academic
18 Centre of Medicine of University of Lisbon (CAML), Portugal

19

20 *Shared first authorship

21 **Shared last authorship

22 Running title: Adherence in secondary prevention of CVD

23

24 Sources of funding: none

25 Conflicts of interest: none to be declared by the authors

26

27 Address correspondence:

28 Roberto F.E. Pedretti, MD, FESC

29 Cardiovascular Department, IRCCS MultiMedica

30 Via Milanese, 30, I-20099, Sesto San Giovanni, Milano, Italy

31 E-mail: robertofrancoenrico.pedretti@multimedica.it

1 **Abstract**

2 A key factor to successful secondary prevention of cardiovascular disease (CVD) is optimal patient adherence to
3 treatment. However, unsatisfactory rates of adherence to treatment for CVD risk factors and CVD have been
4 observed consistently over the last few decades. Hence, achieving optimal adherence to lifestyle measures and
5 guideline-directed medical therapy in secondary prevention and rehabilitation is a great challenge to many
6 healthcare professionals. Therefore, in this European Association of Preventive Cardiology (EAPC) clinical
7 consensus document a modern reappraisal of the adherence to optimal treatment is provided, together with
8 simple, practical, and feasible suggestions to achieve this goal in the clinical setting, focusing on evidence-
9 based concepts.

10

11 Keywords: cardiovascular disease, cardiovascular risk, secondary prevention, adherence

12

13

ACCEPTED MANUSCRIPT

1 **Introduction**

2 In secondary prevention of cardiovascular disease (CVD), significant room for improvement is present as many
3 lifestyle measures and/or guideline-directed medical therapy remain too poor.[1,2] Medication adherence
4 ranges from 50% for primary CVD prevention to 66% for secondary prevention; of all medication-related
5 hospital admissions in the United States, 33 to 69 % and approximately 9% of CVD cases in Europe can be
6 attributed to poor medication adherence.[3–5]

7 In this regard, sufficient treatment adherence is a key element for (i) improving prognosis in CVD and/or high-
8 risk patients, (ii) reducing the burden of morbidity and mortality associated with CVD, and (iii) decreasing costs
9 due to rehospitalizations.[6] The promotion of treatment adherence should embrace all pharmacological and
10 non-pharmacological interventions in secondary CVD prevention, including lifestyle and behavioural changes.
11 In this perspective, multidisciplinary CVD prevention and rehabilitation programs are the most appropriate and
12 cost-effective settings for delivering structured and multi-component interventions on patients' adherence.

13 Despite the realization that treatment adherence is a key aspect of successful secondary CVD prevention,
14 optimisation of treatment adherence remains a great challenge to many healthcare professionals. In coronary
15 artery disease (CAD) patients, ≥ 6 months after hospital discharge, 42% still had a blood pressure $\geq 140/90$
16 mmHg, 71% still had low-density lipoprotein cholesterol ≥ 1.8 mmol/L (≥ 70 mg/dL) and 29% had insufficiently
17 controlled diabetes.[1]. In the EUROASPIRE IV and V surveys, 16259 coronary artery disease (CAD) patients
18 were examined and interviewed during a study visit ≥ 6 months after hospital discharge.[2] Data gathering was
19 fully standardized and the Brief Illness Perception questionnaire was completed by a subsample of 2379
20 patients.[2] Half of those who were smoking prior to hospital admission were still smoking; 37% of current
21 smokers had not attempted to quit and 51% were not considering to do so.[2] The prevalence of obesity was
22 38%, in relation to physical activity, 40% was on target with half of the patients trying to do more everyday
23 activities.[2] Less than half had the intention to engage in planned exercise and only 29% of all patients were
24 on target for all three lifestyle factors[2]. The number of adverse lifestyles was strongly related to the way
25 patients perceive their illness as threatening.[2] Although a lack of adherence to guidelines by healthcare
26 professionals cannot be ruled out, there is a very high likelihood that also patient adherence to treatment or
27 advices is still too poor.

28

29 **Aim**

30 The preventive cardiology community needs a formal clinical consensus document detailing how to optimize
31 patient adherence to treatment for the secondary prevention of CVD. Aims of this clinical consensus document
32 are to provide a modern reappraisal of the concept of adherence together with simple, practical, and feasible

1 suggestions to achieve optimal adherence in the clinical setting, focusing on evidence-based concepts.
2 Although aspects of adherence have been discussed fragmentally in previous guidelines and position
3 statements, the novelty of this paper is thus that all clinically relevant and state-of-the-art knowledge on
4 adherence on all aspects of guideline-directed medical therapy is brought together.

6 **Methods**

7 The accumulation of the current evidence was based on a search strategy of English language published
8 research, consensus documents and policy documents, by using electronic databases (MEDLINE, EMBASE,
9 CINAHL), as selected, evaluated and reviewed by experts from the EAPC, and authors of the original
10 documents. In the development process of this position paper, individuals from relevant healthcare
11 professional groups (e.g. cardiologists, general practitioners, psychologists, psychosomaticists, nutritionists,
12 physiotherapists, nurses) were included. From the collected evidence, consensus statements have been
13 formulated (see Table 1), as well as an agreed approach with respect to adherence optimisation strategies (see
14 Figures 1, 3). Finally, all position statements were carefully aligned with current EAPC/ESC position papers or
15 guidelines.[7–13]

17 **Definition and measurement of adherence**

18 Adherence is defined as the extent to which a person's behaviour – taking medication, following a diet, and/or
19 executing lifestyle changes - corresponds with agreed recommendations from a healthcare provider.[14] The
20 term “adherence,” is preferred to “compliance,” and strong emphasis is placed on the need to differentiate
21 adherence from compliance. The main difference is that adherence requires the patient's agreement
22 (“informed consent”) to the recommendations.[14] Patients should be active partners with healthcare
23 professionals in their own care and thus, good communication between patient and healthcare professional is
24 a must for an effective clinical practice.[14] The process starts with the informed consent of the patient and is
25 followed by the initiation of treatment, when the patient takes the first dose of a prescribed medication or
26 initiates lifestyle changes.[15] The process continues with the implementation of the dosage regimen, defined
27 as the extent to which a patient's actual dosing corresponds to the prescribed dosage regimen, from initiation
28 until the last dose is taken.[15] Discontinuation marks the end of therapy, when the next dose to be taken is
29 omitted and no more doses or lifestyle changes are taken thereafter.[15] Persistence is the length of time
30 between initiation and the last dose or lifestyle action.[15] Non-adherence to medication or healthy lifestyle
31 behaviours can occur in the followingcases: late or non-initiation of the prescribed treatment/therapy, sub-
32 optimal implementation of the dosing regimen or early discontinuation of the treatment/therapy.[15] Non-

1 adherence behaviours include intentional and unintentional components. The former refers to an active and
2 reasoned process that leads the patient to modify the treatment plan, deviating from the agreed prescriptions,
3 while the latter is considered a passive process in which patients are careless, forgetful, or unable to adhere to
4 the treatment plan for other reasons, such as unable to collect their medications or not understanding the
5 information on medications provided.[16] In some cases, i.e. significant cognitive impairment, the patient is not
6 able to agree to the recommendation and in these cases the healthcare provider is responsible for providing
7 the necessary support and/or information. It is also important to note that some behaviours affecting
8 treatment adherence may represent specific mental disorders per se, acknowledged in ICD classification, that
9 needs to be diagnosed and treated. In the ICD-11-CM a specific clinical entity, defined as 'psychological and
10 behavioural factors that may adversely affect the manifestation, treatment, or course of a physical condition by
11 affecting treatment adherence or care-seeking' exists and is coded 6E40.[17] In everyday clinical practice,
12 however, the awareness of these diagnoses is extremely poor and healthcare providers are very reluctant to
13 assess, code, and treat these mental disorders although the mental comorbidity mitigates therapeutic
14 efforts.[18]

15 Measurements of adherence can be direct, including observed administration or measuring the blood
16 concentration of a metabolite, measuring physical activity by step counters/accelerometers, or measuring
17 carbon monoxide (CO) exhalation, or they can be indirect, including patient self-reporting, pill counting,
18 pharmacy refill rates, physical activity or dietary questionnaires, and electronic monitoring systems.[19] Indices
19 such as the medication possession ratio (MPR) or the proportion of days covered (PDC), based on counting the
20 number of days the patient has been in possession of the drug and has actually used it, as derived from the
21 intervals between supplies of the drug. Using PDC for statins and angiotensin-converting enzyme inhibitors,
22 stratification of patients with known CVD as fully adherent ($\geq 80\%$), partially adherent ($\geq 40\%$ to $\leq 79\%$), or
23 nonadherent ($< 40\%$) was able to identify groups with a significantly different event rate.[20] There are
24 numerous methods for measuring adherence by self-reported questionnaires: at least 43 adherence scales
25 exist.[21] Of these, two instruments are particularly used in CVD medicine to assess the degree of patient
26 adherence, which are based on the patients' answers to specific questions. The Morisky Medication Adherence
27 Scale (MMAS) investigates only the domain of the pharmacological treatment [22], while the Hill-Bone
28 Compliance Scale (HBCS) also investigates behavioural domains.[23].

30 **Why are patients non-adherent to cardiovascular prevention recommendations?**

31 The need to integrate the therapeutic routine into one's daily life and to cope with the onset of potential side
32 effects and undesirable changes in lifestyle, or in established habits, represent challenges that many patients

1 face, using their own inner resources in the search for a balance among the need to take care of oneself,
2 preventing relapses, and the need to maintain an acceptable quality of life.[24] The distinction between the
3 intentional and unintentional components of non-adherent behaviours is very important.[16,25,26]
4 Understanding the nature of the non-adherence processes, which can be highly variable (see Table 2), is
5 important not only for the purpose of defining useful strategies to manage their detrimental effects, but also
6 for decreasing these phenomena. Therefore, it is fundamental to understand the emotional and cognitive
7 aspects underlying patients' choices and behaviours regarding treatment. Although the risk factors for CVD are
8 often acknowledged by patients as predisposing them to CVD, their risk perception can still be inadequate, thus
9 affecting preventive behaviours. Moreover, a lower health literacy could also be highly prevalent among
10 patients with CVD risk. As a result, there is a tendency to underestimate the causal link between CVD risk
11 factors and disease manifestations among many patients.[27–31] Indeed, a patient's lower perceived necessity
12 for secondary prevention is related to non-adherence.[28,32] Concerns and irrational beliefs about preventive
13 measures are identified as powerful predictors of (un)intentional non-adherence to treatment.[29] On the
14 other hand, coping skills and the perception of (personal) control over the management of care are important
15 elements capable of increasing the adherence to treatment.[33–35] Patients tend to modify their use of
16 medications in an improper way when they feel they are no longer able to integrate the therapeutic routine
17 into their daily life, due to consequences on their quality of life, which results in their health condition
18 worsening.[34] This highlights the significant role of a high level of self-efficacy in the processes of adherence
19 to treatment.[35] Also the quality of patients' social support, understood as family relationships and available
20 healthcare networks, can affect individual coping and the development of self-care skills:[33] weaker
21 practical/social support is associated with non-participation in rehabilitation programs and non-adherence to
22 medication.[36,37] Also mental disorders (especially mood disorders, depression, anxiety disorder and
23 personality disorders) are associated with poorer adherence to treatment,[34,35,38][39][40] and favor
24 development of irrational beliefs about pharmacotherapy or lifestyle measures. Therefore, it is useful to
25 conduct a careful assessment of the above-mentioned psychosocial variables at entry of prevention and
26 rehabilitation programs, to detect potential contributors to a lower treatment adherence and, by appropriate
27 actions, maximize the patients' adherence to treatment (see Figure 2).

28 **Poor adherence to treatment in patients with specific CVD risk factors and diseases**

30 Next to medication intake, the implementation of lifestyle changes such as a healthy diet, physical
31 activity/exercise training and smoking cessation is recommended by ESC Guidelines in secondary prevention of
32 CVD.[11,13] Poor adherence to long-term therapies, including lifestyle changes, has important public health

1 implications, as it leads to increased morbidity and mortality, as well as significant economic costs (e.g. number
2 of visits, diagnostic procedures, prescribed drugs), and should thus be prevented.[14] Additionally, in specific
3 CVD's and risk factors, some factors seem highly predictive of low adherence to therapy (see Figure 2).

4 5 *Overweight and obesity*

6 The adherence to treatment is generally lower in persons with overweight or obesity.[41] Barriers to lifestyle
7 change include poor motivation, environmental, societal and social pressures, lack of time, health and physical
8 limitations, negative thoughts and moods, socioeconomic constraints, gaps in knowledge or awareness, and
9 lack of enjoyment of exercise.[41] Therefore, a good preparticipation screening is of utmost importance to
10 detect such factors or contributors. On the other hand, the most prominent predictors of greater adherence to
11 lifestyle treatment in obese patients include: early weight loss success, a lower baseline body mass index (BMI),
12 having existing cardiometabolic comorbidities, better baseline mood, being male and older age.[41,42] As the
13 overweight/obesity and unhealthy lifestyle cluster are overrepresented in economically disadvantaged and
14 other more vulnerable populations (including people with psychological issues), they are also important
15 contributors to health disparities. In line with this notion, all lifestyle modifications must be personalized
16 according to the availability of foods, geographic localizations, health status and psychosocial factors of the
17 patient to fully exert their health-promoting effects.[41,42]

18 19 *Hypertension*

20 Despite large evidence confirming the importance of blood pressure (BP) lowering and the availability of many
21 effective and well-tolerated antihypertensive drugs, BP control rates are still unsatisfactory.[1] This is, at least
22 in part, related to poor adherence to lifelong anti-hypertensive therapy. The most common
23 predictors/determinants for a lower adherence to the intake of BP-lowering medications are: lower diastolic
24 blood pressure, higher cost or insurance type/coverage, non-white race/ethnicity, fewer healthcare contacts
25 within six months after the prescription, and ≥ 4 comorbidities.[43] Distrust, (concern for) side effects, and lack
26 of perceived need for the medication (because hypertension is often a symptomless condition it will further
27 lower the adherence to treatment).[43] Crucially, also a lack of patient involvement in the treatment decision-
28 making process will lower the patient's adherence to medication prescription.[44] The lack of adherence to
29 medication prescription should not be confused with difficult-to-treat hypertension, which is BP not optimally
30 controlled despite adherence to an appropriate regimen of three antihypertensive drugs of different classes
31 (including diuretics) in which all drugs are prescribed at appropriate antihypertensive doses.[13] In this regard,
32 pseudo-resistance (such as inaccurate BP measurement, extracellular volume expansion, intake of NSAIDs or

1 stimulants known to elevate BP) as well as a secondary cause of hypertension should be excluded before this
2 diagnosis is accepted.

4 *Dyslipidaemia*

5 Low-density lipoprotein (LDL) cholesterol is a key causal factor of CVD.[45,46] Lipid-lowering medications are
6 often prescribed to decrease the risk of micro- and macro-cardiovascular complications related to
7 dyslipidaemia, in both primary and secondary CVD prevention,[13] including patients who have undergone
8 heart transplantation.[47] Despite widespread prescription of lipid-lowering drugs, including statins, adherence
9 to therapy is a challenge worldwide, in particular in primary prevention.[48] Statins reduce the risk of recurrent
10 ischemic stroke and myocardial infarction (MI) and better adherence to outpatient statin prescriptions lowers
11 the rates of subsequent CVD events.[49] The following characteristics/factors predict a greater adherence to
12 statin prescription: male sex, older age, history of MI or stroke, presence of diabetes, hypertension or co-
13 morbidities, positive patients' beliefs about medicines, and very recent treatment initiation.[48,50,51]
14 However, the adherence to medications for treatment of a symptomless condition, such as dyslipidaemia, is a
15 great challenge: lipid-lowering agents may be discontinued sooner than other oral medications for chronic
16 therapy because of a lack of sensation of improvement in symptoms or benefit. A substantial proportion of
17 patients do not achieve adequate reduction in LDL-cholesterol levels despite intensive statin treatment, cannot
18 tolerate statins, or remain at high residual risk despite being on statin therapy.[52,53] For high-risk patients in
19 whom statin therapy alone is insufficient, add-on treatment with non-statin medications, ezetimibe and
20 proprotein convertase subtilisin/kexin-9 inhibitors (PCSK9i) is a valuable option.[54,55] Importantly,
21 appropriately identifying and characterizing barriers to PCSK9i access, and developing approaches to overcome
22 them, will reduce the clinical and economic burden for patients who are likely to benefit from PCSK9 inhibition
23 and likely result in more cost-effective policies.[56,57]

25 *Diabetes*

26 The current management of diabetes in the secondary prevention of CVD remains suboptimal,[1]
27 notwithstanding the well-established clinically significant relation between a worse glycaemic control and
28 greater risk for adverse CVD events.[58] Sometimes, the treatment of diabetes can be even more challenging
29 when not only glycaemic control is targeted, but also the lipid profile, body weight and blood pressure of the
30 patient with diabetes.[13] This often leads to the need to take different medications in combination with
31 important lifestyle adjustments (e.g. nutrition, quit smoking, and physical activity/exercise training), and
32 stepwise approach is recommended by guidelines,[13] which should be better settled by a shared-decision

1 making process. In this process, health education can be offered: very often the health literacy is low in
2 diabetic patients, which negatively affects adherence to treatment. In addition to the intensiveness of
3 treatment, there are additional predictors for a lower adherence to treatment: anxiety, diabetes distress, older
4 age, poor communication with healthcare professionals, stress, concerns about medicines, cognitive
5 impairment, and low levels of self-care. [26] In particular the experience of frequent hypoglycaemia can
6 significantly lower the adherence to prescriptions of glucose-lowering medications. As a result, it is important
7 to provide a close/regular follow-up of the patient with diabetes, in which such side effects can be remediated
8 timely. On the other hand, a high self-efficacy, social and family support, and the acceptance of illness have a
9 beneficial effect on medication and lifestyle adherence.[26]

10 *Coronary artery disease and heart failure*

11 Poor adherence to prescribed regimens is pervasive and results in preventable hospitalisations, premature
12 deaths and unnecessary healthcare expenditure in CAD and heart failure (HF), regardless of the underlying CVD
13 etiology.[5,14,59–67] Non-adherence to treatment remains high.[68–70] Many factors contribute to
14 medication non-adherence, such as lack of social support, absence of symptoms, cognitive decline, adverse
15 reactions, depression, poor attention span, poor knowledge about medication or treatment, the prescription of
16 multiple medications, difficulty with swallowing (large) pills, and inconveniences of urinary frequency with
17 diuretics.[64] Healthcare providers should continue to provide education, constantly reinforce the importance
18 of taking medication as prescribed, and when feasible, utilize one of the successful evidence-based strategies
19 to increase adherence.[64] In this regard, shared decision making and applying a stepwise approach based on
20 the capacities and preferences of the patient could be of vital importance. A multidisciplinary team approach,
21 such as cardiac rehabilitation (CR) programs, would be the best way to improve medication adherence, since
22 the patient would receive education and resources from every discipline.[14] In addition, a close
23 monitoring/follow-up of the patient may assist in keeping the adherence to treatment high.[11] Telehealth and
24 remote consultations are excellent options to consider.[71]

26 *Stroke*

27 The burden of stroke is immense and rapidly growing and recurrence is a major risk factor since recurrent
28 stroke is more likely to cause death and disability. Medication adherence and persistence rates are low in
29 patients after suffering a stroke as well as adherence to exercise programs. [72,73] Nevertheless, there is a lack
30 of a uniform method of measurement of adherence to exercise or physical activity recommendations in the
31 stroke population.[73] Further research using clear, standardized and objective assessments is needed to

1 clarify the association between cognitive impairment, psychological determinants and medication adherence in
2 stroke survivors.[74,75]

3 4 *Atrial fibrillation*

5 The impact of atrial fibrillation is increasing and an a holistic care approach for atrial fibrillation patients, the
6 'Atrial fibrillation Better Care' (ABC) pathway has been proposed.[76] The ABC pathway stands on three main
7 pillars: 'A': Avoid stroke (with Anticoagulants); 'B': Better symptom management; 'C': Cardiovascular and
8 Comorbidity management and it is recommended in the recent European Society of Cardiology atrial fibrillation
9 management guidelines.[77,78] Adherence to the ABC pathway is associated with a reduction in the risk of
10 major adverse outcomes, however adherence to the ABC pathway is suboptimal, being adopted in one in every
11 five patients.[79]

12 13 *COPD*

14 COPD is a common disease that, if not managed appropriately, causes an enormous strain on health
15 services.[80] Optimal medication adherence in patients with COPD assists in improving disease management
16 and reducing health care costs and patients who adhere to treatment have a lower risk of exacerbating their
17 medical condition as compared to those with poor adherence.[80] Nevertheless, adherence to COPD
18 medication is generally low, with the majority of studies identifying the presence of depression and subjects'
19 concern about the harmful effects of the medicine as barriers to adherence.[80]

20 *Elderly patients*

21 Despite the beneficial effects of secondary prevention, including CR, on clinical outcome in elderly patients
22 with CVD, participation and adherence significantly decrease with age (next to its negative impact on guideline-
23 directed medical therapy adherence).[81,82] The main reasons include transport difficulties and a lack of
24 referral by healthcare providers. Also, elderly patients are more likely to assume that lifestyle changes would
25 not improve their health.[82,83] Key factors that have previously been identified as relevant to increase
26 exercise adherence in elderly patients include supervision, social support from staff and peers, and
27 individualization.[84] Moreover, it is important to provide adequate information about benefits and potential
28 risks, identifying perceived barriers and facilitators, as patients with realistic expectations of change are more
29 likely to be adherent.[84] This may also increase patients' self-efficacy which is related to achieving lifestyle
30 goals. Enjoyment is an immediate reward that is closely related with intrinsic motivation and could lead to
31 better adherence than delayed rewards, such as health benefits in the long-term.[84] Many secondary
32 prevention services have not specifically been designed for the elderly and the implementation requires a high

1 degree of individualization. A comprehensive geriatric assessment including not only CV function, but also
2 peripheral functional evaluation (strength, balance, coordination, aerobic capacity), assessment of disability
3 and comorbidities, nutritional, cognitive and psychosocial components are suggested.[11] Interventions should
4 be tailored to target the main goals of CR for the elderly, including preserved independence, prevention of
5 sarcopenia and frailty, improvement in quality of life and encouragement of social adaptation.[11] Only those
6 programs that are in line with the preferences of patients, improving them globally, can become an actual long-
7 term sustained habit.[84]

9 **Bringing it all together: the five dimensions of adherence to treatment (patient, disease, healthcare provider, 10 therapy, healthcare system) – barriers and strategies**

11 The non-adherence to (non)-pharmacological treatment is common.[1–5] Based on the above-mentioned
12 information, combined with insights from research in the psychology of non-adherence to treatment, barriers
13 and motivators to adherence are presented, originating from the patient him/herself, the (type of) disease, the
14 healthcare professional, the therapy and the healthcare system (see Table 2 and Figure 2).[85–87]

15 Improving the adherence to treatment requires an active process of behavioural change, which is nearly always
16 a challenge. It requires education, motivation, tools, support, monitoring, and evaluation.[88] Multifactorial
17 interventions are more effective,[89] tailored solutions addressing a patient's specific adherence barriers
18 (precision medicine), scaled to the population level (population health), may be a successful strategy to
19 facilitate improved medication adherence on a larger scale.[90]

21 **The patient**

22 *Sex/gender*

23 There is a significant impact of sex/gender on adherence rates to secondary prevention measures, which need
24 to be considered in clinical practice. For example, among 9.283 patients with ACS (in Australia), it was
25 discovered that women had lower odds of attending CR than men (OR [95% CI] 0.87) and at 12 months after
26 discharge, women were less likely to be on $\geq 75\%$ of the indicated medications (OR 0.84).[91] This sex
27 difference in secondary prevention of CVD is a global phenomenon, as also in China it was found that women
28 with established CVD were significantly less likely than men to receive BP-lowering medications (OR 0.79), lipid-
29 lowering medications (OR 0.69), antiplatelets (OR 0.53), or any CVD prevention medication (OR 0.62).[92]
30 Women were less likely to achieve physical activity targets (OR 1.92), but also were less likely to smoke (OR
31 13.89).[92] In the USA, very similar findings were reported.[91] It is also noted that next to a lower referral rate
32 to CR, also the drop-out during CR seems to be greater in women.[93] Potential barriers to women's

1 participation in CR could be greater psychological distress, pressure as the primary caretaker of the family, and
2 the lack of financial resources and social or emotional support.[94]

3 Hence, secondary prevention interventions should be adapted accordingly, and caregivers should be more
4 aware of the issues, to meet these needs and to maximize women's adherence to treatment and participation
5 rates in structured secondary prevention and CR programs.

6 7 *The psychosocial health status and the barriers to their appropriate management*

8 To enhance secondary prevention and ensure the best possible prognosis for patients with CVD, it is
9 paramount to treat not only the underlying disease and ensure management of traditional risk factors, but also
10 to treat mental disorders/issues, such as anxiety, depression, and post-traumatic stress disorder. The sudden
11 confrontation with chronic and potentially life-threatening disease may trigger the onset of one or more
12 mental disorders/issues or increase symptom levels that warrant treatment. Hence, not surprisingly, 20% of
13 CVD patients suffer from depression, anxiety, or both.[95] It is not sufficient to screen patients for mental
14 health problems only at the time of the index event, as the incidence of new-onset anxiety and depression are
15 14% and 11% during 24 months of follow-up in patients without anxiety and depression at baseline.[96] In
16 addition, mental disorders are often undetected and undertreated.[97] Irrespective of whether patients
17 receive a clinical diagnosis or report subthreshold levels, the impact on patient prognosis is potentially large.
18 Mental disorders comprise barriers for lifestyle changes, impair patients' quality of life and health status,
19 increase the risk of refusal or drop-out from CR, non-adherence, hospitalisation, premature death, and
20 increased costs.[98–102]

21 Several barriers exist for the provision of appropriate management of mental disorders in patients with CVD at
22 the patient, society, and healthcare system levels. One barrier is the current organisation of our healthcare
23 system, with its primary focus on treatment of the underlying heart disease, while largely ignoring the
24 interaction between heart and mind and how they through biological and behavioural pathways interact to
25 influence patient and clinical outcomes.[98] Generally, the adherence rate of healthcare providers to the
26 implementation of guideline-based psychosocial interventions in medical settings is poor. Luckily, in some
27 countries and in some healthcare settings (i.e. CR) mental health professionals are part of the multi-disciplinary
28 team At the patients' and society level, while some CVD patients are interested in receiving psychological
29 support and therapy even before the onset of CR,[103] others still feel the stigma associated with going to a
30 psychologist or other mental health professionals; others may lack confidence in these interventions or lack the
31 financial means to go to a psychologist due to lack of reimbursement..

1 Psychological treatments, such as cognitive behavioural therapy, help in reducing psychological distress and
2 increase quality of life in patients with CVD,[104–106] and mental healthcare is effective for the treatment of
3 mental disorders.[13,107] Observational studies with large sample sizes revealed that remission of mental
4 disorders is associated with improvement of cardiac prognosis.[13,107] Nevertheless, some uncertainties
5 remain regarding the magnitude of psychological intervention effects in patients with CVD,[108] and the areas
6 of the mental healthcare impact on cardiovascular outcomes in CVD patients. A systematic Cochrane review
7 and meta-analysis found that psychological interventions had important health benefits among people with
8 CAD, reducing the rate of cardiac mortality and alleviating the psychological symptoms of depression, anxiety,
9 and stress. However, no effects were observed for total mortality, myocardial infarction, or revascularisation.
10 The mixed effects of interventions may also be attributed to a “one-size-fits-all” therapeutic approach in RCTs
11 rather than a precision-medicine approach that is targeted to patients’ specific needs and preferences.[109]; in
12 addition, trials should avoid an over-representation of well-educated and motivated patients.[110] Therefore
13 large-scale trials are still warranted.[108]

16 *Impact of psychological determinants of non-adherence*

17 The ability of a patient to adhere to medical treatments and healthy behaviour changes depends on complex
18 cognitive-emotional capacities and interaction with his or her social environment (e.g., the healthcare system).
19 Emotional factors are symptoms of mental disorders such as anxiety, depression, and other signs of emotional
20 dysregulation.[107] Emotional factors, knowledge (health literacy), and the belief about the consequences of
21 medications strongly influence medication adherence.[111] Other, less essential elements are displayed in
22 Table 3.[111]

23 These factors are all closely related to the level of personality functioning, i.e., the mental capacity of persons
24 to do something good for themselves (self-care), their capacity of self-directedness, and interpersonal skills
25 (communication, being able to ask for help, to cooperate effectively, to trust doctors and to depend on them).
26 Psychological determinants of non-adherence in themselves are a medical problem that has to be tackled
27 explicitly in the treatment.

29 *Health literacy*

30 Health literacy can be defined as the knowledge, motivation, and competencies of people to access,
31 understand and apply health information to make judgments and decisions in daily life about health matters.
32 These skills include reading, writing, numeracy, communication, and increasingly the use of electronic

1 technology. Health literacy therefore plays an important role in CVD secondary prevention, encompassing
2 some of necessary skills, such as understanding health information and active interaction with health
3 professionals, needed to improve self-care.[112,113] Low levels of health literacy have been associated with
4 low educational attainment, low income, and ethnic minority status and have less favorable CVD risk
5 profiles.[114,115] Inadequate health literacy is highly prevalent in patients with CVD and it is associated with
6 poorer control of CVD risk factors and poorer adherence to drugs and changes in lifestyle.[116,117] A high level
7 of health literacy is associated with a lower readmission rate after MI and may be a factor influencing dropout
8 in CR.[116–118] Poor health literacy can be modified through the development of knowledge and skills related
9 to self-care.[119,120] The most commonly used strategies include attention to printed patient educational
10 materials, including elimination of medical jargon by using plain language with clear and concise messages , to
11 ensure that patients understand the advice of healthcare professionals.[121] Digital solutions can improve
12 health literacy by providing patients the opportunity to be a more active participant in their own healthcare.
13 Digital solutions will provide a more person-centred approach in which individuals will have more control over
14 health and data, while staying connected to their healthcare team.[122]

15 16 *From the "awareness" state to the "empowerment" state*

17 The efficacious promotion of treatment adherence requires patients to acquire a solid awareness of their
18 status and then they move to an active engagement in managing their disease. The awareness of the disease
19 and of its potential risks is critical for patient adherence: patients' awareness level is not always high.[123–125]
20 Such a lower awareness is usually associated with various factors, including age, familiar history for a specific
21 risk factor, and unhealthy behavioral habits like poor physical activity, smoking, and heavy alcohol use.[126]
22 The educational status also plays an important role.[127] The sources of information mostly reported are
23 traditional ones and digital media, including social media, print information in newspapers and magazines,
24 healthcare professionals, and family members.[128,129] Educational and informative programs are primarily
25 suggested to promote patients' awareness of their condition and are suitable for interventions directed to
26 large communities, particularly those that consider patients' information needs and offer tailored content and
27 communication strategies.[130] Despite increased knowledge, awareness is insufficient to guarantee
28 prolonged adherence to the treatment. The association between awareness and behavior is usually modest,
29 suggesting that awareness alone does not motivate individual action.[131] Self-management programs are
30 needed to enable patients to have a major role in coping with their condition, controlling their symptoms,
31 understanding and accepting their prescribed treatment, recognizing the time they need medical follow-up, in
32 other words: exerting control over their own situation. This process has been defined as «empowerment»,

1 namely, “the process through which people gain greater control over decisions and actions affecting their
2 health”. [132] Digital solutions are largely employed to enhance patients’ empowerment by providing a large
3 variety of opportunities to be active and engaged in managing their health. [133]

5 *Maintenance self-efficacy and recovery self-efficacy*

6 Unhealthy lifestyles are difficult to change, and, when changes occur, it is hard to maintain them over time.
7 People could make multiple attempts to move from intention to a healthy actual behavior. However, relapses
8 could happen anytime, especially in complex and chronic disease conditions requesting multiple behavioral
9 changes. Maintenance self-efficacy refers to the confidence in one's capability to maintain the behavior despite
10 potential barriers and obstacles. A self-efficacious person responds confidently with efficacious strategies,
11 more effort, and greater perseverance. Greater maintenance self-efficacy correlates with higher medication
12 adherence among CR patients. [134] Patients with a first coronary event and CV high-risk who feel more self-
13 efficacious in coping with potential difficulties related to behavioral changes, are more likely to improve their
14 physical activity over time, [135] while a lower self-efficacy in CVD patients is associated with higher
15 hospitalisation rates and all-cause mortality. [136] Programs focusing on self-efficacy increase patients’
16 engagement in managing their condition with an improvement in clinical outcomes, such as lower blood
17 pressure levels and reduced hospitalizations. [137] A poor self-efficacy can be improved through the sources
18 originally identified by Bandura in psychological counselling programs. [138] The direct experience of mastery
19 and success in increasing difficulty tasks is the primary source of self-efficacy beliefs. Furthermore, self-efficacy
20 could be improved by vicarious experiences. Patients may observe significant and competent patterns, for
21 example, by sharing CR sessions with a practiced patient who serves as a model. A further source of self-
22 efficacy is verbal persuasion by others (doctors, nurses, physiotherapists) to help patients in gaining confidence
23 and esteem.

25 **The disease**

26 *Condition/disease-related factors*

27 Among barriers to adherence co-morbidities adversely impact treatment adherence in case of linked conditions
28 (e.g. CVD and diabetes) or when conditions co-exist (e.g. CVD and orthopaedic limitations), particularly when
29 drug regimens are complex, costly, and influencing activities of daily life. Non-cardiovascular comorbidities play
30 a major role in determining unsatisfactory adherence levels, both to medications and lifestyle, especially in the
31 elderly. [139] Although it is difficult to establish which disease combinations are at highest risk of non-
32 adherence, several situations should be carefully monitored, such as atrial fibrillation and renal impairment

1 after MI.[140] Co-morbidities could also lead to the prescribing cascade, i.e. a situation in which a first drug
2 administered to a patient causes adverse signs and symptoms, that are misinterpreted as a new condition,
3 resulting in a new medication prescription.[141]

4 The duration of disease has an uncertain impact,[142] even though chronic conditions or long duration of acute
5 illnesses reasonably increase the risk for low adherence.

6 The absence of current signs of symptoms (i.e. the “asymptomatic” patient) constitutes per se a condition
7 potentially interfering with adherence, since patients may believe they do not need the medication and might
8 not even follow their prescription.[143] This kind of intentional non-adherence primarily affects dyslipidaemia,
9 hypertension, and subclinical atherosclerosis treatments.

10

11 **The healthcare provider**

12 *Avoid information overload and forgetfulness*

13 Many patients, families and caregivers are exposed to ‘information overload’, often far more than they can
14 remember, exacerbated by the widespread use of social media, emails, and online communications, and the
15 pressure to simultaneously read, produce and exchange information. This is likely to affect the assimilation,
16 understanding, retention and recall of information,[144] which may have an adverse impact on adherence to
17 therapy and lifestyle changes. Therefore, improving access to and delivery of information is important for
18 increasing transparency, patient autonomy and engagement, and improving safety.[145,146]

19 Most patients prefer a written lay summary of health information,[147] but, to avoid information overload and
20 forgetfulness, healthcare professionals should consider the relevance, timing, content, duration, presentation
21 and readability of information and information-processing abilities of patients. Improving recall, understanding
22 and adherence to treatment involves: i) using plain, simple, uncomplicated, and consistent language and
23 terminology, ii) being specific, using some repetition, minimizing jargon and iii) checking a person’s
24 understanding. This can be aided by a variety of information and educational media formats and modes of
25 delivery, encouraging note-taking, clarifying with questions, and using techniques like teach-back and ‘chunk
26 and check’.[148] Shared decision-making [149] taking account of patients’ self-efficacy and autonomy and
27 experience in risk factor modification, can help patients have a more active role and more accurate risk
28 perceptions.[150] How information is portrayed can influence perceptions and adherence.[151]

29

30 *Enhance communication: ask, tell, ask*

31 The physician-patient relationship is critical for establishing a good working alliance and hereby improve the
32 adherence to treatment.[152] Therefore, medical training is supposed to include education in interpersonal

1 and communication skills aiming at effective collaboration with patients, their relatives, and other healthcare
2 professionals.[153] Concerning non-adherence, its detection and effective treatment also depends of
3 physician-patient communication. However, problems with adherence are rarely addressed and recognized by
4 physicians.[18] One teachable method of patient-centred communication is the Ask-Tell-Ask method. This
5 method aims at increasing the involvement of the patient in the treatment process. It consists of asking the
6 patient's understanding of his/her disease and treatment. Based on this information, the physician tells the
7 patient what is needed and then asks again what the patient received and his/her further informational needs.
8 There is continuous feedback between physician and patient to ensure that the patient has understood the
9 information and grasped its meaning and consequences. The physician should use a language style adapted to
10 the health literacy and the emotional state of the patient. The sentences should be short and
11 digestible.[18,154] The Ask-Tell-Ask method needs to be embedded in basic patient-centred communication
12 skills, including active listening and attending to the patient's emotions.[155]

14 *Improve patients' risk perception*

15 Risk perception may be defined as individual thoughts and feelings about the risks they face in behaving in
16 certain manners. The greater the perceived risk for one's health, the greater the motivation for taking
17 protective action.[156] Therefore, risk perception, both absolute ('How I am at risk') and comparative ('How I
18 am at risk comparing to people around me'), is an integral part of many major health behaviour theories,
19 aimed at describing, explaining, and modifying human habits. About 40% of the general population
20 underestimate their risk for developing CVD, while 20% overestimate it.[157,158] Risk underestimation is very
21 common among individuals with CVD. This dysfunctional belief essentially compromises the adoption and the
22 maintenance of healthy habits,[159,160] diminishing the success of CVD secondary prevention. On the other
23 side, excessive overestimation may cause a significant psychological burden. Complex explanations of CVD risk
24 appear insufficient to motivate behaviour change. Providing more medical information to patients may not
25 mitigate the impact that prevailing beliefs have on patients' views on medical issues. They seek personal,
26 meaningful information that can be helpful in making healthcare and lifestyle decisions and a tailored approach
27 should be adopted.[161] Online calculators (such as the ESC CVD Risk app) can be used to estimate the average
28 lifetime benefit of smoking cessation, lipid lowering, and BP lowering on an individual patient level expressed
29 as extra CVD-free life-years. Average lifetime benefit is easy to interpret and may improve the communication
30 of potential therapy benefits to patients in a shared decision-making process. This may increase patient
31 engagement, self-efficacy, and motivation to adhere to lifestyle changes and drug treatment.[13]

1 *Enhance patients' self-efficacy*

2 Self-efficacy is extensively treated above, here is only to be emphasised that each healthcare provider should
3 consider the patient's self-efficacy. It is important to incorporate self-efficacy as a key element in CVD self-
4 management programs. These programs should have a multidisciplinary approach, should be patient-driven
5 and should have a theoretical basis for behaviour change. More research is needed to investigate the causal
6 relationship between self-efficacy, self-control, and clinical outcomes.[137]

7
8 *Healthcare professional: Don't be inert!*

9 Clinical inertia is defined as the failure to initiate or intensify therapy when treatment goals are not met and is
10 a well-recognized barrier to improving patient care and clinical outcomes.[162] The lack of treatment
11 intensification and goal achievement is multifactorial, involving not only healthcare professionals, but also
12 patients, healthcare system, and policy/regulatory factors.[162] One key contributor to therapeutic inertia is
13 poor guideline implementation and slow integration of new knowledge into practice.[162] Educating
14 healthcare professionals on practice guideline changes through continuing education programming is one
15 approach, however, evidence supporting the effectiveness of this strategy is limited.[163] A more effective
16 approach is to provide education outreach visits in which a trained individual provides face-to-face education
17 and feedback on healthcare professional performance. This methodology improves clinical outcomes while also
18 reducing costs. (6) A healthcare professional-patient discussion that helps patients navigate medical
19 misinformation found in online and published media is also extremely important,[164] and educational
20 outreach visits may help healthcare professionals in implementing this in their daily practices. There is also an
21 urgent need to increase guideline dissemination improving readability and dissemination also by smartphone
22 applications and social media.[162] Multidisciplinary team-based care models are more likely to achieve CVD
23 risk factor control and can reach high-risk populations successfully.[162,165] A key aspect of such models is a
24 guideline-based algorithmic approach to treatment, which can significantly reduce therapeutic inertia.
25 Regarding systems approach, the creation of quality improvement programs that incorporate feedback metrics
26 provides healthcare professionals with data needed to drive improvement. In some institutions, these data are
27 available on dashboards where healthcare professionals can compare their control rates for a particular
28 disease, such as hypertension, with others, with the intent to use this information to improve their
29 performance metrics.[162] In a general view of this important topic, patient preference must also be included,
30 as not all patients desire treatment intensification or change, owing to concerns about side effects or personal
31 convictions about prescription-medication use. This underlines the importance of shared decision making with
32 patients to guide treatment decisions that are consistent with the patient's wishes and goals.[162] Finally,

1 studies and efforts aimed to the improvement of therapeutic inertia should be based in implementation
2 science, which is a scientific area focused on determining the best methods for increasing the integration of
3 research findings into clinical practice, with the goal of improving the quality of health services.[166]
4

5 *Promote and use a slogan in your facility: "I am with my therapy!"*

6 According to the Oxford English Dictionary, a motto is "a maxim or saying adopted by a person, family,
7 institution, etc., expressing a rule of conduct or philosophy of life". It's usually simple, catchy, timeless, and
8 easy to remember as well. So defined, the "I am with my therapy!" motto could apply to patients suffering
9 from CVD and was created for the purposes of this consensus statement as a tool to promote treatment
10 adherence. It is not trademarked for protection and could be enriched by an accompanying logo created at a
11 local level. These five words evoke personal empowerment and engagement ("I am", i.e. taking control of own
12 life, and making positive decisions), appropriate relationship between the patient and prescription/prescriber
13 ("with"), and finally recognition of the importance of individualised treatment regimens, tailored to patients'
14 views and embracing all aspects of pharmacotherapy and lifestyle ("my therapy"). This declaimed alliance
15 between patient and therapy definitely overcomes the old concept of passive "compliance" by shifting towards
16 a mutually agreed treatment programme, best appreciated in terms of "concordance" and "persistence". The
17 motto is offered to providers and prescribers, communities, institutions, and healthcare policy makers. By way
18 of example, it could be systematically adopted by multidisciplinary teams for counselling activities during
19 secondary prevention and CR programmes. It could be inserted among educational (posters, pamphlets,
20 booklets, audio tape, tutorial videos) materials prepared for patients. It could be conveyed by websites, apps,
21 and digital health tools, also during telemedicine activities. It could be utilized as slogan for campaigns at a
22 population level or for community activities during phase III CR programmes. It could be even reproduced on T-
23 shirts or presented as jingles for enhancing memory and recall. In other words, it could support the "brand" of
24 CV prevention to 360°, by expanding patient-centred thinking and action.
25

26 **The therapy**

27 Many medications have side effects, require additional monitoring, and serve as a consistent reminder of the
28 patient's illness. All these factors might reduce the patient's persistence/adherence [167]. Furthermore,
29 complicated dosing regimens can lead to inconvenient administration times and contribute to forgetting to
30 take medications. Individuals with multiple medical conditions or conditions that require a large pill burden
31 must adhere to complex regimens and may experience medication interactions and polypharmacy leading to
32 non-adherence. Therefore, the number of diseases as well as the number of prescribed drugs can reduce

1 adherence and adversely affect both secondary prevention of CVD and comorbidity trends. The financial cost of
2 medication can also act as a barrier to adherence and persistence, especially in healthcare systems that have a
3 higher patient cost burden.[5,168] Finally, frequent changes in medication plan pose a greater risk for non-
4 adherence, especially during transition phases between acute and primary care or routine follow-up visits.
5 Medication changes during hospitalization are common and those patients, particularly in the elderly, who are
6 not aware of the changes, may have higher rates of non-adherence.[169] Further, also prolonged disease
7 could lower the adherence to pharmacologic therapy, as well as the absence of symptoms (i.e. the
8 “asymptomatic” patient). [142,143]

9

10 *The Polypill: focus on therapy simplification:*

11 A polypill is a medication that combines multiple active pharmaceutical ingredients. In the prevention of CVD,
12 the types of treatment can be classified into three groups: i) single-pill combinations containing aspirin, a statin
13 and BP-lowering agents mainly focused on prevention and treatment in patients with established
14 atherosclerotic CVD; ii) fixed-dose combinations containing a statin at different dosages and ezetimibe or three
15 or four BP-lowering medications at low doses; and iii) two-drug or three-drug combinations currently on the
16 market, such as two-drug combinations of a BP-lowering drug and a statin, metformin and a statin, and other
17 combinations.[170] The polypill approach aims at controlling multiple risk factors and diseases and it addresses
18 adherence simultaneously, particularly among certain high-risk populations (e.g. low- and middle-income
19 countries, low socioeconomic status).[171] It substantially differs from a precision medicine approach which is
20 individualized and tailors guideline-directed medical therapies, based on measurement of CVD risk
21 factors.[172] However, for secondary prevention of CVD, both approaches could be combined. Patients should
22 be prescribed the components of the polypill according to best medical practice, but providing these
23 components in a combined polypill format simplifies the administration of therapy and improves
24 adherence.[173] In patients with, or at high risk of, CVD polypill-based care with all the three formats described
25 above is more likely than usual care to achieve therapeutic targets for BP, LDL-cholesterol and adherence to
26 antiplatelet therapy simultaneously. [173–175] [176]

27

28 *Digital technologies: m-Health/eHealth*

29 The rapidly growing interest and advances in digital technologies such as mHealth (mobile-Health) and eHealth
30 (electronic-Health) are gaining universal popularity and coverage and have the potential to address the
31 challenge of poor adherence to CVD therapy and lifestyle changes, hereby improving outcomes.

32

1 *m-Health*

2 The WHO defines m-Health technology as “a medical and public health practice supported by mobile devices,
3 such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless
4 devices”.^[177] mHealth provides access to multiple resources and allows monitoring and real-time analysis of
5 health data, and enable patients to become more engaged in the self-management of their condition. For
6 example, mHealth appears to improve health behaviours and medication adherence and to be generally
7 preferred by patients and healthcare professionals to other interventions.^[178–180] It is becoming more user-
8 friendly for older adults and an adjunct to manage CVD risk and improve overall cardiovascular health.^[181] In
9 older adults, mHealth is particularly effective when there is a short message service (texting) component
10 involved. However, there remain distinct barriers to the use of mHealth, such as affordability, usability, privacy,
11 and security issues.^[181] Also, mHealth interventions that incorporate personalized features other than
12 content (e.g. format/visualisation of screen) may improve effectiveness.^[182]

14 *eHealth*

15 eHealth refers to the organisation and delivery of health services and information using the Internet and
16 related technologies, such as web-based technology and mHealth.^[183] eHealth interventions are emerging as
17 an effective alternative model for improving secondary prevention of CVD, where patients receive access to
18 resources at their discretion. For instance, eHealth could be offered to patients who cannot attend traditional
19 CR programmes or as an adjunct and may decrease non-participation and dropout rates due to better
20 adaptation to patients’ needs and preferences.^[184] Utilising eHealth technology in education delivery, which
21 might be more popular among the youngsters, provides easier access for patients and permits them to self-
22 pace through educational materials. An additional advantage of remote delivery of interventions through
23 eHealth platforms is that patients can receive treatment and information during pandemics, such as covid-19.
24 However, it is important to acknowledge patient-related barriers, such as low eHealth literacy, which might
25 inhibit patients’ ability to apply knowledge, make appropriate decisions and achieve better self-
26 management.^[184] To improve health outcomes, eHealth should be designed to foster effective interactions at
27 a distance between patients and healthcare professionals, closer to those which are presential. However, little
28 is known about whether social support offered through eHealth programmes has the same effect on self-
29 management behaviour and psychosocial outcomes as traditional secondary prevention programs. Thus, while
30 eHealth interventions offer the potential of more flexibility, which can overcome barriers of work schedule or
31 geographical distance, further research is needed regarding their acceptability, feasibility, content, delivery and

1 impact, in particular in the elderly and in patients with low socio-economic status and low health/eHealth
2 literacy.

4 **The healthcare system**

5 The epidemiological shift in disease burden from acute to chronic diseases has rendered acute care models of
6 health service delivery inadequate to address the health needs of the population.[14] The healthcare delivery
7 system has the potential to affect patients' adherence behavior.[14] Healthcare systems control access to care.
8 For example, health systems control providers' schedules, length of appointments, allocation of resources, fee
9 structures, communication and information systems, and organizational priorities.[14]

10 The following are examples of the ways in which systems influence patients' behavior:[14]

- 11 ▪ Systems direct appointment length, and providers report that their schedules do not allow time to
12 adequately address adherence behavior;
- 13 ▪ Systems determine fee structures, and in many systems (e.g. fee-for-service) the lack of financial
14 reimbursement for patient counselling and education seriously threatens adherence-focused
15 interventions;
- 16 ▪ Systems allocate resources in a way that may result in high stress and increased demands upon
17 providers which, in turn, have been associated with decreased adherence in their patients;
- 18 ▪ Systems determine continuity of care. Patients demonstrate better adherence behavior when they
19 receive care from the same provider over time;
- 20 ▪ Systems direct information sharing. The ability of clinics and pharmacies to share information on
21 patients' behavior regarding prescription refills has the potential to improve adherence;
- 22 ▪ Systems determine the level of communication with patients. Ongoing communication efforts (e.g.
23 telephone contacts) that keep the patient engaged in healthcare may be the simplest and most cost-
24 effective strategy for improving adherence.

25 Unless variables such as these are addressed, it would be expected that the impact of the efforts of providers
26 and patients would be limited by the external constraints.[14] .

28 *Social media*

29 Social media, defined as "electronic communication, especially applications and websites, through which users
30 create and share information, ideas, and personal messages in an online community", is increasing
31 exponentially. [185,186] Reported social media use by American adults has gone from 5% in 2005 to 69% in
32 2018, and the impact of social media on both adults and youth is both mixed and incompletely

1 understood.[185]. Over recent years, social media have gained powerful influence globally and throughout
2 society. Although initially cautious, healthcare professionals and organizations are increasingly present on
3 social media platforms, with young professionals in particular viewing social media as an integral component of
4 communicating, networking, and keeping up to date with the latest science. While potential problems need to
5 be considered, responsible social media use is likely a beneficial addition to traditional means of obtaining and
6 disseminating medical and scientific education. Healthcare professionals and organizations are advised to
7 actively engage in social media to counterbalance un-reviewed and biased information [7,8]. Future
8 investigations of social media effects should focus on best practices, patient-oriented research, and the costs-
9 benefit of using certain tools or platforms in varying healthcare settings.[187,188]

11 *The role of informal caregivers in adherence to CVD management*

12 Family members and friends can provide practical (e.g., prepare meals, bring a patient to an appointment) and
13 emotional support to improve patients' mood, encourage compliance, and reward them for their efforts.
14 Involving social networks can improve patients' quality of life, self-efficacy and relationship quality and at the
15 same time lower the risk of hospitalisations.[189,190] However, informal carers most often report problems
16 such as lack of time for care and the need for institutional and personal support. In addition, caregivers require
17 information and training (e.g., emergency first aid, practical advice on caring for a bed rest, simple medical
18 procedures, administering medications, patting to prevent pressure ulcers, basic massage and rehabilitation
19 treatments, blood pressure measurement, among others) as well as counselling and the availability of respite
20 care.[191,192] Targeting informal caregivers with behavioural interventions and training may be cost-effective.
21 Carers could help with the multifactorial origin of adherence such as reminding patients to take the medication
22 even if asymptomatic and motivating them to continue with treatment leading to lower rates of
23 hospitalisations or lower use of additional medical resources.[70] Adherence to medication is increased with
24 the support of paid carers. Therefore, providing informal carers with the knowledge of paid professional carers
25 may lead to more successful patient management. [193] Caregivers feel powerless and ignored if they do not
26 engage in relationships with healthcare professionals. This lack of coordination between health caregivers, as
27 well as the lack of access to information, was clearly highlighted in research and stakeholder
28 consultations.[191,194] Therefore, psychosocial support for patients and caregivers can lead towards a more
29 successful management of patients.[195] Adherence to smoking cessation for secondary prevention can be
30 improved by involving family members and friends, with such as a 67% probability for smoking cessation if the
31 spouse of the patient takes the steps to stop smoking.[196]

1 *The role of integrated care: community-based projects*

2 The most common intervention is education (41%), followed by counselling or support (38%), and exercise
3 (28%). Half of the interventions are multi-component. The most common interventionists are health workers.
4 Interventions to lower BP are the most promising, with behaviour change interventions being the most
5 challenging. There is a pattern of successful educational and supportive interventions, initially a more intense
6 phase individual or group based, followed by a less intense phase that often involves individual telephone
7 support or support groups.[197] Increasing accessibility to pharmacists and integrating them in community
8 programs with general practitioners for screening of CVD risk factors or for monitoring patients who have been
9 already diagnosed and require monitoring has proved to be effective in increasing early diagnosis, adherence
10 and follow-up by physicians.[198] The most important barriers are lack of adequate funding, qualified
11 personnel, equipment and material resources, technical support in the field of data management and analysis,
12 training for providers, political support of local authorities and approval of the proposed intervention by the
13 authorities in the local community. The facilitators are motivated local leaders, cross-sector participation and
14 seizing local resources. The evaluation of the project should be based on the process, not on the results
15 indicators.[199] However, the patient adherence to treatment over time seems to be a more complex process
16 in which factors such as individual motivation and professional-patient interaction play an important role.[200]
17 Getting closer to the neighbourhood has proven to be effective. For example, an improved adherence to
18 therapy and management of high BP can be achieved through the involvement of barbershops in CVD
19 prevention.[165]

20

21 **Future directions/research**

22 Regarding future research, suggestions from a recent Policy Statement of the American Heart Association are
23 available (see Table 4).[201] The currently available studies are relatively small and of short duration, and few
24 information about how study designs were performed are provided. These facts significantly limit their ability
25 to be replicated in other settings and with other populations. Several studies used a multi-component
26 interventional design compared to usual care arm. Therefore, it is very difficult to identify the relationship
27 between each intervention and the outcome. The implementation in clinical practice of a policy to improve
28 adherence to optimal therapy is still often disregarded, due to the complexity of the problem and its
29 multidimensional nature. A great hope is in e-Health as a tool to improve adherence by facilitating the
30 relationship and communication between patients and healthcare professionals in the long term. In future
31 studies, it will be of particular importance to isolate the contribution of each component, in order to identify
32 the best target to test in future e-Health tools.

1

2 **Conclusions**

3 Adherence to pharmacological treatments and healthy lifestyle behaviours is poor in secondary CVD
4 prevention. However, adherence to therapy is an extremely complex problem. Probably, it is because of this
5 complexity that, despite the large size of the available literature and the widespread awareness of its
6 importance, effective approaches to address this problem are lacking in daily clinical practice. Since a complex
7 problem necessarily does not have a simple solution, in daily clinical practice every healthcare provider is
8 needed to increase sensitivity to the fact that without considering the future patient's adherence to therapies,
9 every effort done to improve the patient's health status can be insufficient. Each healthcare professional must
10 therefore apply a multidisciplinary approach, focused on adherence to guideline-directed medical therapy and
11 a heart-healthy lifestyle, based on present knowledge. This approach might be based on the following steps: i)
12 the identification of patients at risk of non-adherence, ii) the development of a multidisciplinary intervention
13 pathway useful to support adherence in the long-term, and iii) develop an adequate follow-up strategy in the
14 long term.

ACCEPTED MANUSCRIPT

1 **Author's contribution**

2 RFEP conceived the idea for paper, led the work group, drafted sections of the text, and provided editorial
3 oversight. DH co-led the work group, drafted sections of the text, and provided editorial oversight.
4 MA/MB/MCF/CPZ/AG/DK/MM/EO/SP/RES/MS/PS/DRT/MW/AA drafted sections of the text, reviewed and
5 commented on a final draft of the paper. CV/CHD/DW/IF reviewed and commented on a final draft of the
6 paper. All authors agreed to the final version of the paper.

ACCEPTED MANUSCRIPT

1 **References**

- 2 1. Kotseva K, De Backer G, De Bacquer D *et al.* Lifestyle and impact on cardiovascular risk factor control in
3 coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE
4 V registry. *Eur J Prev Cardiol* 2019;**26**:824–35.
- 5 2. De Bacquer D, Astin F, Kotseva K *et al.* Poor adherence to lifestyle recommendations in patients with
6 coronary heart disease: results from the EUROASPIRE surveys. *European Journal of Preventive Cardiology*
7 2022;**29**:383–95.
- 8 3. Chowdhury R, Khan H, Heydon E *et al.* Adherence to cardiovascular therapy: a meta-analysis of prevalence
9 and clinical consequences. *Eur Heart J* 2013;**34**:2940–8.
- 10 4. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on
11 376,162 patients. *Am J Med* 2012;**125**:882–887.e1.
- 12 5. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**:487–97.
- 13 6. Rea F, Ronco R, Pedretti RFE *et al.* Better adherence with out-of-hospital healthcare improved long-term
14 prognosis of acute coronary syndromes: Evidence from an Italian real-world investigation. *Int J Cardiol*
15 2020;**318**:14–20.
- 16 7. Hansen D, Abreu A, Ambrosetti M *et al.* Exercise intensity assessment and prescription in cardiovascular
17 rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and
18 Rehabilitation Section of the European Association of Preventive Cardiology. *European Journal of Preventive*
19 *Cardiology* 2022;**29**:230–45.
- 20 8. Abreu A, Frederix I, Dendale P *et al.* Standardization and quality improvement of secondary prevention
21 through cardiovascular rehabilitation programmes in Europe: The avenue towards EAPC accreditation
22 programme: A position statement of the Secondary Prevention and Rehabilitation Section of the European
23 Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2020:2047487320924912.
- 24 9. Ladwig K-H, Baghai TC, Doyle F *et al.* Mental Health-Related Risk Factors and Interventions in Patients with
25 Heart Failure. A Position Paper endorsed by the European Association of Preventive Cardiology (EAPC). *Eur J*
26 *Prev Cardiol* 2022:zwac006.
- 27 10. Pedretti RFE, Iliou M-C, Israel CW *et al.* Comprehensive multicomponent cardiac rehabilitation in cardiac
28 implantable electronic devices recipients: a consensus document from the European Association of Preventive
29 Cardiology (EAPC; Secondary prevention and rehabilitation section) and European Heart Rhythm Association
30 (EHRA). *Eur J Prev Cardiol* 2021;**28**:1736–52.
- 31 11. Ambrosetti M, Abreu A, Corrà U *et al.* Secondary prevention through comprehensive cardiovascular
32 rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary
33 Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol*
34 2020:2047487320913379.

- 1 12. A P, S S, S G *et al.* 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular
2 disease. *European heart journal* 2021;**42**, DOI: 10.1093/eurheartj/ehaa605.
- 3 13. Visseren FLJ, Mach F, Smulders YM *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in
4 clinical practice. *Eur Heart J* 2021;**42**:3227–337.
- 5 14. Sabaté E, World Health Organization eds. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva:
6 World Health Organization, 2003.
- 7 15. Vrijens B, De Geest S, Hughes DA *et al.* A new taxonomy for describing and defining adherence to
8 medications. *Br J Clin Pharmacol* 2012;**73**:691–705.
- 9 16. van der Laan DM, Elders PJM, Boons CCLM *et al.* Factors Associated With Nonadherence to Cardiovascular
10 Medications: A Cross-sectional Study. *J Cardiovasc Nurs* 2019;**34**:344–52.
- 11 17. ICD-11 for Mortality and Morbidity Statistics.
- 12 18. Hines R, Stone NJ. Patients and Physicians Beliefs and Practices Regarding Adherence to Cardiovascular
13 Medication. *JAMA Cardiol* 2016;**1**:470–3.
- 14 19. Tomaszewski M, White C, Patel P *et al.* High rates of non-adherence to antihypertensive treatment revealed
15 by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart*
16 2014;**100**:855–61.
- 17 20. Bansilal S, Castellano JM, Garrido E *et al.* Assessing the Impact of Medication Adherence on Long-Term
18 Cardiovascular Outcomes. *Journal of the American College of Cardiology* 2016;**68**:789–801.
- 19 21. Nguyen T-M-U, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring?: a
20 systematic review. *Br J Clin Pharmacol* 2014;**77**:427–45.
- 21 22. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of
22 medication adherence. *Med Care* 1986;**24**:67–74.
- 23 23. Kim MT, Hill MN, Bone LR *et al.* Development and Testing of the Hill-Bone Compliance to High Blood
24 Pressure Therapy Scale. *Progress in Cardiovascular Nursing* 2000;**15**:90–6.
- 25 24. Sav A, King MA, Whitty JA *et al.* Burden of treatment for chronic illness: a concept analysis and review of
26 the literature. *Health Expect* 2015;**18**:312–24.
- 27 25. Khatib R, Marshall K, Silcock J *et al.* Adherence to coronary artery disease secondary prevention medicines:
28 exploring modifiable barriers. *Open Heart* 2019;**6**:e000997.
- 29 26. Świątoniowska-Lonc N, Tański W, Polański J *et al.* Psychosocial Determinants of Treatment Adherence in
30 Patients with Type 2 Diabetes - A Review. *Diabetes Metab Syndr Obes* 2021;**14**:2701–15.
- 31 27. Anderson DR, Emery CF. Irrational health beliefs predict adherence to cardiac rehabilitation: a pilot study.
32 *Health Psychol* 2014;**33**:1614–7.

- 1 28. Allen LaPointe NM, Ou F-S, Calvert SB *et al.* Association between patient beliefs and medication adherence
2 following hospitalization for acute coronary syndrome. *Am Heart J* 2011;**161**:855–63.
- 3 29. Park Y, Park Y-H, Park K-S. Determinants of Non-Adherences to Long-Term Medical Therapy after
4 Myocardial Infarction: A Cross-Sectional Study. *Int J Environ Res Public Health* 2020;**17**:E3585.
- 5 30. Soroush A, Komasi S, Saeidi M *et al.* Coronary artery bypass graft patients' perception about the risk factors
6 of illness: Educational necessities of second prevention. *Ann Card Anaesth* 2017;**20**:303–8.
- 7 31. Sud A, Kline-Rogers EM, Eagle KA *et al.* Adherence to medications by patients after acute coronary
8 syndromes. *Ann Pharmacother* 2005;**39**:1792–7.
- 9 32. Dunlay SM, Witt BJ, Allison TG *et al.* Barriers to participation in cardiac rehabilitation. *Am Heart J*
10 2009;**158**:852–9.
- 11 33. Danielson E, Melin-Johansson C, Modanloo M. Adherence to Treatment in Patients with Chronic Diseases:
12 From Alertness to Persistence. *Int J Community Based Nurs Midwifery* 2019;**7**:248–57.
- 13 34. Mohammed MA, Moles RJ, Chen TF. Medication-related burden and patients' lived experience with
14 medicine: a systematic review and metanalysis of qualitative studies. *BMJ Open* 2016;**6**:e010035.
- 15 35. Yohannes AM, Yalfani A, Doherty P *et al.* Predictors of drop-out from an outpatient cardiac rehabilitation
16 programme. *Clin Rehabil* 2007;**21**:222–9.
- 17 36. Johnson JE, Weinert C, Richardson JK. Rural residents' use of cardiac rehabilitation programs. *Public Health*
18 *Nurs* 1998;**15**:288–96.
- 19 37. Molloy GJ, Perkins-Porras L, Bhattacharyya MR *et al.* Practical support predicts medication adherence and
20 attendance at cardiac rehabilitation following acute coronary syndrome. *J Psychosom Res* 2008;**65**:581–6.
- 21 38. Grace SL, Abbey SE, Shnek ZM *et al.* Cardiac rehabilitation II: referral and participation. *Gen Hosp Psychiatry*
22 2002;**24**:127–34.
- 23 39. Aggarwal B, Mosca L. Lifestyle and psychosocial risk factors predict non-adherence to medication. *Ann*
24 *Behav Med* 2010;**40**:228–33.
- 25 40. Kronish IM, Rieckmann N, Halm EA *et al.* Persistent depression affects adherence to secondary prevention
26 behaviors after acute coronary syndromes. *J Gen Intern Med* 2006;**21**:1178–83.
- 27 41. Burgess E, Hassmén P, Pumpa KL. Determinants of adherence to lifestyle intervention in adults with
28 obesity: a systematic review. *Clin Obes* 2017;**7**:123–35.
- 29 42. Chopra S, Malhotra A, Ranjan P *et al.* Predictors of successful weight loss outcomes amongst individuals
30 with obesity undergoing lifestyle interventions: A systematic review. *Obes Rev* 2021;**22**:e13148.
- 31 43. Cooke CE, Xing S, Gale SE *et al.* Initial non-adherence to antihypertensive medications in the United States:
32 a systematic literature review. *J Hum Hypertens* 2021, DOI: 10.1038/s41371-021-00549-w.

- 1 44. Pathak A, Poulter NR, Kavanagh M *et al.* Improving the Management of Hypertension by Tackling
2 Awareness, Adherence, and Clinical Inertia: A Symposium Report. *Am J Cardiovasc Drugs* 2021, DOI:
3 10.1007/s40256-021-00505-6.
- 4 45. Benjamin EJ, Virani SS, Callaway CW *et al.* Heart Disease and Stroke Statistics-2018 Update: A Report From
5 the American Heart Association. *Circulation* 2018;**137**:e67–492.
- 6 46. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L *et al.* Efficacy and safety of more
7 intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised
8 trials. *Lancet* 2010;**376**:1670–81.
- 9 47. Costanzo MR, Dipchand A, Starling R *et al.* The International Society of Heart and Lung Transplantation
10 Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010;**29**:914–56.
- 11 48. Ingersgaard MV, Helms Andersen T, Norgaard O *et al.* Reasons for Nonadherence to Statins - A Systematic
12 Review of Reviews. *Patient Prefer Adherence* 2020;**14**:675–91.
- 13 49. Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular
14 disease. *Int J Cardiol* 2015;**201 Suppl 1**:S1-7.
- 15 50. Chan SL, Edwards NJ, Conell C *et al.* Age, race/ethnicity, and comorbidities predict statin adherence after
16 ischemic stroke or myocardial infarction. *Eur J Prev Cardiol* 2020;**27**:2299–301.
- 17 51. Lansberg P, Lee A, Lee Z-V *et al.* Nonadherence to statins: individualized intervention strategies outside the
18 pill box. *Vasc Health Risk Manag* 2018;**14**:91–102.
- 19 52. Ferrieres J, De Ferrari GM, Hermans MP *et al.* Predictors of LDL-cholesterol target value attainment differ in
20 acute and chronic coronary heart disease patients: Results from DYSIS II Europe. *Eur J Prev Cardiol*
21 2018;**25**:1966–76.
- 22 53. Serban M-C, Colantonio LD, Manthripragada AD *et al.* Statin Intolerance and Risk of Coronary Heart Events
23 and All-Cause Mortality Following Myocardial Infarction. *J Am Coll Cardiol* 2017;**69**:1386–95.
- 24 54. Koskinas KC, Gencer B, Nanchen D *et al.* Eligibility for PCSK9 inhibitors based on the 2019 ESC/EAS and 2018
25 ACC/AHA guidelines. *Eur J Prev Cardiol* 2021;**28**:59–65.
- 26 55. Koskinas KC, Siontis GCM, Piccolo R *et al.* Effect of statins and non-statin LDL-lowering medications on
27 cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. *Eur Heart J*
28 2018;**39**:1172–80.
- 29 56. O'Brien EC, Roe MT, Fraulo ES *et al.* Rationale and design of the familial hypercholesterolemia foundation
30 CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia registry. *Am Heart J*
31 2014;**167**:342-349.e17.
- 32 57. Myers KD, Farboodi N, Mwamburi M *et al.* Effect of Access to Prescribed PCSK9 Inhibitors on Cardiovascular
33 Outcomes. *Circ Cardiovasc Qual Outcomes* 2019;**12**:e005404.

- 1 58. Prattichizzo F, de Candia P, De Nigris V *et al.* Legacy effect of intensive glucose control on major adverse
2 cardiovascular outcome: Systematic review and meta-analyses of trials according to different scenarios.
3 *Metabolism* 2020;**110**:154308.
- 4 59. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes.
5 *Circulation* 2009;**119**:3028–35.
- 6 60. Oosterom-Calo R, van Ballegooijen AJ, Terwee CB *et al.* Determinants of adherence to heart failure
7 medication: a systematic literature review. *Heart Fail Rev* 2013;**18**:409–27.
- 8 61. Juarez DT, Williams AE, Chen C *et al.* Factors affecting medication adherence trajectories for patients with
9 heart failure. *Am J Manag Care* 2015;**21**:e197-205.
- 10 62. Molloy GJ, O’Carroll RE, Witham MD *et al.* Interventions to enhance adherence to medications in patients
11 with heart failure: a systematic review. *Circ Heart Fail* 2012;**5**:126–33.
- 12 63. Fitzgerald AA, Powers JD, Ho PM *et al.* Impact of medication nonadherence on hospitalizations and
13 mortality in heart failure. *J Card Fail* 2011;**17**:664–9.
- 14 64. Shah D, Simms K, Barksdale DJ *et al.* Improving medication adherence of patients with chronic heart failure:
15 challenges and solutions. *RRCC* 2015;**6**:87–95.
- 16 65. Ruppap TM, Delgado JM, Temple J. Medication adherence interventions for heart failure patients: A meta-
17 analysis. *Eur J Cardiovasc Nurs* 2015;**14**:395–404.
- 18 66. Ruppap TM, Cooper PS, Mehr DR *et al.* Medication Adherence Interventions Improve Heart Failure Mortality
19 and Readmission Rates: Systematic Review and Meta-Analysis of Controlled Trials. *J Am Heart Assoc*
20 2016;**5**:e002606.
- 21 67. Toh C, Jackson B, Gascard D *et al.* Barriers to Medication Adherence in Chronic Heart Failure Patients during
22 Home Visits. *Journal of Pharmacy Practice and Research* 2010;**40**:27–30.
- 23 68. Calvin JE, Shanbhag S, Avery E *et al.* Adherence to evidence-based guidelines for heart failure in physicians
24 and their patients: lessons from the Heart Failure Adherence Retention Trial (HART). *Congest Heart Fail*
25 2012;**18**:73–8.
- 26 69. Silavanich V, Nathisuwan S, Phrommintikul A *et al.* Relationship of medication adherence and quality of life
27 among heart failure patients. *Heart Lung* 2019;**48**:105–10.
- 28 70. Aggarwal B, Pender A, Mosca L *et al.* Factors associated with medication adherence among heart failure
29 patients and their caregivers. *J Nurs Educ Pract* 2015;**5**:22–7.
- 30 71. Dalal HM, Taylor RS. Telehealth technologies could improve suboptimal rates of participation in cardiac
31 rehabilitation. *Heart* 2016;**102**:1155–6.
- 32 72. Zhang J, Gong Y, Zhao Y *et al.* Post-stroke medication adherence and persistence rates: a meta-analysis of
33 observational studies. *J Neurol* 2021;**268**:2090–8.

- 1 73. Levy T, Laver K, Killington M *et al.* A systematic review of measures of adherence to physical exercise
2 recommendations in people with stroke. *Clin Rehabil* 2019;**33**:535–45.
- 3 74. Rohde D, Merriman NA, Doyle F *et al.* Does cognitive impairment impact adherence? A systematic review
4 and meta-analysis of the association between cognitive impairment and medication non-adherence in stroke.
5 Quinn TJ (ed.). *PLoS ONE* 2017;**12**:e0189339.
- 6 75. Crayton E, Fahey M, Ashworth M *et al.* Psychological Determinants of Medication Adherence in Stroke
7 Survivors: a Systematic Review of Observational Studies. *ann behav med* 2017;**51**:833–45.
- 8 76. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*
9 2017;**14**:627–8.
- 10 77. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*
11 2017;**14**:627–8.
- 12 78. Hindricks G, Potpara T, Dagres N *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial
13 fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS).
14 *European Heart Journal* 2021;**42**:373–498.
- 15 79. Romiti GF, Pastori D, Rivera-Caravaca JM *et al.* Adherence to the ‘Atrial Fibrillation Better Care’ Pathway in
16 Patients with Atrial Fibrillation: Impact on Clinical Outcomes—A Systematic Review and Meta-Analysis of
17 285,000 Patients. *Thromb Haemost* 2022;**122**:406–14.
- 18 80. Bhattarai B, Walpola R, Mey A *et al.* Barriers and Strategies for Improving Medication Adherence Among
19 People Living With COPD: A Systematic Review. *Respir Care* 2020;**65**:1738–50.
- 20 81. Ruano-Ravina A, Pena-Gil C, Abu-Assi E *et al.* Participation and adherence to cardiac rehabilitation
21 programs. A systematic review. *Int J Cardiol* 2016;**223**:436–43.
- 22 82. Menezes AR, Lavie CJ, Forman DE *et al.* Cardiac rehabilitation in the elderly. *Prog Cardiovasc Dis*
23 2014;**57**:152–9.
- 24 83. González-Salvado V, Peña-Gil C, Lado-Baleato Ó *et al.* Offering, participation and adherence to cardiac
25 rehabilitation programmes in the elderly: a European comparison based on the EU-CaRE multicentre
26 observational study. *Eur J Prev Cardiol* 2021;**28**:558–68.
- 27 84. Collado-Mateo D, Lavín-Pérez AM, Peñacoba C *et al.* Key Factors Associated with Adherence to Physical
28 Exercise in Patients with Chronic Diseases and Older Adults: An Umbrella Review. *Int J Environ Res Public Health*
29 2021;**18**:2023.
- 30 85. Melloni C, Alexander KP, Ou F-S *et al.* Predictors of early discontinuation of evidence-based medicine after
31 acute coronary syndrome. *Am J Cardiol* 2009;**104**:175–81.
- 32 86. Kripalani S, Henderson LE, Jacobson TA *et al.* Medication use among inner-city patients after hospital
33 discharge: patient-reported barriers and solutions. *Mayo Clin Proc* 2008;**83**:529–35.

- 1 87. Kvarnström K, Airaksinen M, Liira H. Barriers and facilitators to medication adherence: a qualitative study
2 with general practitioners. *BMJ Open* 2018;**8**:e015332.
- 3 88. Kleinsinger F. The Unmet Challenge of Medication Nonadherence. *Perm J* 2018;**22**:18–033.
- 4 89. Nieuwlaat R, Wilczynski N, Navarro T *et al.* Interventions for enhancing medication adherence. *Cochrane*
5 *Database Syst Rev* 2014:CD000011.
- 6 90. Zullig LL, Blalock DV, Dougherty S *et al.* The new landscape of medication adherence improvement: where
7 population health science meets precision medicine. *Patient Prefer Adherence* 2018;**12**:1225–30.
- 8 91. Hyun K, Negrone A, Redfern J *et al.* Gender Difference in Secondary Prevention of Cardiovascular Disease
9 and Outcomes Following the Survival of Acute Coronary Syndrome. *Heart Lung Circ* 2021;**30**:121–7.
- 10 92. Xia S, Du X, Guo L *et al.* Sex Differences in Primary and Secondary Prevention of Cardiovascular Disease in
11 China. *Circulation* 2020;**141**:530–9.
- 12 93. Oosenbrug E, Marinho RP, Zhang J *et al.* Sex Differences in Cardiac Rehabilitation Adherence: A Meta-
13 analysis. *Can J Cardiol* 2016;**32**:1316–24.
- 14 94. Sanderson BK, Bittner V. Women in cardiac rehabilitation: outcomes and identifying risk for dropout. *Am*
15 *Heart J* 2005;**150**:1052–8.
- 16 95. Lichtman JH, Froelicher ES, Blumenthal JA *et al.* Depression as a risk factor for poor prognosis among
17 patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from
18 the American Heart Association. *Circulation* 2014;**129**:1350–69.
- 19 96. Pedersen SS, Nielsen JC, Wehberg S *et al.* New onset anxiety and depression in patients with an implantable
20 cardioverter defibrillator during 24 months of follow-up (data from the national DEFIB-WOMEN study). *Gen*
21 *Hosp Psychiatry* 2021;**72**:59–65.
- 22 97. Hoogwegt MT, Kupper N, Theuns DAMJ *et al.* Undertreatment of anxiety and depression in patients with an
23 implantable cardioverter-defibrillator: impact on health status. *Health Psychol* 2012;**31**:745–53.
- 24 98. Pedersen SS, von Känel R, Tully PJ *et al.* Psychosocial perspectives in cardiovascular disease. *Eur J Prev*
25 *Cardiol* 2017;**24**:108–15.
- 26 99. Pogosova N, Saner H, Pedersen SS *et al.* Psychosocial aspects in cardiac rehabilitation: From theory to
27 practice. A position paper from the Cardiac Rehabilitation Section of the European Association of
28 Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology. *Eur J Prev Cardiol*
29 2015;**22**:1290–306.
- 30 100. Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-
31 regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart
32 disease. *J Psychosom Res* 2014;**77**:439–48.

- 1 101. Luppá M, Heinrich S, Angermeyer MC *et al.* Cost-of-illness studies of depression: a systematic review. *J*
2 *Affect Disord* 2007;**98**:29–43.
- 3 102. Rodwin BA, Spruill TM, Ladapo JA. Economics of psychosocial factors in patients with cardiovascular
4 disease. *Prog Cardiovasc Dis* 2013;**55**:563–73.
- 5 103. Shields GE, Wright S, Wells A *et al.* Delivery preferences for psychological intervention in cardiac
6 rehabilitation: a pilot discrete choice experiment. *Open Heart* 2021;**8**:e001747.
- 7 104. Reavell J, Hopkinson M, Clarkesmith D *et al.* Effectiveness of Cognitive Behavioral Therapy for Depression
8 and Anxiety in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Psychosom Med*
9 2018;**80**:742–53.
- 10 105. Schneider LH, Hadjistavropoulos HD, Dear BF *et al.* Efficacy of internet-delivered cognitive behavioural
11 therapy following an acute coronary event: A randomized controlled trial. *Internet Interv* 2020;**21**:100324.
- 12 106. Helmark C, Ahm R, Andersen CM *et al.* Internet-based treatment of anxiety and depression in patients
13 with ischaemic heart disease attending cardiac rehabilitation: a feasibility study (eMindYourHeart). *European*
14 *Heart Journal - Digital Health* 2021;**2**:323–35.
- 15 107. Michal M, Beutel M. Mental disorders and cardiovascular disease: what should we be looking out for?
16 *Heart* 2021;**107**:1756–61.
- 17 108. Richards SH, Anderson L, Jenkinson CE *et al.* Psychological interventions for coronary heart disease:
18 Cochrane systematic review and meta-analysis. *Eur J Prev Cardiol* 2018;**25**:247–59.
- 19 109. Andersson G, Estling F, Jakobsson E *et al.* Can the patient decide which modules to endorse? An open trial
20 of tailored internet treatment of anxiety disorders. *Cogn Behav Ther* 2011;**40**:57–64.
- 21 110. Cajita MI, Cajita TR, Han H-R. Health Literacy and Heart Failure: A Systematic Review. *J Cardiovasc Nurs*
22 2016;**31**:121–30.
- 23 111. E C, M F, M A *et al.* Psychological Determinants of Medication Adherence in Stroke Survivors: a Systematic
24 Review of Observational Studies. *Annals of behavioral medicine : a publication of the Society of Behavioral*
25 *Medicine* 2017;**51**, DOI: 10.1007/s12160-017-9906-0.
- 26 112. Berkman ND, Davis TC, McCormack L. Health literacy: what is it? *J Health Commun* 2010;**15 Suppl 2**:9–19.
- 27 113. Kickbusch I, Pelikan JM, Apfel F *et al.* *Health Literacy: The Solid Facts*. World Health Organization. Regional
28 Office for Europe, 2013.
- 29 114. Sørensen K, Pelikan JM, Röthlin F *et al.* Health literacy in Europe: comparative results of the European
30 health literacy survey (HLS-EU). *Eur J Public Health* 2015;**25**:1053–8.
- 31 115. van der Heide I, Wang J, Droomers M *et al.* The relationship between health, education, and health
32 literacy: results from the Dutch Adult Literacy and Life Skills Survey. *J Health Commun* 2013;**18 Suppl 1**:172–84.

- 1 116. Kripalani S, Goggins K, Nwosu S *et al.* Medication Nonadherence Before Hospitalization for Acute Cardiac
2 Events. *J Health Commun* 2015;**20 Suppl 2**:34–42.
- 3 117. Ghisi GL de M, Chaves GS da S, Britto RR *et al.* Health literacy and coronary artery disease: A systematic
4 review. *Patient Educ Couns* 2018;**101**:177–84.
- 5 118. Aaby A, Friis K, Christensen B *et al.* Health Literacy among People in Cardiac Rehabilitation: Associations
6 with Participation and Health-Related Quality of Life in the Heart Skills Study in Denmark. *Int J Environ Res*
7 *Public Health* 2020;**17**:E443.
- 8 119. Aaby A, Friis K, Christensen B *et al.* Health literacy is associated with health behaviour and self-reported
9 health: A large population-based study in individuals with cardiovascular disease. *Eur J Prev Cardiol*
10 2017;**24**:1880–8.
- 11 120. van Schaik TM, Jørstad HT, Twickler TB *et al.* Cardiovascular disease risk and secondary prevention of
12 cardiovascular disease among patients with low health literacy. *Neth Heart J* 2017;**25**:446–54.
- 13 121. Magnani JW, Mujahid MS, Aronow HD *et al.* Health Literacy and CVD: Fundamental Relevance to Primary
14 and Secondary Prevention: A Scientific Statement From the AHA. *Circulation* 2018;**138**:e48–74.
- 15 122. Conard S. Best practices in digital health literacy. *Int J Cardiol* 2019;**292**:277–9.
- 16 123. Boateng D, Wekesah F, Browne JL *et al.* Knowledge and awareness of and perception towards
17 cardiovascular disease risk in sub-Saharan Africa: A systematic review. *PLoS One* 2017;**12**:e0189264.
- 18 124. Caligiuri SPB, Austria JA, Pierce GN. Alarming Prevalence of Emergency Hypertension Levels in the General
19 Public Identified by a Hypertension Awareness Campaign. *Am J Hypertens* 2017;**30**:236–9.
- 20 125. Shal’nova S Svetlana, Deev A, Metelskaya V *et al.* Awareness and treatment specifics of statin therapy in
21 persons with various cardiovascular risk: The study ESSE-RF. *Cardiovascular Therapy and Prevention* 2016;**15**:29–
22 37.
- 23 126. Wang C, Yu Y, Zhang X *et al.* Awareness, treatment, control of diabetes mellitus and the risk factors:
24 survey results from northeast China. *PLoS One* 2014;**9**:e103594.
- 25 127. Tchicaya A, Braun M, Lorentz N *et al.* Social inequality in awareness of cardiovascular risk factors in
26 patients undergoing coronary angiography. *Eur J Prev Cardiol* 2013;**20**:872–9.
- 27 128. Finken LR, Coomes E, Bajaj RR *et al.* HAS GOOGLE REPLACED TRADITIONAL SOURCES OF CARDIOVASCULAR
28 DISEASE AND RISK FACTOR INFORMATION? *Canadian Journal of Cardiology* 2014;**10 Supplement**:S180.
- 29 129. Redmond N, Baer HJ, Clark CR *et al.* Sources of health information related to preventive health behaviors
30 in a national study. *Am J Prev Med* 2010;**38**:620–627.e2.
- 31 130. Noar SM, Harrington NG. Tailored communications for health-related decision-making and behavior
32 change. *Handbook of Health Decision Science*. New York, NY, US: Springer Science + Business Media, 2016,
33 251–63.

- 1 131. Alzaman N, Wartak SA, Friderici J *et al.* Effect of patients' awareness of CVD risk factors on health-related
2 behaviors. *South Med J* 2013;**106**:606–9.
- 3 132. Nutbeam D, Kickbusch I. Health promotion glossary. *Health promotion international* 1998;**13**:349–64.
- 4 133. Karni L, Dalal K, Memedi M *et al.* Information and Communications Technology-Based Interventions
5 Targeting Patient Empowerment: Framework Development. *J Med Internet Res* 2020;**22**:e17459.
- 6 134. Greer AE, Milner K, Marcello R *et al.* Health Action Process Approach: Application to Medication
7 Adherence in Cardiac Rehabilitation (CR) Patients. *Educational Gerontology* 2015;**41**:685–94.
- 8 135. Steca P, Pancani L, Cesana F *et al.* Changes in physical activity among coronary and hypertensive patients:
9 A longitudinal study using the Health Action Process Approach. *Psychol Health* 2017;**32**:361–80.
- 10 136. Sarkar U, Ali S, Whooley MA. Self-efficacy as a marker of cardiac function and predictor of heart failure
11 hospitalization and mortality in patients with stable coronary heart disease: findings from the Heart and Soul
12 Study. *Health Psychol* 2009;**28**:166–73.
- 13 137. Katch H, Mead H. The role of self-efficacy in cardiovascular disease self-management: a review of effective
14 programs. *PI* 2010;**2**:33–44.
- 15 138. Salim U. Bandura, A.(1997). Self Efficacy The Exercise of Control. New York: WH Freeman and Company.
- 16 139. Griffo R, Ambrosetti M, Tramarin R *et al.* Effective secondary prevention through cardiac rehabilitation
17 after coronary revascularization and predictors of poor adherence to lifestyle modification and medication.
18 Results of the ICAROS Survey. *Int J Cardiol* 2013;**167**:1390–5.
- 19 140. Brieger D, Chow C, Gullick J *et al.* Improving patient adherence to secondary prevention medications 6
20 months after an acute coronary syndrome: observational cohort study. *Intern Med J* 2018;**48**:541–9.
- 21 141. Rochon PA, Gurwitz JH. Drug therapy. *Lancet* 1995;**346**:32–6.
- 22 142. Gast A, Mathes T. Medication adherence influencing factors-an (updated) overview of systematic reviews.
23 *Syst Rev* 2019;**8**:112.
- 24 143. Miller NH. Compliance with treatment regimens in chronic asymptomatic diseases. *Am J Med*
25 1997;**102**:43–9.
- 26 144. Liu C-F, Kuo K-M. Does information overload prevent chronic patients from reading self-management
27 educational materials? *Int J Med Inform* 2016;**89**:1–8.
- 28 145. Delbanco T, Berwick DM, Boufford JI *et al.* Healthcare in a land called PeoplePower: nothing about me
29 without me. *Health Expect* 2001;**4**:144–50.
- 30 146. Bell SK, Mejilla R, Anselmo M *et al.* When doctors share visit notes with patients: a study of patient and
31 doctor perceptions of documentation errors, safety opportunities and the patient-doctor relationship. *BMJ*
32 *Qual Saf* 2017;**26**:262–70.

- 1 147. Fritz Z, Schlindwein A, Slowther A-M. Patient engagement or information overload: patient and physician
2 views on sharing the medical record in the acute setting. *Clin Med (Lond)* 2019;**19**:386–91.
- 3 148. Teach-Back.
- 4 149. Navar AM, Stone NJ, Martin SS. What to say and how to say it: effective communication for cardiovascular
5 disease prevention. *Curr Opin Cardiol* 2016;**31**:537–44.
- 6 150. Stacey D, Légaré F, Lewis K *et al*. Decision aids for people facing health treatment or screening decisions.
7 *Cochrane Database Syst Rev* 2017;**4**:CD001431.
- 8 151. Navar AM, Wang TY, Mi X *et al*. Influence of Cardiovascular Risk Communication Tools and Presentation
9 Formats on Patient Perceptions and Preferences. *JAMA Cardiol* 2018;**3**:1192–9.
- 10 152. Fuertes JN, Mislowack A, Bennett J *et al*. The physician-patient working alliance. *Patient Educ Couns*
11 2007;**66**:29–36.
- 12 153. *Textbook of Palliative Care Communication*. Oxford University Press
- 13 154. Härter M, Dirmaier J. 4.3. Arzt-Patient-Kommunikation.
14 https://books.publisso.de/de/publisso_gold/publishing/books/overview/46/175 2020, DOI:
15 10.5680/OLMPS000062.
- 16 155. Hashim MJ. Patient-Centered Communication: Basic Skills. *Am Fam Physician* 2017;**95**:29–34.
- 17 156. Renner B, Gamp M, Schmäzle R *et al*. Health Risk Perception. *International Encyclopedia of the Social &*
18 *Behavioral Sciences*. Elsevier, 2015, 702–9.
- 19 157. Hengen KM, Alpers GW. What's the Risk? Fearful Individuals Generally Overestimate Negative Outcomes
20 and They Dread Outcomes of Specific Events. *Front Psychol* 2019;**10**:1676.
- 21 158. Webster R, Heeley E. Perceptions of risk: understanding cardiovascular disease. *Risk Manag Healthc Policy*
22 2010;**3**:49–60.
- 23 159. Davidson PM, Salamonson Y, Rolley J *et al*. Perception of cardiovascular risk following a percutaneous
24 coronary intervention: a cross sectional study. *Int J Nurs Stud* 2011;**48**:973–8.
- 25 160. Plana N, Ibarretxe D, Cabré A *et al*. Prevalence of atherogenic dyslipidemia in primary care patients at
26 moderate-very high risk of cardiovascular disease. Cardiovascular risk perception. *Clin Investig Arterioscler*
27 2014;**26**:274–84.
- 28 161. Goldman RE, Parker DR, Eaton CB *et al*. Patients' perceptions of cholesterol, cardiovascular disease risk,
29 and risk communication strategies. *Ann Fam Med* 2006;**4**:205–12.
- 30 162. Dixon DL, Sharma G, Sandesara PB *et al*. Therapeutic Inertia in Cardiovascular Disease Prevention: Time to
31 Move the Bar. *Journal of the American College of Cardiology* 2019;**74**:1728–31.

- 1 163. Chan WV, Pearson TA, Bennett GC *et al.* ACC/AHA Special Report: Clinical Practice Guideline
2 Implementation Strategies: A Summary of Systematic Reviews by the NHLBI Implementation Science Work
3 Group: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical
4 Practice Guidelines. *J Am Coll Cardiol* 2017;**69**:1076–92.
- 5 164. Hill JA, Agewall S, Baranchuk A *et al.* Medical Misinformation. *Circulation* 2019;**139**:571–2.
- 6 165. Victor RG, Lynch K, Li N *et al.* A Cluster-Randomized Trial of Blood-Pressure Reduction in Black
7 Barbershops. *N Engl J Med* 2018;**378**:1291–301.
- 8 166. Bauer MS, Damschroder L, Hagedorn H *et al.* An introduction to implementation science for the non-
9 specialist. *BMC Psychol* 2015;**3**:32.
- 10 167. Choudhry NK, Krumme AA, Ercole PM *et al.* Effect of Reminder Devices on Medication Adherence: The
11 REMIND Randomized Clinical Trial. *JAMA Intern Med* 2017;**177**:624–31.
- 12 168. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical
13 utilization and spending and health. *JAMA* 2007;**298**:61–9.
- 14 169. Harris CM, Sridharan A, Landis R *et al.* What happens to the medication regimens of older adults during
15 and after an acute hospitalization? *J Patient Saf* 2013;**9**:150–3.
- 16 170. Chow CK, Meng Q. Polypills for primary prevention of cardiovascular disease. *Nat Rev Cardiol*
17 2019;**16**:602–11.
- 18 171. Roshandel G, Khoshnia M, Poustchi H *et al.* Effectiveness of polypill for primary and secondary prevention
19 of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *The Lancet* 2019;**394**:672–83.
- 20 172. Joyner MJ, Paneth N. Cardiovascular Disease Prevention at a Crossroads: Precision Medicine or Polypill?
21 *JAMA* 2019;**322**:2281–2.
- 22 173. Thom S, Poulter N, Field J *et al.* Effects of a fixed-dose combination strategy on adherence and risk factors
23 in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA* 2013;**310**:918–29.
- 24 174. Patel A, Cass A, Peiris D *et al.* A pragmatic randomized trial of a polypill-based strategy to improve use of
25 indicated preventive treatments in people at high cardiovascular disease risk. *Eur J Prev Cardiol* 2015;**22**:920–
26 30.
- 27 175. Selak V, Elley CR, Bullen C *et al.* Effect of fixed dose combination treatment on adherence and risk factor
28 control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care. *BMJ*
29 2014;**348**:g3318.
- 30 176. Selak V, Webster R, Stepien S *et al.* Reaching cardiovascular prevention guideline targets with a polypill-
31 based approach: a meta-analysis of randomised clinical trials. *Heart* 2019;**105**:42–8.
- 32 177. WHO Global Observatory for eHealth. *MHealth: New Horizons for Health through Mobile Technologies:*
33 *Second Global Survey on EHealth.* World Health Organization, 2011.

- 1 178. Burke LE, Ma J, Azar KMJ *et al.* Current Science on Consumer Use of Mobile Health for Cardiovascular
2 Disease Prevention. *Circulation* 2015;**132**:1157–213.
- 3 179. Thakkar J, Kurup R, Laba T-L *et al.* Mobile Telephone Text Messaging for Medication Adherence in Chronic
4 Disease: A Meta-analysis. *JAMA Internal Medicine* 2016;**176**:340–9.
- 5 180. Gandapur Y, Kianoush S, Kelli HM *et al.* The role of mHealth for improving medication adherence in
6 patients with cardiovascular disease: a systematic review. *European Heart Journal - Quality of Care and Clinical
7 Outcomes* 2016;**2**:237–44.
- 8 181. Schorr EN, Gepner AD, Dolansky MA *et al.* Harnessing Mobile Health Technology for Secondary
9 Cardiovascular Disease Prevention in Older Adults: A Scientific Statement From the American Heart
10 Association. *Circulation: Cardiovascular Quality and Outcomes* 2021;**14**:e000103.
- 11 182. Tong HL, Quiroz JC, Kocaballi AB *et al.* Personalized mobile technologies for lifestyle behavior change: A
12 systematic review, meta-analysis, and meta-regression. *Prev Med* 2021;**148**:106532.
- 13 183. Frederix I, Caiani EG, Dendale P *et al.* ESC e-Cardiology Working Group Position Paper: Overcoming
14 challenges in digital health implementation in cardiovascular medicine. *Eur J Prev Cardiol* 2019;**26**:1166–77.
- 15 184. Brørs G, Pettersen TR, Hansen TB *et al.* Modes of e-Health delivery in secondary prevention programmes
16 for patients with coronary artery disease: a systematic review. *BMC Health Services Research* 2019;**19**:364.
- 17 185. LaBarge G, Broom M. Social Media in Primary Care. *Mo Med* 2019;**116**:106–10.
- 18 186. Dictionary by Merriam-Webster: America's most-trusted online dictionary.
- 19 187. Social Media Use 2018: Demographics and Statistics. *Pew Research Center: Internet, Science & Tech* 2018.
- 20 188. Ladeiras-Lopes R, Baciú L, Grapsa J *et al.* Social media in cardiovascular medicine: a contemporary review.
21 *European Heart Journal - Digital Health* 2020;**1**:10–9.
- 22 189. Martire LM, Schulz R, Keefe FJ *et al.* Couple-Oriented Education and Support Intervention for
23 Osteoarthritis: Effects on Spouses' Support and Responses to Patient Pain. *Fam Syst Health* 2008;**26**:185–95.
- 24 190. Nichols LO, Martindale-Adams J, Burns R *et al.* Translation of a dementia caregiver support program in a
25 health care system--REACH VA. *Arch Intern Med* 2011;**171**:353–9.
- 26 191. Morris SM, King C, Turner M *et al.* Family carers providing support to a person dying in the home setting: A
27 narrative literature review. *Palliat Med* 2015;**29**:487–95.
- 28 192. Ploeg J, Matthew-Maich N, Fraser K *et al.* Managing multiple chronic conditions in the community: a
29 Canadian qualitative study of the experiences of older adults, family caregivers and healthcare providers. *BMC
30 Geriatr* 2017;**17**:40.
- 31 193. Aggarwal B, Liao M, Mosca L. Medication adherence is associated with having a caregiver among cardiac
32 patients. *Ann Behav Med* 2013;**46**:237–42.

- 1 194. Ventura AD, Burney S, Brooker J *et al.* Home-based palliative care: a systematic literature review of the
2 self-reported unmet needs of patients and carers. *Palliat Med* 2014;**28**:391–402.
- 3 195. Blair J, Volpe M, Aggarwal B. Challenges, needs, and experiences of recently hospitalized cardiac patients
4 and their informal caregivers. *J Cardiovasc Nurs* 2014;**29**:29–37.
- 5 196. Trivedi RB, Bryson CL, Udris E *et al.* The influence of informal caregivers on adherence in COPD patients.
6 *Ann Behav Med* 2012;**44**:66–72.
- 7 197. Walton-Moss B, Samuel L, Nguyen TH *et al.* Community-based cardiovascular health interventions in
8 vulnerable populations: a systematic review. *J Cardiovasc Nurs* 2014;**29**:293–307.
- 9 198. Snella KA, Canales AE, Irons BK *et al.* Pharmacy- and community-based screenings for diabetes and
10 cardiovascular conditions in high-risk individuals. *J Am Pharm Assoc (2003)* 2006;**46**:370–7.
- 11 199. Belizan M, Chaparro RM, Santero M *et al.* Barriers and Facilitators for the Implementation and Evaluation
12 of Community-Based Interventions to Promote Physical Activity and Healthy Diet: A Mixed Methods Study in
13 Argentina. *Int J Environ Res Public Health* 2019;**16**:E213.
- 14 200. Taylor AJ, Bindeman J, Feuerstein I *et al.* Community-based provision of statin and aspirin after the
15 detection of coronary artery calcium within a community-based screening cohort. *J Am Coll Cardiol*
16 2008;**51**:1337–41.
- 17 201. Piña IL, Di Palo KE, Brown MT *et al.* Medication adherence: Importance, issues and policy: A policy
18 statement from the American Heart Association. *Prog Cardiovasc Dis* 2021;**64**:111–20.

19

20

1 **Table 1** Take-home messages and consensus statements

- 2 ° In the secondary prevention of CVD, it is crucial to optimize the adherence to therapy since most CVD risk
3 factors and lifestyle measures are far from optimally controlled in many patients.
- 4 ° Considering the multifactorial process that can lead to suboptimal adherence to treatment, secondary CVD
5 prevention should be deployed in a multidisciplinary setting or context.
- 6 ° In general, a low self-efficacy, poor health literacy and risk perception, and certain psychosocial issues (e.g.
7 depression, anxiety, cognitive decline, poor social support and socio-economic status) predict a low adherence
8 to therapy. Hence, these factors should be screened at entry of a secondary prevention program and targeted
9 accordingly.
- 10 ° For each CVD risk factor or condition separately, additional specific predictors for a low adherence to therapy
11 are established, and should thus be taken into account by healthcare providers.
- 12 ° To optimize the adherence to therapy, it is important to work on its five dimensions simultaneously,
13 including: the patient, the disease, the healthcare provider, the therapy, and the healthcare system.

14

15

1 **Table 2** General barriers to adherence to treatment

Patient-centred barriers to adherence to treatment
Low education level
Low health literacy with poor knowledge of illness and medication
Lack of competence in self-management
Misbeliefs (alternative belief systems as media and neighbours medication information)
Lack of motivation
Fear for medication side-effects
Low economic status
Depression or cognitive disturbances
Old age
Poor vision
Alcohol or drug abuse
Disease-driven barriers to adherence to treatment
Absence of symptoms
Chronicity
Good prognosis
Healthcare professional-centred barriers to adherence to treatment
Not enough time for consults (short consult period)
Poor practitioner-patient relationship
Unsatisfactory skills in coaching self-management treatment
No satisfactory full list of medication review (too time-consuming)
Difficulties to obtain the accurate knowledge of home medication (generics, past medication maintained)
Healthcare professional authoritarian approach to patients
Medication-driven barriers to adherence to treatment
Complexity of medication
Polypharmacy
Doubts on duration of medication (temporary, chronic)

Medication withdrawal
Drugs adverse effects and toxicity
Drug-to-drug interaction
Existence of different generic drugs (different names and boxes for the same drug)
Costs (economic, personal, social)
Inconvenience
Time
Unavailability
Healthcare system-driven barriers to adherence to treatment
Provided poor access to healthcare (distance, costs, reimbursement)
Poor communication within the system
Problems in keeping the list of medication up-to-date
Lack of enough healthcare professionals with multitask appointments and short time for consults

1

2 **Table 3** Psychological determinants of non-adherence

<ul style="list-style-type: none"> • Skills (language skills, planning, and organization skills): Poorer skills yield worse adherence • Beliefs about capabilities: Helplessness impairs adherence, perceived control improves adherence • Memory: Memory deficits were related to poorer adherence • Social Influences: Perceived discrimination due to race, ethnicity, education, or income was linked to a higher risk of non-adherence. Increasing inertia appeared was related to increased non-adherence

3

4

1 **Table 4** Gaps in current knowledge – need for future studies

2

3 ° Which interventions have the broadest impact on maximising adherences to therapy across patient groups or
4 health conditions? Which interventions work best for which component of the CVD therapy?

5 ° What is the direct impact of improved adherence to medication and improved adherence to lifestyle in
6 specific patient populations or health conditions on actual healthcare outcomes and costs?

7 ° Does the adherence to medications for multiple medical conditions differ from adherence if only one medical
8 condition is present? If yes what additional tools, resources needed?

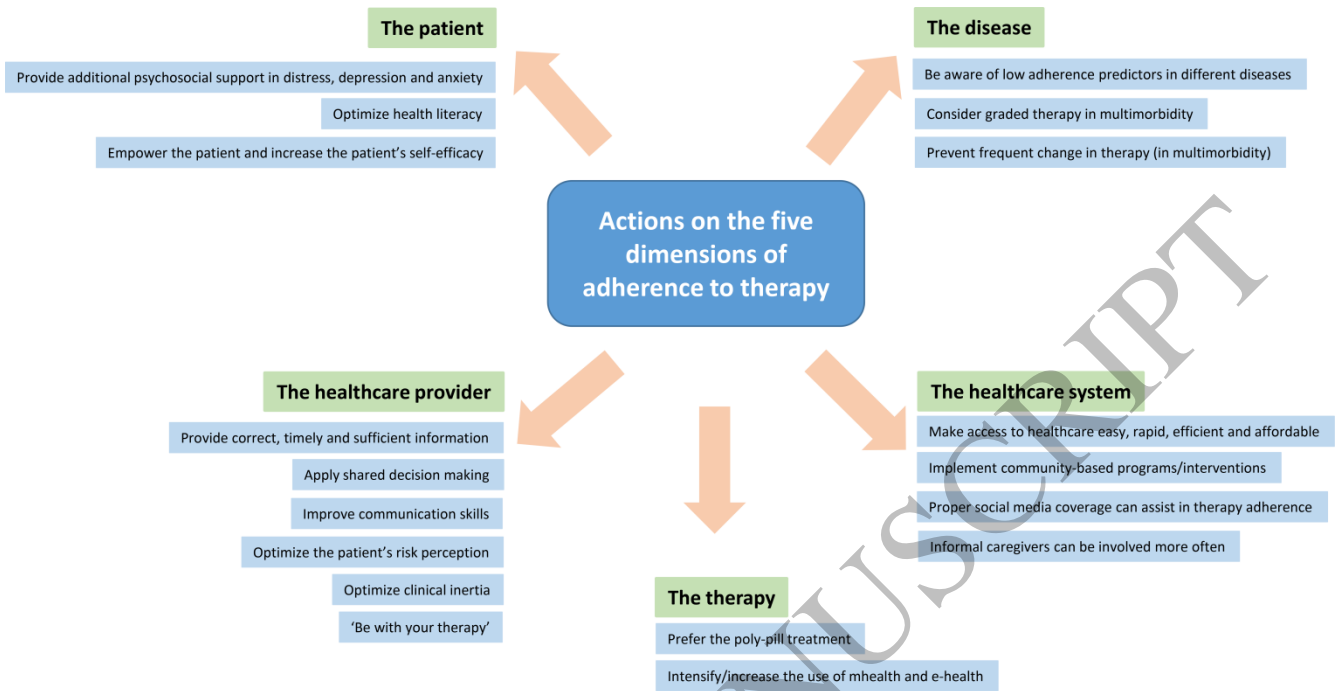
9 ° Are there patient subgroups for whom spending on adherence interventions yields more benefit in terms of
10 reducing future healthcare costs than other patient subgroups?

11 ° What healthcare provider-patient communication strategies mostly impact adherence to heart healthy
12 therapies (i.e medication and lifestyle) in a positive direction?

13 ° To what degree does payment reform and incentives impact medication adherence rates on the long-term?

14

15



1 **Figure 1** How to optimize therapy adherence in CVD

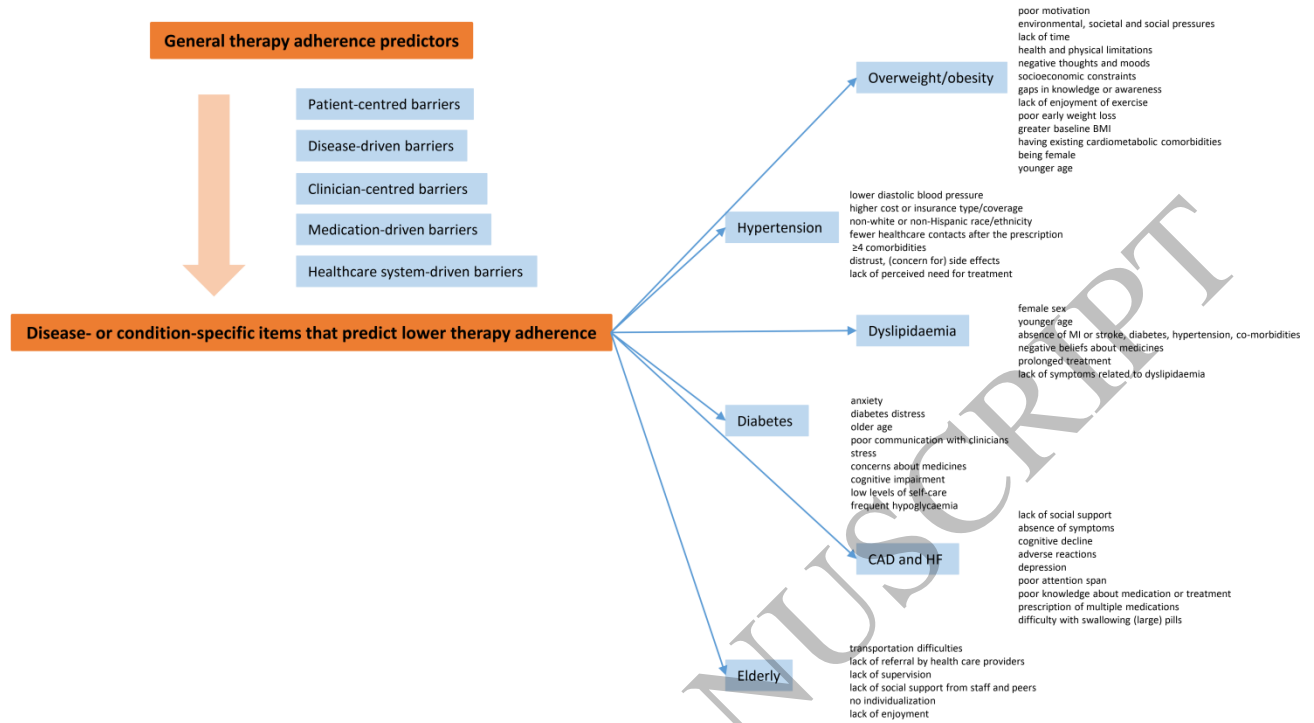
2

3

4

Figure 1
305x173 mm (x DPI)

ACCEPTED MANUSCRIPT



1 **Figure 2** Predictors of therapy adherence in specific CVD's or risk factors

2 **Figure 2**
3 301x187 mm (x DPI)

4

Figure 3 Graphical abstract

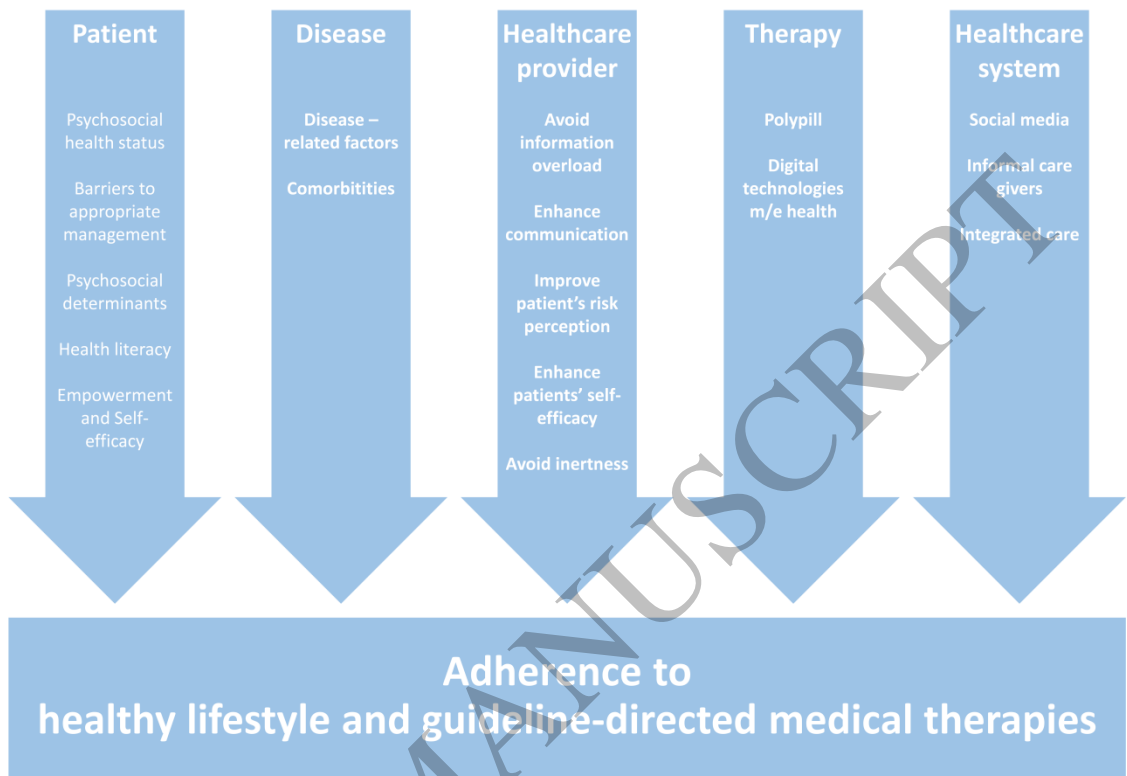


Figure 3
295x180 mm (x DPI)

1
2
3