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Dyslipidaemia and hypertension – brothers in crime?!

Minoski, Darko [a]; Dieterle, Thomas [a,b,c]

[a] Klinik Arlesheim AG, Arlesheim, Switzerland
[b] Department of Clinical Research, University Hospital Basel, Switzerland
[c] University of Basel, Faculty of Medicine, Basel, Switzerland

Introduction

Cardiovascular disease (CVD) remains the major cause of mortality and healthcare costs worldwide. Prevalent cases of total CVDs have nearly doubled from 271 million in 1990 to 523 million in 2019 [1]. In Europe alone, CVD accounts for more than 4 million deaths each year [2]. It is well known that metabolic, environmental and occupational, as well as behavioural risk factors contribute to the burden of CVD [1]. According to the Global Burden of Disease study, high blood pressure and high low-density lipoprotein cholesterol (LDL-C) were the leading metabolic, attributable, modifiable risk factors for CVD in 2019, followed by high body mass index, high fasting plasma glucose and kidney dysfunction [1].

According to the World Health Organization, 1.13 billion people were affected by arterial hypertension globally in 2019 [3]. With more than 10 million hypertension-related deaths, arterial hypertension was the leading contributor to deaths caused by CVDs [4, 5]. In addition, arterial hypertension remains the most important risk factor for ischaemic heart disease, ischaemic and haemorrhagic stroke, peripheral artery disease, and heart failure – diseases that themselves are associated with high mortality and a high burden in terms of hypertension-related disabilities [6]. Hypertension often aggregates with other metabolic and/or behavioural cardiovascular (CV) risk factors, such as high cholesterol, high blood glucose, overweight and obesity, smoking and physical inactivity, exponentially increasing morbidity and mortality [7, 8]. In fact, data from the REACH (Reduction of Atherothrombosis for Continued Health) registry indicate that the majority of patients had at least one other CV risk factor in addition to hypertension, with hypercholesterolaemia being the most prevalent [9]. In Swiss patients included in the Swiss Hypertension Cohort Study (HccH), 1–2 and 3 or more additional cardiovascular risk factors were found in 19.7% and 27.3% of patients, respectively, and dyslipidaemia was the most prevalent additional risk factor in addition to arterial hypertension [10].

The goal of this article is to outline the importance of early and effective risk factor management in patients with arterial hypertension and dyslipidaemia as well as the benefits of a combined approach to CV risk factor treatment with a special emphasis on lowering blood pressure and lipids. The concepts presented are largely based on the recommendations of the 2018 European Society of Hypertension / European Society of Cardiology (ESH/ESC) guidelines for the management of arterial hypertension and the European Society of Cardiology / European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias published in 2019 [11, 12].

High blood pressure and cholesterol and cardiovascular risk

It is well known that increasing blood pressure and low-density lipoprotein cholesterol (LDL-C) is associated with an increasing risk for ischaemic heart disease, stroke and vascular disease-related mortality [13, 14]. A meta-analysis of 61 prospective studies demonstrated that, within each decade of age at death, the proportional difference in the risk of vascular death associated with a given absolute difference in usual blood pressure is about the same down to a blood pressure of at least 115/75 mm Hg. Each difference of 20/10 mm Hg was associated with a two-fold increase in death rate from stroke, ischaemic heart disease and other vascular causes of death [13]. A similar trend was observed with regards to cholesterol where 1 mmol/l lower non-high-density lipoprotein (HDL) cholesterol, mostly LDL-C, was associated with about one third lower mortality from ischaemic heart disease [14].

For a long time, hypertension guidelines have focused on blood pressure as the only and main variable determining the need for antihypertensive treatment. In 1994, the ESC, ESH, and the EAS developed recommendations on prevention of coronary heart disease (CHD) that emphasised basing therapeutic decisions on total CV risk [15]. Many CV risk assessment systems are available and most project 10-year risk. Since 2003, the European guidelines on CVD prevention recommended the Systematic Coronary Risk Evaluation (SCORE) system because it is based on large, representative European cohort data-sets [16]. The SCORE system provides an estimate of the 10-year risk of a first fatal atherosclerotic event based on information on age, sex, smoking status, total cholesterol level and systolic blood pressure, and provides the basis for CV risk stratification as outlined in the 2018 ESH/ESC guidelines for the

Correspondence:
Prof. Thomas Dieterle, MD, MHBA
Division of Cardiology
Klinik Arlesheim AG and
Department of Clinical Research
University Hospital Basel
Pfeffingerweg 1
CH-4144 Arlesheim
thomas.dieterle[at]klinik-arlesheim.ch

management of arterial hypertension and the 2019 ESC/EAS guidelines for the management of dyslipidaemias [11, 12]. The presence of multiple risk factors in an individual patient exponentially increases CV risk [11]. The presence of a single risk factor increases the risk of myocardial infarction (MI) approximately 2–3-fold, the presence of multiple risk factors such as hypertension, diabetes, dyslipidemia and smoking increase CV risk more than 20-fold [12].

However, it must be emphasised that stratification of total CV risk should not be based on the SCORE charts alone since they do not take into account further risk factors such as diabetes mellitus, heart rate, family history of premature CVD, sedentary lifestyle, and psychosocial and socioeconomic factors. Moreover, the presence of hypertension-mediated organ damage (HMOD), such as arterial stiffening, left ventricular hypertrophy, microalbuminuria, retinopathy, or a low ankle-brachial index, and/or established CV and/or renal disease should be searched for and considered in the process of estimating total CV risk [11, 12]. Patient characteristics defining low, moderate, high and very high CV risk are summarised in table 1.

Rationale for lowering blood pressure and cholesterol

Despite the availability of effective therapies for high blood pressure, high cholesterol and high blood glucose, many patients still have major CV events, demonstrating the continuing need for improved risk factor management to reduce CV mortality and disability. Numerous trials have clearly and convincingly demonstrated that lowering of blood pressure andLDL-C significantly reduce CV risk [17–19]. A meta-regression analysis based on 123 studies that included 613,815 participants demonstrated that every 10 mm Hg reduction in systolic blood pressure led to a 20% reduction in major CV events, a 13% reduction in coronary heart disease (CHD), a 27% reduction in stroke and a 28% reduction in heart failure, resulting in a 13% reduction in all-cause mortality in the populations studied [19]. Reduction of LDL-C by 1 mmol/l were associated with a relative risk reduction for vascular events of 23–25% [17].

Mendelian randomisation studies indicate that the beneficial effects of lowering LDL-C and blood pressure on the risk of CHD may accumulate over time [20, 21]. Ference and colleagues have shown that similar blood pressure values, either due to a favourable genetic background or achieved later in life in the context of blood pressure lowering clinical trials, were associated with an almost 50% vs a 17–25% reduction in CVD [20]. Similar results were found when genetically determined lower LDL-C levels were compared with LDL-C levels that were lowered during treatment within randomized controlled trials [21].

A further Mendelian randomisation study analysed the association of lifetime exposure to lower blood pressure and lower LDL-C levels with the lifetime risk of CVD in 438,952 patients (mean age 65.2 years, 54.1% women) enrolled in theUK Biobank between 2006 and 2010 and followed up until 2018 [22]. A total of 24,980 patients experienced a first major coronary event during follow-up [22]. Genetic LDL-C and systolic blood pressure scores were used to divide the participants into subgroups with lifetime exposure to lower or higher LDL-C levels or systolic blood pressure , with genetic scores higher than the median being associated with lower LDL-C or systolic blood pressure [22]. Genetic LDL-C and systolic blood pressure scores higher than the median were associated with a 0.377 mmol/l lower LDL-C and a 2.9 mm Hg lower SBP, and a 27% and 18%, respectively, lower rate of major coro-

Table 1: :
Cardiovascular risk categories.

Risk estimate	Patient characteristics	ESH/ESC	EAS
Very high	Documented CVD, either clinical or unequivocal on imaging	X	X
	Clinical CVD: acute MI, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, peripheral artery disease	X	X
	Unequivocal documented CVD on imaging: significant plaque (i.e. ≥50% stenosis) on (coronary) angiography, CT scan, or ultrasound	X	X
	DM with target organ damage, e.g. proteinuria or with a major risk factor (grade 3 hypertension, hypercholesterolemia)	X	
	DM with target organ damage, or at least three major risk factors, or early onset of T1D of long duration (≥20 years)		X
	Severe CKD (eGFR <30 ml/min/1.73m²)		X
	A calculated 10-year SCORE ≥10%	X	X
	FH with atherosclerotic CVD or with another major risk factor	X	X
High	Marked elevation of a single risk factor, particularly cholesterol >8 mmol/l, e.g. FH or grade 3 hypertension (BP ≥180/110 mm Hg)	X	
	Markedly elevated single risk factor, in particular TC >8 mmol/l, LDL-C >4.9 mmol/l, or BP ≥180/110 mm Hg		X
	FH without other major risk factors	X	X
	DM (except some young people with T1DM and without major risk factors, who may be at moderate risk		
	DM without target organ damage, with diabetes duration ≥10 years or another additional risk factor	X	X
	Hypertensive LVH	X	
	Moderate CKD (eGFR 30–59 ml/min/1.73 m²)	X	X
	A calculated 10-year SCORE of ≥5% to <10%	X	X
Moderate	A calculated 10-year SCORE of ≥1% to <5%	X	
	Grade 2 hypertension	X	
	T1DM <35 years/T2DM <50 years with DM duration <10 years, without other risk factors		X
Low	A calculated 10-year SCORE of <1%	X	X

BP: blood pressure; CKD: chronic kidney disease; CVD: cardiovascular disease; DM: diabetes mellitus; FH: familial hypercholesterolaemia; T1DM: Type 1 DM; T2DM: Type 2 DM; eGFR: estimated glomerular filtration rate; LVH: left ventricular hypertrophy; MI: myocardial infarction; TC: total cholesterol; TIA: transitory ischaemic attack. Table compiled from the ESC/ESH guidelines for the management of arterial hypertension [11] and the ESC/EAS Guidelines for the management of dyslipidaemias [12].

nary events.The combination of both genetic scores higher than the median was associated with a 0.352 mmol/l lower LDL-C, a 3.1-mm Hg lower SBP, and a 39% lower rate of major coronary events [22]. Increasing genetic risk scores were associated with a dose-dependent lower event rate, with a combined exposure to about 1 mmol/l lower LDL-C and a 10 mm Hg lower SBP being associated with a 78% reduction of major coronary events and a 68% reduction of CV death [22].

Taken together, the results from randomised controlled trials as well as from Mendelian randomisation studies suggest that early and consistent lowering of blood pressure and LDL-C is associated with a substantial decrease in CV risk.

Trials investigating combined lowering of blood pressure and cholesterol

In a systematic review and meta-analysis published by Wang and colleagues, the effects of combined blood pressure and LDL-C lowering therapy compared with antihypertensive therapy alone on major CV outcomes in hypertensive patients were analysed [23]. The meta-analysis included eight randomised controlled trials with 38,618 patients. Combined antihypertensive and lipid-lowering therapy significantly reduced the risk of major adverse CV events, MI and stroke [23]. However, there was no significant effect on cardiac and all-cause mortality compared with antihypertensive therapy alone [23]. It is important to note that medication with statins per se contributes to small but statistically significant reductions of blood pressure with slightly more pronounced effects in patients with hypertension [24, 25]. A further meta-analysis of 14 randomised controlled trials including 69,984 patients with or without CVD indicated that statin therapy reduced cardiac death to the same extent in hypertensive and non-hypertensive patients independent of the percentage of hypertensive patients at baseline [26].

In this regard, a closer look should be taken on the results of the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA). ASCOT-LLA investigated the effects of atorvastatin versus placebo on CHD events in patients with arterial hypertension and a total cholesterol of ≤6.5 mmol/l who were previously randomised to an amlodipine- or atenolol-based antihypertensive treatment regimen within the Blood-Pressure Lowering Arm of ASCOT (ASCOT-BPLA) [27]. The CHD event rate calculated with the Framingham Risk Score was 22.8 per 1000 patient years. After 3.3 years, by the time ASCOT-LLA was stopped, the actual CHD event rate was 4.8 per 1000 patient years, equaling a 79% risk reduction or a number needed to treat of about 55 to prevent one CHD event per year in patients treated with both a blood pressure and lipid lowering therapy [27]. The beneficial effect of statin treatment with the goal to lower LDL-C levels of <3.0 mmol/ in patients without previous CV events has been strengthened by the results of the JUPITER and HOPE-3 studies. Lowering LDL-C in patients with baseline values <3.4 mmol/l reduced the incidence of CV events by 44 and 24%, justifying the use of statins in hypertensive patients at moderate to high CV risk [11].

Initiation of treatment and treatment targets [11, 12]

The treatment of high blood pressure should always be based on lifestyle changes such as healthy diet, regular exercise and weight loss. It is important to note that the implementation of such changes must not delay the initiation of antihypertensive drug treatment when indicated (see table 2). Office blood pressure drug treatment thresholds according to the ESC/ESH guidelines for the management of arterial hypertension continue to be ≥140/90 mm Hg, except for elderly patients ≥80 years of age where initiation of antihypertensive drug treatment is recommended at blood pressure values of ≥160/90 mm Hg. Dual combination consisting of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker and a calcium channel blocker or a diuretic should be considered for initiating antihypertensive drug therapy. Initial monotherapies should be restricted to low-risk grade 1 hypertensive, very old or frail patients. Office blood pressure targets are given in table 2. When these targets are not reached with a dual combination, therapy should be switched to a triple combination consisting of an ACE inhibitor or an angiotensin receptor blocker, a calcium channel blocker, and a diuretic, which may be further intensified by adding spironolactone. Beta-blockers may be considered at any treatment step if there is a specific indication such as heart failure, angina, after MI, atrial fibrillation, or in younger women with, or planning, pregnancy.

Based on the study results outlined above, the 2018 ESH/ESC hypertension guidelines state that statins are recommended in hypertensive patients at high or very high risk and should be considered in patients at low to moderate CV risk [11]. According to the 2019 EAS guidelines for the management of dyslipidaemia, the management of dyslipidaemia - like the management of arterial hypertension - should be based on lifestyle modifications. The cut-off for LDL-C for the initiation of lipid-lowering drugs together with the currently recommended LDL-C targets are given in table 3. The EAS guidelines recommend initiating lipid-lowering therapy with a high potency statin at the highest recommended tolerated dose. When treatment targets are not reached, statin therapy should be complemented by ezetimibe. In primary prevention and very high CV risk but without familial hypercholesterolaemia, adding a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor should be considered, whereas in patients in primary prevention and familial hypercholesterolaemia or in secondary prevention, a PCSK9 inhibitor should be added when treatment targets are not reached.

Adherence to preventive therapies

The most recent EAS recommendations have considerably increased the proportion of patients with arterial hypertension who are candidates for statin treatment [12]. However, despite guideline recommendations and a well-established substantial reduction of CV risk by combined lipid-lowering and antihypertensive therapies, statin therapy is not adequately implemented in patients with hypertension in many European countries [28]. Even in a high-risk population investigated in the EUROASPIRE V survey, 42%

of patients still had a blood pressure ≥140/90 mm Hg, and 71% had an LDL-C level ≥1.8 mmol/l 6 months after a coronary event and/or intervention [29]. Though 80% of patients were taking statins, 50% were treated with high-intensity drugs/combinations with the potential to reduce LDL-C by >50%, and 76% reported complete adherence with their medication regimen, 68% of patients did not have an LDL-C level <1.8 mmol/l [29]. These numbers demonstrate that there is still a substantial need for improving the adherence to lifestyle changes as well as control rates of major CV risk factors, even in the highest risk patients who suffered a CV event [29].

Poor adherence to lipid-lowering therapies strongly impedes primary and secondary prevention measures [12]. In fact, 77% of patients discontinue their statin therapy within 2 years [12]. The same is true for the treatment of hypertension, where physician inertia and poor patient adherence to antihypertensive medication were identified as major factors that contribute to poor blood pressure control, with the latter being much more important than previously recognised [11]. A meta-analysis including almost two million participants from 44 studies demonstrated that poor adherence to CV medications accounted for 9.1% of all adverse CV events. Good adherence to statins reduced the risk of developing CVD by 15% and the risk of death by 45% [29]. The corresponding numbers for good adherence to antihypertensive medication were 19% and 29%, respectively [30]. Importantly, CV risk attributable to low adherence increases exponentially in patients treated for multiple CV risk factors [31]. Risk of death from stroke in patients non-adherent to statin but adherent to antihypertensive therapy was 1.8-fold increased, where as it was 1.3-fold increased in patients adherent to statin but not to blood pressure lowering therapy, and 7.4-fold increased compared to fully adherent patients [31].

Non-adherence to preventive therapies – causes and approaches

Barriers to adherence are related, among other factors, to communication and motivation [32]. Speaking different languages, older patient age, low functional literacy, substance abuse or mental illness can make effective communication about a complex disease and medication regimen difficult. Poor understanding of the disease, a limited perception of the need for or the benefits of, and presumed adverse events related to the treatment may negatively affect the patient´s motivation. Moreover, the selection of drugs, dosing frequency and pill burden may substantially impact treatment adherence with significantly lower adherence rates in therapy regimens that require multiple doses per day compared to once or twice-daily regimens [33]. Therefore, both the European dyslipidemia guidelines and the European hypertension guidelines recommend simplifying dosing regimens, whenever possible, and to prescribe single-pill combinations (SPC), where available, to improve adherence to medication because of significantly higher adherence rates with SPCs versus usual care [11, 12, 34]. In fact, a meta-analysis of six retrospective studies including 30´000 patients with hypertension demonstrated

Table 2:
Initiation of blood pressure lowering interventions and treatment targets (modified from [11]).

Blood pressure	Lifestyle advice	Drug therapy	Office blood pressure treatment targets
High normal 130-139/ 80-89 mmHg	All patients	Consider drug treatment in very high risk patients with CVD, especially CAD	Patients with **Hypertension**. Patients with **Hypertension + Diabetes/CAD/Stroke/ TIA**: *18-65 years:* ≤130 (if tolerated) / 70-79 mmHg, systolic BP not <120 mmHg; ≥ *65 years:* 130-139 (if tolerated) / 70-79 mmHg. Patients with **Hypertension + CKD**: *a ll patients:* 130-139 (if tolerated) / 70-79 mmHg
Grade 1 hypertension 140-159/ 90-99 mmHg		Immediate drug treatment in high/very high risk patients with CVD, renal disease or HMOD. Drug treatment in low/moderate risk patients without CVD, renal disease or HMOD after 3-6 months of lifestyle intervention if blood pressure not controlled	
Grade 2 hypertension 160-179/ 100-109 mmHg		Immediate drug treatment in all patientsAim for blood pressure control within 3 months	
Grade 3 hypertension ≥180/ ≥ 110 mmHg		Immediate drug treatment in all patients. Aim for blood pressure control within 3 months	

BP: blood pressure; CAD: coronary artery disease; CKD: chronic kidney disease; CVD: cardiovascular disease; HMOD: hypertension-mediated organ damage; TIA: transitory ischaemic attack.

Table 3: :
Initiation of lipid-lowering interventions and treatment goals (modified from [12]).

Total cardiovascular risk (SCORE %)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug treatment	LDL-C target
Primary prevention				
Low (<1%)	<3.0 mmol/l	3.0 – <4.9 mmol/l	≥4.9 mmol/l	<3.0 mmol/l
Moderate (≥1 to <5%)	<2.6 mmol/l	2.6 – <4.9 mmol/l	≥4.9 mmol/l	<2.6 mmol/l
High (≥5 to <10%)	<1.8 mmol/l	1.8 – 2.6 mmol/l	≥2.6 mmol/l	<1.8 mmol/l and ≥50% reduction from baseline
Very high (≥ 10%)	<1.4 mmol/l	1.4 – <1.8 mmol/l	≥1.8 mmol/l	<1.4 mmol/l and ≥50% reduction from baseline
Secondary prevention				
Very high risk	All patients	<1.4 mmol/l	≥1.8 mmol/l	<1.4 mmol/l and ≥50% reduction from baseline

that the use of an SPC improved therapy adherence by 29% when compared to the free-drug combination [34].

Considering the potential CV benefits and taking into account the current European recommendations, the combination of a statin, angiotensin converting enzyme inhibitor/angiotensin receptor antagonist and a calcium antagonist/diuretic may significantly improve CV risk in patients with hypertension. In this respect, the combination of amlodipine, perindopril, and atorvastatin used in the ASCOT trial (and available as an SPC in Switzerland) was proven to provide greater CV protection compared to the combination of atenolol, bendroflumethiazide, and atorvastatin, with a 24% reduction in total CV events and procedures, a 31% reduction in total coronary events, a 39% reduction in the composite of non-fatal MI, fatal CHD, and coronary revascularization, and a 42% reduction of CV mortality, MI, and stroke [35].

Summary and conclusions

With the consistent use of modern CV drugs, CVD death and morbidity have become mostly preventable. Lessons from genetic studies suggest that early blood pressure- and LDL-C-lowering may provide better CV risk reductions and protection than interventions later in life. Thus, CV prevention should be started early and always be based on lifestyle interventions as an essential part of any therapy. Data on the benefits of a combined risk factor intervention targeting both hypertension and dyslipidemia are convincing, and statins are now recommended in the guidelines for patients at high or very high and should be considered in patients at low to moderate CV risk. Achieving and maintaining a good adherence to preventive therapies is a core aspect of patient management since non-adherence may increase the risk for future CV events. In this respect, the use of single-pill combinations is strongly recommended since it may increase adherence and substantially improve CV risk compared to therapy regimens using several pills.

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