Aus der Klinik für Innere Medizin III

(Kardiologie, Angiologie und Internistische Intensivmedizin)

Direktor: Prof. Dr. med. Michael Böhm

Fachbereich Klinische Medizin

Universität des Saarlandes, Homburg/Saar

Evaluation of placebo-adjusted cough on angiotensin-converting-enzyme inhibitors and hyperkalemia on mineralocorticoid-receptor-antagonists in patients with cardiovascular disease

Dissertation zur Erlangung des Grades eines Doktors der Medizin

der Medizinischen Fakultät

Der UNIVERSITÄT DES SAARLANDES

2020

vorgelegt von:

Davor Dragoslava Vukadinović

geb. am 06.10.1985 in Kruševac, Serbien

Content

Abbreviations

ACE-I	Angiotensin converting enzyme inhibitor
MRA	Mineralocorticoid receptor antagonist
HF	Heart failure
AE	Adverse events
RAASi	Renin angiotensin aldosterone system inhibitors
AT1	Angiotensin receptor subtype 1
ACTH	Adrenocorticotropic hormone
CHF	Chronic heart failure
EF	Ejection fraction
BP	Blood pressure
CAD	Coronary artery disease
LV	Left ventricle
STEMI	ST-elevation myocardial infarction
NSTEMI	None ST-elevation myocardial infarction
HFrEF	Heart failure with reduced ejection fraction
SE	Side effects
CVD	Cardiovascular disease
CKD	Chronic kidney disease
DM	Diabetes mellitus
NYHA	New York Heart Association
AHA	American Heart Association
RR	Risk ratio
CI	Confidence interval
IRR	Incidence risk ratio
CVI	Cerebrovascular insult
TIA	Transitory ischemic attack
PAD	Periphery artery disease
ACB	Aortocoronary bypass
COPD	Chronic obstructive pulmonary disease
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
GFR	Glomerular flitration rate
SPS	Sodium polystyrene sulphonate
FDA	Food and Drug Administration
ZS-9	Zirconium cyclosilicate
NT-proBNP	N-terminal pro-B-type natriuretic peptide

1 Summary

1.1 Deutsche Zusammenfassung

Medikamente wie Angiotensin-Converting-Enzym (ACE) Hemmer und Mineralocorticoid-Rezeptor-Antagonisten (MRA) sind bedeutsam für die Verhinderung kardialer Ereignisse wie Tod oder Hospitalization bei Patienten mit kardiovaskulären Erkrankungen wie arterielle Hypertonie, koronare Herzkrankheit und Herzinsuffizienz. Daten aus zahlreichen Registern zeigen, dass Patienten mit diesen Substanzen erheblich untertherapiert und unterdosiert behandelt werden. Das liegt unter anderem darin, dass diese Arzneimittel abgesetzt werden, wenn unerwünschten Nebenwirkungen (UN) wie Husten bei ACE-Hemmern oder Hyperkaliämie bei MRA auftreten. Häufig geschieht dies aus Angst von schwerwiegenden Wechselwirkungen wie Hyperkaliämie. Bei einer beträchtlichen Zahl von Patienten traten die Husten und Hyperkaliämie in kontrollierten klinischen Studien zu diesen Medikamenten auch unter Placebo auf. Wir haben uns die Frage gestellt, ob die Nebenwirkungsrate bei ACE-Hemmern und Hyperkaliämie bei MRA als spezifische Ursachen überschätzt sind, da diesen UN mit Placebo ebenfalls vorkommen. Das ist von besonderer klinischer Bedeutung, da die Nicht-Therapie oder das Absetzen der ACE-Hemmer und/oder MRA insbesondere bei Patienten mit Herzinsuffizienz mit einer schlechteren Prognose assoziert ist und die eigentliche Ursache von Husten und Hyperkaliämie häufig nicht abgeklärt werden.

Wir schlossen alle geeigneten randomisierten, placebokontrollierten Studien mit ACE-Hemmern und MRA bei Patienten mit kardiovaskulären Erkrankungen in eine Metaanalyse ein, bei denen Ereignisse von Interesse (Husten bei ACE-Hemmer und Hyperkaliämie bei MRA) adäquat berichtet wurden. Die Datenbank PUBMED sowie Cochrane-library wurden nach geeigneten Studien durchgesucht. Zusätzlich wurden alle Studien, die in den aktuellen Leitlinien der Europäischen Gesselschaft für Kardiologie für arterielle Hypertonie, akuten Myokardinfarkt und Herzinsuffizienz aufgenommen wurden, erfasst.

Wir ermittelten die Placebo-adjustierte Rate für Husten bei ACE-Hemmern und Hyperkaliämie bei MRA, die den zuzurechnenden Anteil an Husten / Hyperkaliämie bei exponierten Personen darstellten, die spezifisch auf die Exposition zu bestimmten Medikamenten zurückzuführen sind. Die Placebo-adjustierte Rate von UN bei Medikamenten (%) wurde definiert als Differenz zwischen den Raten von UN bei Patienten der Medikamenten-Gruppe und Placebo-Gruppe, dividiert durch die Gesamtrate von UN der Medikamenten-Gruppe. Dieses Beispiel für Husten bei ACE-Hemmern erläutert das Vorgehen: Placebo-adjustierter Husten der Medikamenten-Gruppe% = (Medikament-Gruppe Husten% - Placebo-Gruppe Husten%) / Medikament-Gruppe Husten%.

Die vorgelegte Analyse konnte zeigen, dass eine relevante Anzahl von Husten- und Hyperkaliämie-Fällen bei ACE-Hemmern bzw. bei MRA nicht allein durch die Wirkung dieser Medikamenten erklärt werden konnte, da die placebokorrigierte Rate für Husten 37% und für Hyperkaliämie 54% betrug. Dies würde in einem hypothetisch schlimmsten Fall zu Folge haben, dass etwa die Hälfte der Patienten mit Husten (63%) bei ACE-Hemmern und mit Hyperkaliämie (46%) bei MRA diese lebensverlängerde Therapie, nicht erhalten würden. Dies basiert auf der falschen Annahme, dass die Genese dieser UN in jedem einzelnen Fall ausschließlich durch die Wirkung dieser Medikamenten zu erklären sind, wodurch die wahren Ursache nicht diagnostiziert bleiben.

Unsere Analyse zeigt, dass das Absetzen von diesen lebensrettenden Medikamenten vor allem bei Patienten mit Herzinsuffizienz nicht vorgenommen werden sollte. Die Leitlinie empfehlen, die kurzfristige Unterbrechung der Therapie, bevor die Ursache der Entstehung von UN eindeutig abgeklärt ist.

1.2 Abstract

Studies on the treatment with drugs like angiotensin-converting-enzyme inhibitors (ACE-Is) and mineralocorticoid-receptor-antagonists (MRAs) have achieved evidence for their beneficial effects on cardiac events in patients with cardiovascular diseases like arterial hypertension, coronary heart disease and heart failure. However, real-world data like those from numerous registries consistently show that patients are undertreated with these drugs. One of the reasons for inadequate treatment in recommendations are concerns of physicians regarding adverse events (AE) accompanied by the use of these drugs, such as cough on ACE-Is and hyperkalemia on MRAs, due to a widespread opinion that AE are always the causally related to these drugs.

In a considerable number of patients enrolled in controlled clinical trials with these drugs cough and hyperkalemia occurred also on placebo. We addressed the question whether the “true” rates of cough on ACE-Is and hyperkalemia on MRAs are overestimated or other often unrecognized causes are underestimated, because the rate of these AE on placebo are usually not been taken into consideration. This is of particular clinical importance, since withholding or interruption of ACE-I and/or MRA application may be associated with a worse prognosis and other causes may be underdiagnosed.

We included all eligible randomized, placebo-controlled trials with ACE-Is and MRAs in patients with cardiovascular disease where events of interest (cough on ACE-I and hyperkalemia on MRA) were adequately reported. Database PUBMED and Cochrane library were searched for eligible trials. To avoid any relevant study to be missed, we crosschecked the identified studies with those referenced in the

current European Association of Cardiology guidelines for arterial hypertension, acute myocardial infarction with and without ST-segment elevation and heart failure.

We determined placebo-adjusted rates of cough on ACE-Is and of hyperkalemia on MRAs, which present the attributable fraction of total cough/hyperkalemia rate in the exposed individuals that can be attributed specifically to the exposure. Placebo-adjusted rate of AE on drug (%) was calculated as the difference between the rates of AE in patients on drug and those on placebo, divided by the total rate of AE on drug. Example for cough on ACEIs: placebo-adjusted drug-cough = (drug-cough – placebo-cough) / drug-cough. This analysis was based on the assumption that incidence of specific AE on placebo represents spontaneous rate of AE in populations with cardiovascular disease.

According to our analysis, a relevant number of cough cases on ACE-Is and hyperkalemia cases on MRAs might not be caused due to the treatment with these drugs, as placebo-adjusted rate for cough was 37% and for hyperkalemia 54%. In hypothetical worst-case scenario, which means withdrawal of ACE-I from all patients with cough and MRA from patients with hyperkalemia, about half of patients with cough (63%) on ACE-Is and with hyperkalemia (46%) on MRAs would not receive these life-saving therapies due the misconception that all cases of these AE are exclusively caused by these drugs. In turn, other causes of AE, might remain underdiagnosed.

This study highlights the importance of a comprehensive approach in excluding other potential causes for cough on ACE-Is and hyperkalemia on MRAs in this population of patients before withdrawal of these drugs in order to avoid undertreatment with these well proven and beneficial drugs.

2 Introduction

2.1 Pathophysiology of renin-angiotensin-aldosterone-system in cardiovascular diseases

The renin-angiotensin-aldosterone-system (RAAS) represents a specific neurohormonal cascade playing a pivotal role in maintaining homeostasis of the fluid and electrolytes balance as well as a role in the regulation of blood pressure. Low levels of sodium, decreased renal perfusion pressure (driven by hypovolemia and/or hypotension) and increased sympathetic activity stimulate release of renin from juxtaglomerular cells in the kidney (GUYTON et al., 1972). Renin represents the proteinase, which cleaves angiotensin I from angiotensinogen, predominantly synthesized in the liver. Further fragmentation of angiotensin I (decapeptide) into angiotensin II (octapeptide) occurs in the lung, the kidneys, the vessels and in the heart by angiotensin-converting-enzyme (ACE), which is bound to the endoluminal side of the endothelial cells (NAVAR, 2014).

Angiotensin II increases sodium and maintains blood pressure by acting on AT1 receptors. It induces secretion of aldosterone from the adrenal gland, causes constriction, stimulates sympathetic activity and tubular sodium reabsorption.

According to pre-clinical data aldosterone promotes up-regulation of angiotensin II receptors and its activation, thus, creating a vicious cycle between these two hormones, which can be antagonized with the administration of MRA spironolactone (ULLIAN et al., 1992). Further, maladaptive effects by angiotensin II such as cardiac fibrosis, inflammation and oxidative stress could be diminished by administration of spironolactone, thereby pointing to mutual maladaptive role of angiotensin II and aldosterone (ZHAO et al., 2006).

The two main secretagogues for aldosterone are angiotensin II and hyperkalemia (GUYTON et al., 1972; STRUTHERS, 2004). Beside these two stimuli, adrenocorticotropic hormone (ACTH) stimulates production of aldosterone (BROWN, 2003). It is produced by the zona glomerulosa of the adrenal gland. In addition to this and according to evidence from experimental studies aldosterone is also produced locally by endothelial cells and vascular smooth muscle cells (HATAKEYAMA et al., 1994; TAKEDA et al., 1996) in tissues such as blood vessels (TAKEDA et al., 1995), brain (GOMEZ-SANCHEZ et al., 1997) and myocardium (MIZUNO et al., 2001; SILVESTRE et al., 1998; YOUNG et al., 2001). Stimuli for synthesis of locally generated aldosterone seem to be the same as those at adrenal gland (SILVESTRE et al., 1998). The phenomenon called “aldosterone escape” describes the rise of aldosterone after initial fall following introduction of angiotensin-converting-enzyme inhibitors (ACE-Is), which normally should

decrease the levels of this hormone by preventing the generation of angiotensin-II. "Aldosterone escape" has been documented in patients with arterial hypertension (SATO, SARUTA, 2001), after myocardial infarction (BORGHI et al., 1993) and with heart failure (MACFADYEN et al., 1999) on the long-term treatment when alternative pathways (e.g. hyperkalemia) can activate the chronically inhibited and go to same pathway.

Aldosterone exhibit pleiotropic mechanisms of action, such as fibrosis, but the best known and understood is regulation of body fluid, blood pressure and homeostasis of sodium and potassium through activation of Na^+/K^+ pump in the epithelial cells of distal tubules and collecting ducts of the kidney nephron. Binding of aldosterone to intracellular mineralocorticoid receptors (MR) generates cascades of intracellular reactions resulting in stimulation of Na^+/K^+ pump, whereby sodium is actively reabsorbed and potassium excreted from and into the tubular fluids, respectively (ARRIZA et al., 1987; BHARGAVA et al., 2001; FEJES-TOTH et al., 1998). As sodium is osmotically active, its reabsorption is followed by passive reabsorption of water, indicating the main mechanism by which aldosterone indirectly regulates blood volume and blood pressure.

It is well documented in experimental and clinical studies that aldosterone exerts many adverse pathophysiological effects on cardiovascular system beyond its role in homeostasis of the fluid and electrolytes, regardless of effects of angiotensin II (STRUTHERS, 2004). Aldosterone has been linked with endothelial dysfunction (STRUTHERS, 2004), myocardial fibrosis/remodelling (BAUERSACHS, FRACCAROLLO, 2011; MACFADYEN et al., 1997; ZANNAD et al., 2000), inflammation/injury of myocardial, cerebral and renal tissue (ROCHA, STIER, 2001) and arterial hypertension (LIM et al., 1999). Cardiac remodelling is mediated through cardiomyocyte-specific MR, as its inactivation ameliorates adverse heart remodelling into HF after ischemia or pressure overload (FRACCAROLLO et al., 2011; LOTHER et al., 2011). Myocardial toxicity of aldosterone is best supported by the facts: i) MR are founded in the heart (LOMBES et al., 1995), ii) higher aldosterone levels are linked with poor cardiac outcome (SWEDBERG et al., 1990), iii) antagonism of MR had beneficial effects on survival in patients with chronic heart failure (CHF) (PITT et al., 1999) and those after myocardial infarction with reduced ejection fraction (EF <40%) (PITT et al., 2003).

2.2 Mechanism of action and clinical evidence for use of ACE-I in treatment of cardiovascular diseases: current status

ACE-I blocks conversion of angiotensin I into angiotensin II, thus decreasing levels of angiotensin II and aldosterone thereby reducing their pathological effects on the cardiovascular system. Furthermore, ACE-I

blocks kininase II responsible for degradation of bradykinin (as well as other biologic peptides such as substance P), thus leading to accumulation of bradykinin, which through stimulation of B2 receptors induce synthesis of nitric oxide and arachidonic acid derivates (vasoactive prostaglandins) (LINZ et al., 1995). There is evidence that ACE-Is cause vascular effects that could be partially explained through effect of accumulation of bradykinin (HORNIG et al., 1997).

The mechanism of action of all ACE-Is is the same rather than binding affinity to the tissue ACE and pharmacokinetic characteristics of the individual substance, which may be responsible for different tissue concentration of ACE-Is and its clinical effect. There is evidence suggesting that suppression of ACE in different tissues is more relevant than suppression of plasma ACE on the long term (DZAU et al., 2001).

ACE-Is reduce peripheral vascular resistance inducing venous and arterial vasodilation, which combined with enhanced natriuresis results in lowering of blood pressure without any relevant impact on the heart rate (BROWN, VAUGHAN, 1998). Further, administration of ACE-I improves endothelial dysfunction in patients with arterial hypertension (TADDEI et al., 1998), coronary artery disease (HORNIG et al., 2001) and those with heart failure (HORNIG et al., 1998), exhibit antiproliferative effects thereby reducing ventricular remodelling (KLINGBEIL et al., 2003; PAUL, GANTEN, 1992). ACE-Is adjust fibrinolytic homeostasis regulating synthesis of plasminogen activator and opposing platelet aggregation (VAUGHAN, 1997).

Based on the large body of evidence concerning effectiveness of ACE-Is in BP reduction, this class of drugs has been recommended by the guidelines of European Society of Cardiology as initial therapy alone or in combination with other antihypertensive drugs in patients with arterial hypertension (recommendation class I, level of evidence A) (WILLIAMS et al., 2018). Of note, every 10 mmHg reduction in SBP significantly reduced risk of stroke, CAD, HF and mortality, irrespective of baseline BP values (ETTEHAD et al., 2016). Therapy with ACE-I in patients with stable CAD in absence of LV systolic dysfunction decreased risk of non-fatal myocardial infarction, stroke, all-cause mortality and onset of HF (DAGENAIS et al., 2006), which, therefore, should be considered in these patients (class IIa, level of evidence A) (PONIKOWSKI et al., 2016). Early treatment with ACE-I in hemodynamic stable patients suffering STEMI with evidence of HF (AIRE study) (AIRE-INVESTIGATORS, 1993) or LV systolic dysfunction EF ≤40% (SAVE study) (PFEFFER et al., 1992) reduces all-cause mortality and is, therefore, strongly recommended in the current guidelines (class I, level of evidence A) (IBANEZ et al., 2018). In absence of contraindications, ACE-Is are recommended in all patients after STEMI (class IIa, level of evidence A) (IBANEZ et al., 2018). In patients with NSTEMI associated with left ventricular EF ≤40%, heart failure, hypertension or diabetes treatment with ACE-I is strong recommended (class I, level

of evidence A) (ROFFI et al., 2016) unless not contraindicated in order to reduce risk of heart failure onset, re-hospitalization and mortality. Use of ACE-Is in patients with HFrEF reduced risk of HF hospitalization and death as demonstrated in SOLVD (YUSUF et al., 1991) and CONSENSUS study (CONSENSUS-GROUP, 1987). Therefore, their use is strongly recommended in these patients according to the current HF guidelines (class I, level of evidence A) (PONIKOWSKI et al., 2016).

2.3 Mechanism of action and clinical evidence for the use of MRAs in the treatment of cardiovascular diseases: current status

MRAs exert their effects by competitively blocking the intracellular MR, thereby preventing aldosterone to act. Currently, there are two MRAs widely used in a clinical praxis, spironolactone as a first generation and eplerenone as a second generation of this class of drugs. The MRA of a third generation, finerenone represent a substance used in clinical trials only (FILIPPATOS et al., 2016; PITT et al., 2013). While eplerenone is available only as oral drug, spironolactone can be administered orally and intravenously. Although all three agents basically have the same mechanism of action there are some major differencies regarding structure and pharmacokinetics, reflected by various levels of clinically beneficial and adverse effects.

Spironolactone represents a non-selective MRA that has a similar structure as progesterone. Owing to this, it shows affinity for androgen and progesteron receptors producing unwanted side effects such as gynecomastia in men and menstrual irregularities in women. Conversely, eplerenone is a more selective MRA that shows 100-1000-fold lower affinity compared with spironolactone for androgen and progesterone receptors. Consequently, use of eplerenone is usually not associated with these sexual side effects (STRUTHERS, UNGER, 2011). Spironolactone as a pro-drug exerts its effect after conversion into several active metabolites with long half-lives (from 13.8 up to 16.5 h) (STRUTHERS, UNGER, 2011) as opposed to eplerenone which has shorter half-life (4-6 h) and no active metabolites (SICA, 2005). Furthermore, spironolactone has 20-fold higher in vitro affinity for MR than eplerenone (MULDOWNEY et al., 2009). According to one trial where both drugs were directly compared regarding their effects on BP and safety profiles in patients with primary aldosteronism, spironolactone expressed more pronounced reduction of BP and higher rate of adverse events than eplerenone (PARTHASARATHY et al., 2011). This finding support the inofficial view among some clinicans that eplerenone exhibit lower potency than spironolactone concerning inhibition of aldosterone effects, driven by the aforementioned features of both agents. Of note, shorter half-life of eplerenone versus spironolactone might be beneficial for a more rapid resolution of side effects after drug discontinuation.

However, to the best of our knowledge there are no reported data from clinical or observational trials concerning period of time until resolution of hyperkalemia after stopping the MRAs. The lack of data regarding this issue is probably caused by a need for the urgent administration of different potassium lowering agents, instead of discontinuation of the MRA treatment only and waiting for spontaneous hyperkalemia resolution.

Spironolactone is recommended as add-on therapy in patients with resistant hypertension (Class I, Level B) (WILLIAMS et al., 2018) according to the results from PATHWAY-2 trial (WILLIAMS et al., 2015). Nevertheless, one systematic analysis showed that eplerenone is effective as BP lowering agent, which could be a treatment option in patients with mildly to moderately elevated BP (PELLICCIA et al., 2014). Administration of MRA is strongly recommended in patients following myocardial infarction and EF≤40% with heart failure (Class I, Level B) (IBANEZ et al., 2018) based on results from EPHESUS trial (PITT et al., 2003). However, individual patient-level meta-analysis showed reduced mortality with treatment of spironolactone and eplerenone in patients with ST-elevation myocardial infarction in absence of heart failure (BEYGUI et al., 2018). MRAs are strongly recommended (Class I, Level A) (PONIKOWSKI et al., 2016) in patients with HF and reduced ejection fraction (HFrEF), who remain symptomatic despite treatment with beta-blockers and ACE-Is/ARBs in order to reduce the risk of mortality and HF hospitalization, based on results from RALES (PITT et al., 1999) and EMPHASIS-HF trial (ZANNAD et al., 2011). It has been shown that MRAs have no pronounced effect, on systolic and diastolic BP reduction in HF patients, suggesting its use according to the guidelines regardless of baseline BP values (BAZOUKIS et al., 2018). Recently published individual patient-level meta-analysis showed that the use of MRA is associated with reduction of sudden cardiac death in HFrEF patients (ROSSELLO et al., 2018).

2.4 Cough on angiotensin-converting-enzyme inhibitors and hyperkalemia on mineralocorticoid receptor antagonists as the leading reasons for withdrawal of the treatment

Although it has been well documented that ACE-Is and MRAs represent life-saving drugs in patients with CVD recommended by many guidelines, their utilization among eligible patients is not sufficient (CHIN et al., 2016; DEV et al., 2015). Some of the main reasons for this are the side effects (SE) associated with the use of these classes of drugs. Dry cough has been identified as one of the most frequently reported SE and the main reason for withdrawal of ACE-Is (BART et al., 1999), while hyperkalemia as a potential life-threatening complication has been recognized as the most limiting factor of therapy with MRAs.

Cough

Incident cough on ACE-Is varies from 3.6% (BART et al., 1999) to 37% (DICPINIGAITIS, 2006; YUSUF et al., 1991), reflecting a huge variation in reported incidence, which could be explained by different definitions used (adverse effects vs. reason for withdrawal), the patient cohort studied (arterial hypertension vs. heart failure, clinical trials vs. registries) or the way of evaluation (systematic queries or self-reported). It represents a class effect common for all ACE-Is, which is not dose-related (OMBONI, BORGHI, 2011). Cough on ACE-I is usually described as dry, non-productive and persistent, usually followed with tickling sensations in the throat. Although its considered as an benign side effect it could in severe cases be pretty annoying, worse sleep and cause vomiting and hoarseness (OMBONI, BORGHI, 2011), thus, impacting negatively the quality of life in affected patients. Furthermore, its occurrence might lead to unneeded, expensive and misleading diagnostic examinations, which could further potentiate patients' discomfort.

The occurrence of ACE-I associated cough usually takes place after several weeks or in rare occasions months after initial drug administration (DICPINIGAITIS, 2006). Coughing completely disappears after a couple of days or weeks after cessation and mostly reoccurs with reintroduction of the drug, thus, ascertaining whether the ACE-I is causally related to cough (ISRAILI, HALL, 1992).

The pathomechanisms of the ACE-I induced cough are not entirely resolved, but the main hypothesis labels the accumulation of bradykinin and substance P, which degradation is inhibited by ACE-Is (Figure 1) (ISRAILI, HALL, 1992). Both substances could stimulate afferent vagal nerve fibers causing cough (OMBONI, BORGHI, 2011). Further, bradykinin facilitates production of arachidonic acid derivates and nitric oxide, which can promote cough driven by proinflammatory mechanisms (TRIFILIEFF et al., 1993). There is evidence suggesting that ACE-I might intensify the cough reflex itself, thereby facilitating the onset of cough due to some other cause (MORICE et al., 1989). Still, some but not all patients develop cough on ACE-I indicating some kind of predisposition in affected individuals to develope cough on ACE-I, like bradykinin receptor gene polymorphism (MUKAE et al., 2000) or decreased activity of aminopeptidase-P (NIKPOOR et al., 2005), an enzyme important for degradation of bradykinin. Cough is more frequent among women (COULTER, EDWARDS, 1987; VISSER et al., 1995), patients of Asiatic ethnicity (MCDOWELL et al., 2006; TSENG et al., 2010) and Afro- Americans (ELLIOTT, 1996).

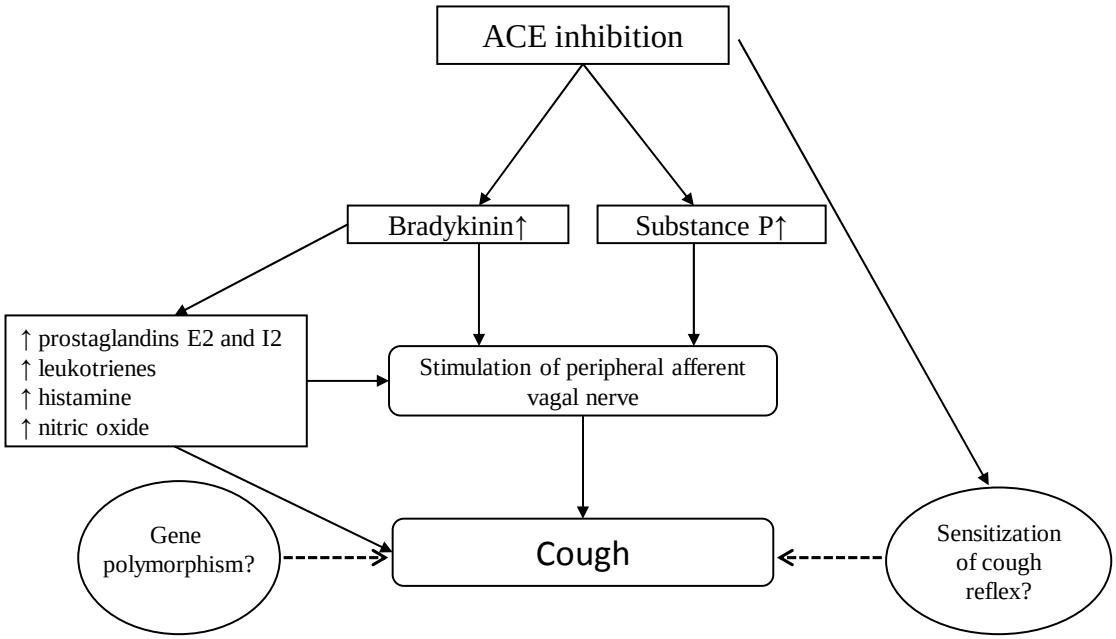

Figure 1. Pathomechanism of cough caused by treatment with ACE-I

Hyperkalemia/Hypokalemia

Potassium (K^+) represents the most important intracellular electrolyte, which is essential for cellular and electrical activity. The 90% of whole body content of K^+ is located intracellularly, 8% in bones and cartilages and only about 2% in extracellular fluids (COHN et al., 2000). Theirs extra-/intracellular cation ratio of 1:10 causes a steep K^+ concentration gradient between the intracellular and the extracellular space, which is essential for cellular membrane potentials and transmission of the electrical impulses in the cardiovascular and central nervous system. K^+ values between 3.5 mmol/l – 5 mmol/l has been defined as normal values (COHN et al., 2000). Albeit 2% of whole body K^+ is located in the extracellular fluid, its concentration is precisely maintained in a narrow range through K^+ shift, renal excretion and intestinal secretion. Therefore, changes in K^+ concentration may provoke and aggravate abnormalities in cardiac conduction system, which can lead to life-threating arrhythmias, thereby increasing mortality. This applies for K^+ disturbances in both directions such as hypo- and hyperkalemia, revealing a nonlinear U-shaped association between level of K^+ and mortality in patients with CVD (ALDAHL et al., 2017; KROGAGER et al., 2017; NUNEZ et al., 2018).

Hyperkalemia can be further classified into mild (K^+ of 5-5.5 mmol/l), moderate (K^+ of 5.5-6 mmol/l) and serious (K^+>6 mmol/l), thereby graduating the level of potential danger for affected individuals. It has been marked as one of the major co-morbidities in patients with HF stressing the importance of better understanding and management of hyperkalemia, the condition which should contribute to better outcomes of patients with HF. MRAs as a part of the cornerstone therapies for patients with HFrEF express certain dichotomy. While on the one hand they unequivocally improve outcomes of these patients and on the other hand they are identified as a one of the major culprits for increased risk of hyperkalemia in this cohort of patients (PONIKOWSKI et al., 2016). Since the physiological function of mineralocorticoid receptor in the kidney is to excrete potassium and to retain sodium maintaining the fluid and electrolyte balance, MRA treatment is physiologically associated with the risk of hyperkalemia. Development of hyperkalemia often results in discontinuation or down-titration of protective and life-saving treatments with RAAS-inhibitors (RAASi) and MRAs among eligible patients, which is in both cases associated with higher mortality (KOMAJDA et al., 2016; MAGGIONI et al., 2013; OUWERKERK et al., 2017). Data from registries demonstrate a strong underuse of the life-saving therapy with MRA, applied at 9-55% among eligible patients (HIRT et al., 2016; RASSI et al., 2013).

Chronic kidney disease (CKD) and diabetes mellitus (DM) as highly prevalent comorbidities in patients with CVD represent itself risk factors for hyperkalemia and factors which concomitant presence facilitate the occurrence of this SE on MRAs, given on top of RAASi (PITT et al., 2008; ROSSIGNOL et al., 2014; VARDENY et al., 2014). Pathophysiology of hyperkalemia on MRA in patients with CVD represents a complex interplay of many factors (Figure 2). Its prevalence on MRAs varies from 3-18% in randomized trials (PITT et al., 2003; PITT et al., 1999) to 21% according to one survey from patients with HF (KOMAJDA et al., 2016).

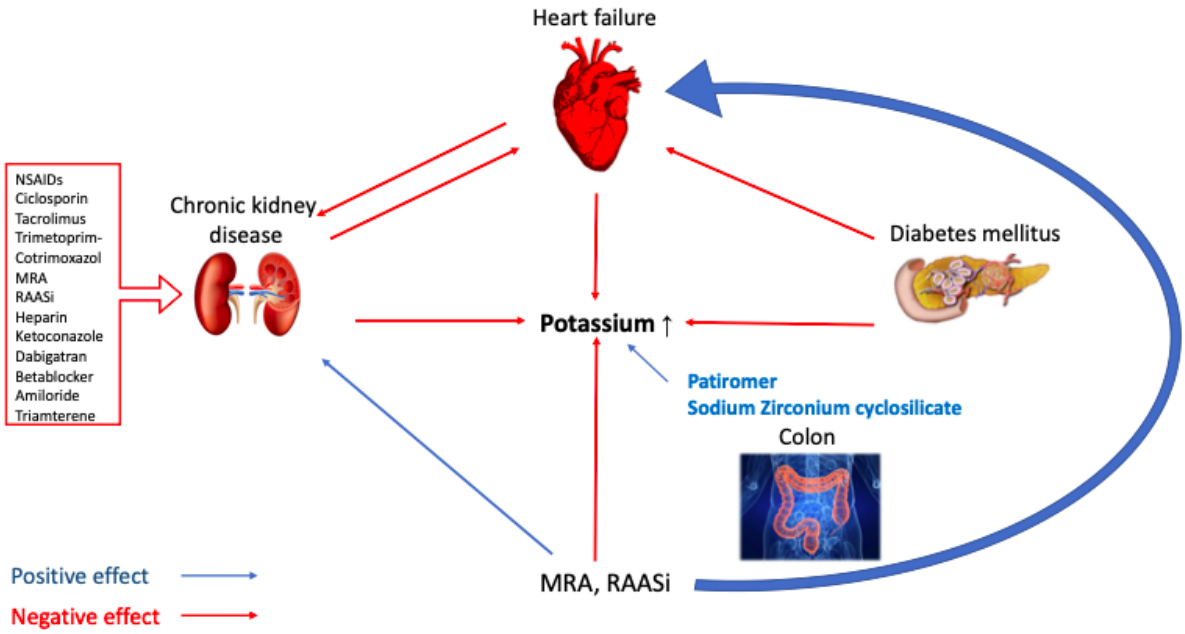

Figure 2. Pathomechanism of hyperkalemia on MRA in patients with CVD

Development of hyperkalemia in patients on MRAs with HF results from complex interactions, visualized using blue (positive effect) and red arrows (negative effect). Diabetes mellitus and chronic kidney disease as two prevalent comorbidities in HF-patients represent at the same time risk factors for both, HF and hyperkalemia. In turn, HF aggravates renal function and is itself risk factor for hyperkalemia. Many drugs may impair renal function (depicted at the left side), the most important organ for potassium homeostasis, thus, facilitating occurrence of hyperkalemia. Treatment with MRAs and RAASi in patients with CKD and HF is associated with better outcome, but these groups of drugs are recognized as the leading risk factors for hyperkalemia. Patiromer and sodium zirconium cyclosilicate are the new potassium-binders that stimulate its excretion in colon, leading to normalization of potassium values.

2.5 Aim of the analysis

An attributable exposure risk (also called attributable fraction) represents the proportion of the disease/side effects in the exposed group which can be attributed to the exposure/exposed factor (ROCKHILL et al., 1998). With other words, it is the proportion of the disease/side effect which could be prevented with elimination of the potential cause. Using this measure of association it can be easily computed to what extent some drug is responsible for a specific side effect, knowing the incidence of side effects in a comparable group of patients without exposure to the investigated drug (i.e. placebo group). It is calculated by taking the risk difference between exposed (i.e. investigated) and non-exposed (i.e. placebo) group, dividing it by the incidence in the exposed group, and then multiplying it by 100 to convert it into a percentage.

As the aforementioned side effects, such as cough on ACE-I and hyperkalemia on MRA occur in considerable number of patients on placebo in placebo-controlled clinical trials, we aimed to explore the attributable proportion for these side effects by including all randomized, placebo-controlled clinical trials with ACE-Is and MRAs in patients with CVD. We named the attributable proportion as "*placebo-adjusted rate*", which was our primary endpoint.

As our secondary endpoint we aimed to explore the overall risk and incidence of cough on ACE-Is and hyperkalemia/hypokalemia on MRAs.

3 Methods

3.1 Study protocol

This analysis has been done according to a predefined protocol. We included all randomized, placebo-controlled clinical trials with ACE-Is and MRAs which reported cough on ACE-I and hyperkalemia on MRA in patients with arterial hypertension, coronary heart disease and heart failure. All trials had to have a minimum of 100 individuals and a follow-up of at least 4 weeks. Further, only trials with approved spironolactone and eplerenone from MRAs were considered for inclusion. Exclusion criteria were articles that analyzed effects of ACE-I/MRA in cohort of patients with other underlying conditions like diabetes, nephropathy, retinopathy, cerebrovascular disease, metabolic syndrome and others. Studies where effects of ACE-Is were evaluated as combined drug composed from two or more active substances vs. placebo were also excluded. We evaluated only published peer-reviewed articles for inclusion.

Reporting and conducting of this meta-analysis has been carried out in accordance with the PRISMA (MOHER et al., 2009) statement for meta-analysis and with the scientific statement from the American Heart Association (RAO et al., 2017).

3.2 Literature search and selection strategy

We searched PubMed, Cochrane library databases for eligible articles published until January 2017. For purpose of the search for articles with ACEIs and MRAs the following terms were used: i) "*angiotensin converting enzyme inhibitor*", "*cough*", "*ACE-I related cough", "ACE-I",* in combination with *"placebo-controlled"* for ACE-I and ii) "*aldosterone receptor antagonist*" and/or "*mineralocorticoid receptor antagonist*", "*MRA*", "*spironolactone*" and/or "*eplerenone*", "*hyperkalemia*" in combination with "*placebo-controlled*" for MRA. Additionally, we marked filter "*clinical trial*" in PubMed and "*trials*" in Cochrane library database. In order to avoid any relevant study being missed, we reviewed the potential studies cited in the current European Society of Cardiology guidelines for arterial hypertension (WILLIAMS et al., 2018), myocardial infarction with and without ST-segment elevation (IBANEZ et al., 2018; ROFFI et al., 2016) and heart failure (PONIKOWSKI et al., 2016).

We performed an additional search for clinical registries reporting hyperkalemia on MRAs, which will be used within a sensitivity analysis. PubMed and Cochrane library were searched using the terms "*aldosterone receptor antagonist*" and/or "*hyperkalemia*" and/or "*register*" and/or "*survey*" and "*mineralocorticoid receptor antagonist*".

The search results were screened for relevance according to their title and abstract. In case the content of the abstract corresponded to the inclusion criteria, the full-text review followed. The inclusion of each study in the analysis was based on a consensus between D.V. and M.B.

3.3 Data extraction and assessment of study quality

After inclusion the following items were extracted from each study: events of interest (cough for studies with ACE-Is and hyper- and hypokalemia for studies with MRAs), characteristics of the investigated population (arterial hypertension, myocardial infarction, heart failure, NYHA functional class, ejection fraction, age, study size), used substance, average time of follow-up and clinical outcome. Quality of each included study was assessed using Jadad score (JADAD et al., 1996), which accounts for randomization (no randomization 0, randomization 1, data concerning adequate randomization reported 2 points), blinding (no blinding 0, blinding 1, data about appropriate blinding present 2 points) and lost to follow-up (no data present 0, data present 1 point). A score ≥ 3 is considered as a high level of quality and ≤ 2 as low level of quality. Jadad score proved to be reliable with low interobserver variability and is therefore recommended from AHA (OLIVO et al., 2008; RAO et al., 2017). Moreover, we evaluated whether some trial have been discontinued earlier for benefit.

3.4 Statistical analysis

We performed a study-level meta-analysis of the summary statistics from the individual trials that explored the effect of investigated treatment with ACE-I and MRA compared with placebo. Differences in the occurrence of events of interest (cough on ACE-I and hyper- and hypokalemia on MRA) among groups were computed and presented as risk ratios (RR) together with corresponding 95% confidence intervals (CI) for each trial. All results were based on intention-to-treat analysis. We used RR as a measure of the relative risk. The results from each trial were pooled using fixed (Mantel-Haenszel, Rothman-Boice)- or random-effects (DerSimonian-Laird) model, as appropriate. Heterogeneity between the trials was evaluated by applying Cochran's Q test and I^2 statistic. Relevant statistical heterogeneity was present if Cochran's Q test $p<0.05$ and $I^2 >50\%$. In this case, we used random-effects model to pool the data.

To adjust a different length of follow-up between the trials, we calculated the incidence rate ratio (IRR) for cough and hyperkalemia. Trials were standardized by multiplying the number of patients in each trial (investigated group and placebo group) with the number of months of follow-up, determining person-month as person-time data. Results of the main analysis would be further explored within appropriate

sensitivity analyses, such as exploring the effect of different underlying diseases (arterial hypertension, coronary heart disease, heart failure) or different cough definition (defined as adverse effect or reason for withdrawal/discontinuation) on final results, by determining the p for interaction between appropriate subgroups (ALTMAN, BLAND, 2003). Further, we assessed if and to what extent the hyperkalemia on MRAs from noninterventional studies correlates with the results obtained from clinical trials, by estimating the RR from combined data, that is, by adding the data from registries to data from clinical trials.

A potential presence of publication bias was assessed visually by looking for the presence of asymmetry in obtained Funnel plot and formally using the Egger's regression asymmetry test.

All statistical analyses were performed by applying the statistical program StatsDirect version 3.0.150 (Cheshire, UK) and RevMan 5.3. All P values were 2-sided, with $p<0.05$ considered as significant.

3.5 Placebo-adjusted rate of cough on ACE-Is and hyperkalemia on MRAs

Attributable proportion of total cough on ACE-Is and hyperkalemia on MRAs that can be attributed specifically to the exposure of investigated treatment, taking thereby into account all cases with spontaneous cough or hyperkalemia as in placebo group, we called "placebo-adjusted rate". For example, the placebo-adjusted rate of cough on ACE-Is was determined as the difference between the rates of cough in patients on ACE-Is and those on placebo, divided by the total rate of cough on ACE-Is, as demonstrated in the equation: Placebo-adjusted ACE-I cough = (ACE-I cough – Placebo cough)/ACE-I cough. The same equation refers for placebo-adjusted rate of hyperkalemia on MRA. This analysis is based on the assumption that incidence of cough or hyperkalemia on placebo corresponds to the rates of spontaneous cough/hyperkalemia in the investigated populations.

4 Results

4.1 Cough on ACE-Is

Initial search identified 4,210 potentially eligible trials. After reviewing the titles and abstracts manually, 4,078 trials were excluded. The main reasons for exclusion were that ACE-I was not the objective or primary objective of investigation, absence of randomization and/or control/placebo-group or small number of analyzed patients. The remaining 132 trials were full-text reviewed, of which 110 did not meet the predefined inclusion criteria (patients with nephropathy, data about cough not adequately reported, ACE-Is used in combination with other drugs vs. placebo, absence of placebo group). 22 studies met the criteria for inclusion: (BLACK et al., 1997; BORGHI et al., 1998; BRAUNWALD et al., 2004; CUSHMAN et al., 1998; FERRARI, 2006; FOX, 2003; KOBER et al., 1995; LÜDERS et al., 2008; MERCATOR, 1992; NISSEN et al., 2004; OMBONI, BORGHI, 2011; PFEFFER et al., 1992; PITT et al., 2001; PROGRESS, 2001; ROULEAU et al., 2008; RUGGENENTI et al., 2004; RUILOPE et al., 2004; SWEDBERG et al., 1992; YUSUF et al., 1991, 1992; YUSUF et al., 2000).

The study selection process is depicted in the flow diagram (Figure 3). The final analysis included 65,054 patients from 22 randomized, placebo-controlled trials. A total of 32,586 patients were on ACE-Is and 32,468 on placebo. Baseline data of the studies are visualized in Table 1. There were 6 studies where arterial hypertension was the underlying disease (n=8,636), 12 with coronary disease (n=45,641) and 4 with HF (n=10,777). All studies were judged as high-quality studies (Table 1). None of the studies were stopped earlier for benefit. Asymmetric left-right distribution of plots in funnel plot and results of Egger's regression asymmetry test (Egger statistic = 2.29, p=0.0083) indicates presence of publication bias (Figure 4).

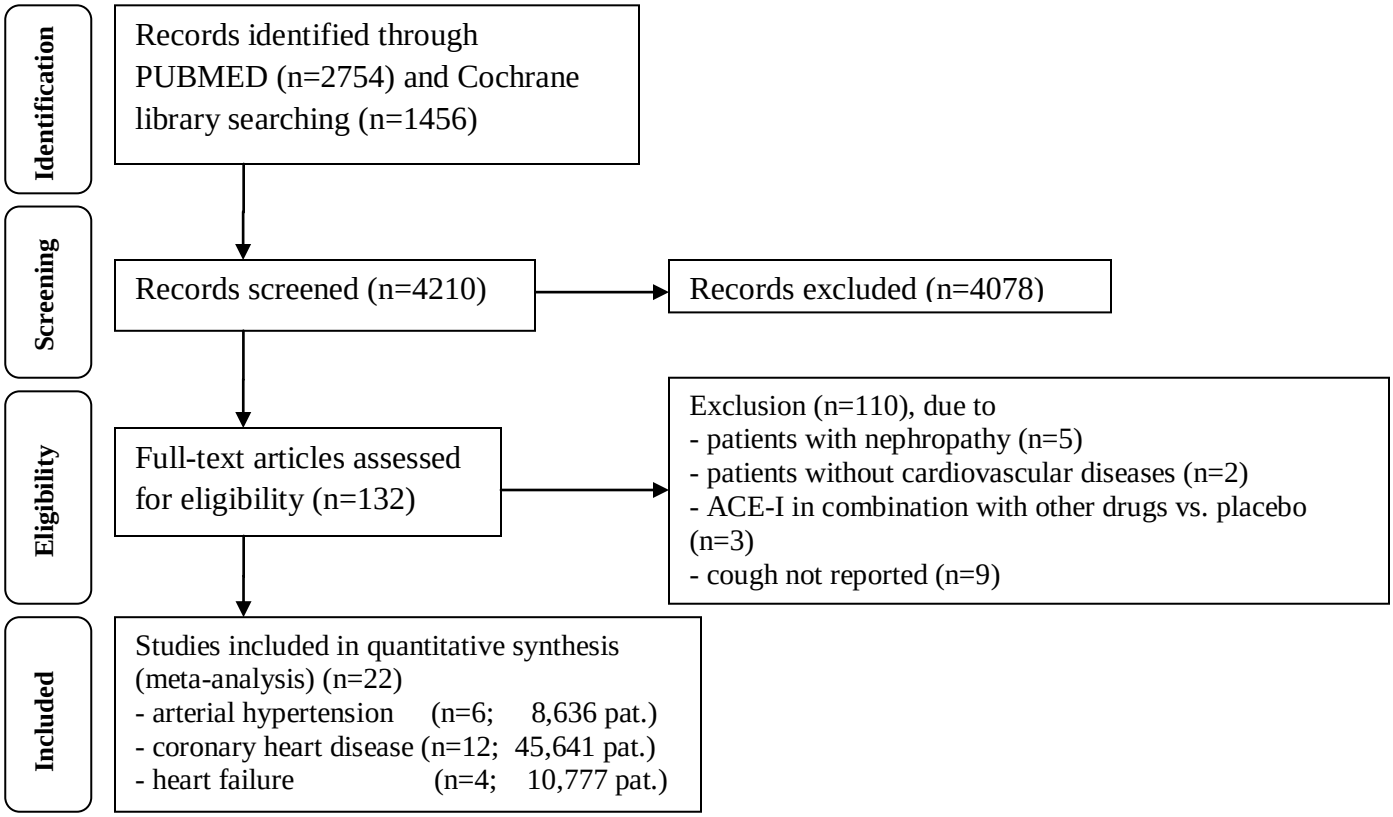

Figure 3. PRISMA flow diagram of the studies, showing study selection process for studies with cough on ACE-I

Table 1. Characteristics of the included studies

ACE Inhibitors	Study	Drug	Inclusion Criteria	EF Drug/ Placebo	Smokers* Drug/ Placebo (%)	Patients (n)	Primary Outcome	Jadad score	Follow up
Arterial hypertension	PROGRESS	Perindopril	Patients with CVI/TIA within 5y	/	20 / 20	6,105	Fatal or non-fatal CVI	5	48
	BENEDICT	Trandolapril	Hypertension and diabetes type 2	/	13.6 / 12.3	601	Development of persistent albuminuria	5	43
	PRADID	Trandolapril	High normal BP or isolated syst. hypertension + diabetes type 2	/	/	258	SBP <135 and DBP <85	4	4
	PHARAO	Ramipril	High normal BP, 50-85y	/	61 / 84	1,008	Development of hypertension	3	36
	Black et al	Lisinopril	Hypertension, 21-80y	/	/	370	Comparing treatments regimen Valsartan vs. Lisinopril	5	3
	Cushman et al	Enalapril	Hypertension, >21y	/	/	294	Monotherapy vs. combinations	3	3
Coronary disease	CAMELOT	Enalapril	Stable angina pectoris, 30-79y	>40%	24.8 / 27.9	1,328	CV Events under Amlodipin or Enalapril	5	20
	HOPE	Ramipril	CAD, CVI, PAD, >55y	>40%	13.9 / 14.5	9,541	Composite of MI, CVI and death	5	60
	PEACE	Trandolapril	Stable CAD, >50y	>40%	14 / 15	8,290	CV death or non-fatal MI	5	57.6
	QUIET	Quinapril	Stable CAD, 18-75y	>40%	21 / 23	1,750	CV Events	5	27
	MERCATOR	Cilazapril	Stable CAD, <75y	/	14 / 20	693	Efficacy of Cilazapril in reducing of restenosis	4	6
	EUROPA	Perindopril	Post-MI patients, >18y	/	/	12,218	Composite of CV death, MI, cardiac arrest	5	50.4
	PREAMI	Perindopril	Myocardial infarction, >65y	>40%	19 / 19	1,252	Composite of death and hospitalizations due to HF	5	12
	CONSENSUS II	Enalapril	Myocardial infarction	/	37.2 / 36	6,090	Mortality	5	6

Table 1 continued

Coronary disease	SMILE	Zofenopril	Anterior MI, 18-80y	/	41 / 41	1,556	Death due to HF	5	1.2
	SMILE-Ischemia	Zofenopril	Myocardial infarction	>40%	23 / 26	349	CV Events	5	6
	IMAGINE	Quinapril	Patients after ACB, >18y	>40%	20 / 20	2,553	CV Events	5	36
	FAMIS	Fosinopril	Anterior MI, Thrombolysis therapy, 17-75y	49 ±11; 51 ±10	56 / 48.2	285	Efficacy and safety of Fosinopril in prevention LV-enlargement	5	24
Heart failure	TRACE	Trandolapril	Patients with LV-dysfunction after MI, >18y, NYHA I-40%	≤35%	73 / 75**	1,749	Mortality	5	24-50
	SAVE	Captopril	Patients with LV-dysfunction after MI, 21– 80y	≤ 40%	53 / 53	2,231	Mortality	5	42
	SOLVD	Enalapril	HF, <80y, NYHA I,II-55%, III-30%	≤35%	22.8 / 21.4	2,569	Mortality und hospitalizations due to HF	5	41.4
	SOLVD Prevention	Enalapril	Patients with asymptomatic LV dysfunction, without HF	≤35%	22.8 / 24.1	4,228	Mortality, development and hospitalizations due to HF	5	37.4

CVI- cerebrovascular insult; TIA - transitory ischemic attack; BP - blood pressure; SBP, DBP- systolic, diastolic blood pressure; CV - cardiovascular; MI - myocardial infarction; CD - coronary disease; PAD- peripheral artery disease; HF- heart failure; ACB - aorto-coronary bypass; LV- left ventricle; *- current smokers at baseline, **- current and previous smoker reported together.

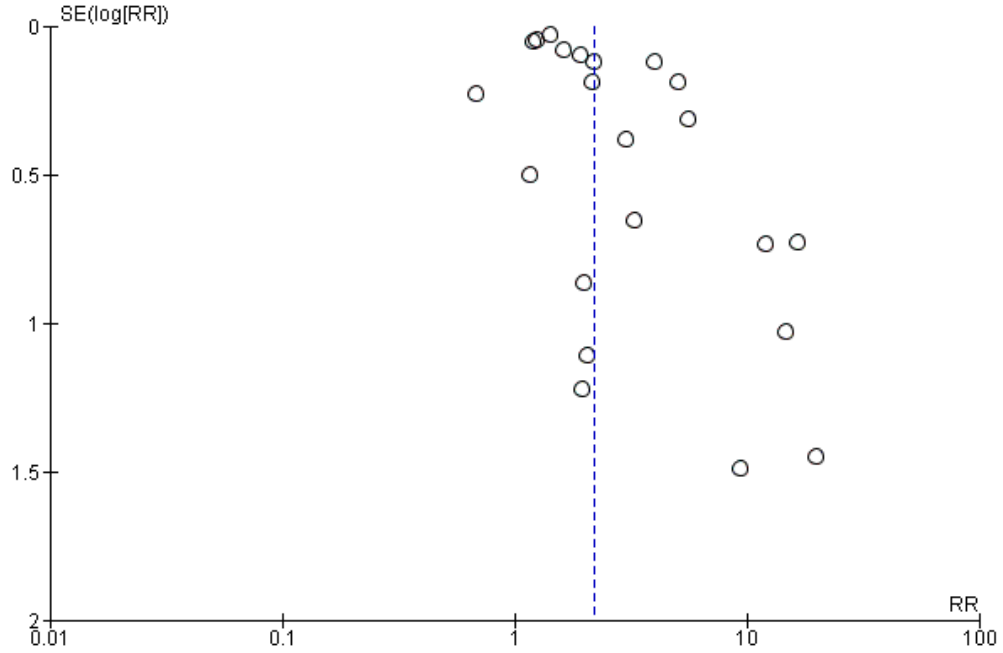

Figure 4. Funnel plot showing standard error of each trial (with ACE-Is) against log risk ratio

Cough occurred in 4,410/32,586 (13.5%) patients on ACE-Is and in 2,769/32,468 (8.5%) on placebo ($p<0.0001$) (Figure 5). RR for cough in patients on ACE-Is was 2.19 (95% CI: 1.78-2.70, $p<0.0001$) vs. placebo (Figure 5). Estimated RR was determined using the random-effects (Der-Simonian-Laird) model since there were signs of relevant statistical heterogeneity (Cochran Q $p<0.0001$, $I^2=91.2\%$) regarding risk of cough among analyzed studies. The pooled incidence rate ratio (IRR) was 2.18 (95% CI: 1.75-2.73, $p<0.0001$) using random effects ($p<0.0001$ for Cochran Q and $I^2=89.8\%$).

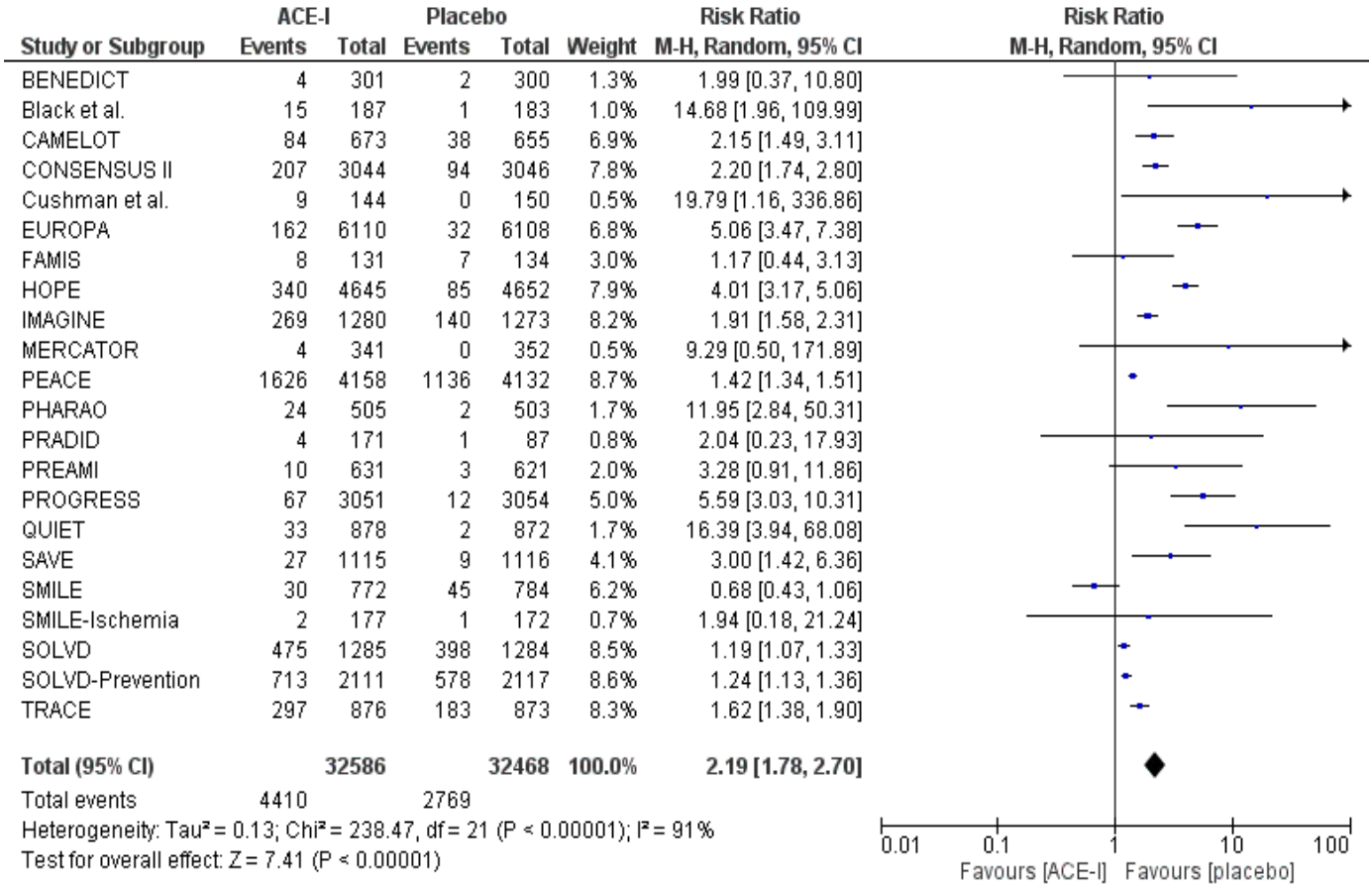

Figure 5. Forest plot demonstrating the RR for cough with corresponding 95% CI. The size of the square represents the percentage of the contribution of each study in the final result. The rhombus represents the pooled effect of the investigated factor, i.e.cough.

By calculating the difference between the rates of cough on ACE-Is (13.5%) and on placebo (8.5%), divided by total rate of cough on ACE-Is, we determined the placebo-adjusted rate of cough on ACE-Is, which was 37% of 13.5% of all cough cases on ACE-Is. This indicates that 8.5% of cases on placebo are equivalent to 63% of 13.5% reported cases on ACE-Is, suggesting that 63% of all cough cases on ACE-Is were potentially not associated with these drugs, as this rate of cough is the same as on placebo, i.e. in absence of exposure to ACE-I (Figure 6).

Cough was reported as an AE in 15 studies and in 7 as a reason for withdrawal/discontinuation (Figure 7). Rate of cough reported as an AE on ACE-Is was 22.8% (3,790/16,629) and 16% (2,633/16,509) in patients on placebo. RR for cough defined as AE in patients on ACE-Is was 1.59 (95 CI: 1.36-1.85, $p<0.0001$) compared to placebo (Figure 7). Placebo-adjusted cough on ACE-Is defined as AE amounts 30%, indicating that all cough cases on placebo are equivalent to 70% of all cough cases on ACE-Is.

Rate of cough defined as a reason for withdrawal/discontinuation as reported in seven included studies, was on ACE-Is 3.8% (620/15,957) and 0.8% (136/15,959) on placebo. Thus, RR for cough defined as a reason for withdrawal in patients on ACE-Is was 4.50 (95% CI: 3.65-5.55, $p<0.0001$) compared to placebo. Placebo-adjusted rate of such defined cough amounts to 78%, indicating that all cough cases on placebo are equivalent to 22% of all cough cases on ACE-Is.

Subgroup analysis revealed a significant interaction (p for interaction $p<0.0001$) regarding effect size of risk for cough between group where cough was reported as AE (RR 1.59) and group where cough was reported as a reason for withdrawal/discontinuation (RR 4.50) (Figure 7), due to substantial lower rate of cough on placebo reported as reason to withdrawal (0.8%) than reported as AE (16%).

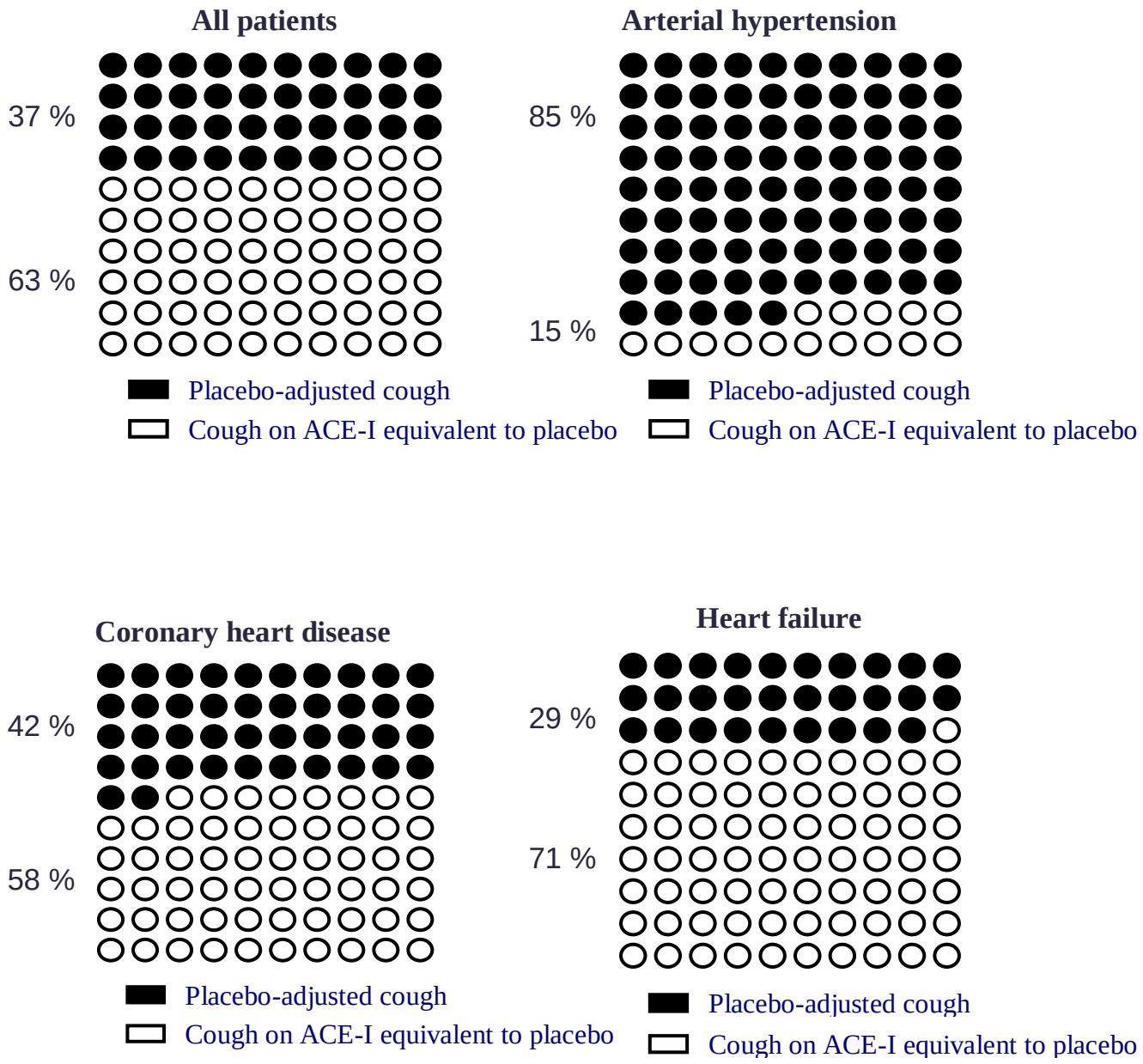

Figure 6. Dot plot demonstrating placebo-adjusted cough on ACE-Is versus cough on ACE-Is equivalent to placebo in all patients and across different underlying conditions, i.e. with arterial hypertension, coronary disease and heart failure.

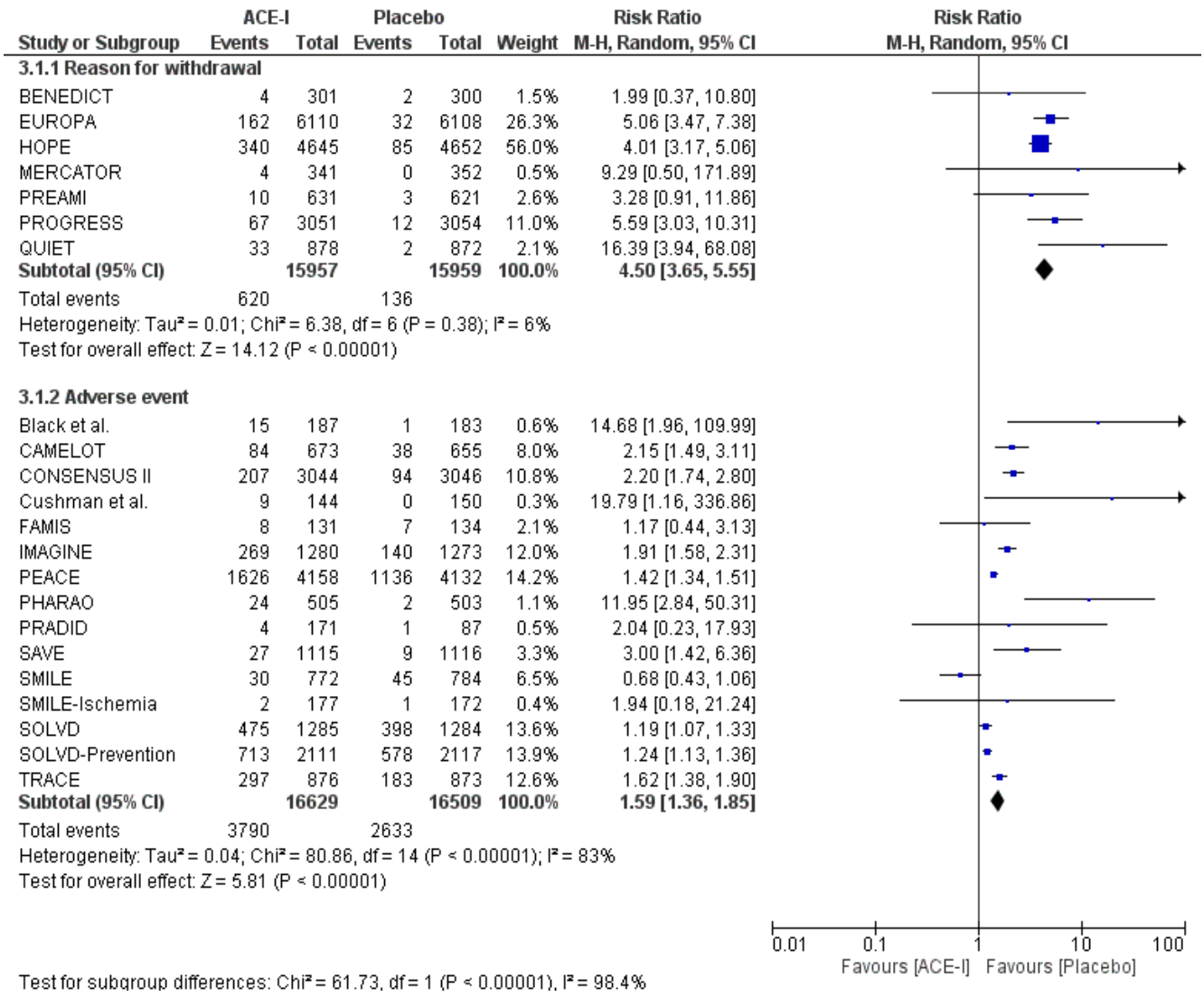

Figure 7. Forest plot demonstrating RR for cough based on different cough definition

Cough in different patient populations

We explored the risk of cough separately in different patient populations, i.e. patients with arterial hypertension, coronary disease and those with HF. In cohort of patients with arterial hypertension, cough has been reported in 123/4,359 (2.8%) patients on ACE-Is and in 18/4,277 (0.4%) patients on placebo. RR for cough on ACE-Is was 5.87 (95% CI: 3.5-9.85, p<0.0001) (Figure 8). Estimated placebo-adjusted rate of cough on ACE-Is with arterial hypertension as underlying disease was 85%, thereby reflecting that all cough cases on placebo are equivalent to 15% of cases on ACE-Is (Figure 6).

In cohorts of patients with coronary disease as underlying disease cough on ACE-Is has been reported in 2,775/22,840 (12.1%) and in 1,583/22,801 (6.9%) on placebo. RR for cough on ACE-Is compared with placebo was 2.30 (95% CI: 1.61-3.28, p<0.0001) (Figure 8). Calculated placebo-adjusted rate of cough on ACE-Is was 42%, indicating thus all cough cases on placebo are equivalent to 58% of cases on ACE-Is in patients with coronary disease (Figure 6).

In cohort with HF as underlying disease cough has been documented in 1,512/5,387 (28%) patients on ACE-Is and in 1,168/5,390 (21.6%) on placebo. RR for cough on ACE-Is compared with placebo in this population was 1.38 (95% CI: 1.16-1.64, p=0.0004) (Figure 8). Estimated placebo-adjusted cough on ACE-Is was 29%, indicating that all cough cases on placebo are equivalent to 71% of cough cases on ACE-Is in patients with HF (Figure 6).

There was a substantial heterogeneity regarding the risk of cough on ACE-Is across different underlying diseases, i.e. in patients with arterial hypertension, coronary disease and HF (I^2=93.4%, p for interaction <0.0001, Figure 8).

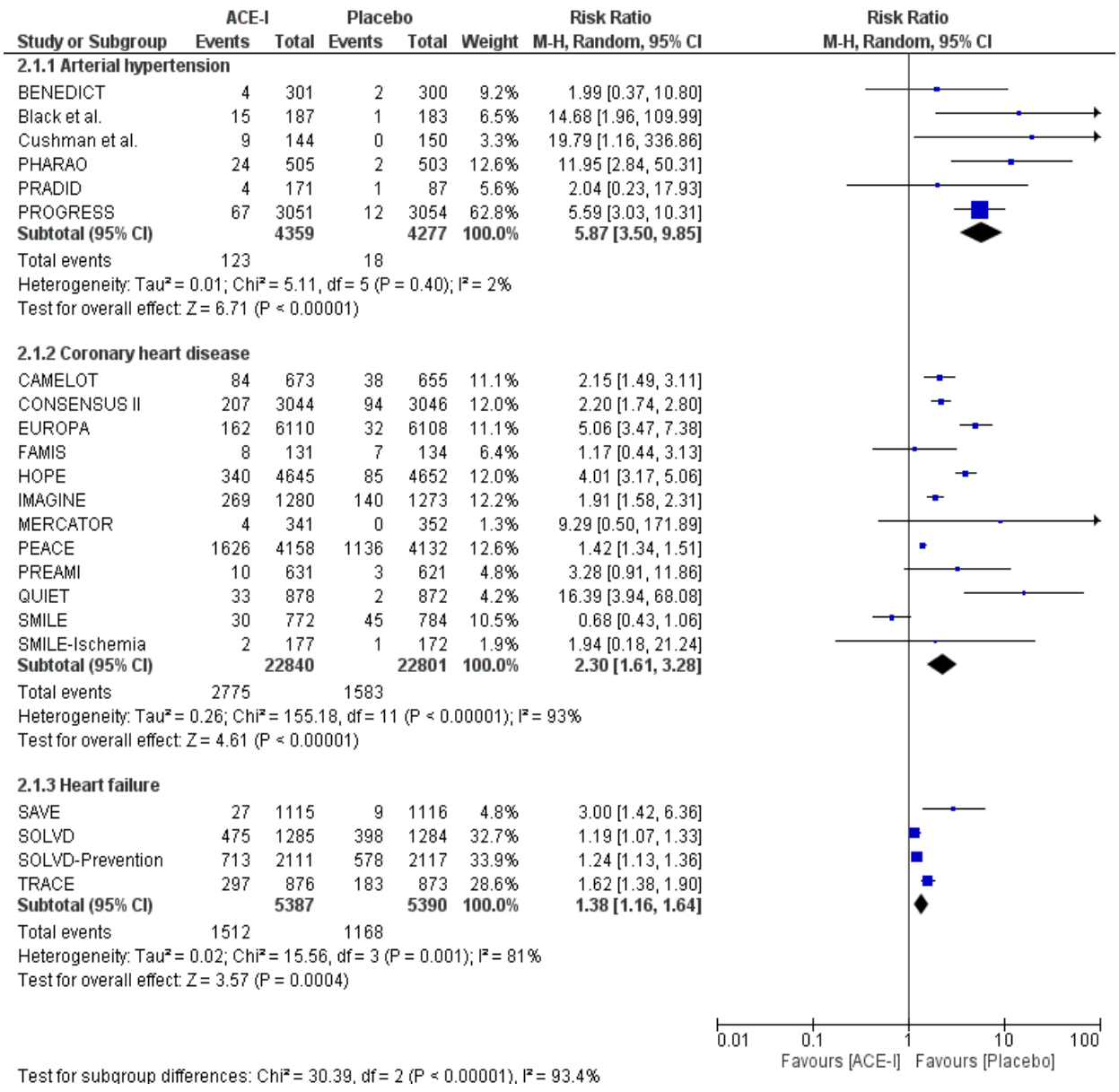

Figure 8. Forest plot demonstrating different risk of cough on ACE-Is across different underlying conditions

Rate of smoking, defined in the most trials as "current smoker", was reported in 18 from 22 trials (Table 1, Figure 9). The rates of so-called "ex-smokers" were underrepresented. The patients with HF had the highest average rate of smokers with 43% followed with 26% in patients with CAD while the patients with arterial hypertension had the lowest rate of smokers with 17% (Figure 9). There was a relevant statistical difference between the rates of smokers across the groups of patients with different underlying diseases (i.e. HF, CAD and arterial hypertension).

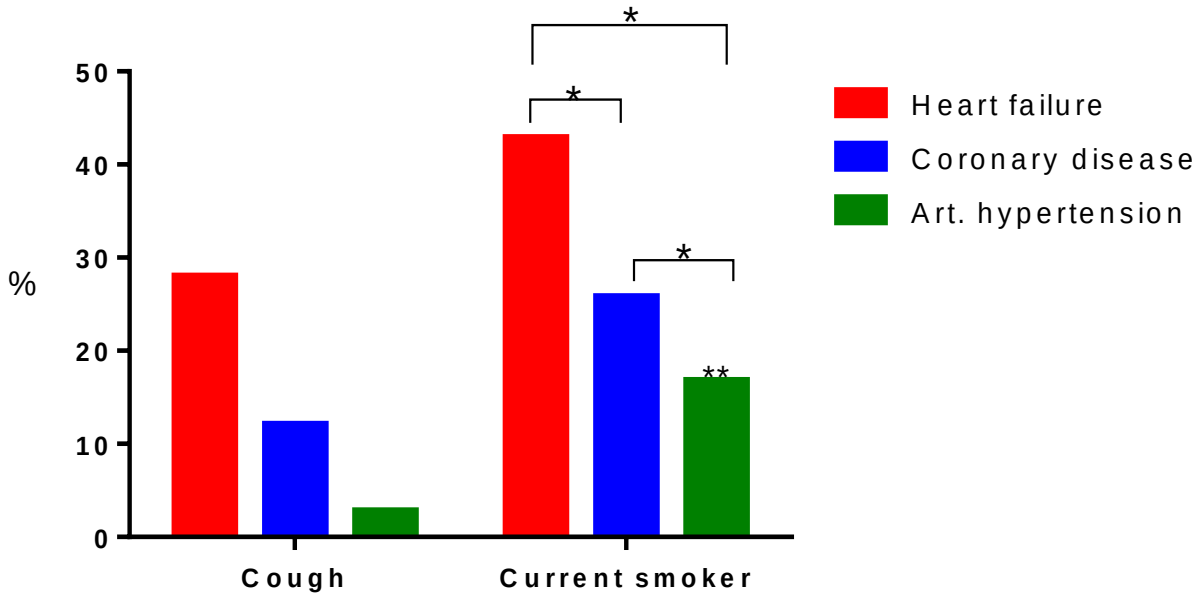

Figure 9. Comparison of reported rates of cough and current smokers (at baseline) in drug-treatment group across different underlying conditions, *****- p<0.0001,

******- reported rate of smokers from PHARAO trial was considered as implausible with 61% on ACE-I and 85% on placebo of current smokers, and was, therefore, excluded.

4.2 Hyperkalemia on MRAs

From the databases, 682 potentially appropriate trials were identified. After reviewing the titles and abstracts, 665 inappropriate trials were excluded. The primary reasons for exclusion were that MRA was not the objective or primary objective of investigation, lack of randomization or placebo-group, small number of analyzed patients and evaluation of the effect of MRA in other clinical settings we found inappropriate (i.e. patients with nephropathy). From remaining 17 full-text reviewed trials, 8 did not met the predefined inclusion criteria due to small number of patients (<100); in 1 trial, rate of hyperkalemia was not adequately reported; and in 1 trial, intervention with canrenone was used. Seven trials met the criteria for inclusion (EDELMANN et al., 2013; MONTALESCOT et al., 2014; PITT et al., 2014; PITT et al., 2003; PITT et al., 1999; UDELSON et al., 2010; ZANNAD et al., 2011) (Table 2). Study selection process is depicted in the flow diagram (Figure 10). A total of 16,065 individuals from 7 randomized, placebo-controlled trials entered the final analysis, of those 8,030 were on MRA and 8,035 on placebo. Baseline characteristics of the included studies are visualized in Table 2. In two studies were analyzed patients after myocardial infarction (n= 7,602), in three patients with chronic HF and reduced ejection fraction (n= 4,618), and in two patients suffering from HF with preserved ejection fraction (n= 3,845).

The initial search for non-interventional registry studies identified 118 potential appropriate articles for inclusion in sensitivity analysis. Of those 78 articles were excluded after screening the titles and abstracts. From the remaining 40 articles, where complete full-text review were performed, 2 studies (HERNANDEZ et al., 2012; WANG et al., 2016) (Table 3 and 4) met the inclusion criteria whose data regarding hyperkalemia were pooled together with the data from the interventional trials.

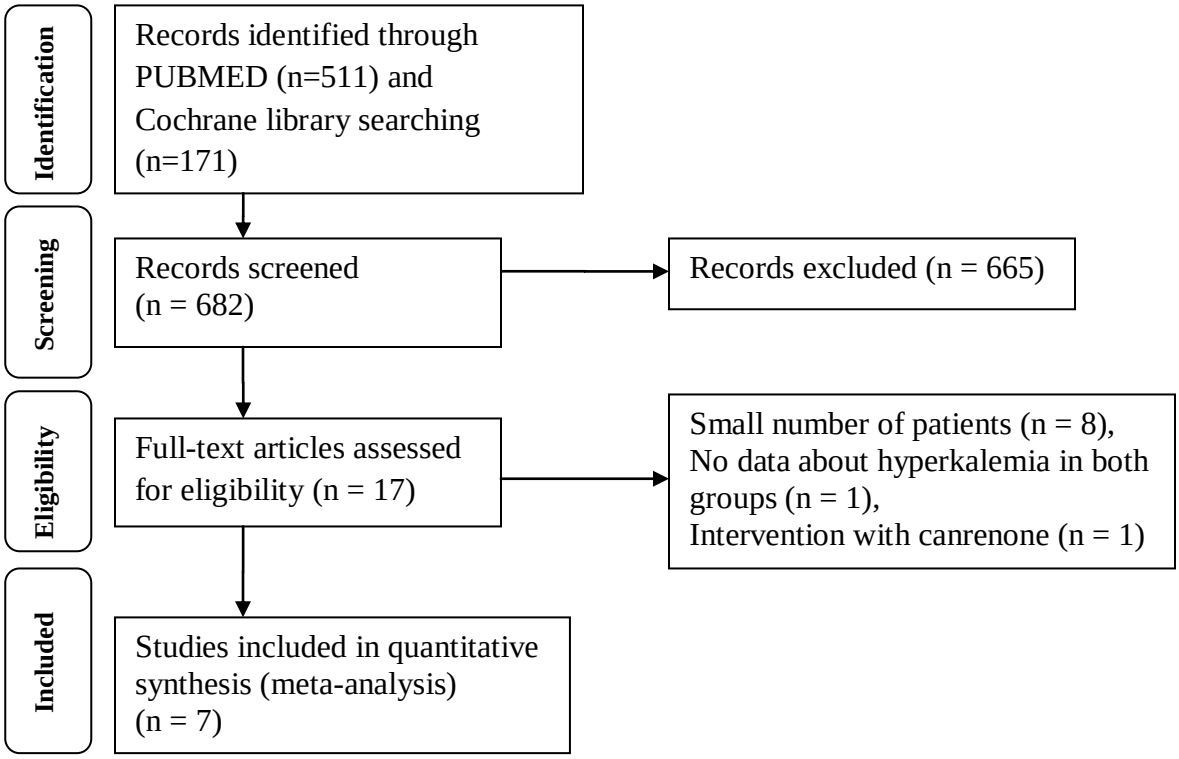

Figure 10. PRISMA flow diagram showing the study selection strategy for trials with hyperkalemia on MRA

Table 2. Baseline characteristics of the studies included in the meta-analysis

	Study	Drug	Inclusion Criteria	EF	N	Primary outcome	Jadad Score	Follow up*
Post myocardial infarction	EPHESUS	Eplerenone	AMI and left ventricular dysfunction and heart failure or diabetes	≤40%	6,608	Mortality/Mortality or Hospitalization from CV cause	5	16
	REMINDER	Eplerenone	Within 24h after STEMI	≥40%	994	CV Mortality or Hospitalization	5	10.5
Heart Failure	RALES	Spironolactone	HF, NYHA III-IV	≤35%	1,663	Mortality	5	24
	EMPHASIS-HF	Eplerenone	HF, NYHA II, >55y	≤35%	2,729	CV Mortality/ Hospitalization due to HF	5	21
	TOPCAT	Spironolactone	HF and preserved EF, NYHA II, III; average EF 56% in both groups, >50y	≥45%	3,445	CV Mortality/ Hospitalization due to HF	5	39.6
	ALDO-DHF	Spironolactone	HF and preserved EF, NYHA II/III, >50y, diastolic dysfunction/ atrial fibrillation	≥50%	400	Improving of diastolic function	5	12
	Udelson et al.	Eplerenone	HF, NYHA II/III, >21y	≤35%	226	Effect on remodeling	5	9

AMI, acute myocardial infarction; CV, cardiovascular; HF, heart failure; EF, ejection fraction; NYHA, New York Heart Association functional class; STEMI, ST segment elevation myocardial infarction; * duration in months.

Table 3. Characteristics of registries used in sensitivity analysis

Register	Substance	Inclusion Criteria	EF	N	Outcome	Follow up*
Wang TY et al.	97% Spironolactone, 3% Eplerenone	>65y, STEMI/NSTEMI and HF signs or diabetes, without contraindication for MRA	≤40%	12,080	Mortality, rehospitalization, hyperkalemia or decrease of renal function	24
Hernandez AF et al.	Aldosterone antagonist	>65y, hospitalized for HR, without contraindication for MRA	≤35%	5,887	Mortality, rehospitalization, hyperkalemia	36

* duration in months

Table 4. Results on MRA presciption at discharge among eligible patients and rates of hyperkalemia after one month

	Study	MRA prescribed at discharge	MRA not prescribed at discharge	Hyperkalemia after one month	
				MRA prescribed	MRA not prescribed
Post myocardial Infarction	Wang TY et al.	1310 (10.8%)	10,770	29 (2.2%)	164 (1.5%)
Heart failure	Hernandez AF et al.	1070 (18.2%)	4,817	31 (2.9%)	58 (1.2%)

All studies were evaluated as high-quality studies (Table 2). None of the studies were stopped earlier for benefit. Funnel plot with symmetric left-right distribution of plots and results of Egger's regression asymmetry test (Egger statistic = -0.22, p=0.85) indicates no presence of publication bias (Figure 11).

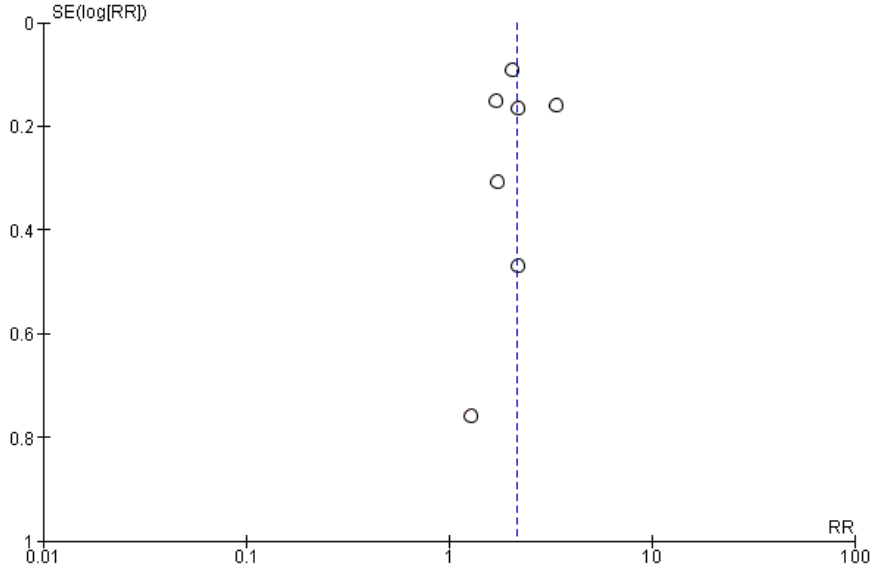

Figure 11. Funnel plot showing standard error of each trial (with MRA) against log risk ratio

Hyperkalemia as an adverse event was predefined in most of the included trials as potassium values ≥ 5.5mmol/l and in one trial ≥ 6mmol/l (UDELSON et al., 2010). Hyperkalemia has been reported in 746/8,030 (9.3%) patients on MRA and in 345/8,035 (4.3%) patients on placebo (p<0.0001). The estimated RR for hyperkalemia on MRA was 2.17 (95% CI: 1.92-2.45, p<0.0001) (Figure 10). The determined RR was calculated using the fixed-effects model since there were no signs of substantial heterogeneity (Cochran Q p=0.07, I^2=49%). Synthesis of the data regarding hyperkalemia using random-effect model had the similar results with the RR of 2.16 (95% CI: 1.76-2.66, p<0.0001).

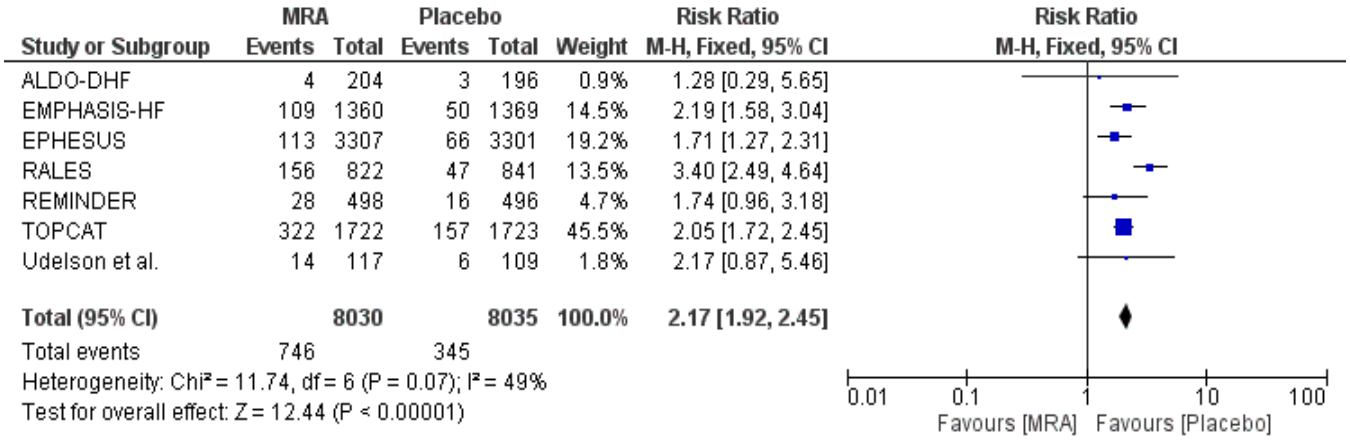

Figure 10. Forest plot showing risk (RR) of hyperkalemia on MRA vs. placebo

Pooled incidence rate ratio was 2.15 (95% CI: 1.88-2.44, p<0.0001), using fixed-effect (no heterogeneity p=0.09, I^2=44.9%), indicating that different length of follow-up across the trials had no major impact on the final results.

Since the data from the TOPCAT trial had the major impact on pooled RR (weight 45% using fixed-effect and 27% using random effect), we performed sensitivity analysis by excluding the data of this trial. The pooled RR computed in this way was 2.18 (95% CI: 1.63-2.91, p<0.0001).

Pooled RR for hyperkalemia on MRAs obtained from the combined data from registries and clinical trials was 2.09 (95% CI: 1.74-2.5, p<0.001), using random effect model to pool the data (Cochran Q p=0.04, I^2=49%).

We determined the placebo-adjusted rate of hyperkalemia on MRA, by calculating the difference between the rates of hyperkalemia on MRA (9.3%) and on placebo (4.3%), divided by the rate of hyperkalemia on MRA. The placebo-adjusted rate on MRA shows that 54% of 9.3% reported hyperkalemia cases on MRA are indeed MRA-associated, while 46% of 9.3% reported hyperkalemia-cases on MRA might represent non-MRA related hyperkalemia, as this number of hyperkalemia cases are equivalent to those on placebo

(Figure 13). This analysis was based on the assumption that incidence of hyperkalemia on placebo represents spontaneous hyperkalemia rate in this population.

The rates of hyperkalemia were differentiated according to the use of spironolactone as a non-selective MRA and eplerenone as a selective MRA (Figure 14). In trials with spironolactone, hyperkalemia was reported in 482/2,748 (17.5%) on drug and in 207/2,760 (7.5%) on placebo. The RR for hyperkalemia on spironolactone vs. placebo was 2.34 (95% CI: 2.01-2.73, $p<0.0001$) (Figure 15). The placebo-adjusted rate on spironolactone was 57% of all reported hyperkalemia cases on this drug, suggesting that 43% of hyperkalemia cases reported on this drug were non-spironolactone related hyperkalemia (Figure 13). In trials with eplerenone, hyperkalemia occurred in 264/5,282 (5%) patients on eplerenone and in 138/5,275 (2.6%) on placebo. The RR for hyperkalemia on eplerenone vs. placebo was 1.91 (95% CI: 1.56-2.34, $p<0.0001$) (Figure 15). The placebo-adjusted rate of hyperkalemia on eplerenone was 48% of 5% reported cases, indicating that 52% of all hyperkalemia cases on eplerenone were not eplerenone-related (Figure 13).

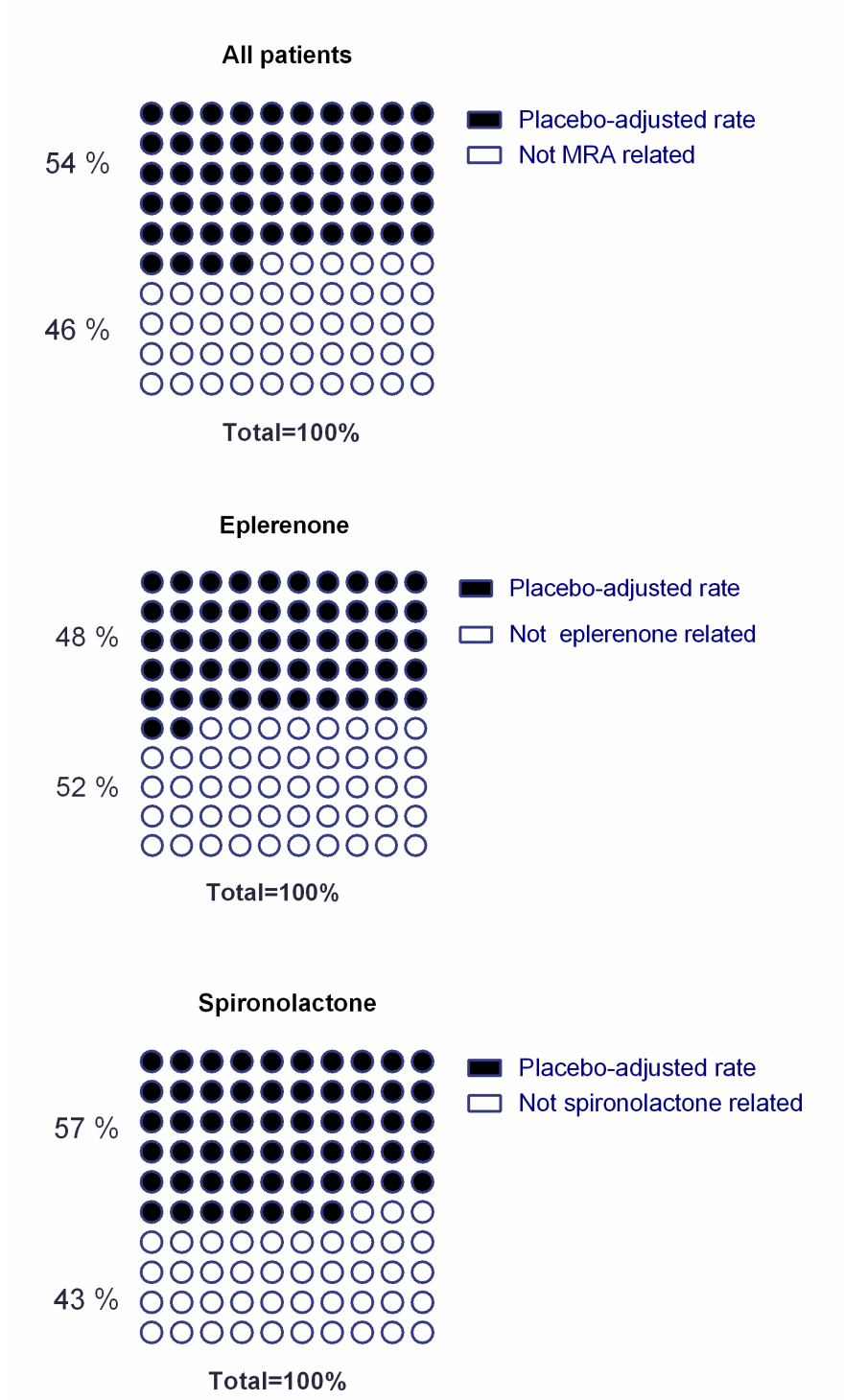

Figure 13. Dot plot demonstrating placebo-adjusted rate of hyperkalemia on MRA versus hyperkalemia equivalent to placebo in all patients and across selective/non-selective MRA, i.e. eplerenone and spironolactone

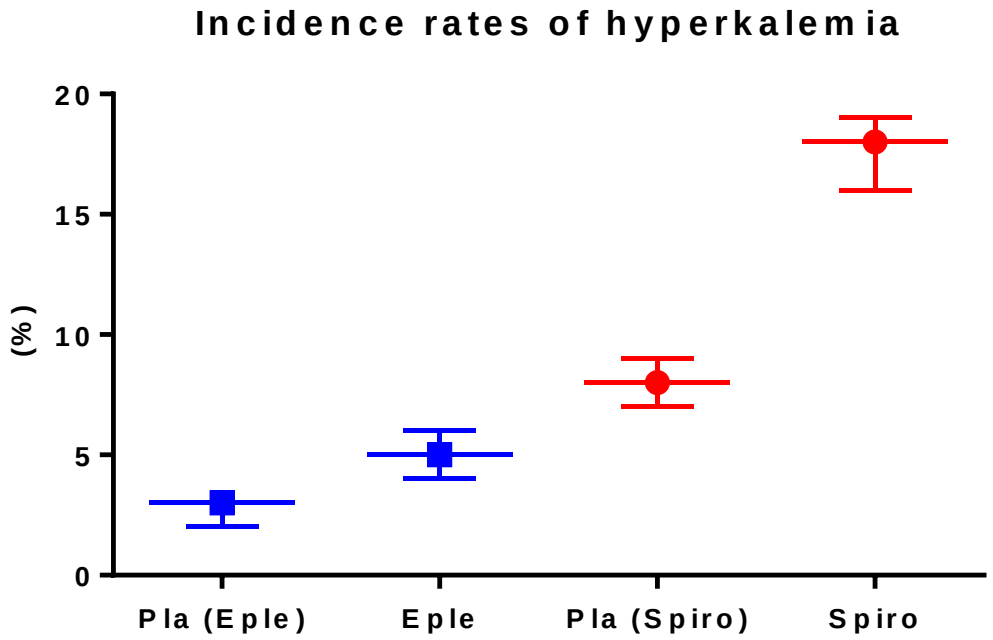

Figure 14. Incidence rate of hyperkalemia with 95% confidence intervals

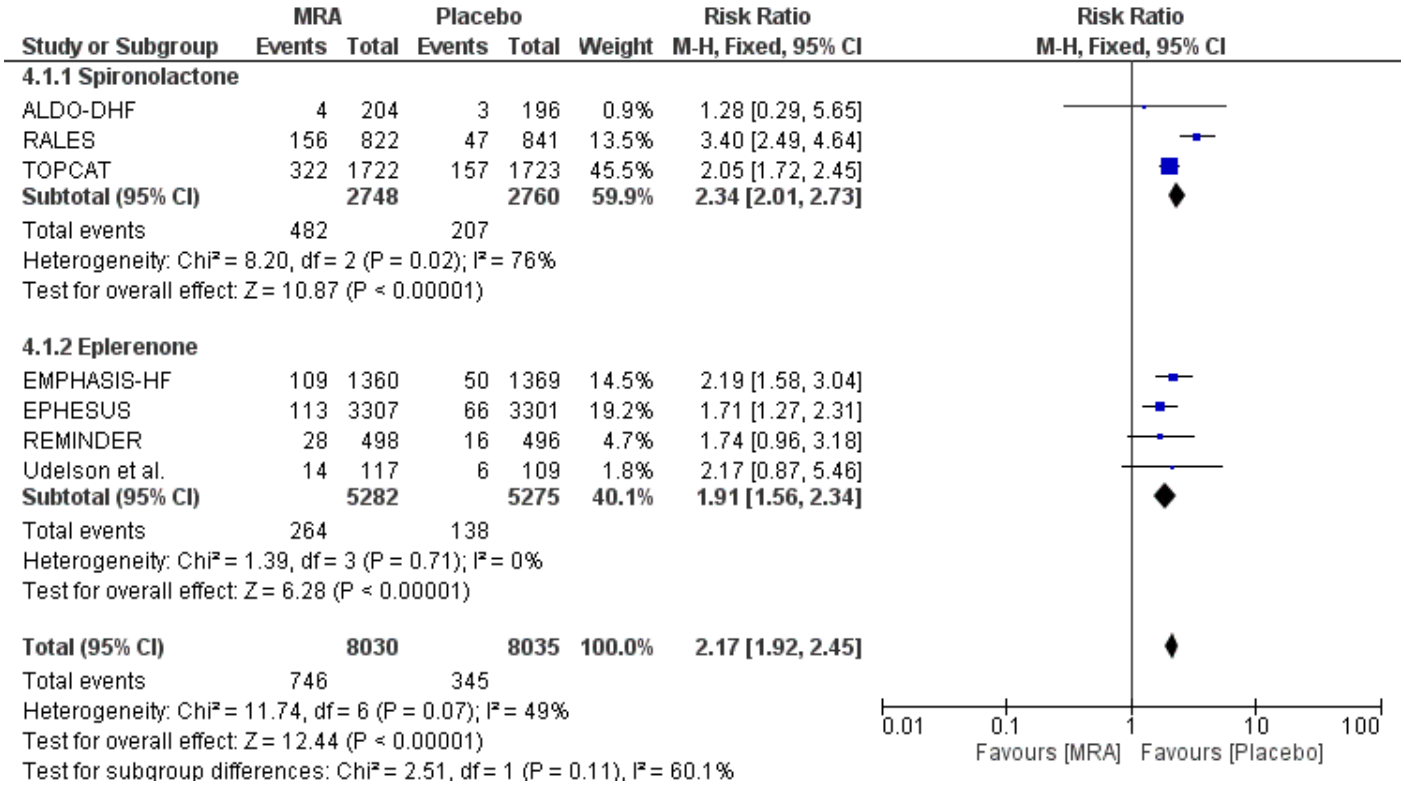

Figure 15. Forest plot with estimated RR for hyperkalemia differentiated according to the different MRA used, i.e. spironolactone vs. eplerenone.

4.3 Hypokalemia on MRAs

Data about hypokalemia, which was predefined as potassium values <3.5mmol/l, has been reported in 5 trials from 15,266 patients (Figure 16). Hypokalemia was reported in 712/7,648 (9.3%) patients on MRA and in 1,130/7,618 (14.8%) patients on placebo (p<0.0001). The RR for hypokalemia on MRA was 0.57 (95% CI: 0.46-0.71, p<0.0001) (Figure 16). There was a substantial statistical heterogeneity across the trials (Cochran Q p=0.00009, I^2=79%), so we used a random-effect model to pool the data. There were no signs for publication bias (Egger statistic =-3.36, p=0.09) (Figure 17).

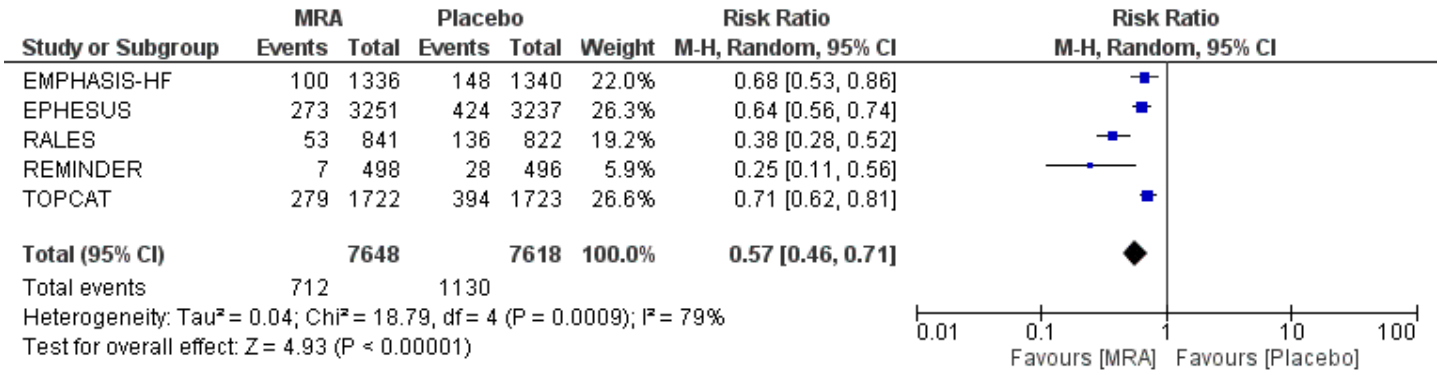

Figure 16. Forest plot demonstrating RR for hypokalemia on MRA vs. placebo

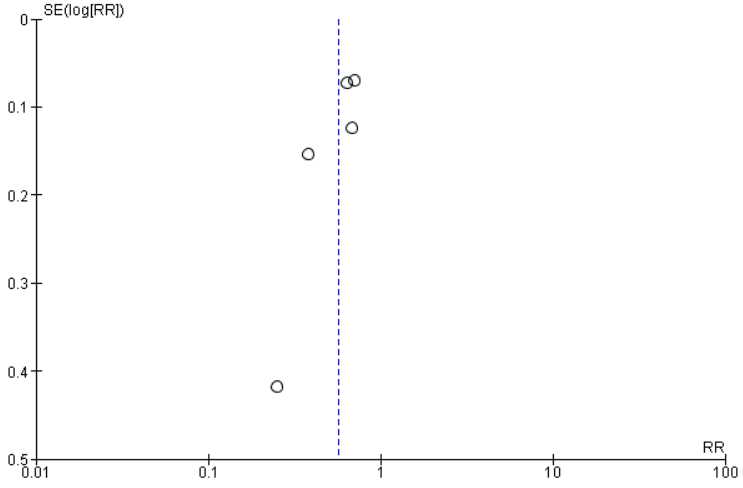

Figure 17. Funnel plot suggesting no presence of publication bias

5 Discussion

The key findings of this quantitative analysis based on a large number of data from controlled trials exploring cough on ACE-I treatment and hyperkalemia on MRA treatment were that about one third (37%) of all cough cases on ACE-I and about half (54%) of all hyperkalemia cases on MRA might be explained solely by the use of these drugs, i.e. are specifically related to the treatment with ACE-I and MRA, respectively. In turn, all cough cases on placebo were equivalent to about two thirds (63%) of all cough cases on ACE-I and all hyperkalemia cases on placebo were equivalent to about half (46%) of all hyperkalemia cases on MRA. Furthermore, treatment with MRA reduced the risk of hypokalemia, electrolyte imbalance which has been associated with increased mortality.

These results provide new insights into dealing with the problem of these specific adverse events, which are recognized as the leading causes for withdrawal of these life-saving treatments in patients with cardiovascular diseases. They demonstrate physicians' perception that side effects are ultimately owing to drugs, thereby dismissing other potential causes leading to interruption of treatment and underdiagnosing others underlying conditions. These new insights fill the gap concerning safety profile of drugs, by revealing the fact, that not all cough cases on ACE-Is and hyperkalemia on MRAs are necessarily caused by these drugs. In view of these novel findings, a comprehensive work up for other potential reasons for cough and hyperkalemia is necessary in every single case.

5.1 Cough on ACE-Is

According to the results from our analysis the rate of cough on ACE-Is was 13.5% based on data from 32,586 patients from randomized, clinical trials. There were variations in incidence of cough depending on the underlying conditions. In patients with arterial hypertension the incidence was 2.8%, in patients with coronary disease 12.1% and in patients with HF 28%. However, according to the same subgroup analysis estimated risk effects for cough were inversely proportional to the rates of cough across the subgroups being the highest in patients with arterial hypertension (RR of 5.87) and the lowest in patients with HF (RR of 1.38). There was a relevant heterogeneity concerning estimated risk for cough between these subgroups (p for interaction p=0.0004).

According to the several postmarketing surveillance studies and studies based on the data from general population, rate of ACE-I associated cough was lower (1-4%), which is in distinction with our results (COOPER et al., 1987; HUCKELL et al., 1993; INMAN et al., 1988). Reasons for these different findings may be due to different study designs (postmarketing surveillance and general population studies vs. randomized controlled trials), different subpopulation (general population vs. patients with CVD), number of evaluated individuals and the most probably due to way how cough was ascertained (spontaneous, self-reported or based on systematic query).

Furthermore, the rate of cough was 3.8% by accounting only the cases with cough reported as a reason for withdrawal/discontinuation, which is very similar to the real-world data published in the SPICE registry, where the incidence of cough reported as a reason for withdrawal in HF patients was 3.6% (BART et al., 1999). Not every episode of cough should lead to ACE-I withdrawal. Lower rate of cough defined on this way justifies drug re-exposure with a work-up of underlying other potential causes. There was a relevant difference in estimated risk effect between subgroups where cough was defined as a reason for withdrawal (RR of 4.50) and as adverse effect (RR of 1.59), with p for interaction $p<0.0001$.

The third issue to be appreciated beside underlying condition, and cough definition, is taking the rate of cough on placebo into consideration. Estimated placebo-adjusted rate of cough on ACE-I was 37%. Therefore, we could expect that these drugs are genuinly responsible for cough in every third case of cough on ACE-I. This rate varied substantially across different underlying conditions, showing the lowest rate in HF (29%), higher in coronary disease (42%) and the highest in patients with arterial hypertension (85%).

Findings from our analysis that cough on ACE-I was more common in patients with HF than in patients with other underlying conditions are consistent with previous observations (RAVID et al., 1994). The fact that rates of cough in patients with HF on placebo was also relative high (21.6%) and that placebo-adjusted rate on the drug was the lowest across all underlying conditions (Figure 6), indicates that HF patients are prone to develop cough irrespective of use of ACE-Is. There are some possible explanations for this observation. HF as a syndrome characterized by breathlessness as a result of reduced cardiac output and/or elevated intracardiac pressure leads to pulmonary congestion, which causes cough (PONIKOWSKI et al., 2016). Additionally these patients are more prone to develop pulmonary infections, which could be also manifested with cough either. Further, chronic obstructive pulmonary disease (COPD) is a common comorbidity present in up to 25% of patients with HF (MENTZ et al., 2012). It is reasonable to assume that COPD with cough as one of its main symptoms/signs could contribute to some extent to prevalent and incident cough in HF patients. Data from the OPTIMIZE-HF registry with HF patients, with concomitant COPD, support these considerations. According to this registry, patients with HF and COPD were less likely to be on ACE-I than those without COPD, potentially reflecting a high cough incidence (MENTZ et al., 2012). Unfortunately COPD was underreported (only in one trial)(LÜDERS et al., 2008) among studies included in our analysis, thus disabling detailed exploration of this issue. Furthermore, the rate of smoking as a possible cause of COPD in these patients was higher in the subpopulation of patients with HF compared to patients with arterial hypertension and coronary disease (Table 1, Figure 9). Rate of smoking referred to as “current smokers” while the rate of so-called ex-smokers were underrepresented, depicted in only three trials. Higher rates of smokers in patients with HF might be associated with a higher burden with obstructive lung disease in these patients.

Applying the results from our analysis that the placebo-adjusted rate of cough on ACE-Is is about 40%, into clinical practice would means in a hypothetical worst-case scenario that more than half (approximately 60%, Figure 6) of patients with CVD would not be on this life-saving and well proven treatment due to the misconception that ACE-Is are necessarily responsible for all cough cases in patients receiving this treatment. To define whether these drugs are really the cause of cough among affected individuals, ideally a re-challenge with the drug should be performed following cough resolution after drug discontinuation. In case cough reoccurs after re-challenge to the ACE-I would strongly suggest that ACE-I is actually the cause of cough. However, there are limited data addressing this concept. It has been shown that a re-challenge with lisinopril decreased the rate of cough by 30% in individuals with cough initially thought to be caused solely by lisinopril (LACOURCIERE et al., 1994). The occurrence of cough on ACE-I would in the majority of cases instantly lead to a change of therapies and switching to

angiotensin receptor blockers (ARBs), based on findings that ARBs are equally effective but without increased rate of cough on ARBs. In patients with arterial hypertension this concept is equally recommended (LACOURCIERE et al., 1994; PASTER et al., 1998).

Undertreatment with ACE-Is may be even more pronounced in patiens with coronary artery disease and with HF due the fact that rates of cough were higher but the placebo-adjusted rates were lower by 42% and 29%, respectively. Patients with HF who are treated with submaximal doses or those who withdraw eternally from RAAS inhibitors had poorer outcomes in comparison with those on maximum recommended doses (EPSTEIN et al., 2015). In addition, treatment of patients with coronary artery disease and HF with ACE-I in comparison with ARB has a much larger amount of evidence-based data regarding reduction of death, risk of hospitalization and prevention of HF. In the current guidelines for HF, ACE-Is (Class I, Level A) should be preferred over ARBs, which should be considered only in patients who are unable to tolerate ACE-I (Class I, Level B) (PONIKOWSKI et al., 2016).

ACE-I related cough may occur shortly after initiation but its onset could occur also later after couple of months or even years after treatment with these drugs has been started (OVERLACK, 1996). Cough cessation triggered by ACE-I usually takes 1 to 4 weeks after the treatment with ACE-I has been stopped, but it can last up to 3 months (ISRAILI, HALL, 1992). Trials included in our analysis differed in their duration of follow-up, which may affect the final results concerning the rate of cough. We take this into consideration by computing the incidence rate ratio that exhibits risk of cough based on person-month data, which were calculated by multiplying the number of persons from each trial with the number of months of follow-up. Thus, we adjusted the different time of follow-up across the trials. This exploratory analysis showed almost the same results as the primary analysis did (IRR of 2.18 vs. RR of 2.19), pointing out that different length of follow-up had no major impacts on risk of cough.

Although the rates of cough may differ across different ACE-Is cough represents an adverse event associated with ACE-Is as a class of drugs. According to one large meta-analysis the rate of cough was not affected after reducing the dose of ACE-I, indicating that this adverse event is not dose dependent (LAW et al., 2003). There were several approaches how to diminish the cough on ACE-I like with the use of baclofen (DICPINIGAITIS, 1996), cromolyn (ALLEN, GORA-HARPER, 1997), theophylline (CAZZOLA et al., 1993) and local anesthetics. However, in absence of strong evidence showing that these approaches are actually effective in cough supression associated with ACE-I they are abandoned and represent not the standard procedure how to deal with this problem. Once cough occurs believed to be related to ACE-I the only appropriate treatment is stopping the administration of ACE-I.

5.2 Hyperkalemia on MRAs

The most important findings from this analysis were that approximately an half of the all hyperkalemia cases in patients on MRA in controlled clinical trials were specifically related to MRA treatment, whereby the other half were MRA-unrelated. Results were very similar for both investigated substances spironolactone and eplerenone, applied in patients after myocardial infarction and with HF. In addition, treatment with MRA significantly reduced the occurrence of hypokalemia.

As the activation of mineralocorticoid receptor located in the kidney stimulates excretion of potassium, an inactivation of potassium excretion through blockade of these receptors with MRA is associated with the risk of hyperkalemia. A publication of the RALES trial in 1999 establishing the MRA, as a cornerstone therapy in patients with HFrEF was linked with increased hospitalization and in-hospital mortality by hyperkalemia in the following years (JUURLINK et al., 2004). It has been assumed that widespread prescription of MRAs and its inappropriate use, with high doses, lack of consideration of renal function and concomitant treatments have increased the number of hyperkalemia cases (DEV et al., 2015). This observation raised concerns among physicians resulting in substantial underuse of these life-saving and protective drugs, which are according to the data from registries adequately applied in only 9-55% of eligible patients (HIRT et al., 2016; LOPEZ-DE-SA et al., 2011; RASSI et al., 2013). The risk of hyperkalemia (and the fear of it) has been recognized as the most relevant factor that prevents the implementation of the MRA in eligible patients (MAGGIONI et al., 2013). However, there are other reasons probably responsible for underuse. Shortage of time during hospital stay may act as a limiting factor for initiation and titration of several new guidelines recommended drugs in a safe manner, to avoid deterioration of renal function or drops in blood pressure. This is primarily related to patients with newly diagnosed HF, i.e. in therapy naive patients without ACE-Is/ARBs or ARNI and/or beta-blockers as basis therapy. Of note, most of the individuals included in this analysis were already on beta-blockers and ACE-I/ARB. Other reasons for underuse of MRA that need to be considered are lack of knowledge, presence of poly-pharmacy limiting the adherence to the therapy, high price (eplerenone), or worry concerning capabilities of appropriate biochemical monitoring after hospital discharge (CHIN et al., 2016).

We demonstrated that the placebo-adjusted rate of hyperkalemia on MRA is 54% of all patients who developed hyperkalemia on the MRA-treatment in clinical trials. In a hypothetical worst-case scenario that means discontinuation of this drug from all hyperkalemia cases, about half (46%) of patients with hyperkalemia would not be on this evidence-based and strongly recommended drug for treatment of HF

due to erroneous notion that all cases of hyperkalemia on MRA are mandatory generated by the use of MRA. Considering that a relative high number of patients on placebo (4.3%) had hyperkalemia in relation to hyperkalemia-cases on MRA (9.3%), highlights the role of some other risk factors in facilitating hyperkalemia in this population of patients irrespective of the use of MRA. High comorbidity load in these patients like diabetes mellitus and/or chronic kidney disease, representing itself risk factors for hyperkalemia (PALMER, 2004), may be responsible for this electrolyte disturbance in absence of the MRAs. Furthermore, a post hoc analysis of the RALES trial shows that positive effect of spironolactone in term of mortality reduction is persistent even in presence of moderate (>5.5mmol/l) hyperkalemia, stressing that although MRA represent a risk factor for hyperkalemia, it also appears to protect from death in comparison with patients with similar level of potassium in the absence of MRAs (VARDENY et al., 2014).

Trials included in our analysis differed in their duration of follow-up, which might affect the final results. We addressed this question by performing an additional exploratory analysis by computing the incidence rate ratio, an estimate that exhibits risk of hyperkalemia based on person-month data, thus, accurate for exposure time, which was calculated by multiplying the number of persons from each trial with the number of months of follow-up. In this way, we adjusted different time of follow-up across the included trials. According to this exploratory analysis different duration of follow-up had no major impact on the final results, as the results were very similar to results from primary analysis (IRR of 2.15 vs. RR of 2.17). According to data from included trials hyperkalemia usually occurs within first month after drug initiation (PITT et al., 2014; PITT et al., 2003; ZANNAD et al., 2011). This critical period of time has also been acknowledged by the guidelines of European Society of Cardiology who recommended close potassium monitoring on the regular basis 1 and 4 weeks after introduction of the drug and/or increasing the dose of the drug. In case there is no sign of hyperkalemia, controls should be carried out less frequently once monthly until 3 months after MRA initiation, and thereafter every 3 months until one year after MRA initiation. Although these practical guidance, which are easy to follow, should help in minimizing the risk to miss the rise of potassium values there are many evidence from clinical practice which shows an inadequate potassium monitoring, thus, putting the patients at increased risk for hyperkalemia associated mortality and morbidity (COOPER et al., 2015; SHAH et al., 2005). This could be managed by establishing the quality improvement programmes which should improve laboratory potassium controls after MRA initiation, especially in high risk patients, i.e. with impaired renal function and patients with diabetes mellitus.

As the data from TOPCAT trial had numerically the great impact on final results of our analysis and because there were substantial regional variations in rates of hyperkalemia observed among individuals

included in this study (PFEFFER et al., 2015; ROSSIGNOL, ZANNAD, 2015), we conducted a sensitivity analysis by excluding the data from this trial. The results were similar to the results of primary analysis, reflecting consistency of hyperkalemia rates across the included trials.

Incidence rate of hyperkalemia on MRA in our analysis was 9.3% which reflected the rate of hyperkalemia in patients from controlled clinical trials. However, in the real-world setting the rate of hyperkalemia could be much higher up to 50% (PALMER, 2004), particularly when these medications are used in unselected patient population. We performed an additional analysis incorporating the data from two registries. This additional analysis showed similar results with primary analysis (RR of 2.09 vs. RR of 2.17). Of note, the rates of hyperkalemia in both registries were relatively low because hyperkalemia was defined as a reason for hospitalization, possibly reflecting serious hyperkalemia, only.

Incident hyperkalemia was more frequent on spironolactone (17.5%) in comparison with eplerenone (5%), whereas corresponding placebo population in trials with spironolactone (7.5%) also had higher rate of hyperkalemia compared with trials with eplerenone (2.5%) (Figure 14) However, this level of data is not appropriate to allow a valid comparison of these two drugs, as the patients were not directly randomized to spironolactone or eplerenone, despite the fact that these two group of patients (on spironolactone and on eplerenone) were in many clinical aspects very different.

Reported difference in incidence rate of hyperkalemia between these two drugs might be explained due to more patients with more severe HF based on higher proportion of patients with NYHA functional class III and IV, higher use of diuretics and a lower average glomerular filtration rate in trials with spironolactone (RALES) (PITT et al., 2014; VARDENY et al., 2014) compared with trials with eplerenone (EMPHASIS-HF, EPHESUS) (PITT et al., 2003; ZANNAD et al., 2011). Differences might reflect a higher proportion of patients with cardiorenal syndroms with more severe kidney dysfunction in patients on spironolactone, thus facilitating development of hyperkalemia on MRA. The longer half-life of active metabolites of spironolactone and its higher binding capacity for mineralocorticoid receptor compared with eplerenone might also play a role (MULDOWNEY et al., 2009; SICA, 2005). The average dose of spironolactone was slightly higher than equivalent dose, of eplerenone. In summary, according to the available data from our analysis no conclusion could be made concerning question which drug is associated with higher risk of hyperkalemia, as these two drugs were not directly compared.

In case of hyperkalemia occurrence during treatment with MRA, differential causes should be comprehensively considered before MRA discontinuation. The first step in evaluation of hyperkalemia should be excluding the presence of pseudohyperkalemia, i.e. increased serum potassium concentration with normal plasma potassium concentration (CARRARO et al., 2000; SEVASTOS et al., 2008).

Hyperkalemia may occur as a result of increased potassium intake, potassium shift from intra- to extracellular space, decreased potassium excretion or combination of these factors. Ingestion of food, rich in potassium, like certain fruits (bananas, kiwis, citrus fruits, melons, mangos, dried fruits, strawberries), vegetables (avocado, tomato, beans, carrots, broccoli) or salt substitutes (where is Na-chloride substitute with K-chloride) may be the cause for potassium imbalance (LLUBANI et al., 2018). However, increased potassium intake may cause hyperkalemia in case renal potassium excretion is impaired (ROSANO et al., 2018). Potassium shift from intracellular to extracellular fluid due to abnormal potassium release may occur due to metabolic acidosis, trauma, use of digoxin and strenuous exercise (DUNN et al., 2015).

Under normal conditions the kidneys are responsible for 90-95% of potassium elimination from the body and for the rest 5-10% the gastrointestinal system, precisely the colon. According to the post-hoc analyses of RALES, EPHESUS and EMPHASIS-HF trials a lower baseline GFR, history of diabetes and high baseline potassium values were independent predictors of hyperkalemia (PITT et al., 2008; ROSSIGNOL et al., 2014; VARDENY et al., 2014). Because potassium elimination is mainly regulated by the kidneys any drug or condition that impairs kidney function may indirectly facilitate hyperkalemia. Therefore, renal function should be carefully estimated for the presence of acute renal failure or deterioration of chronic kidney dysfunction in every patient on MRA. Parameters like kreatinin, urea, GFR, urine output should be checked. Further, signs of volume overload like leg edema, pulmonary crackles, dilated neck veins, increase in body weight and/or determination of natriuretic peptides which might indicate cardiac decompensation should be evaluated. In turn, presence of volume depletion by history of excessive vomiting, prolonged diarrhea, overtreatment with diuretics or in case of severe infection should also be checked. After evaluation of the renal function a critical review of the patients' co-medication is needed in order to rule out the use of drugs which impaire renal function like nonsteroidal anti-inflammatory drugs, cyclosporine, tacrolimus, some antibiotics (aminoglykoside, vancomycin, trimetoprim-cotrimoxazol) and use of potassium-sparing diuretics such as amilorid and triamterene or intake of potassium supplements. Furthermore, conditions associated with impaired renal function like diabetes and advanced age are also recognized as risk factors for hyperkalemia (PALMER, 2004). Triple therapy with MRA, ACE-I and ARB in patients with HF is strongly discouraged due to substantial higher risk for hyperkalemia (recommendation class III, level of evidence A) (PONIKOWSKI et al., 2016). Conversely, the addition of MRA is recommended for all patients with HF already on beta-blockers and ACE-I (ARB in ACE-I intolerant patients) or ARNI (recommendation class I, level of evidence A).

Results from a large individual patient-level meta-analysis which analyzed data from 1 217 986 participants from 27 international cohorts (10 from general population, 7 with high cardiovascular risk and 10 with chronic kidney disease), unequivocally showed that a lower GFR represent a strong risk

factor for hyperkalemia (KOVESDY et al., 2018). In line with this and similar earlier observations that decreased renal function is associated with the increased risk for hyperkalemia, many physicians hesitatate to introduce RAASi including MRA in patients with cardiovascular disease and concomitant mild or moderate renal insufficiency. One another large meta-analysis addressed the question whether worsening renal function (defined as 20-30% decrease from baseline value) after initiation of these drugs might predict worse outcome in these patients or just reflects the pharmacological effect of these drugs (CLARK et al., 2014). This meta-analysis combined data from five large randomized placebo controlled trials SAVE, SOLVD, RALES, EPHESUS and Val-HeFT. It has been shown that worsening renal function is associated with higher mortality. However, treatment with RAASi reduced all cause mortality significantly more in patients with worsening renal function in comparison with those without worsening renal function. The authors concluded that physicians should not be detered to use the RAASi in eligible patients in the setting of worsening renal function.

If potassium values rises over 5.5 mmol/L or estimated GFR declines to <30mL/min per 1.73m^2, the dose of MRA should be halved, and in case potassium values rise over 6 mmol/L or estimated GFR drops <20 ml/min per 1.73m^2, MRA should be temporarily stopped. Normalization of the potassium values after cessation or reduction of the MRA would be the confirmation that MRA could have contribute to hyperkalemia. However, among included trials in our analysis these data were not captured and therefore could not be analyzed in this analysis.

It has been observed that patients with diabetes mellitus have increased risk to develop hyperkalemia in comparison with general population, thus showing that diabetes mellitus represents a risk factor for occurrence of hyperkalemia (PALMER, 2004). Genesis of hyperkalemia in diabetic patients often represents a combination of multiple risk factors like lack of insulin or insulin resistance, diabetic nephropathy causing decreased glomerular filtration of potassium and potassium shift from intra- to extracellular space due to diabetic ketoacidosis. However, the most important mechanism for chronic hyperkalemia in these patients is the syndrome of hyporeninemic hypoaldosteronism, where the reduced renin release results in decline of aldosterone production. This syndrome is more common in patients with mild to moderate impaired renal function caused by diabetic nephropathy and chronic interstitial nephritis (SOUSA et al., 2016).

There are several therapeutic measures which could be undertaken to decrease the level of potassium, thereby preventing deleterious rhythm disorders. It should be distinguished between measures in acute and chronic settings. In acute settings intravenous infusion of calcium carbonate could be administered in order to stabilize cell membrane of myocardial cells; insulin in combination with hyperosmolar glucose

and/or beta adrenoceptor agonists (salbutamol inhalation or infusion) and/or sodium bicarbonate to stimulate potassium transfer into the cells (ROSANO et al., 2018). As the later measures promote potassium redistribution into the cells without affecting on potassium excretion and total amount of potassium in the body, they are suitable for rapid decrease of potassium values. However, these measures exhibit only temporary benefit as in the most cases after a few hours rebound effect with rise of potassium values may occur, where potassium level could reach the baseline values. Therefore other measures that stimulate potassium excretion out of the body like loop diuretics, sodium infusion and even dialysis as ultima ratio should be strongly considered. Furthermore, potassium binders which are primarily intended for treatment of chronic hyperkalemia and for long-term use should be administered in parallel with other measures in acute settings as add-on treatment. Since the sodium polystyrene sulphonate (SPS), the first potassium binder which was approved from the Food and Drug Administration (FDA) in the 1958 (STERNS et al., 2010), has been associated with colonic necrosis, volume overload and hypernatremia making it especially inappropriate in patients with HF and arterial hypertension, there was an unmet need for the new potassium binders that would have a better safety profile (ROSANO et al., 2018). Furthermore, SPS has never been investigated for efficacy and safety in a placebo-controlled clinical trial for hyperkalemia treatment (STERNS et al., 2010). Meanwhile there are two novel potassium binders patiromer (PITT et al., 2011; WEIR et al., 2015) and sodium zirconium cyclosilicate (ZS-9) (PACKHAM et al., 2015), which showed its efficacy in treatment of acute hyperkalemia, maintaining normokalemia and preventing of new hyperkalemia in high risk patients associated with good safety profile in randomized, placebo-controlled clinical trials. Both substances act predominantly in the colon by increasing faecal excretion of potassium. Patiromer uses calcium as the counter-exchange ion while ZS-9 uses sodium as a counter ion. Of note, the colonic excretion could increase in case of reduced renal function. In patients with end-stage kidney disease colonic excretion may be up to threefold higher in comparison with patients with normal renal function (ROSANO et al., 2018). This indicates that the colon have an important role in regulation of potassium homeostasis as compensatory mechanism when renal excretion of potassium is reduced. Use of novel potassium binding agents allows optimal use of life-saving drugs like RAASi/MRA in patients who are at the same time at risk to develop hyperkalemia and who would have the most benefit of this therapy.

Besides spironolactone and eplerenone, a novel non-steroidal MRA of a third generation with greater selectivity than spironolactone and binding affinity than eplerenone to mineralocorticoid receptor has been developed. In comparison with spironolactone in patients with HFrEF and moderate CKD use of finerenone shows comparable efficacy concerning decreasing N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a biomarker of haemodynamic stress. Of note, patients treated with finerenone had lower

rate of hyperkalemia (5.3% vs 12.7%, p=0.048) and worsening renal function (PITT et al., 2013). In another trial efficacy and safety of finerenone was compared with eplerenone in patients who were hospitalized due to worsening of chronic HFrEF. Treatment with finerenone was associated with 30% reduction of NT-proBNP levels and lower rate of all cause mortality and cardiovascular hospitalizations in comparison with eplerenone (FILIPPATOS et al., 2016). Based on these promising results finerenone might represent a valuable alternative to spironolactone and eplerenone in the future in patients at higher risk for hyperkalemia.

5.3 Hypokalemia on MRAs

In the past decade hyperkalemia has been highlighted as a relevant comorbidity in patients with HF, thereby being in the focus of scientific community as relevant potassium disorder which can adversely affect patient outcome both through rhythm disorders and through preventing them from being treated with these life-saving drugs. However, in many studies where has been shown that hyperkalemia had negative impact on patients outcome the curve which visualize the ratio between potassium levels and mortality has been nonlinear U-shaped, meaning that potassium abnormalities beyond the range of normal values in both directions (i.e. <3.5 and >5mmol/l) are associated with poor outcome. Hypokalemia increased mortality in patients with arterial hypertension (KROGAGER et al., 2017), patients with acute heart failure following myocardial infarction treated with diuretics (KROGAGER et al., 2015) and with chronic HF (ALDAHL et al., 2017). According to the data from our analysis hypokalemia could be expected in every sixth patient with HF as the rate of hypokalemia in patients on placebo was almost 15%. Our data are similar with previous findings where the rate of hypokalemia among hospitalized patients could be up to 20%, in outpatient settings 2-3% (VIERA, WOUK, 2015). Individuals taking diuretics exhibit even higher risk, where 56% of individuals are likely to develop hypokalemia (PEPIN, SHIELDS, 2012). The hypokalemia in these patients is mostly secondary due to effect of loop diuretics administered in almost every HF patient as symptomatic therapy to reduce dyspnea and to avoid volume overload. Increased sodium delivery following administration of diuretics to the distal segment of distal tubule stimulate aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium, thus resulting in the loss of potassium by urine. Use of MRA may inhibit this reabsorption by blocking the aldosterone-sensitive sodium pump. According to our results use of MRA shows relative risk reduction of 42% in comparison with patients on placebo. Preventing hypokalemia and with its associated rhythm disorders might in part be responsible for reduction of mortality in these patients. This hypothesis is supported with the results of one individual patient-level meta-analysis where it has been showed that treatment with MRA is associated with reduction of sudden cardiac death (ROSSELLO et al., 2018). Furthermore, correction of hypokalemia and potassium normalization has been associated with lowering of mortality risk (NUNEZ et al., 2018). This stresses how important it is to avoid and to treat hypokalemia.

6 LIMITATIONS

6.1 Analysis for cough on ACE-Is

Although this analysis explored the rate of cough on large number of patients from high quality trials, thus, presenting scientific facts important for daily clinical decision making, several limitations need to be mentioned. This analysis represents post-hoc meta-analyses of controlled clinical trials based on the data reported in the original publications. It needs to be appreciated that underreporting of comorbidities disabled us to identify the combined causes of cough related or not related to ACE-Is. Also the underreporting of cough that may have led to drug discontinuation during the run-in period in both groups may have influenced the results. Additionally, the results from this analysis are confined to population of patients included in these trials which may differ from those patients in daily clinical practice. Cough cessation after discontinuation of the ACE-I would show that cough was secondary caused by ACE-I. However, these data were not reported in the publications, thus, preventing further investigation regarding this issue. Furthermore, a re-challenge seems to be mandatory before patients are permanently kept off ACE-Is. Presence of asymmetry in distribution of plots visualized by funnel plot indicates presence of publication bias (small study effect). During the search, nine eligible trials were identified without adequately reported data concerning cough and therefore were not included. This could in some part explain the presence of publication bias. In addition, the substantial between-study heterogeneity (I^2=91.2%) might influenced the results of detection bias tests. Due to paucity of the data concerning details about cough events it was not possible to judge about the specific causes of cough and their relation to ACE-I treatment. In none of the included trials was not reported information on re-exposure to ACE-I after withdrawal.

6.2 Analysis of hyperkalemia on MRAs

The presented analysis is one post-hoc meta-analysis of randomized, controlled clinical trials based on the data and numbers reported in original publications. Therefore, the level of available data was not sufficient to further specify combined causes of hyperkalemia related to and not related to MRAs. Of note, underreporting of comedication, comorbidities and/or appropriate NYHA class of patients with HF might disable further exploration of the results. In particular, different stages of renal failure could predispose a higher risk of hyperkalemia regardless of treatment with MRAs. In most of the included trials (EDELMANN et al., 2013; PITT et al., 2014; PITT et al., 2003; UDELSON et al., 2010; VARDENY et al., 2014; ZANNAD et al., 2011) advanced chronic kidney disease (GFR < 30 ml/min per $1.73m^2$) and potassium values > 5 mmol/l were exclusion criteria. The effect of MRA cessation on hyperkalemia and its potential resolution could not be evaluated, as these data were not reported in none of the included study. At the end, the presented results are confined to individuals from included trials that might differ from patients in daily clinical practice.

7 Conclusion

In summary, in contrast to the general perception of many physicians, results from this meta-analysis show the facts regarding cough on ACE-Is and hyperkalemia on MRAs in randomized clinical trials from one another perspective by taking the rates of cases with adverse events on placebo into consideration. Demonstrating that more than half of cough events (63%) on ACE-Is and almost half of hyperkalemia events (46%) on MRAs in patients with cardiovascular disease are equivalent to cough and hyperkalemia cases on placebo, respectively, strongly suggest that other causes for cough than the ACE-I treatment and for hyperkalemia MRA treatment have to be considered and ruled out before cessation of treatment with these protective drugs. In addition, treatment with MRA in patients with CVD significantly prevents hypokalemia, a highly prevalent and hazardous electrolyte disorder in these patients.

With no intention to downplay the risk of ACE-I-related cough and MRA-related hyperkalemia, it is clinically of huge importance to rule out other causes of these adverse events before cessation of the ACE-I and MRA treatment in order to avoid undertreatment and/or underdosage with these life-saving drugs.

References

1. AIRE-Investigators (1993) Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 342:821-828
2. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P (2017) Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J 38:2890-2896
3. Allen TL, Gora-Harper ML (1997) Cromolyn sodium for ACE inhibitor-induced cough. Ann Pharmacother 31:773-775
4. Altman DG, Bland JM (2003) Interaction revisited: the difference between two estimates. BMJ 326:219
5. Arriza JL, Weinberger C, Cerelli G, Glaser TM, Handelin BL, Housman DE, Evans RM (1987) Cloning of human mineralocorticoid receptor complementary DNA: structural and functional kinship with the glucocorticoid receptor. Science 237:268-275
6. Bart BA, Ertl G, Held P, Kuch J, Maggioni AP, McMurray J, Michelson EL, Rouleau JL, Warner Stevenson L, Swedberg K, Young JB, Yusuf S, Sellers MA, Granger CB, Califf RM, Pfeffer MA (1999) Contemporary management of patients with left ventricular systolic dysfunction. Results from the Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Registry. Eur Heart J 20:1182-1190
7. Bauersachs J, Fraccarollo D (2011) Pre-clinical data on involvement of mineralocorticoid receptor activation in healing and remodelling post-myocardial infarction. European Heart Journal Supplements 13:B10-B14
8. Bazoukis G, Thomopoulos C, Tse G, Tsioufis C (2018) Is there a blood pressure lowering effect of MRAs in heart failure? An overview and meta-analysis. Heart Fail Rev 23:547-553
9. Beygui F, Van Belle E, Ecollan P, Machecourt J, Hamm CW, Lopez De Sa E, Flather M, Verheugt FWA, Vicaut E, Zannad F, Pitt B, Montalescot G (2018) Individual participant data analysis of two trials on aldosterone blockade in myocardial infarction. Heart 104:1843-1849
10. Bhargava A, Fullerton MJ, Myles K, Purdy TM, Funder JW, Pearce D, Cole TJ (2001) The serum- and glucocorticoid-induced kinase is a physiological mediator of aldosterone action. Endocrinology 142:1587-1594
11. Black HR, Graff A, Shute D, Stoltz R, Ruff D, Levine J, Shi Y, Mallows S (1997) Valsartan, a new angiotensin II antagonist for the treatment of essential hypertension: efficacy, tolerability and

safety compared to an angiotensin-converting enzyme inhibitor, lisinopril. J Hum Hypertens 11:483-489

12. Borghi C, Boschi S, Ambrosioni E, Melandri G, Branzi A, Magnani B (1993) Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. J Clin Pharmacol 33:40-45
13. Borghi C, Marino P, Zardini P, Magnani B, Collatina S, Ambrosioni E (1998) Short- and long-term effects of early fosinopril administration in patients with acute anterior myocardial infarction undergoing intravenous thrombolysis: results from the Fosinopril in Acute Myocardial Infarction Study. FAMIS Working Party. Am Heart J 136:213-225
14. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, Pfeffer MA, Rice MM, Rosenberg YD, Rouleau JL (2004) Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 351:2058-2068
15. Brown NJ, Vaughan DE (1998) Angiotensin-converting enzyme inhibitors. Circulation 97:1411-1420
16. Brown NJ (2003) Eplerenone: cardiovascular protection. Circulation 107:2512-2518
17. Carraro P, Servidio G, Plebani M (2000) Hemolyzed specimens: a reason for rejection or a clinical challenge? Clin Chem 46:306-307
18. Cazzola M, Matera MG, Liccardi G, De Prisco F, D'Amato G, Rossi F (1993) Theophylline in the inhibition of angiotensin-converting enzyme inhibitor-induced cough. Respiration 60:212-215
19. Chin KL, Skiba M, Tonkin A, Reid CM, Liew D, Krum H, Hopper I (2016) The treatment gap in patients with chronic systolic heart failure: a systematic review of evidence-based prescribing in practice. Heart Fail Rev 21:675-697
20. Clark H, Krum H, Hopper I (2014) Worsening renal function during renin-angiotensin-aldosterone system inhibitor initiation and long-term outcomes in patients with left ventricular systolic dysfunction. Eur J Heart Fail 16:41-48
21. Cohn JN, Kowey PR, Whelton PK, Prisant LM (2000) New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. Arch Intern Med 160:2429-2436
22. CONSENSUS-Group (1987) Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 316:1429-1435
23. Cooper LB, Hammill BG, Peterson ED, Pitt B, Maciejewski ML, Curtis LH, Hernandez AF (2015) Consistency of Laboratory Monitoring During Initiation of Mineralocorticoid Receptor Antagonist Therapy in Patients With Heart Failure. JAMA 314:1973-1975

24. Cooper WD, Sheldon D, Brown D, Kimber GR, Isitt VL, Currie WJ (1987) Post-marketing surveillance of enalapril: experience in 11,710 hypertensive patients in general practice. J R Coll Gen Pract 37:346-349
25. Coulter DM, Edwards IR (1987) Cough associated with captopril and enalapril. Br Med J (Clin Res Ed) 294:1521-1523
26. Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK (1998) Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. Am J Hypertens 11:23-30
27. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S (2006) Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 368:581-588
28. Dev S, Lacy ME, Masoudi FA, Wu WC (2015) Temporal Trends and Hospital Variation in Mineralocorticoid Receptor Antagonist Use in Veterans Discharged With Heart Failure. J Am Heart Assoc 4
29. Dicpinigaitis PV (1996) Use of baclofen to suppress cough induced by angiotensin-converting enzyme inhibitors. Ann Pharmacother 30:1242-1245
30. Dicpinigaitis PV (2006) Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest 129:169s-173s
31. Dunn JD, Benton WW, Orozco-Torrentera E, Adamson RT (2015) The burden of hyperkalemia in patients with cardiovascular and renal disease. Am J Manag Care 21:s307-315
32. Dzau VJ, Bernstein K, Celermajer D, Cohen J, Dahlöf B, Deanfield J, Diez J, Drexler H, Ferrari R, van Gilst W, Hansson L, Hornig B, Husain A, Johnston C, Lazar H, Lonn E, Lüscher T, Mancini J, Mimran A, Pepine C, Rabelink T, Remme W, Ruilope L, Ruzicka M, Schunkert H, Swedberg K, Unger T, Vaughan D, Weber M (2001) The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. Am J Cardiol 88:1l-20l
33. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B (2013) Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA 309:781-791
34. Elliott WJ (1996) Higher incidence of discontinuation of angiotensin converting enzyme inhibitors due to cough in black subjects. Clin Pharmacol Ther 60:582-588

35. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J (2015) Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care 21:S212-220
36. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K (2016) Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 387:957-967
37. Fejes-Toth G, Pearce D, Naray-Fejes-Toth A (1998) Subcellular localization of mineralocorticoid receptors in living cells: effects of receptor agonists and antagonists. Proc Natl Acad Sci U S A 95:2973-2978
38. Ferrari R (2006) Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. Arch Intern Med 166:659-666
39. Filippatos G, Anker SD, Böhm M, Gheorghiade M, Kober L, Krum H, Maggioni AP, Ponikowski P, Voors AA, Zannad F, Kim SY, Nowack C, Palombo G, Kolkhof P, Kimmeskamp-Kirschbaum N, Pieper A, Pitt B (2016) A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 37:2105-2114
40. Fox KM (2003) Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 362:782-788
41. Fraccarollo D, Berger S, Galuppo P, Kneitz S, Hein L, Schutz G, Frantz S, Ertl G, Bauersachs J (2011) Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction. Circulation 123:400-408
42. Gomez-Sanchez CE, Zhou MY, Cozza EN, Morita H, Foecking MF, Gomez-Sanchez EP (1997) Aldosterone biosynthesis in the rat brain. Endocrinology 138:3369-3373
43. Guyton AC, Coleman TG, Cowley AV, Jr., Scheel KW, Manning RD, Jr., Norman RA, Jr. (1972) Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. Am J Med 52:584-594
44. Hatakeyama H, Miyamori I, Fujita T, Takeda Y, Takeda R, Yamamoto H (1994) Vascular aldosterone. Biosynthesis and a link to angiotensin II-induced hypertrophy of vascular smooth muscle cells. J Biol Chem 269:24316-24320
45. Hernandez AF, Mi X, Hammill BG, Hammill SC, Heidenreich PA, Masoudi FA, Qualls LG, Peterson ED, Fonarow GC, Curtis LH (2012) Associations between aldosterone antagonist

therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. JAMA 308:2097-2107

46. Hirt MN, Muttardi A, Helms TM, van den Bussche H, Eschenhagen T (2016) General practitioners' adherence to chronic heart failure guidelines regarding medication: the GP-HF study. Clin Res Cardiol 105:441-450
47. Hornig B, Kohler C, Drexler H (1997) Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. Circulation 95:1115-1118
48. Hornig B, Arakawa N, Drexler H (1998) Effect of ACE inhibition on endothelial dysfunction in patients with chronic heart failure. Eur Heart J 19 Suppl G:G48-53
49. Hornig B, Landmesser U, Kohler C, Ahlersmann D, Spiekermann S, Christoph A, Tatge H, Drexler H (2001) Comparative effect of ace inhibition and angiotensin II type 1 receptor antagonism on bioavailability of nitric oxide in patients with coronary artery disease: role of superoxide dismutase. Circulation 103:799-805
50. Huckell VF, Belanger LG, Kazimirski M, Subramanian T, Cox AJ (1993) Lisinopril in the treatment of hypertension: a Canadian postmarketing surveillance study. Clin Ther 15:407-422
51. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 39:119-177
52. Inman WH, Rawson NS, Wilton LV, Pearce GL, Speirs CJ (1988) Postmarketing surveillance of enalapril. I: Results of prescription-event monitoring. BMJ 297:826-829
53. Israili ZH, Hall WD (1992) Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 117:234-242
54. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1-12
55. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA (2004) Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 351:543-551
56. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE (2003) A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 115:41-46

57. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC (1995) A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 333:1670-1676
58. Komajda M, Anker SD, Cowie MR, Filippatos GS, Mengelle B, Ponikowski P, Tavazzi L (2016) Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. Eur J Heart Fail 18:514-522
59. Kovesdy CP, Matsushita K, Sang Y, Brunskill NJ, Carrero JJ, Chodick G, Hasegawa T, Heerspink HL, Hirayama A, Landman GWD, Levin A, Nitsch D, Wheeler DC, Coresh J, Hallan SI, Shalev V, Grams ME (2018) Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. Eur Heart J 39:1535-1542
60. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Kober L, Gislason G, Torp-Pedersen C, Sogaard P (2015) Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. Eur Heart J Cardiovasc Pharmacother 1:245-251
61. Krogager ML, Torp-Pedersen C, Mortensen RN, Kober L, Gislason G, Sogaard P, Aasbjerg K (2017) Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. Eur Heart J 38:104-112
62. Lacourciere Y, Brunner H, Irwin R, Karlberg BE, Ramsay LE, Snavely DB, Dobbins TW, Faison EP, Nelson EB (1994) Effects of modulators of the renin-angiotensin-aldosterone system on cough. Losartan Cough Study Group. J Hypertens 12:1387-1393
63. Law MR, Wald NJ, Morris JK, Jordan RE (2003) Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 326:1427
64. Lim PO, Rodgers P, Cardale K, Watson AD, MacDonald TM (1999) Potentially high prevalence of primary aldosteronism in a primary-care population. Lancet 353:40
65. Linz W, Wiemer G, Gohlke P, Unger T, Scholkens BA (1995) Contribution of kinins to the cardiovascular actions of angiotensin-converting enzyme inhibitors. Pharmacol Rev 47:25-49
66. Llubani R, Vukadinović D, Werner C, Marx N, Zewinger S, Böhm M (2018) Hyperkalaemia in Heart Failure-Pathophysiology, Implications and Therapeutic Perspectives. Curr Heart Fail Rep 15:390-397
67. Lombes M, Alfaidy N, Eugene E, Lessana A, Farman N, Bonvalet JP (1995) Prerequisite for cardiac aldosterone action. Mineralocorticoid receptor and 11 beta-hydroxysteroid dehydrogenase in the human heart. Circulation 92:175-182

68. Lopez-de-Sa E, Martinez A, Anguita M, Dobarro D, Jimenez-Navarro M (2011) [Aldosterone receptor antagonist use after myocardial infarction. Data from the REICIAM registry]. Rev Esp Cardiol 64:981-987

69. Lother A, Berger S, Gilsbach R, Rosner S, Ecke A, Barreto F, Bauersachs J, Schutz G, Hein L (2011) Ablation of mineralocorticoid receptors in myocytes but not in fibroblasts preserves cardiac function. Hypertension 57:746-754

70. Lüders S, Schrader J, Berger J, Unger T, Zidek W, Böhm M, Middeke M, Motz W, Lubcke C, Gansz A, Brokamp L, Schmieder RE, Trenkwalder P, Haller H, Dominiak P (2008) The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. J Hypertens 26:1487-1496

71. MacFadyen RJ, Barr CS, Struthers AD (1997) Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res 35:30-34

72. MacFadyen RJ, Lee AF, Morton JJ, Pringle SD, Struthers AD (1999) How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? Heart 82:57-61

73. Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L (2013) Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 15:1173-1184

74. McDowell SE, Coleman JJ, Ferner RE (2006) Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. Bmj 332:1177-1181

75. Mentz RJ, Fiuzat M, Wojdyla DM, Chiswell K, Gheorghiade M, Fonarow GC, O'Connor CM (2012) Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: findings from OPTIMIZE-HF. Eur J Heart Fail 14:395-403

76. MERCATOR (1992) Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MERCATOR study: a multicenter, randomized, double-blind placebo-controlled trial. Multicenter European

Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR) Study Group. Circulation 86:100-110

77. Mizuno Y, Yoshimura M, Yasue H, Sakamoto T, Ogawa H, Kugiyama K, Harada E, Nakayama M, Nakamura S, Ito T, Shimasaki Y, Saito Y, Nakao K (2001) Aldosterone production is activated in failing ventricle in humans. Circulation 103:72-77
78. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151:264-269, W264
79. Montalescot G, Pitt B, Lopez de Sa E, Hamm CW, Flather M, Verheugt F, Shi H, Turgonyi E, Orri M, Vincent J, Zannad F (2014) Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. Eur Heart J 35:2295-2302
80. Morice AH, Brown MJ, Higenbottam T (1989) Cough associated with angiotensin converting enzyme inhibition. J Cardiovasc Pharmacol 13 Suppl 3:S59-62
81. Mukae S, Aoki S, Itoh S, Iwata T, Ueda H, Katagiri T (2000) Bradykinin B(2) receptor gene polymorphism is associated with angiotensin-converting enzyme inhibitor-related cough. Hypertension 36:127-131
82. Muldowney JA, 3rd, Schoenhard JA, Benge CD (2009) The clinical pharmacology of eplerenone. Expert Opin Drug Metab Toxicol 5:425-432
83. Navar LG (2014) Physiology: hemodynamics, endothelial function, renin-angiotensin-aldosterone system, sympathetic nervous system. J Am Soc Hypertens 8:519-524
84. Nikpoor B, Duan QL, Rouleau GA (2005) Acute adverse reactions associated with angiotensin-converting enzyme inhibitors: genetic factors and therapeutic implications. Expert Opin Pharmacother 6:1851-1856
85. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ, Investigators C (2004) Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA 292:2217-2225
86. Nunez J, Bayes-Genis A, Zannad F, Rossignol P, Nunez E, Bodi V, Minana G, Santas E, Chorro FJ, Mollar A, Carratala A, Navarro J, Gorriz JL, Lupon J, Husser O, Metra M, Sanchis J (2018) Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality. Circulation 137:1320-1330
87. Olivo SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ (2008) Scales to assess the quality of randomized controlled trials: a systematic review. Phys Ther 88:156-175

88. Omboni S, Borghi C (2011) Zofenopril and incidence of cough: a review of published and unpublished data. Ther Clin Risk Manag 7:459-471

89. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M, Zwinderman AH (2017) Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J 38:1883-1890

90. Overlack A (1996) ACE inhibitor-induced cough and bronchospasm. Incidence, mechanisms and management. Drug Saf 15:72-78

91. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B (2015) Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 372:222-231

92. Palmer BF (2004) Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 351:585-592

93. Parthasarathy HK, Menard J, White WB, Young WF, Jr., Williams GH, Williams B, Ruilope LM, McInnes GT, Connell JM, MacDonald TM (2011) A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. J Hypertens 29:980-990

94. Paster RZ, Snavely DB, Sweet AR, Draper RA, Goldberg AI, Soffer BA, Sweet CS (1998) Use of losartan in the treatment of hypertensive patients with a history of cough induced by angiotensin-converting enzyme inhibitors. Clin Ther 20:978-989

95. Paul M, Ganten D (1992) The molecular basis of cardiovascular hypertrophy: the role of the renin-angiotensin system. J Cardiovasc Pharmacol 19 Suppl 5:S51-58

96. Pelliccia F, Patti G, Rosano G, Greco C, Gaudio C (2014) Efficacy and safety of eplerenone in the management of mild to moderate arterial hypertension: systematic review and meta-analysis. Int J Cardiol 177:219-228

97. Pepin J, Shields C (2012) Advances in diagnosis and management of hypokalemic and hyperkalemic emergencies. Emerg Med Pract 14:1-17; quiz 17-18

98. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 327:669-677

99. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T,

Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B (2015) Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 131:34-42

100. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341:709-717
101. Pitt B, O'Neill B, Feldman R, Ferrari R, Schwartz L, Mudra H, Bass T, Pepine C, Texter M, Haber H, Uprichard A, Cashin-Hemphill L, Lees RS (2001) The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. Am J Cardiol 87:1058-1063
102. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 348:1309-1321
103. Pitt B, Bakris G, Ruilope LM, DiCarlo L, Mukherjee R (2008) Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). Circulation 118:1643-1650
104. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ (2011) Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J 32:820-828
105. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, Nowack C, Kolkhof P, Kim SY, Zannad F (2013) Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J 34:2453-2463
106. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM (2014) Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 370:1383-1392
107. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M, Document R (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart

failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18:891-975

108. PROGRESS (2001) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 358:1033-1041

109. Rao G, Lopez-Jimenez F, Boyd J, D'Amico F, Durant NH, Hlatky MA, Howard G, Kirley K, Masi C, Powell-Wiley TM, Solomonides AE, West CP, Wessel J (2017) Methodological Standards for Meta-Analyses and Qualitative Systematic Reviews of Cardiac Prevention and Treatment Studies: A Scientific Statement From the American Heart Association. Circulation 136:e172-e194

110. Rassi AN, Cavender MA, Fonarow GC, Cannon CP, Hernandez AF, Peterson ED, Peacock WF, Laskey WK, Rosas SE, Zhao X, Schwamm LH, Bhatt DL (2013) Temporal trends and predictors in the use of aldosterone antagonists post-acute myocardial infarction. J Am Coll Cardiol 61:35-40

111. Ravid D, Lishner M, Lang R, Ravid M (1994) Angiotensin-converting enzyme inhibitors and cough: a prospective evaluation in hypertension and in congestive heart failure. J Clin Pharmacol 34:1116-1120

112. Rocha R, Stier CT, Jr. (2001) Pathophysiological effects of aldosterone in cardiovascular tissues. Trends Endocrinol Metab 12:308-314

113. Rockhill B, Newman B, Weinberg C (1998) Use and misuse of population attributable fractions. Am J Public Health 88:15-19

114. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Group ESD (2016) 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European Heart Journal 37:267-315

115. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C, Coats AJS, Drexel H, Filippatos G, Kaski JC, Lund L, Niessner A, Ponikowski P, Savarese G, Schmidt TA, Seferovic P, Wassmann S, Walther T, Lewis BS (2018) Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular

Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother 4:180-188

116. Rossello X, Ariti C, Pocock SJ, Ferreira JP, Girerd N, McMurray JJV, Van Veldhuisen DJ, Pitt B, Zannad F (2018) Impact of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with heart failure and left-ventricular systolic dysfunction: an individual patient-level meta-analysis of three randomized-controlled trials. Clin Res Cardiol

117. Rossignol P, Dobre D, McMurray JJ, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Messig M, Vincent J, Girerd N, Bakris G, Pitt B, Zannad F (2014) Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Circ Heart Fail 7:51-58

118. Rossignol P, Zannad F (2015) Regional differences in heart failure with preserved ejection fraction trials: when nephrology meets cardiology but east does not meet west. Circulation 131:7-10

119. Rouleau JL, Warnica WJ, Baillot R, Block PJ, Chocron S, Johnstone D, Myers MG, Calciu CD, Dalle-Ave S, Martineau P, Mormont C, van Gilst WH (2008) Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. Circulation 117:24-31

120. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, Rubis N, Gherardi G, Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini AR, Remuzzi G (2004) Preventing microalbuminuria in type 2 diabetes. N Engl J Med 351:1941-1951

121. Ruilope LM, Usan L, Segura J, Bakris GL (2004) Intervention at lower blood pressure levels to achieve target goals in type 2 diabetes: PRADID (PResion Arterial en DIabeticos tipo Dos) study. J Hypertens 22:217-222

122. Sato A, Saruta T (2001) Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in essential hypertensive patients with left ventricular hypertrophy. J Int Med Res 29:13-21

123. Sevastos N, Theodossiades G, Archimandritis AJ (2008) Pseudohyperkalemia in serum: a new insight into an old phenomenon. Clin Med Res 6:30-32

124. Shah KB, Rao K, Sawyer R, Gottlieb SS (2005) The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. J Am Coll Cardiol 46:845-849

125. Sica DA (2005) Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. Heart Fail Rev 10:23-29

126. Silvestre JS, Robert V, Heymes C, Aupetit-Faisant B, Mouas C, Moalic JM, Swynghedauw B, Delcayre C (1998) Myocardial production of aldosterone and corticosterone in the rat. Physiological regulation. J Biol Chem 273:4883-4891
127. Sousa AG, Cabral JV, El-Feghaly WB, de Sousa LS, Nunes AB (2016) Hyporeninemic hypoaldosteronism and diabetes mellitus: Pathophysiology assumptions, clinical aspects and implications for management. World J Diabetes 7:101-111
128. Sterns RH, Rojas M, Bernstein P, Chennupati S (2010) Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? J Am Soc Nephrol 21:733-735
129. Struthers AD (2004) The clinical implications of aldosterone escape in congestive heart failure. Eur J Heart Fail 6:539-545
130. Struthers AD, Unger T (2011) Physiology of aldosterone and pharmacology of aldosterone blockers. European Heart Journal Supplements 13:B27-B30
131. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L (1990) Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 82:1730-1736
132. Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H (1992) Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med 327:678-684
133. Taddei S, Virdis A, Ghiadoni L, Mattei P, Salvetti A (1998) Effects of angiotensin converting enzyme inhibition on endothelium-dependent vasodilatation in essential hypertensive patients. J Hypertens 16:447-456
134. Takeda Y, Miyamori I, Yoneda T, Iki K, Hatakeyama H, Blair IA, Hsieh FY, Takeda R (1995) Production of aldosterone in isolated rat blood vessels. Hypertension 25:170-173
135. Takeda Y, Miyamori I, Yoneda T, Hatakeyama H, Inaba S, Furukawa K, Mabuchi H, Takeda R (1996) Regulation of aldosterone synthase in human vascular endothelial cells by angiotensin II and adrenocorticotropin. J Clin Endocrinol Metab 81:2797-2800
136. Trifilieff A, Da Silva A, Gies JP (1993) Kinins and respiratory tract diseases. Eur Respir J 6:576-587
137. Tseng DS, Kwong J, Rezvani F, Coates AO (2010) Angiotensin-converting enzyme-related cough among Chinese-Americans. Am J Med 123:183.e111-185
138. Udelson JE, Feldman AM, Greenberg B, Pitt B, Mukherjee R, Solomon HA, Konstam MA (2010) Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of

aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. Circ Heart Fail 3:347-353

139. Ullian ME, Schelling JR, Linas SL (1992) Aldosterone enhances angiotensin II receptor binding and inositol phosphate responses. Hypertension 20:67-73

140. Vardeny O, Claggett B, Anand I, Rossignol P, Desai AS, Zannad F, Pitt B, Solomon SD (2014) Incidence, predictors, and outcomes related to hypo- and hyperkalemia in patients with severe heart failure treated with a mineralocorticoid receptor antagonist. Circ Heart Fail 7:573-579

141. Vaughan DE (1997) The renin-angiotensin system and fibrinolysis. Am J Cardiol 79:12-16

142. Viera AJ, Wouk N (2015) Potassium Disorders: Hypokalemia and Hyperkalemia. Am Fam Physician 92:487-495

143. Visser LE, Stricker BH, van der Velden J, Paes AH, Bakker A (1995) Angiotensin converting enzyme inhibitor associated cough: a population-based case-control study. J Clin Epidemiol 48:851-857

144. Wang TY, Vora AN, Peng SA, Fonarow GC, Das S, de Lemos JA, Peterson ED (2016) Effectiveness and Safety of Aldosterone Antagonist Therapy Use Among Older Patients With Reduced Ejection Fraction After Acute Myocardial Infarction. J Am Heart Assoc 5

145. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B (2015) Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 372:211-221

146. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ (2015) Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 386:2059-2068

147. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 39:3021-3104

148. Young MJ, Clyne CD, Cole TJ, Funder JW (2001) Cardiac steroidogenesis in the normal and failing heart. J Clin Endocrinol Metab 86:5121-5126

149. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293-302

150. Yusuf S, Pitt B, Davis CE, Hood WB, Jr., Cohn JN (1992) Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 327:685-691

151. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G (2000) Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342:145-153

152. Zannad F, Alla F, Dousset B, Perez A, Pitt B (2000) Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. Circulation 102:2700-2706

153. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B (2011) Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 364:11-21

154. Zhao W, Ahokas RA, Weber KT, Sun Y (2006) ANG II-induced cardiac molecular and cellular events: role of aldosterone. Am J Physiol Heart Circ Physiol 291:H336-343

9 Publications, Abstracts and Awards

9.1. Publications

1. Vukadinović D, Lavall D, Vukadinović AN, Pitt B, Wagenpfeil S, Böhm M. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: A meta-analysis. *Am Heart J*. 2017;188:99-108.

2. Nikolovska Vukadinović A, Vukadinović D, Borer J, Cowie M, Komajda M, Lainscak M, Swedberg K, Böhm M. Heart rate and its reduction in chronic heart failure and beyond. *Eur J Heart Fail*. 2017;19:1230-1241.

3. Llubani R, Vukadinović D, Werner C, Marx N, Zewinger S, Böhm M. Hyperkalaemia in Heart Failure-Pathophysiology, Implications and Therapeutic Perspectives. *Current heart failure reports*. 2018;15:390-397.

4. Vukadinović D, Vukadinović AN, Lavall D, Laufs U, Wagenpfeil S, Böhm M. Rate of Cough During Treatment With Angiotensin-Converting Enzyme Inhibitors: A Meta-Analysis of Randomized Placebo-Controlled Trials. *Clinical pharmacology and therapeutics*. 2019;105:652-660.

5. Vukadinović D, Schirmer SH, Vukadinović AN, Ukena C, Scheller B, Mahfoud F, Böhm M. Interventional closure vs. medical therapy of patent foramen ovale for secondary prevention of stroke: updated meta-analysis. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2019;108:157-166.

6. Vukadinović D, Scholz SS, Messerli FH, Weber MA, Williams B, Böhm M, Mahfoud F. Peripheral edema and headache associated with amlodipine treatment: a meta-analysis of randomized, placebo-controlled trials. *J Hypertens*. 2019;37:2093-2103.

7. Scholz SS, Vukadinović D, Lauder L, Ewen S, Ukena C, Townsend RR, Wagenpfeil S, Böhm M, Mahfoud F. Effects of Arteriovenous Fistula on Blood Pressure in Patients With End-Stage Renal Disease: A Systematic Meta-Analysis. *Journal of the American Heart Association*. 2019;8:e011183.

8. Tadic M, Vukadinovic D, Cvijanovic D, Celic V, Kocica M, Putnik S, Ivanovic B. The impact of the metabolic syndrome on the outcome after aortic valve replacement. *Journal of cardiovascular medicine (Hagerstown, Md)*. 2014;15:745-51.

9.2. Abstracts

Vukadinović D., Scholz S., Böhm M., Mahfoud F. (2019). Peripheral edema and headache associated with with amlodipine treatment: a meta-analysis of randomized, placebo-controlled trials. Congress of European Society of Cardiology 2019. Oral presentation by D.Vukadinović.

Vukadinović D., Schirmer SH., Nikolovska Vukadinović A., Scheller B., Mahfoud F., Böhm M. (2018). Interventional patent foramen ovale closure or medical therapy only for the prevention of recurrent strokes: a meta-analysis of available randomized trials. Congress of European Society of Cardiology 2018. Poster Presentation by D.Vukadinović.

Vukadinović D., Lavall D., Nikolovska Vukadinović A., Wagenpfeil S., Böhm M. (2017). The true rate of drug-related cough of the angiotensin converting enyzme inhibitors in placebo controlled clinical trials in cardiovascular medicine: a meta-analysis. 83. Jahrestagung der Deutschen Gesellschaft für Kardiologie 2017. Poster Presentation by D.Vukadinović.

9.3. Awards

Vukadinović D., Lavall D., Wagenpfeil S., Böhm M. (2016). Wahre Rate von unerwünschten Arzneimittelwirkungen auf die Kalium-Homöostase der Renin-Angiotensin-Aldosterone-System-Inhibitoren in placebokontrollierten Studien: Eine Meta-Analyse. Participation in the final competition for Young Investigator Award as one of the best six abstracts. 122. Internistenkongress der Deutschen Gesellschaft für Innere Medizin 2016. Oral presentation by D.Vukadinović.

10 Acknowledgement

I would like to take this opportunity to thank Prof. Dr. M. Böhm on the selfless support and time he spent with me in the creation of this work. In particular, his ideas and enthusiasm encouraged me often to deliver performance beyond my own capabilities, thus reaching always a higher level. Moreover, I am especially grateful for the support provided in attending the numerous national and international congresses of cardiology, where I had the unique opportunity to be in line with some of the greatest scientist in the field of the cardiology of today. This valuable experience helped me a lot in my further professional development.

Further, I would like to express my gratitude for the support and great cooperation to Prof. Dr. F. Mahfoud. I would also like to thank the colleagues from the department of Innere Medizin III, Klinik für Kardiologie, Angiologie und internistische Intensivmedizin III for the good time during last six years we spent together during which I acquired a lot of skills practicing medicine.

Finally, one special and big thank you goes to my family who were always there for me, thus being an inexhaustible source of support and power which helped me to move on further. Full understanding and support often putting my interests ahead of their own interests in order to facilitate my professional development show their selflessness and modesty, to which I am especially proud and immensely grateful. I dedicate this work to them.

11 CURRICULUM VITAE

Aus datenschutzrechtlichen Gründen wird der Lebenslauf in der elektronischen Fassung der Dissertation nicht veröffentlicht.

Tag der Promotion:	**24.11.2020**
Dekan:	**Univ. –Prof. Dr. med. Michael D. Menger**
Berichterstatter:	**Prof. Dr. med. Michael Böhm**
	Prof. Dr. med. Veit Flockerzi
	Prof. Dr. med. Norbert Frey