TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

APPLICATION OF CHRONOTHERAPY IN CARDIOVASCULAR DISEASES: A SYSTEMATIC REVIEW

DANIA HASSAN DARKAZANLI

MASTER THESIS

A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF
HEALTH SCIENCES NEAR EAST UNIVERSITY

DEPARTMENT OF PHARMACOLOGY

Supervisor:
Prof. Dr. Nurettin ABACIOĞLU
Co-advisor: Assist. Prof. Dr. Abdikarim ABDI

Northern Cyprus, Nicosia
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NEAR EAST UNIVERSITY

THESIS APPROVAL

Directorate of Institute of Health Sciences

Thesis submitted to the Institute of Health Sciences of Near East University
in partial fulfillment in of the requirement for the degree
Master of Science in Pharmacology.

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ACKNOWLEDGMENTS

First and fore most I have to thank Allah (SWT) who gave me good health and wellbeing that were necessary to complete this thesis. Secondly, special thanks to my parents and my brothers, sister for their love and endless support throughout my life.

My sincere appreciation goes to my advisor. Prof. Dr. Nurettin Abacıoğlu for his valuable guidance, advice, and encouragement to always aim high, whose hard work always inspires me, He's ever ready to share his knowledge with his student, even to make us better.

I also thank the members of the graduate committee and thesis examiners in Near East University for their guidance and suggestions, especially Assist. Prof. Dr. Abdikarim Abdi. Without their assistance and dedicated involvement in every step throughout the process, this paper would have never been accomplished.

Special thanks also to all my classmates while studying the master of pharmacology together. Lastly but not least I would like to thank all the medical staff who participated in the study without whom this study could not have been completed. I would also like to thank everyone who supported and helped me to do and complete this thesis.

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LIST OF ABBREVIATIONS

ABBREVIATION	EXPLANATION
CVD	Cardiovascular disease
CCBs	calcium channel blockers
ACEs	angiotensin-converting-enzyme inhibitor
BP	Blood pressure
AMI	Acute myocardial infraction
PE	pulmonary embolism
LDL-C	low-density lipoprotein cholesterol
HCP	Health care provider
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
HTN	hypertension
CKD	Chronic kidney disease
ABPM	Ambulatory Blood Pressure Monitoring
VTA	Ventricular techy arrhythmia
CAD	Coronary artery disease
ARBs	Angiotensin II receptor blockers

Application of Chronotherapy in Cardiovascular Diseases: A Systematic Review

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Abstract

Chronotherapy involves altering the timing of medication administration to improve the overall control of disease and to minimize treatment side-effects and is an emerging concept in the field of therapeutics. The aim of this review is to conduct an in-depth analysis of the recent literature in order to identify and evaluate current knowledge regarding chronotherapy in cardiovascular diseases.

Aim of the Study: To investigate the "time of administration" recommendations based on chronotherapy of commonly-prescribed medicines in cardiovascular diseases. The relationship between chronotherapy and its actual benefits on cardiovascular disease was highlighted.

Moreover, to determine the effects of chronotherapy strategies to CVD -related medications that been prescribed to the patients.

Method: "PubMed" and ''Web of Science'' databases were used to search eligible articles. The selection criteria for the inclusion of articles in the review included (year's 2009–2019), the search was done by using the English language. The used keywords were ("Time of administration" OR Chronotherapy OR "circadian rhythm") AND ("cardiovascular diseases" OR cardiology OR hypertension OR blood pressure OR CAD OR "ischemic heart disease" OR "heart failure" OR hyperlipidemia OR Arrhythmia OR atrial fibrillation) and their combinations. A systemic review of the literature was done in agreement with the PRISMA guideline.

Results: This research revealed a total of 4,226 related journals were identified of which 3,994 not included because they were not clinical studies (neither randomized

or cohort), 232 articles were not included because of different reasons such as irreverent article (180) ,article duplicated (20) or only abstract available (18). Finally, 15 articles were selected for review. (Fig. 3)

Conclusion: In recent years, the application of chronotherapy technique has increased; this strategy is characterized by more accurate identification of times when patients are at greater risk and therefore the most need for preventive or therapeutic action. It also gives ways to design the most appropriate medication regimens. Heart attack, acute myocardial infarction, sudden cardiac death factors that impact daily differences in cardiovascular disorders include physiological determinants, such as platelet aggregation and heart rate - and external factors, such as daily activity, stress, and food intake.

Our results support that many cardiovascular disorders, such as AMI and hypertension, occur in the morning between 06:00 a.m. and 12:00 p.m. in the general population.

In chronotherapy, we can exploit daily differences in pathological conditions and pharmacological properties of drugs to improve prevention and treatment. Our study suggests that the following chronotherapy is beneficial and can protect against blood clots, high blood pressure, persistent stable angina, and acute myocardial infarction.

Chronotherapy is a wide technique and can help in improving the patient's outcome. An increase in studies investigating the chronotherapeutic effects in all medical fields and not only in the field of cardiovascular disease is needed and highly recommended.

Keywords: Cardiovascular disease, chronotherapy, circadian rhythm, antihypertensive.

Kardiyovasküler Hastalıklarda Kronoterapi Uygulaması: Sistematik Bir İnceleme

Öğrencinin adı: Dania Hassan Darkazanli

Danışman: Prof. Dr. Nurettin Abacıoğlu

Bölüm: Farmakoloji

Öz

Kronoterapi, hastalığın genel kontrolünü iyileştirmek ve tedavinin yan etkilerini en aza indirmek için ilaç uygulamasının zamanlamasını değiştirmeyi içerir ve terapötikler alanında ortaya çıkan bir kavramdır. Bu derlemenin amacı, kardiyovasküler hastalıklarda kronoterapi ile ilgili güncel bilgileri belirlemek ve değerlendirmek için son literatürün derinlemesine bir analizini yapmaktır.

Çalışmanın Amacı: Kardiyovasküler hastalıklarda yaygın olarak reçete edilen ilaçların kronoterapisine dayalı olarak "uygulama zamanı" önerilerini araştırmak. Kronoterapi ile kardiyovasküler hastalık üzerindeki gerçek faydaları arasındaki ilişki vurgulanmıştır. Ayrıca kronoterapi stratejilerinin hastalara reçete edilen KVH ile ilgili ilaçlara etkisinin belirlenmesi.

Yöntem: Uygun makaleleri aramak için "PubMed" ve "Web of Science" veritabanları kullanıldı. Makalelerin incelemeye dahil edilmesine ilişkin seçim kriterleri (2009–2019 yılı) dahil, arama İngilizce dili kullanılarak yapıldı. Kullanılan anahtar kelimeler ("Uygulama zamanı" VEYA Kronoterapi VEYA "sirkadiyen ritim") VE ("kardiyovasküler hastalıklar" VEYA kardiyoloji VEYA hipertansiyon VEYA kan basıncı VEYA CAD VEYA "iskemik kalp hastalığı" VEYA "kalp yetmezliği" VEYA hiperlipidemi VEYA Aritmi VEYA atriyal idi fibrilasyon) ve bunların kombinasyonları. PRISMA kılavuzuna uygun olarak literatürün sistemik bir incelemesi yapıldı.

Bulgular: Bu araştırma, 3.994'ü klinik çalışmalar olmadığı için (ne randomize ne de kohort) dahil edilmeyen toplam 4,226 ilgili derginin tespit edildiğini, sayısız makale (180), makale çoğaltılması gibi farklı nedenlerden dolayı 232 makalenin dahil edilmediğini ortaya koymuştur. (20) veya sadece özet mevcut (18). Son olarak, inceleme için 15 makale seçildi (Şekil 3).

Sonuç: Son yıllarda kronoterapi tekniğinin uygulanması artmıştır; Bu strateji, hastaların daha fazla risk altında olduğu ve bu nedenle önleyici veya terapötik eyleme en çok ihtiyaç duyulan zamanların daha doğru tanımlanmasıyla karakterize edilir. Aynı zamanda en uygun ilaç rejimlerini tasarlamanın yollarını verir. Kalp krizi, akut miyokard enfarktüsü, kardiyovasküler bozukluklarda günlük farklılıkları etkileyen ani kardiyak ölüm faktörleri arasında trombosit agregasyonu ve kalp hızı gibi fizyolojik belirleyiciler ve günlük aktivite, stres ve yiyecek alımı gibi dış faktörler yer alır.

Sonuçlarımız, AMI ve hipertansiyon gibi birçok kardiyovasküler bozukluğun sabah 06:00 ile 12:00 saatleri arasında ortaya çıktığını desteklemektedir. Genel popülasyonda.

Kronoterapide, önleme ve tedaviyi iyileştirmek için patolojik durumlardaki ve ilaçların farmakolojik özelliklerindeki günlük farklılıkları kullanabiliriz. Çalışmamız, aşağıdaki kronoterapinin yararlı olduğunu ve kan pıhtılarına, yüksek tansiyona, kalıcı stabil anjinaya ve akut miyokard enfarktüsüne karşı koruma sağlayabileceğini göstermektedir.

Kronoterapi geniş bir tekniktir ve hastanın sonucunu iyileştirmeye yardımcı olabilir. Sadece kardiyovasküler hastalıklar alanında değil, tüm tıbbi alanlarda kronoterapötik etkileri araştıran çalışmalarda artışa ihtiyaç vardır ve şiddetle tavsiye edilir.

Anahtar Kelimeler: Kardiyovasküler hastalık, kronoterapi, sirkadiyen ritim, antihipertansif.

1. INTRODUCTION

1.1 Back Ground and Aim

Cardiovascular disease is the chief cause of death worldwide (World Health Organization {WHO}, 2011; Mozaffarian et al., 2014; Townsend et al., 2014). Available therapies have had only limited success in improving the long-term survival of patients. Recently, there have been several studies indicating time-of-day variations in drug toxicity and efficacy (Smolensk, 2007) daily cardiovascular gene and protein expression (Martino et al., 2009; Durgan et al., 2010; Paschos et al., 2010), and there are reports of new pharmacological compounds targeting the circadian mechanism (Chen et al., 2013; Kojetin et al., 2014).

Chronotherapy is a behavioral technique in which bedtime is systematically delayed, which follows the regular propensity of human science (Czeisleret et al., 1981). Chronotherapy includes the administration of medicine in a joint effort with the body's circadian rhythm to maximize effectiveness and/or minimize/avoid adverse effects (Kauret, 2016).

The underlying foundation for cardiovascular chronotherapy stems from observations that biological processes in humans (and other mammals) exhibit 24-h daily rhythms, and these are controlled by molecular circadian clocks in the brain, heart, and other organs (Tsimakouridze et al., 2015). Heart rate, blood pressure, and endothelial function show diurnal variations within a day. The onset of cardiovascular disorders such as acute coronary syndrome, atrial arrhythmia, and subarachnoid hemorrhage also exhibits diurnal oscillation. Recent progress in studying the functions and molecular mechanisms of the biological clock brought forth the idea that intrinsic circadian rhythms are tightly related to cardiovascular pathology (Takeda and Maemura, 2011).

It has now been established that the time of administration of many medicines changes the viability and danger due to the influence of circadian rhythms. Medication administration at different times of the day may improve the therapeutic outcome (Ohdo, 2003).

The understanding of circadian rhythms in the risk of disease, symptom patterns, and evidence of circadian variability in drug pharmacokinetics, therapeutic effects and safety constitute the rationale for chronotherapy (Ohdo, 2010).

Knowledge of 24-hour rhythm in the risk of disease, plus evidence of a 24-hour rhythm dependency in medication pharmacokinetics, therapeutic effects and safety constitutes the rationale for pharmacotherapy. One way to increase the efficiency of pharmacotherapy is the organization of drugs at times at which they are most effective and/or best tolerate (Ohdo, 2010).

This study comprises five chapters which include an introduction to the concept of chronotherapy and its practice on cardiovascular diseases; and the purpose of this study; proceeded by a review of related literature: here we review the current knowledge regarding cardiovascular disorder; timing in therapy (chronotherapy); chronotherapy in cardiovascular disease and awareness HCP on the application of chronotherapy in cardiovascular diseases (CVD).

To investigate the “time of administration” recommendations based on chronotherapy of commonly-prescribed medicines in cardiovascular diseases. The relationship between chronotherapy and its actual benefits on cardiovascular disease was highlighted. Moreover, to determine the effects of chronotherapy strategies to CVD - related medications that been prescribed to the patients.

2. LITERATURE REVIEW

2.1. Chronotherapy Definition and Circadian Rhythm

Biological rhythms have been well describing in plants, animals, and humans and are defined as a regularly cyclic component in a series of evaluations of a biologic variable obtained as a function of time (Lemmer, 2000).

Circadian rhythms are governed by a network of hierarchical master clocks present at various locations in the brain and peripheral tissues, such as the liver. Of these clocks, the most important are the paired suprachiasmatic nuclei (SCN) located in the hypothalamus, which coordinate the multitude of these other clock networks via endocrine signals (Lemmer B, 2012; Schulz P, Steimer T, 2009).

The study of biological rhythms and their underlying mechanisms are known as chronobiology. The best known and most studied biological rhythm patterns in humans are the circadian rhythms with a frequency of about 24 h. (Skene DJ et al., 2006).

Chronotherapy needs an understanding of circadian patterns in the potency of disease symptoms and rhythmic patterns in the human body's handling of medicines, which decide the therapeutic and adverse effects of a drug. (Kaur, 2016).

Pharmacists can exploit the knowledge of circadian rhythms by employing chronotherapy principles, which involve the timing of the administration of dosage forms, conventional or special, to deliver medication in coordination with the body's circadian rhythms to maximize therapeutic effectiveness whilst also minimizing or avoiding adverse effects (Smolensky, M.H. et al., 2012).

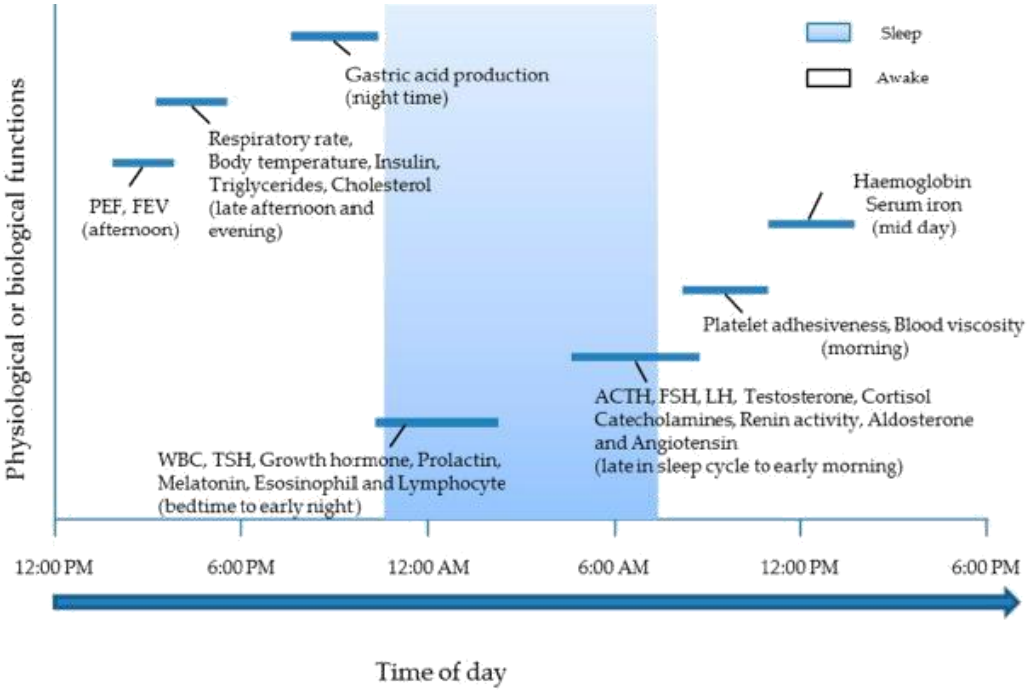

Figure 1. Time of day when physiological or biochemical functions are at peak. PEF, peak expiratory flow rate; FEV, forced expiratory volume; WBC, white blood count; TSH, thyroid stimulating hormone; ACTH, adrenocortical tropic hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone.

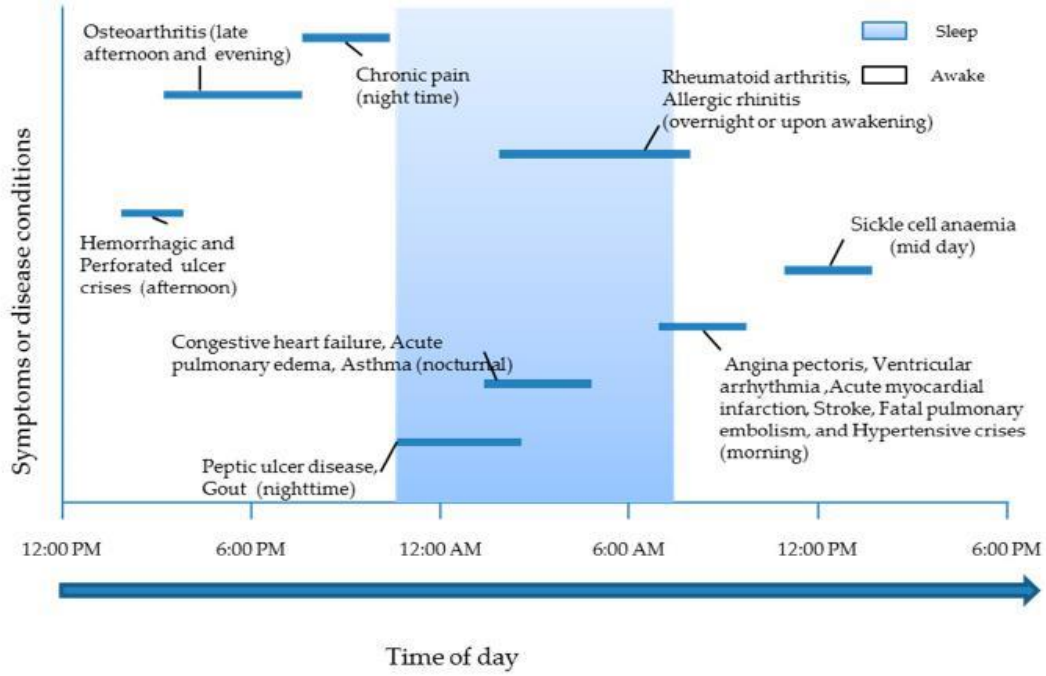

Figure 2. Time of day when symptoms or events of diseases are most frequent.

2.2. Definition

Chronobiology:

The branch of biology concerned with biological phenomena that display cyclical patterns. The field of chronobiology may be classified into chronophysiology, chronopharmacology, and chronopathology (Scott et al, 2001).

Chronopharmacology:

The branch of chronobiology that explores the effects of medication on the timing of biologic events and rhythms, and the relation of biologic timing to the effects of medications. It is used as an important tool in drug optimization, i.e. to maximize the desired effect and/or to minimize the undesired effect of the drug. (Reinberg A, 1976).

Since pharmacology is the study of the effect of medications on the human body (both therapeutic and adverse/toxic effects), it is proposed that chronopharmacology may be further classified into chronotoxicology and chronotherapy (Ohdo, 2003).

Chronophysiology:

The branch of chronobiology that explores rhythmic occurrences in the physiological processes and behaviors of the human body. It aims to understand the mechanisms and functional significance of biological timing (Kaur et al, 2013).

Chronopathology:

The branch of chronobiology explores biological rhythms in the manifestation of disease or symptoms of disease and mechanisms underlying these rhythmic manifestations or the occurrence of diseases (Smolensky et al., 1988).

Chronotoxicology:

The branch of chronopharmacology explores circadian rhythms in the manifestation and the severity of side effects of a drug and/or a patient's intolerance to chemical, physical, or other agents (including poisons, pollutants, and overdoses of drugs) (Kaur et al., 2013).

It has been reported that if a medication is administered at the inappropriate circadian time, the induced toxicity could be more severe than when administered at other times, thus compromising treatment outcomes. (Smolensky et al., 2005).

Chronopharmaceutices:

The branch of pharmaceutics devoted to the design and evaluation of a drug delivery system that releases a bioactive agent at a rhythm that ideally matches the biological requirement of given disease therapy.

Chronopharmacokinetics:

It refers to rhythmic changes in drug bioavailability as well as excretion.

Chronosthesy:

It refers to rhythmic variation detected in the systems. It also includes susceptible variations detected in parasites, bacteria, tumors.

Chronergy:

The rhythmic changes in its effects and side effects, this depends on the Pharmacokinetics of drugs & Chronosthesy of various systems.

Chronotherapy:

This may be defined as the delivery of drugs in synchrony with the circadian rhythms inherent in the human body. Chronotherapy is the therapeutic application of chronopharmacology.

It integrates chronopathological, chronopharmacological and chronotoxicological information to enhance both effectiveness and tolerance of a drug by determining optimal medication administration times from a circadian perspective. (Kaur et al., 2013).

Chronotherapy may be accomplished by the appropriate timing of administration using conventionally formulated dosage forms and also through special drug delivery systems (chronoformulations) to synchronize medication concentration to circadian rhythms in disease activity (Ohdo, 2007).

2.3. Rational drug use and Chronotherapy in practice

The World Health Organization (WHO) defines the rational and safe use of drugs as a series of steps where appropriate diagnoses and prescribing are followed by appropriate usage of medicines (WHO, 2016). According to an estimate by WHO, over half of all medicines are inappropriately prescribed, dispensed and about half of all patients fail to adhere to instruction.

The reasons for this irrationality can be summarized to include: ignorance, incompetence, and inadequate resources (WHO, 2012).

As a result, the WHO has stipulated principles that recommend that the patient have to be informed about their medication, understand the importance of the prescribed treatment and take the drug s as required and at the correct time (WHO, 2012).

Rational use of drugs requires that patients receive medications appropriate to their clinical needs in doses that meet their own requirements, for an adequate period of time, and at the lowest cost to them and their community (Ohdo, 2003).

Chronotherapy needs an understanding of circadian type in the severity of disease symptoms and regular patterns in the human body's handling of drugs, which dictate the therapeutic and side effects of drugs (Ohdo, 2003).

Chronotherapy in Clinical Practice One approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated.

The chronotherapy of medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity (Ohdo, 2003).

Pharmacy practitioners should take into account that the time of administration may play an important role in maximizing benefits and eliminating the risk of toxicity of certain medications (Chukwunyere & Abacıoğlu, 2017).

Pharmacists can use this knowledge of circadian rhythms by utilizing the chronotherapy concept, which covers the timing of the administration of dosage forms, conventional or special, to deliver a drug in coordinate with the body's circadian

rhythms to maximize therapeutic efficacy whilst also minimizing or avoiding side effects (Smolensky, 2012).

Impact of finding on practice:

• There are medication and disease conditions where old research proposes an optimal circadian time of drug administration.

• Practitioners need to stratify this knowledge to relevant drugs and states to maximize clinical effects.

• When advising patients about the 'time' when prescriptions should be taken, pharmacy practitioners should be given consideration to the circadian impact on medications and disease.

• The chronotherapy literature utilizes terms and definitions rather than interchangeably. The model that consolidates the relational advantage of the varied terms utilized in this field may be a good reference for practitioners.

2.4. Chronotherapy for Cardiovascular Medicine

The efficiency & toxicity of many drugs differ depending on dosing time related with 24 hours rhythm of biochemical, physiological & behavioral processes under the control of circadian clock such chronopharmacological phenomenon are affected by not only the pharmacokinetics but also pharmacodynamics of a drug .Now a day Chronopharmacological principle is applied in the therapy of various cardiovascular diseases such as hypertension, myocardial infarction, angina pectoris, and pulmonary embolism (Krishna et al., 2012).

Moreover, new technology makes possible chronotherapy, that is an increase of the efficiency and safety of medications by proportioning their concentrations during the 24 hours in synchrony with biological rhythm determinants of disease. The chronotherapy of cardiovascular disease achieved by evening dosing (Smolensky et al., 1999).

2.4.1. Various Cardiovascular Diseases:

Blood pressure (B.P) / Hypertension:

The differences in patterns of disorder between day and night for cardiovascular diseases such as hypertension, angina, heart attack, sudden cardiac death, and stroke have been documented.

Chronotherapeutics approach offers a more proper determination of the time when patients are at the highest risk and in greatest demand of therapy. For example – it has often been found that the blood pressure of hypertensive patients rises rapidly in the morning after awakening, typically peaks in the middle to the late time of the day decline in the evening and is lowest when the patient sleeps at night. (Hofstra, 2008).

To create a chronotherapy for hypertensive patients, it is essential to identify the BP parameters that can predict cardiovascular outcomes, and which then can become therapeutic goals (Takeda, 2011).

It is well known that there is a 24-h variation in BP with a peak in the morning. This variation in BP within a day is considered as representative of both intrinsic and exogenous factors. Intrinsic factors include autonomic nervous activity and hormonal factors such as cortisol, renin, aldosterone, vasoactive intestinal peptide, Of course, exogenous factors such as physical activity, emotional state, meals, and the sleep/awake states also affect BP variations. (Hermida et al., 2007).

Chronotherapy with anti-hypertensive medication can be most successfully achieved by adjusting the time of medication within a day. Most of the anti-hypertensive drugs, such as calcium channel blockers (CCBs), b- adrenoreceptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs), could exert significant effects on the day/night BP (Hermida et al., 2007).

Thus, the 24 h alteration in the B.P is representative of both endogenous diurnal rhythms and exogenous factors. (Young ME, 2006). Blood pressure is characterized by a circadian rhythm, both in hypertensive and in normotensive subjects; this manner is related with lower B.P values during sleeping time and time of minimal activity and higher B.P levels during wakeup and mental and physical activity (Takeda et al., 2010).

Recently, chronotherapy issue a means of individualizing treatment of hypertension according to the circadian BP profile of each patient comprise a new option in optimizing BP control and reducing risk. Nocturnal hypertension increases the risk of cardiovascular and cerebrovascular case nephron sclerosis and development to end-stage kidney failure in renal patients (Hermida et al., 2005).

Chronotherapeutics is advancing hypertension treatments beyond once-daily dosing by synchronizing the maximum levels of medication during times when cardiovascular risk highest. Using novel oral delivery methods, chronotherapeutic medication synchronizes the delivery of BP drugs within the period of risk, significantly reducing both absolute BP and, especially important, the rate of BP increases. These therapies have also shown the ability to maintain adequate BP levels during the trough period. (Hermida, 2007).

Commonly, the therapeutic strategies used to improve Blood Pressure control in a hypertensive patient include the increase of the therapeutic dose of the medication, sequential change of antihypertensive drugs or application of drug combinations having synergic effects. All these therapeutic strategies have, in practice, one common element: the administration of antihypertensive medication in a single morning dose, not only with a single prescribed drug but also with combination therapy.

Graded-release long-acting diltiazem (Cardizem, Biovail Pharmaceuticals) was approved by the FDA in 2003 for once-daily dosing either in the morning or evening.

COER-verapamil constitutes the first chronotherapy of hypertension. , it controls the rapid morning rise and daytime excess of BP of hypertensive patients in a nearly dose-dependent manner.

Moreover, the proportioning of verapamil to a low concentration nocturnally, when BP declines to lowest levels during the 24 hours in most hypertensive patients minimizes the risk of excessive dipping of BP during nighttime sleep, especially for doses in the range of up to 360 mg. (White WB, et al., 1995) (White WB, et al.,1998).

The effect of COER-verapamil on the sleep-time BP level of patients with normal dipper essential hypertension who show a 10% to 20% decline in BP overnight is moderated by the purposeful reduction in drug concentration nocturnally.70 White et al75 investigated whether COER-verapamil can be used to normalize the sleep-time

BP of so-called non-dipper hypertensive patients whose BP fails to decline by 10% to 20% from daytime levels. The results of this study found that bedtime dosing of COER-verapamil helps normalize the abnormal 24-hour BP pattern of non-dipper hypertensive patients. This finding indicates that the concentration of verapamil that exists during sleep, the time of the trough of drug concentration during the 24 hours, is sufficient to exert a significant pharmacodynamic effect in patients with nocturnal hypertension. (Smolensky, 1999).

The calcium channel blocker controlled-onset, extended-release (COER) Verapamil was the first special drug-delivery tablet medication specifically designed for the chronotherapy of hypertension. The drug-delivery technology of this tablet medication delays the release of verapamil for approximately 4-5 h following its recommended bedtime ingestion. Medication is released thereafter so the highest blood concentration is achieved in the morning around the time of awakening, generally between 6 and 10 a.m., with an elevated level sustained throughout the diurnal activity. The half-life kinetics of verapamil results in a progressive decline of drug level in the evening and overnight, so reduced concentration occurs during nighttime sleep when BP in uncomplicated essential hypertension is generally lowest (Longstreth et al., 1995).

Table 1. Common Onset Time of Cardiovascular System

Disease	**Common Onset Time**
Atrial fibrillation	Morning/ night
Ventricular tachycardia/fibrillation	Morning
Acute coronary syndrome	Early morning
Pulmonary embolism	Early morning
Cerebral infraction	Morning
Subarachnoid hemorrhage	Day time

Acute myocardial infarction (AMI) /pulmonary embolism (PE):

Acute myocardial infarction (AMI) continues to be a significant health concern, as patients who suffer from coronary heart disease have worse short-term and long-term morbidity and mortality compared with the general population (Piironen, 2017).

It is well known that AMI or PE frequently occurs in the early morning and, also systemic BP & heart rate increase and augment the oxygen demand of the heart. And it has been found that the peak in the frequency of AMI happens between 6:00 AM and noon.4,5 Prior studies found that AMI could be triggered by several factors, both environmental and physiologic, including circadian variations in cardiovascular and metabolic functioning (Fabbian et al., 2017).

In addition, the vascular tone of the coronary artery rises and coronary blood flow decreases in the morning. This increases in oxygen demand & decreases in oxygen supply exaggerate a mismatch of oxygen demand and supply in the morning plays a major role in the circadian variation of the onset of AMI.

It may also be important to recognize that the risk of a heart attack appears to be greatest during the early morning hours after awakening. For instance, capillary resistance and vascular reactivity are higher in the morning and decreases later in the day (Fabbian, 2017).

Patients receiving beta-blocker do not show morning increase in the incidence of AMI, angina, & sudden death (Fabbian et al, 2017).

A few studies have shown that sustained-release β-adrenergic and calcium channel antagonist chemotherapies influence, protection against the excess of AMI cases in the morning (Behrens,1997 ; Peters,1989 ; Willich,1989).

Arrhythmia:

Beta-Adrenergic blockers:

Blockers have been demonstrated to be potent in diminishing myocardial infarction rate (Jama, 1982). Myocardial localized necrosis shows a circadian example with a higher incidence in morning hours, and a second peak later in the day (Muller et al.,

1985). In healthy subjects, an investigation of the pharmacokinetics of propranolol at various times of the day (Langner et al., 1988).

In conclusion, information actually available shows that dose, frequency, and time of B-blocker administration must be modified to be changed in accordance with accomplishing viable B-blocker all through 24 hours. Long-acting p-blockers must be regulated around evening time, while drugs with shorter half-life esteem must be given at suitable intervals to be best toward the beginning of the day and evening (Manfredini Roberto, 1994).

Calcium antagonists:

Evidence has gathered that calcium antagonist is efficient in decreasing or preventing myocardial ischemia. Verapamil, 120 to 160 mg three times each day, altogether decreased the rise in pulse during the early morning time and protected circadian rhythm.

Conversely, studies on healthy subjects are seen that the Nifedipine administration modifies the circadian rhythm of heart rate and blood glucose level as a because of adrenergic activation, (Manfredini et al., 1991).

A study of Mulcahy et al., demonstrated that nifedipine, compared with atenolol, had little action on the recurrence or total duration of ischemic incidence and did not alter the circadian pattern of ischemic incidence. In another research accomplish after standard exercise treadmill testing and 48-hour ambulatory electrocardiographic ST-segment monitoring, nifedipine reduced both the total number and period of ischemic incidence compared to placebo; the rise of ischemia observed at baseline by subjects taking placebo was almost eliminate with nifedipine therapy.

Diltiazem, at 360 mg/day, has been appeared to reduce the circadian pattern in patients with spontaneous angina and quiet ischemia. (Pepine, 1990) Felodipine additionally gives an anti-ischemic action to 24 hours in chronic stable angina (Santoro, 1991) and in Prinzmetal's angina (Ardissino, 1991) Amlodipine has likewise been demonstrated to be effective both in the control of BP (Raftery et al., 1991) and in the treatment of myocardial ischemia. (Taylor, 1989).

Consequently the effectiveness of calcium antagonists, described by short and broadened half-life esteems, has been shown, be that as it may, the previous gathering requires a few portions day by day and chronophammcology reflects just their pharmacokinetics. For calcium rivals with broadened half-life esteems, whose subterranean insect ischemic impacts keep going for 24 hours, a once-every day evening organization may be suggested (Manfredini, Roberto, 1994).

Nitrates:

In healthy volunteers, pharmacokinetics and hemodynamic effects of oral nitrates show to be circadian phase-dependent, depending on the galenic formulation, absorption, and gastrointestinal perfusion. However, a drug-free interval has become standard for nitrates to minimize the likelihood of tolerance progress. On the whole of the circadian variation in cardiovascular ischemia, the nitrate-free period is generally at night, while the patient is sleeping. (Pepine, 1991) A long-acting nitrate preparation could be taken on awakening. (Hoekenga, 1984) With its rapidity of action, the nitrate preparation releases the regulate drug dosage rapidly and provides defense within a few minutes against ischemic events that usually happen within 3 hours after awakening (Manfredini, Roberto, 1994).

Hyperlipidemia:

Statins are the drug of choice for hyperlipidemia as a lipid-lowering agent regarding the principal clinical practice guidelines (Stone, 2014). Statins lowering level of lipids in plasma by inhibiting some cholesterol biosynthesis initial steps (Smith, 2009).

Every 24-hours cholesterol biosynthesis is repeated depending on circadian rhythm generally at night (between 12: 00 am and 6:00 am). (Izquierdo-Palomares,et al., 2016).

However, in clinical practice statins are administered once per day, without specifying the time of day when they should be taken and, therefore, without taking into consideration the circadian rhythm of cholesterol (San Vicente, 2008).

This time-dependent synthesis would give a chance for statin therapy to be adjusted regarding biologic rhythms, which is known as chronotherapy. The chronotherapy

concept is depending on the idea that drugs effect can be altered depending on the admini stration time (Sánchez, 2005).

Statins have been shown to decrease the risk of CVD for secondary prevention. In principle, statins with a shorter half-life (one to five hours) would be more effective if taken in the evening, whereas those with a longer half-life could be equally effective when taken at any hour of the day (Izquierdo-Palomares et al., 2016).

A study conducted by Plakogiannis, et al. found that atorvastatin (40 mg) showed no significant difference in the lipid-lowering effect between morning and evening administration.

For simvastatin, the literature search identified seven studies, and most reported a chronotherapeutic benefit with evening administration.

For example, a placebo-controlled, double-blind study compared the effectiveness of morning vs. evening administration of simvastatin for two different doses (2.5 and 5 mg). After 12 weeks of treatment, the percent decrease in LDL-C concentrations when compared to baseline was greater in patients taking simvastatin in the evening than in the morning. The reduction in LDL-cholesterol concentration for evening administration was statistically significant for the 5 mg dose when compared to morning administration.

This is because the period of greatest activity for short half-life statins (i.e. lovastatin, simvastatin) would coincide with the cholesterol biosynthesis peak. A systematic review evaluated the effect of statins on blood cholesterol levels according to the time they were taken (morning versus evening) and concluded that there were sufficient data to support the evening administration of simvastatin to achieve an optimal lowering of LDL-C levels. (Plakogiannis, 2007).

The review also concluded that rigorous and robust trials was necessary to determine the best administration time to achieve optimal LDL-C lowering for lovastatin, pravastatin, rosuvastatin, atorvastatin, and fluvastatin (Plakogiannis, 2007).

However, some studies have suggested that a morning administration of some statins is associated with a smaller reduction in LDL-C levels, as compared to evening administration (specifically, 8.5 mg/dL smaller) (Izquierdo-Palomares et al., 2016).

2.5. Application of chronotherapy in cardiovascular disease

Recent evidence supports the idea that the diurnal variation of cardiovascular physiology and pathology is tightly related to an intrinsic biological rhythm, named the circadian clock and the onset of cardiovascular disease (CVD) exhibits a diurnal oscillation (Takeda, 2011).

Circadian rhythms are involved in physiology and the development of cardiovascular disease. Many of these diseases have a 24-h rhythm in incidence and disease burden. (Guo, 2003).

Heart rate and blood pressure (BP) exhibit daily rhythms that peak during wake time and trough during sleep. There are also circadian rhythms in the timing of onset of acute cardiovascular events. For example, myocardial infarction (MI, heart attack) is more likely to occur between _6:00 AM and 12:00 noon versus any other time of day or night. (Muller et al., 1989).

The severity of MI appears to be driven in part by the circadian mechanism (Durgan et al., 2010). There is also a morning peak in ventricular arrhythmias and sudden cardiac death. Moreover, rhythms are relevant to hypertension (high BP) and a reduced nocturnal BP (dipper) profile is better for the heart in hypertensive patients (Manfredini, 2016).

From one study. It is established that is circadian medicine is applicable to many aspects of cardiovascular diseases; one example of application is timing drug therapies, or chronotherapy, with the body's circadian rhythms. Experimentally it was shown that considering time-of-day of administration improves some cardiovascular therapies, such as angiotensin-converting enzyme inhibitors (ACEI) if given at sleep time (Martino, et al., 2011). Mechanistically, genes and products of the renin-angiotensin system exhibit daily rhythmicity, and thus timing drugs for when targets are high is more effective than when they are low. Indeed, many medications target the products of rhythmic genes and may benefit from time-of-day dosing (Zhang, 2014). Chronotherapy is also applicable to other areas of clinical cardiology.

To summarize, in humans, circadian rhythms have been studied extensively in the cardiovascular system. Many cardiovascular functions, such as endothelial function,

thrombus formation, blood pressure, and heart rate, are now known to be regulated by the circadian clock. Additionally, the onset of acute myocardial infarction, stroke, arrhythmias, and other adverse cardiovascular events show circadian rhythmicity. (Guo, 2003).

2.6. Awareness of HCP towards chronotherapy

HPC has a key role in providing medicine-related information, including counseling about the optimal time for medication administration. Where applicable, the principles of chronotherapy should underlie this aspect of medication counseling.

Information on circadian patterns in the occurrence of many cardiovascular disorders is enabling HCP to tailor treatment in ways that may lead to improved patient outcomes.

Knowledge about circadian rhythms and chronotherapy is increasingly becoming relevant to healthcare professionals, including pharmacists (Stranges, et al., 2015).

Thus, it is not surprising that pharmacists have a key role in counseling on all aspects of medication use, and, given their supply role, are usually the last health professional to advise patients prior to actual consumption (Deakin West, 2013). For drug/diseases where evidence for chronotherapy has been observed, it is important that pharmacists, who provide patients with education about optimal drug use, are well informed and aware Patients 'queries (Kaur et al., 2016).

It was interesting to note that the level of awareness of participants on chronotherapy bases did not appear to be associated with the length of experience in pharmacy practice. Most participants reported being unsure about the circadian variability of blood pressure and some were not familiar with the concept of ambulatory blood pressure monitoring.

Furthermore, results from a previous study indicate that many participants reported that they possessed little or no knowledge of circadian rhythms affecting disease symptoms or mode of action/pharmacokinetics of drugs. They attributed this to the fact that the concept of circadian rhythms affecting medication use was not included in their undergraduate pharmacy program. (Kaur at el.,2016).

In addition, participants believed that pharmacists have an important role to play in supporting patients with medicine-related issues, e.g. counseling about administration time, and were willing to apply chronotherapy principles to improve health outcomes. They acknowledged that compared to GPs, pharmacists need to explain drug usage in greater detail to patients, enabling them to focus on counseling about the most appropriate time of drug administration (Kaur et al.,2016).

Results of the previous study presented in Nigeria showed that positive attitudes from practicing community pharmacists towards chronotherapy and willingness to learn and apply principles of chronotherapy in practice (Chukwunyere & Abacıoğlu, 2017).

Clinical health care providers have a wide range of responsibilities amongst which include improving access and quality health care for the population. There have been significant awareness in the area of chronotherapy and understanding the basic principles is a prerequisite for better application in clinical settings regarding the pharmacological management of some disease conditions including cardiovascular diseases.

3. METHODOLOGY

3.1. Inclusion and Exclusion criteria

Inclusion criteria:

Original articles of randomized controlled trials involving a cardiovascular drug from 2009 to 2018 reporting the outcome of interest were considered eligible for inclusion. Cardiovascular diseases that were included in the study: Hypertension, Arrhythmia, Hyperlipidemia, and Heart failure. Also, systematic reviews and meta-analysis covering the same topic were included in the analysis.

Exclusion criteria:

Studies not assessing chronotherapy therapeutic effect medication were excluded.

3.2. Search strategy:

We searched the major electronic databases, PubMed and Web of Science. The bibliography of the included studies was hand-search to identify additional studies.

3.3. Search, data collection and analyzing

Research Database: PubMed and web of science.

A systemic review of the literature was done in agreement with the PRISMA guideline. Data screening and extraction: Two investigators systematically review the database search independently by reading the title & abstract of the identified studies and screen out the irrelevant ones. Included studies were read in full text for suitability of the Criteria independently, Variance was managed by consensus.

Population: Investigators independently reviewed all relevant articles to identify studies for inclusion. Any discrepancies were discussed and a consensus decision was reached. Data components collected directly from included article(s) were (a) patient characteristics (age, sex), (b) trial inclusion and exclusion criteria, (c) medications used, doses, and route of administration, (d) efficacy of intervention at controlling rapid ventricular response or converting to sinus rhythm, (e) timing of rate/rhythm control after drug administration, and (f) adverse events including bradycardia hypotension. Data extracted from relevant publications included: first author, data

collection year, publication year, number of participants, mean age, follow-up period, and outcomes reported.

3.4. Study Selection

Search Terms: ("Time of administration" OR Chronotherapy OR "circadian rhythm") AND ("cardiovascular diseases" OR cardiology OR hypertension OR blood pressure OR CAD OR "ischemic heart disease" OR "heart failure" OR hyperlipidemia OR Arrhythmia OR atrial fibrillation.

Study design: Randomize clinical trials that were published between (year's 2009-2019). And systematic reviews also included.

3.5. Outcome measures

The major outcome of this review is any improvement in cardiovascular events such as (decreasing in lipid profile, blood pressure, heart rate).

4. RESULTS

This research revealed a total of 4,226 related journals were identified of which 3,994 not included because they were not clinical studies (neither randomized or cohort), 232 articles were not included because of different reasons such as irreverent article (180),article duplicated (20) or only abstract available (18). Finally, 15 articles were selected for review. (Fig. 3)

Therefore, 15reports evaluating different populations were considered: 3 from the USA, 6 from Spain and 1 from Japan, 2 from China, Switzerland, England, and Hungary. The authors calculated the total number of patients included in all studies in whom the circadian pattern was evaluated to be 19551 patients.

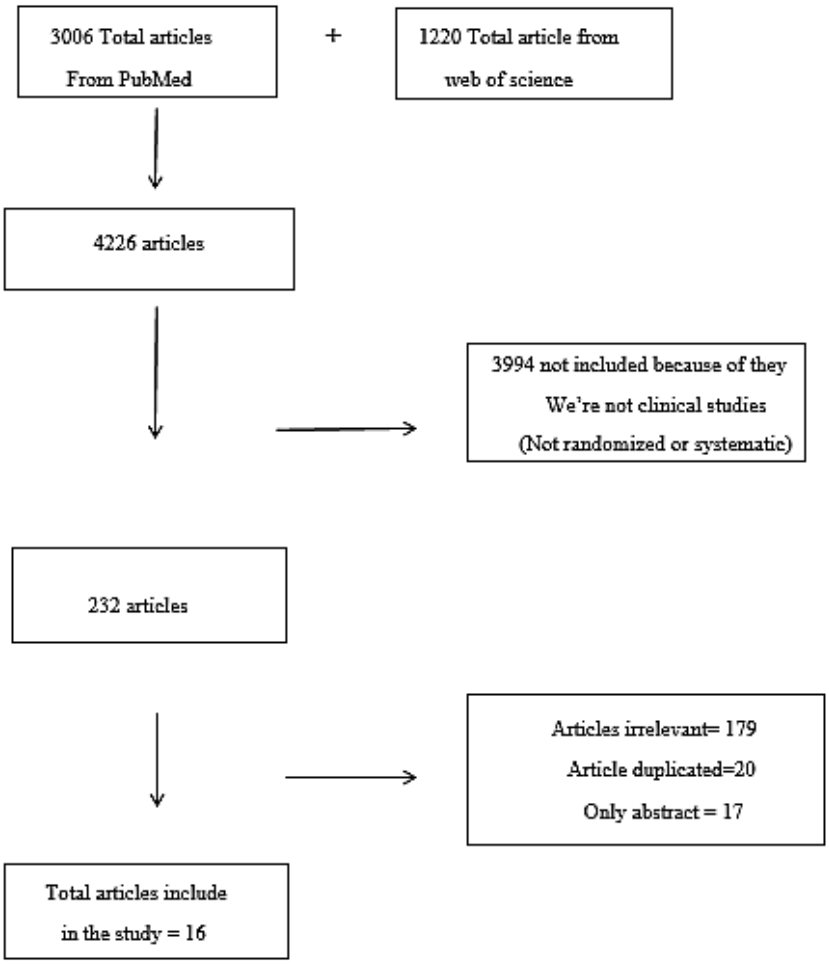

Figure 3. PubMed & Web of Science flow chart of the electronic search for study selection

Effect of Chronotherapy on hypertension:

In table1, three studies investigating the effectiveness of taking one or more antihypertensive medications at night show that bedtime antihypertensive drugs decrease SBP and DBP during the sleep. Moreover, those three studies reported a significant 48% decrease in relative risk of adverse CV event occurrence in patients ingesting their medications in the evening compared to that in the morning.

The results of one of these studies on beta-blocker (Nebivolol) drugs have been found Nebivolol is given in the morning or the evening significantly reduces 24-hour BP parameters. Evening dosed Nebivolol may confer to determine the effect of the timing (morning vs. evening) of nebivolol administration.

Similarly, one clinical trial that compared the effect of morning and bedtime administration of an ARBs and CCB combination reported that morning dosing reduced nocturnal brachial and central SBP and DBP whereas bedtime dosing only reduced nocturnal central DBP.

However, trials on specific drug combinations have demonstrated mixed results.

Prospective clinical trials with irbesartan, olmesartan, telmisartan, and valsartan emphasize that important ingestion-time differences in therapeutic effects are independent of drug terminal half-life.

A prospective open-label trial examining the impact of taking every antihypertensive drug at sleep compared to the morning resulted in improved 24-h BP control.

The chronotherapeutic effects of olmesartan in hypertensive patients have been published and found that compared with morning dosing; evening dosing of olmesartan was a better dose regimen for the treatment of hypertension, whereas other research groups did not support the merits of chronotherapy of olmesartan.

In this study, the percent of dipper BP pattern was similar between the olmesartan-M (46%) and olmesartan-E (42%) groups, which suggests that the influence of a dosing-time of olmesartan on BP dipping state was small in hypertensive patients with a non-dipper BP pattern during valsartan treatment at morning.

Further, a systematic review conducted to evaluate the improved effectiveness of aspirin by changing the timing of administration on the primary and secondary prevention of CVD that described outcomes of BP. In general, studies that examined younger populations with untreated mild HTN or pre-HTN reported reduced 24-h SBP and DBP when aspirin was administered in the evening.

Most patients treated for hypertension take once-every day regimens (monotherapy or combination therapy) because of the therapeutics' 24-h efficacy or to increase treatment adherence however, the long terminal half-life of, for example, the ARBs telmisartan (~ 24 h), Hermida et al. report additional benefits of taking the drug at night including increased nighttime sleep decline of BP. The group presented similar findings related to olmesartan which has a terminal half-life of ~13 h.

Notably, Ushijima et al conducted a study on the chronotherapeutic effects of valsartan dosing and found an increase of patients achieving dipper patterns. However, the BP reduction was too small when dosing time changed from morning to evening. This unexpected outcome can be attributed to the low valsartan dose of 40-80mg used in the study.

Another study investigating the chronotherapeutic effects of valsartan done by Zappe et al found a similar 24-h BP control regardless of dosing time and when compared to administration of a long-acting ARBs taken in the morning. The aforementioned outcome can also be explained due to the high dose of 320mg used in the study.

In contrast, Sazder, et al, state that twice-daily administration of an ACEI or ARBs were more effective in converting non-dippers to dippers compared to once-daily dosing of either drug in the evening.

By the findings of a clinical trial by Hermida et al. previously untreated hypertensive patients -Ramipril dosing on awakening and at bedtime showed similar efficacy in reducing the awake BP mean. The enrolled (n=2484) patients randomly allocated to first-line treatment with a CCB the home blood pressures in the morning and evening were measured for 5 days off treatment before randomization and for 5 days after 2 to 4 weeks of randomized drug treatment. We assessed BPL and BPV changes as estimated by variability independent of the mean and compared cardiovascular outcomes. The home BPL response in each group was significant.

Effect of chronotherapy on chronic kidney disease:

Chronic kidney disease (CKD) is considered an accelerator of CVD and an independent risk factor for adverse CV events. Moreover, nocturnal hypertension and non-dipping are frequently found in patients with chronic kidney disease (CKD).

A pilot randomized clinical trial by C. Wang in 2012 investigated the dosing time effects of ARBs (valsartan) on CKD patients with non-dipping BP patterns. The study found a reduction in nighttime BP pattern and even a change to dipping pattern in some patients when dosing was changed from awakening to bedtime.

Another randomized clinical trial by J. J. Crespo examining the chronotherapeutic effects of hypertension treatments on patients with CKD found a significant reduction of systolic and diastolic blood pressure when at least one medication was ingested at bedtime when compared to ingestion all medications upon awakening.

Furthermore, the study found a 50% reduction in riser BP pattern (the highest between BP patterns in CVD risk) when *all* the medication was ingested at bedtime.

A similar prospective, randomized, open-label, and blinded endpoint clinical trial by C. Hermida also confirmed improved blood pressure control in CKD patients both in sleep-time BP decline and mean.

Another study by C. Wang in 2016, which utilized the aforementioned three studies, demonstrated the benefits of chronotherapy in controlling nocturnal BP in hypertensive CKD patients via systematic review and meta-analysis. It also recommended and encouraged further clinical testing on the potential benefits of chronotherapy.

Effects of chronotherapy on AMI (Myocardial Infraction):

Studies: one study was found (systematic review).

For Acute Myocardial Infarction (AMI), the systematic reviews reported on a circadian variety for the beginning of AMI distinguishing an expanded morning recurrence in the period somewhere in the range of 06:00 A.M and 12:00 A.M

They evaluated that over 27% of morning AMIs and over 22% of abrupt heart passing were owing to a morning abundance of hazard.

Effects of chronotherapy on Hyperlipidemia:

The results in one randomized clinical demonstrated that no differences between Chronomodulated treatment with statins in people with hyperlipidemia as compared to conventional treatment with statins. Thus, Taking statins in the evening does not have an effect on the improvement of lipid levels with respect to morning administration.

Table 2. Characteristics of included Studies regarding chronotherapy of cardiovascular disease

N	Title	Authors & publication Year	Country	Population	Mean age	Aim of Study	Study design	Primary outcomes	Result
1	Time of administration important Morning versus evening dosing of valsartan	Dion H. Zappe,et al (2015)	Switzerland	1093	61.5	Comparing the antihypertensive effects of the morning (a.m.) and evening (p.m.) dosing of valsartan on 24-h BP	Randomized double-blind study	Mean 24-h ambulatory SBP change from baseline to Weeks 12 and 26 were comparable between valsartana.m. (–10.6 and –13.3mmHg) and p.m. (–9.8 and –12.3 mmHg) and lisinopril (–10.7 and –13.7 mmHg).	There was no benefit of valsartan p.m. versus a.m. on the night-Time BP, early morning BP and morning BP surge. Evening dosing also did not improve BP lowering in patients requiring add-on HCTZ or in no dippers at baseline.
2	Different chronotherapeutic effects of valsartan and olmesartan in non-dipper hypertensive patients during valsartan treatment at morning	Kentaro Ushijia, et al, (2014)	Japan	94	64.55	Evaluating the differences in chronotherapeutic effects of angiotensin-II Receptor blockers, valsartan and olmesartan in hypertensive patients with non-dipper blood pressure (BP) pattern during valsartan in morning.	Open-label, randomized, parallel group design	The effect of antihypertensive drugs can be influenced by a dosing-time, and appropriate timing of dosing is likely to correct an abnormal BP pattern.	These data suggest that dipper BP pattern could be obtained by chronotherapeutic approach nursing valsartan and olmesartan in non-dipper patients with Valsartan in the morning. Morning and evening olmesartan, but not evening valsartan improved renal function in these patients

3	Treatment of Hypertension Favorable Effect of the Twice-Daily Compared to the Once-Daily (Evening) Administration of Perindopril and Losartan	Szauder et al, (2015)	Hungary	164	55.7	Assess the effect of two widely used long acting drugs: perindopril and losartan in the treatment of hypertension comparing the once daily (evening) vs. twice-daily (morning and evening) administration with the same daily doses	Randomized controlled trial	The mean BP, the percent time elevation index, and the hyperbaric impact decreased in both drug groups	The mean BP, the percent time elevation index, and the hyperbaric impact decreased in both drug groups. A Significant difference was observed in the diurnal index in the case of twice-daily administration VS once-daily evening dosing
4	Effect of Valsartan With Bedtime Dosing on Chronic Kidney Disease Patients With Non-dipping Blood Pressure Pattern	Cheng Wang, et al (2013)	China	60	36	To investigate the effect of Valsartan With Bedtime Dosing on Chronic Kidney Disease Patients With Non-dipping Blood Pressure Pattern	Randomized clinical trails	valsartan with a bedtime dose decreased nighttime SBP compared with patients with awakening dose in the non-dipper group	The results indicate that bedtime dosing of valsartan in CKD patients with a non-dipping BP pattern showed better renal and CV protection

5	Bedtime Dosing of Antihypertensive Medications Reduces Cardiovascular Risk in CKD	Hermida ,et al (2011)	Spain	661	59.4	To determine how the circadian patterns of BP can be affected by the time ingestion of the hypertension medications	Randomized clinical trials	patients who took at least one BP-lowering medication at bedtime had an adjusted risk for total cardiovascular events that was approximately one-third that of patients who took all medications upon awakening	Patients' with CKD and hypertension, taking at least one antihypertensive medication at bedtime improve control of BP and reduces the risk for cardiovascular events.
6	Administration-Time-Dependent Effects of Hypertension Treatment on Ambulatory Blood Pressure in Patients With Chronic Kidney Disease	Juan J. Crespo, et al (2013)	Spain	2659	64.6	To investigate the influence of hypertension treatment time on the circadian BP pattern and degree of BP control of hypertensive patients with CKD evaluated by 48-h ABPM.	Randomized clinical trails	Patients who ingested medication at the bed time had lower asleep SBP and DBP more than those who had the medications during the awakening time.	Ingestion of ≥1 medication at bedtime was significantly associated with lower asleep systolic (SBP) and diastolic (DBP) BP means than treatment with all medications upon awakening.
7	Cardiovascular Risk of Resistant Hypertension: Dependence on Treatment-Time Regimen of Blood Pressure–Lowering Medications	Diana E. Ayala et al (2007)	Spain	776	61.6	This randomized trial investigated if bedtime therapy with at least one hypertension medication exerts better BP control and CVD risk reduction than conventional, morning-time therapy with all medications	Prospective, open-label blinded endpoint trial.	Among patients with resistant hypertension, ingestion of at least one hypertension medication at bedtime, compared with all medication upon waking, resulted in improved ambulatory BP control and fewer hard and soft CVD events	After a median follow-up of 5.4 yrs. (range, .5–8.5 yrs.), participants ingesting ≥1 hypertension medications at bedtime showed a significantly lower hazard ratio (HR) of total CVD events.

8	Both morning and evening dosing of nebivolol reduces trough mean blood pressure surge in hypertensive patients	Maria Czarina Acelajado, et al (2012)	England	42	52	To determine the effect of the timing (morning vs. evening) of nebivolol administration on the diurnal pattern of BP particularly the morning surge and nocturnal BP.	prospective, randomized, double-blind trial	Nebivolol was effective in reducing daytime, nighttime 24- hour ambulatory BP and systolic trough to morning MBPS	Both morning and evening dosed Nebivolol significantly lowered daytime, nighttime, and 24-hour BP after 3 weeks of treatment. Evening (but not morning) dosing significantly reduced pre waking systolic BP from baseline (8.64 _ 26.46 mm Hg, P ¼.048). Nebivolol is given in the morning or the evening significantly reduces 24-hour BP parameters. Evening dosed Nebivolol may confer some advantage over morning dosing in reducing pre waking systolic BP
9	Chronotherapy versus conventional statins therapy for the treatment of hyperlipidemia	Tabera JM,et al (2016)	Spain	767	47.5	Evaluate the effects of chronotherapy on the effectiveness and safety of treatment with statins for hyperlipidemia.	Randomized controlled trials	That no differences between Chronomodulated treatment with statins in people with hyperlipidemia as compared to conventional treatment with statins	Taking statins in the evening does not have an effect on the improvement of lipid levels with respect to morning administration.

10	Circadian Periodicity of Ischemic Heart Disease	Fabbian, et al (2017)	USA	13235		To evaluate the risk of AMI during the morning versus the other hours of the day.	systematic reviews	The first report on a circadian variation for the onset of AMI detecting an increased morning frequency in the period between 06:00 and 12:00 A.M	They found the incidence of AMI onset was 40% higher in the morning than throughout the rest of the day. Furthermore, they estimated that more than 27% of morning AMIs and more than 22% of sudden cardiac deaths were attributable to a morning excess of risk. Furthermore, several factors have been found to modify or attenuate the circadian pattern of AMI including demographic factors medications, and comorbidities have seen major changes in lifestyle and Significant improvements in medical intervention.

11	Chronotherapy for Hypertension	Bowles, et al (2018)	USA		younger populations	To clarify that circadian rhythmicity is existed in all of the cells and organs regarding the beneficial outcomes of chronotherapy for hypertension and other diseases.	Meta-analysis and systematic review.	The participants with HTN resistant showed an improved in the ambulatory BP control in participants who had anti-hypertension medication at night more than those who had it during the day time.	The efficacy of Aspirin was conducted in a systematic review to assess its avoidance toward primary and secondary CVD by changing the time of administration. The results showed that taking the aspirin during night time will reduce the SBP and DBP within 24-h for patients with mild-HTN and pre-HTN. 170 clinical trials adjusted during the daytime compared with five clinical trials adjusted at evening and the result of this comparison showed that patients who used their antihypertensive medication at evening reduced the risk of CV events by 48% according to meta-analysis. As a conclusion that dosing during the evening is not harmful as well as it seems that it has high beneficial outcomes of clinical trials with HTN patients.

12	Treatment of Hypertension With Chronotherapy: Is It Time?	Stranges, et al (2014).	USA	4086	≥60	To proof the consequences of administrating antihypertensive at bedtime and the possibility of reducing CV events.	Prospective studies	Dosing at bedtime showed a result of stimulating the normal circadian BP and decreased the risk of morbidity and mortality of CV events compared with dosing in the morning.	Despite growing evidence and promise as a cost-effective strategy for reducing cardiovascular risk, chronotherapy is not uniformly recommended in the treatment of hypertension. Careful selection of patients and antihypertensive for chronotherapy is required.
13	Chronotherapy for hypertension in patients with chronic kidney disease: a systematic review and meta-analysis in non-black patients	Wang,et al (2016).	China.	3380	64.6	To investigate the effects of chronotherapy on blood pressure in patients with chronic kidney disease (CKD).	Systematic review and meta-analysis.	Compared with morning dosing regimen drug therapy, chronotherapy was associated with a significant decrease of 3.55% in sleep-time relative decline of systolic blood pressure (SBP) (mean difference [MD], 95% CI, [0.22, 6.88])	This meta-analysis suggests that chronotherapy could reduce nocturnal BP in hypertensive CKD patients. Chronotherapy benefited hypertensive CKD patients in nocturnal BP and should be encouraged in the clinical setting.

14	Role of Time-of-Day of Hypertension Treatment on the J-Shaped Relationship Between Blood Pressure and Cardiovascular Risk	Hermida, et al (2012).	Spain	2156	55.6 13.6 years	The role of hypertension treatment time scheme on the nature of the relationship between the achieved clinic and ambulatory BP and CVD risk.	Prospective open-label blinded-endpoint trial,	After a median follow-up of 5.6 yrs. a J-shaped relationship was detected between total CVD events and the clinic as well as a wake BP mean but only for the group of patients ingesting all medications upon awakening.	Our findings indicate that bedtime hypertension treatment is not associated with a J-shaped relationship between achieved BP and CVD risk the decreased CVD risk associated with the progressive reduction in a sleep BP, more feasible by bedtime than morning hypertension treatment.
15	Chronotherapy with conventional blood pressure medications improves management of hypertension and reduces cardiovascular and stroke risks	hermida, et al (2015).	Spain	802		The goal of all hypertension treatment strategies is the reduction of SBP and DBP as a means of preventing end-organ injury and decreasing CVD, stroke, renal disease and other life-threatening risks.	Review (Prospective clinical trials).	this finding is based primarily on outcome trials targeting correction of only the daytime OBPM level as opposed to correction of features—mainly asleep SBP mean and sleep time relative SBP decline—of the 24 h BP pattern known to be more strongly associated with CVD risk.	previously untreated hypertensive patients -wakening or bedtime 5mg ramipril monotherapy and who were assessed by 48 h ABPM before and after 6 weeks of treatment. In addition, the results of another study by utilizing an identical investigative protocol and involving untreated hypertensive Patients demonstrate that the differential

									treatment-time effects of ACEIs upon the 24 h BP profile are independent of drug half-life. Prospective clinical trials with irbesartan, olmesartan, telmisartan, and valsartan validate that significant ingestion-time differences in therapeutic effects are independent of drug terminal half-life. Most hypertension patients required treatment with more than one blood pressure-lowering medication to achieve target BP goal.

5. DISCUSSION

Chronotherapy provided scope for individual treatment of hypertension, achieving optimal blood pressure control, and reducing the risk of cardiovascular disease and organ damage, stroke, kidney disease, and other life-threatening risks.

The aim of this study was that we find the benefit of chronotherapy for CVD disease and found that chronotherapy medication strategy reduced DBP and SBP nocturnal blood pressure and during the early hours of sleep were associated with lower cardiovascular risk and improved kidney disease independent of the prescribed drug category.

Research conducted in recent years generally shows improved blood pressure 24-h BP profiles with at least one medication taken in the evening.

Studies on the chronotherapeutic effects of medications controlling blood pressure patterns on patients with chronic kidney disease agree with our findings on the therapeutic benefits gained in utilizing chronotherapy. Most notably the consistent improvement in outcome when dosing of at least one medication is administered at bedtime.

Considering the frequent co-occurrence and the importance of controlling hypertension in CKD patients, the utilization of chronotherapy provided essential improvements in the patients' outcomes.

However, due to the small increase in morning SBP when dosing is done in the evening, patients with uncontrolled BP may suffer adverse chronotherapeutic effects and evening dosing is not recommended.

Hence, a careful and customized treatment time according to the patient's specific state is essential in achieving optimal patient outcomes.

All remaining outcomes recommend that taking the medication in the evening should be supported in all cases because of the ability to benefit especially for nocturnal BP and enhance the dipping status, and in some cases overall 24-h BP, and in some cases, hard clinical CV outcomes and without an increase in injury.

Of the same doses of ACE and ARB on the day/night blood pressure ratio. Effect of the most commonly utilized long-term antihypertensive ACE inhibitors and ARBs drugs: perindopril and losartan in the treatment of hypertension comparing once-daily the administration (in the evening) in daily administration (morning and evening) were investigated twice in the same dose with 24-hour blood pressure monitoring (ABPM).

Daily (evening) dose of perindopril (8 mg) and losartan (100 mg) and administration twice daily (morning and evening 4-4 mg of perindopril and 50-50 mg of losartan).

A study on the chronotherapeutic effects of olmesartan in hypertensive patients has been published, and conflicting data observed. Some research groups found that, compared with morning dosing, evening dosing of olmesartan was a better dose regimen for the treatment of hypertension, whereas other research groups did not support the merits of chronotherapy of olmesartan. In this study, the percent of dipper BP pattern was similar between the olmesartan-M (46%) and olmesartan-E (42%) groups, which suggests that the influence of a dosing-time of olmesartan on BP dipping state was small in hypertensive patients with a non-dipper BP pattern during valsartan treatment at morning. We do not have definitive explanations for apparent diverse findings, and further clinical studies are needed to confirm the chronotherapeutic effects of olmesartan.

Most hypertension patients required treatment with more than one blood pressure-lowering medication to achieve target BP goal.

Demonstrate that bedtime ingestion of any given class of BP-lowering medication is consistently associated with lower HRs of CVD injury than ingestion upon awakening; these outcomes, indicating lower CVD risk with bedtime as compared with awakening ingestion of CCBs, β-blockers, and ARBs we need more investigation and studies about it

The latter study proposes that for some medication classes, twice-daily dosing may be required to obtain target BP control.

The incidence of AMI was higher in the morning 40% more than at night, this was the result of a meta-analysis of 30 studies on AMI which include more than 66.000 patients (Gilpin et al., 1997)

For Acute Myocardial Infarction (AMI), the first report on a circadian variation for the onset of AMI detecting an increased morning frequency in the period between 06:00 and 12:00 was published in 1985 by Muller and colleagues. (Muller JE, 1985)

Furthermore, they estimated that more than 27% of morning AMIs and more than 22% of sudden cardiac deaths were attributable to a morning excess of risk. The current authors' results seem to confirm the previous findings with a weighted ratio between the number of events per hour during the morning and the number of events per hour during the other hours of the day to be 1.56 (95% CI, 1.48–1.65).

Prior evidence shows that although the onset of AMIs is lowest during the first part of the night when sleeping, the prevalence increases in the second part of the night and increases further during the first hours of daytime activity.

6. CONCLUSION AND RECOMMENDATION

In recent years, the application of chronotherapy technique has increased, this strategy is characterized by more accurate identification of times when patients are at greater risk and therefore the most need for preventive or therapeutic action. It also gives ways to design the most appropriate medication regimens. Heart attack, acute myocardial infarction, sudden cardiac death factors that impact daily differences in cardiovascular disorders include physiological determinants, such as platelet aggregation and heart rate - and external factors, such as daily activity, stress, and food intake.

Our results support that many cardiovascular disorders, such as AMI and hypertension, occur in the morning between 06:00 a.m. and 12:00 p.m. in the general population.

In chronotherapy, we can exploit daily differences in pathological conditions and pharmacological properties of drugs to improve prevention and treatment. Our study suggests that the following chronotherapy is beneficial and can protect against blood clots, high blood pressure, persistent stable angina, and acute myocardial infarction.

Chronotherapy is a wide technique and can help in improving the patient's outcome. An increase in studies investigating the chronotherapeutic effects in all medical fields and not only in the field of cardiovascular disease is needed and highly recommended.

Strengths:

In this study, the studies used are exclusively randomized studies and/or systematic reviews, only select databases, Web of Science Database and PubMed, due to their high quality. Nonetheless, all of the mentioned studies in this research were integrated together due to the interrelation of cardiovascular diseases.

Limitation:

Although these results confirm those of previous studies of what is already known, our study should be interpreted in light of its limitations. Several of the reports analyzed had different study designs (Heterogeneously) and unable to generalize their findings, as well as this study designed in systematic review only and didn't include meta-analysis, also the study didn't include all databases and the included studies were only between (2009-2018).

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