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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk stratification of patients who present with chest pain and have normal troponins using a machine learning model

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Abstract

BACKGROUND

Risk stratification tools exist for patients presenting with chest pain to the emergency room and have achieved the recommended negative predictive value (NPV) of 99%. However, due to low positive predictive value (PPV), current stratification tools result in unwarranted investigations such as serial laboratory tests and cardiac stress tests (CSTs).

AIM

To create a machine learning model (MLM) for risk stratification of chest pain with a better PPV.

METHODS

This retrospective cohort study used de-identified hospital data from January 2016 until November 2021. Inclusion criteria were patients aged > 21 years who presented to the ER, had at least two serum troponins measured, were subsequently admitted to the hospital, and had a CST within 4 d of presentation. Exclusion criteria were elevated troponin value (> 0.05 ng/mL) and missing values for body mass index. The primary outcome was abnormal CST. Demographics, coronary artery disease (CAD) history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, obesity, and smoking were evaluated as potential risk factors for abnormal CST. Patients were also categorized into a high-risk group (CAD history or more than two risk factors) and a low-risk group (all other patients) for comparison. Bivariate analysis was performed using a χ^2 test or Fisher's exact test. Age was compared by *t* test. Binomial regression (BR), random forest, and XGBoost MLMs were used for

prediction. Bootstrapping was used for the internal validation of prediction models. BR was also used for inference. Alpha criterion was set at 0.05 for all statistical tests. R software was used for statistical analysis.

RESULTS

The final cohort of the study included 2328 patients, of which 245 (10.52%) patients had abnormal CST. When adjusted for covariates in the BR model, male sex [risk ratio (RR) = 1.52, 95% confidence interval (CI): 1.2-1.94, $P < 0.001$)], CAD history (RR = 4.46, 95%CI: 3.08-6.72, $P < 0.001$), and hyperlipidemia (RR = 3.87, 95%CI: 2.12-8.12, $P < 0.001$) remained statistically significant. Incidence of abnormal CST was 12.2% in the high-risk group and 2.3% in the low-risk group (RR = 5.31, 95%CI: 2.75-10.24, $P < 0.001$). The XGBoost model had the best PPV of 24.33%, with an NPV of 91.34% for abnormal CST.

CONCLUSION

The XGBoost MLM achieved a PPV of 24.33% for an abnormal CST, which is better than current stratification tools (13.00%-17.50%). This highlights the beneficial potential of MLMs in clinical decision-making.

Key Words: Machine learning; Chest pain; Risk stratification; Risk factors; Cardiac stress test; Cardiac catheterization

Core Tip: For patients with chest pain, current stratification tools result in unwarranted investigations due to low (13.0%-17.5%) positive predictive values (PPVs). This retrospective cohort study aimed to create a machine learning model (MLM) for risk stratification of patients with chest pain with a better PPV. Demographics, coronary artery disease history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, obesity, and smoking were the covariates. The XGBoost MLM achieved a PPV of 24.33% for an abnormal cardiac stress test, which is better than current stratification tools. This model highlights the potential use of MLMs in clinical decision-making.

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INTRODUCTION

The annual cost of cardiovascular disease and stroke has been estimated to be more than $200 billion in the United States[1]. Chest pain, in particular, led to over 40 million hospital visits from 2006-2016 and had an associated cost of $6.2 billion from 2014-2016[2]. For each hospital admission, the average cost has been reported to be $11700 per patient in the United States[3]. This cost represents a significant burden on the patients and the healthcare system and emphasizes the need for a better stratification tool to safely identify patients who present with chest pain for early discharge without unnecessary testing.

Patients who present with chest pain are considered to be low risk if their probability of a major adverse cardiac event is < 1%, according to clinical practice guidelines of the American College of Cardiology and American Heart Association[4]. The two most widely used stratification tools that calculate the probability of major adverse cardiac event include the history, electrocardiogram (ECG), age, risk factors, and initial troponin pathway accelerated diagnostic protocol (HEART pathway-ADP) and the emergency department assessment of chest pain score (EDACS)-ADP[5-8]. The HEART pathway-ADP and EDACS-ADP have demonstrated excellent sensitivity and a negative predictive value (NPV) of 99%, as recommended by the American College of Cardiology and the American Heart Association[5-8]. However, both the HEART pathway-ADP and EDACS-ADP have low positive predictive values (PPVs) of 13.0% and 17.5%, respectively[7,9]. This low PPV leads to unnecessary additional testing, such as serial laboratory tests and cardiac stress tests (CSTs). Furthermore, the main focus of these two stratification tools has been the 30-d outcome of acute myocardial infarction (AMI) and all-cause mortality.

Many medical devices are already using artificial intelligence and machine learning algorithms[10]. However, these domains are underutilized in clinical decision-making despite their huge potential. The National COVID Cohort Collaborative facilitated the creation of machine learning models (MLMs) for

accurate prediction of coronavirus disease 2019 severity with proven efficacy[11]. The same concept of machine learning can be applied to patients who present with chest pain in the emergency room (ER), and the use of patient data points (such as demographics and risk factors) can build predictive models with better specificity and PPV.

Stewart *et al*[12] reported in a recent systematic review of 23 studies that MLM outperformed traditional risk stratification scores for chest pain. Although the outcome varied among the included studies, data and the specifics of the MLMs, such as hyperparameters, were not shared, which complicates replication and validation[12]. Most recently, Doudesis *et al*[13] published the myocardial-ischemic-injury-index (MI^3) algorithm with high PPV (70.4%) and NPV (99.8%) for myocardial infarction. They have not provided the specifics of their MLM either.

The HEART pathway-ADP, the EDACS-ADP, and other recently developed MLMs include both normal and abnormal troponin levels in their stratification[7,8,12,14,15]. However, risk stratification is more challenging when the troponin level is normal. In addition, the HEART pathway-ADP and the EDACS-ADP do not address the risk of non-obstructive coronary artery disease (CAD) or the risk of AMI over an extended period of time (over a year). Lastly, recently developed MLMs claim to have better stratification, but essential information about their models have not been shared, limiting the potential for reproducibility. Given these challenges to risk stratification among patients with chest pain and the need to improve patient outcomes and reduce unnecessary healthcare costs, we hypothesized that an MLM could be created to better predict abnormal CST among patients who present with chest pain and have normal troponin values. CST can identify wide spectrum of CAD, including non-obstructive CAD, and it provides risk assessment for 1 year rather than just 30 d. Due to the current enhanced computing capabilities, MLMs have the potential to achieve better PPV and lower false-positive rates, which can reduce unnecessary testing. MLMs can gain the reproducibility needed to build trust through data sharing and transparency, which can further improve risk stratification and deliver the most cost-effective healthcare.

This study aimed to create an MLM that can use patient characteristics to provide risk stratification for further clinical intervention for patients who present with chest pain and have normal troponin values. The hypothesis of this study was that patient characteristics can be used to create MLMs for risk stratification for patients who present to the ER with chest pain and have normal troponin values with a PPV of 25% or more and an NPV of at least 99%.

MATERIALS AND METHODS

Study design

This study used a retrospective cohort design involving de-identified data available in the i2b2 common data model repository of the University of Kansas Medical Center. Database queries for patients observed in the health system between January of 2016 and November of 2021 were conducted using Healthcare Enterprise Repository for Ontological Narration, a search discovery tool that allows cohort building for observational research using de-identified data[16,17]. Institutional Review Board approval was not required because the data was de-identified. Identification and/or definitions of computable phenotypes used in this study are provided in the Supplementary material.

Selection criteria

Inclusion criteria: All patients aged 21 years or older who presented to the ER, had their first troponin test carried out within the first 6 h of arrival to the ER and at least one troponin test completed after 6 h, were subsequently admitted to the hospital, and had a nuclear CST carried out within 4 d of presentation to the ER were included in the study.

Exclusion criteria: Patients with elevated troponin levels (> 0.05 ng/mL) and those with missing body mass index values were excluded. Patients with elevated troponin levels are considered high risk, and hospital admission with further clinical intervention is more appropriate for this class of patients. Without body mass index data, obesity could not be defined as one of the risk factors/covariates in this study.

Risk stratification

CAD history, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, obesity, and smoking history were the risk factors included in this study. For comparison, patients included in the final cohort were also categorized into a high-risk group (CAD history or > 2 risk factors) and a low-risk group (no prior CAD history and ≤ 2 risk factors).

Encounters

Only the first encounter was included in the study for patients with more than one ER encounter that met the above inclusion and exclusion criteria.

Outcome

The outcome of the study was the incidence of abnormal CST. Abnormal CST was defined as CST followed by cardiac catheterization and/or coronary artery bypass graft within 30 d. Cardiac catheterization and coronary artery bypass graft were used as a surrogate to identify abnormal CST in this study.

Statistical analysis

Bivariate analysis: Except for age, the association between the incidence of abnormal CST and sex, race, and risk factors was assessed by χ^2 test or Fisher's exact test. High-risk and low-risk groups were also compared using a χ^2 test, and the risk ratio was calculated. Age was compared by t test. Alpha criterion was set at 0.05.

Binomial regression: Binomial regression (BR) was used to adjust for confounding factors and infer the degree of association between the risk factors and the outcome. All BR assumptions were assessed, including assumptions of no multi-collinearity and no outliers. To ensure model adequacy, Hosmer-Lemeshow goodness-of-fit test was also performed. Alpha criterion both for BR as well as Hosmer-Lemeshow goodness-of-fit test was set at 0.05.

MLMs: BR was also used for prediction, and it used the same predictor variables as for inference. Besides BR, the random forest and XGBoost MLMs were also used. In the random forest MLM, proximity and importance were set as "True". In order to minimize overfitting, the number of trees was set at 25 in training and testing. In the XGBoost MLM, hyperparameters were set as: Booster = "gbtree"; objective = "binary:logistic"; eval_metric = "auc"; eta = 0.1; max.depth = 10; gamma = 0; min_child_weight = 1; and colsample_bytree = 1. In order to minimize overfitting, 25 rounds were used in the XGBoost MLM.

Bootstrapping with replacement was used for internal validation of all the above models. Data were randomly split into training (75%) and testing (25%) during each iteration of bootstrapping. The model with training data was first fitted, and then testing data were applied to assess internal validation during each iteration of bootstrapping. Finally, the results were averaged. In order to produce more precise estimates, 500 iterations were used in bootstrapping for all models, and 95% confidence intervals (CIs) were created. Prediction cutoff values were calibrated manually, and the value with the best metrics (sensitivity, specificity, PPV, and NPV) was then selected for each model. All statistical analyses were performed using R software (version 4.1.2).

RESULTS

The final cohort sample included 2328 unique patients, of which 245 (10.52%) patients had abnormal CST requiring cardiac catheterization and/or coronary artery bypass graft (Figure 1). There were 196 duplicate encounters, which were removed, and only the patient's first encounter was included in the study. The basic demographic characteristics of the patients are presented in Table 1. Male sex and Caucasian race were significantly associated with the incidence of abnormal CST.

In the bivariate analysis, obesity was not significantly associated with abnormal CST. Smoking history was significantly associated with abnormal CST, but the association was weak. As shown in Table 2, all other risk factors were significantly associated with abnormal CST. High-risk patients were found to have a risk ratio of 5.31 (95%CI: 2.75-10.24) for abnormal CST when compared to low-risk patients (Table 3).

Age, race, and obesity were removed from the final BR model because they were not statistically significant, did not have any confounding relationship with other covariates, and their contribution to the prediction was not significant. These three covariates together resulted in an increased area under the receiver operating characteristic curve (AUC) by only 1.35%. The final model met all assumptions of BR, including the assumption of no multi-collinearity and no outliers, and appeared to fit the data adequately (Hosmer-Lemeshow goodness-of-fit test, P = 0.9). Only male sex, CAD history, and hyperlipidemia were statistically significant when adjusted for covariates in the final BR model. Covariates that were included in the final BR model and their estimated risk ratios are shown in Table 4.

Prediction models

BR: The same covariates used for inference in the BR model were also used for prediction. These covariates included sex, CAD history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, and smoking history. First, all data were used together, which yielded an AUC of 74.51% (Figure 2A). The internal validation of the BR model yielded similar results (Figure 2B). A prediction cutoff value of 0.2 provided a sensitivity of 45.06%, specificity of 80.46%, a PPV of 21.34%, and an NPV of 92.55%.

Random forest: In the random forest model, all covariates were included. This model showed a much

Table 1 Demographics

Characteristics	Abnormal cardiac stress test requiring cardiac catheterization and/or CABG		Degree of association (95%CI)	*P* value
	Yes, *n* = 245	No, *n* = 2083		
Age, mean ± SD	63.02 ± 11.67	61.99 ± 12.46	Mean different: 1.03 (-0.53, 2.59)	0.200
Sex male	153 (62.4%)	965 (46.3%)	RR: 1.8 (1.41, 2.30)	< 0.001
Race				
Caucasian	163 (66.5%)	1182 (56.7%)	RR: 1.8 (1.08, 3.00)	0.020 (combined)
African American	65 (26.5%)	650 (31.2%)	RR: 1.35 (0.79, 2.32)	
Asian	2 (0.8%)	43 (2.1%)	RR: 0.66 (0.16, 2.79)	
Other	15 (6.1%)	208 (10.0%)	Reference	

CABG: Coronary artery bypass graft; CI: Confidence interval; RR: Risk ratio; SD: Standard deviation.

Table 2 Bivariate analysis of the risk factors

Risk factors	Abnormal cardiac stress test requiring cardiac catheterization and/or CABG		Risk ratio (95%CI)	*P* value
	Yes, *n* = 245	No, *n* = 2083		
CAD history, yes	216 (88.2%)	1063 (51.0%)	6.11 (4.18, 8.92)	< 0.001
Obesity, yes	136 (55.5%)	1121 (53.8%)	1.06 (0.84, 1.35)	0.620
Diabetes mellitus, yes	112 (45.7%)	760 (36.5%)	1.41 (1.11, 1.78)	0.005
Hypertension, yes	232 (94.7%)	1783 (85.6%)	2.77 (1.61, 4.78)	< 0.001
Hyperlipidemia, yes	236 (96.3%)	1602 (76.9%)	6.99 (3.62, 13.50)	< 0.001
CKD history, yes	88 (35.9%)	540 (25.9%)	1.52 (1.19, 1.94)	< 0.001
Smoking history, yes	153 (62.4%)	1133 (54.4%)	1.35 (1.05, 1.72)	0.020

CABG: Coronary artery bypass graft; CAD: Coronary artery disease; CI: Confidence interval; CKD: Chronic kidney disease.

Table 3 Comparison between the high-risk group and the low-risk group

Risk category	Abnormal cardiac stress test requiring cardiac catheterization and/or CABG		Risk ratio (95%CI)	*P* value
	Yes, *n* = 245	No, *n* = 2083		
High risk	236 (96.3%)	1700 (81.61%)	5.31 (2.75, 10.24)	< 0.001
Low risk	9 (3.7%)	383 (18.39%)		

CABG: Coronary artery bypass graft; CI: Confidence interval.

better fit for all data combined (Figure 2C). During internal validation of the random forest model, the AUC dropped significantly (Figure 2D). A prediction cutoff value of 0.18 provided a sensitivity of 13.92%, specificity of 93.66%, a PPV of 20.55%, and an NPV of 90.24 % for the random forest model.

XGBoost: All covariates were used in the XGBoost model. It provided a better AUC for all data combined compared to BR (Figure 2E). Like the random forest model, the AUC dropped significantly during internal validation of the XGBoost model (Figure 2F). A prediction cutoff value of 0.27 was used for the XGBoost model, and it yielded a sensitivity of 30.54%, specificity of 88.51%, a PPV of 24.33%, and an NPV of 91.34%. A comparison of the three models is presented in Table 5.

Table 4 Adjustment of risk factors association with the abnormal cardiac stress test *via* binomial regression

Covariate	Risk ratio	95%CI	*P* value
Sex, male	1.52	1.2, 1.94	< 0.001
CAD history, yes	4.46	3.08, 6.72	< 0.001
Hypertension, yes	1.35	0.82, 2.44	0.280
Hyperlipidemia, yes	3.87	2.12, 8.12	< 0.001
Diabetes mellitus, yes	1.06	0.83, 1.34	0.650
CKD history, yes	1.02	0.80, 1.30	0.860
Smoking history, yes	1.06	0.84, 1.35	0.620

CAD: Coronary artery disease; CI: Confidence interval; CKD: Chronic kidney disease.

Table 5 Comparison of the models for the prediction of an abnormal cardiac stress test

Feature	BR	RF	XGBoost
Prediction cutoff value	0.20	0.18	0.27
Sensitivity (95%CI)	45.06 (44.23, 45.88)	13.92 (13.50, 14.33)	30.54 (29.30, 31.79)
Specificity (95%CI)	80.46 (80.14, 80.79)	93.66 (93.53, 93.80)	88.51 (88.15, 88.86)
PPV (95%CI)	21.34 (21.09, 21.60)	20.55 (20.05, 21.04)	24.33 (23.46, 25.20)
NPV (95%CI)	92.55 (92.42, 92.69)	90.24 (90.14, 90.35)	91.34 (91.12, 91.56)

BR: Binomial regression; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; RF: Random forest.

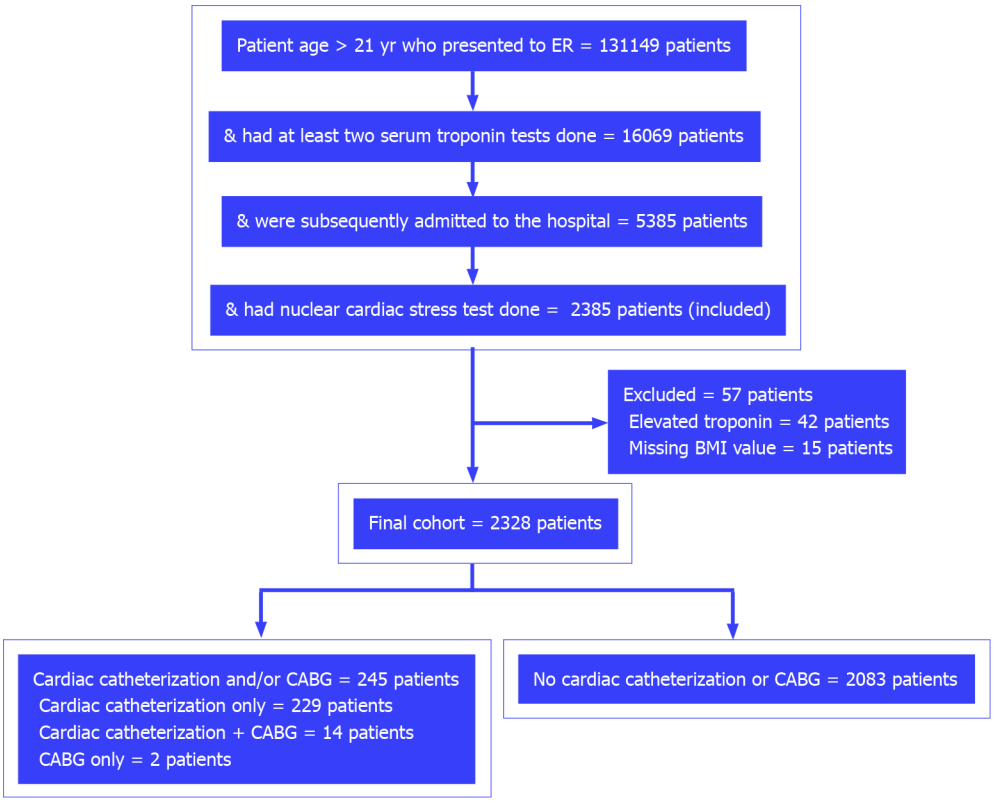

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Figure 1 Flowchart of the cohort selection. BMI: Body mass index; CABG: Coronary artery bypass graft; ER: Emergency room.

DISCUSSION

This study found statistically significant associations between abnormal CST and several factors, including male sex, CAD history, and hyperlipidemia, among patients with chest pain who presented to the hospital, had normal troponin tests, and completed a CST. The incidence rate of abnormal CST among low-risk patients was only 2.30%, while it was 12.19% among high-risk patients. NPV for all MLMs in this study did not reach the recommended value of 99%. However, the XGBoost MLM in this study provided a much better PPV of 24.33%.

Both the HEART pathway-ADP and EDACS-ADP have excellent sensitivity and NPV (99%), but the PPV (13.0% and 17.5%, respectively) is considerably low. This likely leads to unnecessary clinical intervention[7,8]. Despite the retrospective nature and limited explanatory variables in modeling in this study, the XGBoost MLM resulted in an increased PPV (24.33%). Patients who had CAD with the need for revascularization and who did not follow up within 30 d could not be identified in the HEART pathway-ADP and EDACS-ADP studies. Likewise, further clinical intervention was not completed for low-risk patients, who were subsequently discharged in the HEART pathway-ADP and EDACS-ADP studies. Therefore, no objective data exists to suggest that those discharged patients did not have CAD (such as non-obstructive CAD). Nevertheless, in our study, nuclear CST was part of the inclusion criteria to ensure there was objective data on CAD for all patients. Therefore, the inclusion criteria were stricter for our study.

In the HEART pathway-ADP and EDACS-ADP, ECG and all troponin tests (normal and abnormal) were predictor variables[7,8]. If a patient has elevated troponin values, then the resulting clinical decision is to recommend further clinical intervention the majority of the time. However, it is challenging to identify patients who have normal troponin values and need further clinical intervention. This study undertook the challenge of including only patients with normal troponin values, which is another reason that the selection criteria for this study cohort was restricted. However, it mirrors real-life clinical practice and the challenges that come with it. ECG was not included in this study and is a significant limitation. Since it was a retrospective study based on de-identified data, access to actual ECG data was not possible. Machine readings of the ECG are available. However, due to the poor PPV of machine readings for abnormal findings on ECG, machine readings were not included[18,19]. Incorporating incorrect interpretations of ECG machine readings could have resulted in erroneous results and conclusions.

There has been increased interest in using MLMs and artificial intelligence in clinical decision-making in the past 8-10 years[12,14,15]. For patients who presented with chest pain to the ER, Stewart *et al*[12] conducted a systematic review of 23 studies that used MLMs to stratify these patients. There is significant heterogeneity in the studies included in this systematic review with differences noted in study design, type of MLM used, selected outcomes, comparisons made, data sharing, and validation. Despite the limitations, Stewart *et al*[12] reported that MLMs outperformed traditional risk stratification scores. Using high-sensitivity serum troponins, Doudesis *et al*[13] recently developed the MI^3 using gradient boosting MLM with sex, age, serial serum troponin concentrations, and the time interval between the serum troponin sampling as their parameters. This model also included both normal and abnormal troponin assays. MI^3 has reported a PPV of 70.4% for myocardial infarction if the MI^3 score was > 49.6 and an NPV of 99.8% if the MI^3 score was < 1.6. The specifics of their gradient boosting MLM have not been shared.

Zhang *et al*[14] conducted a study using MLMs for chest pain stratification, which shares some similarities in methodology to our study. The retrospective arm of their study was based on data from the electronic medical records. They excluded patients who had no follow-up data and did not include ECG for technical reasons (with no further explanation). The main differences in the study by Zhang *et al*[14] and our study included different outcomes (30-d AMI and all-cause mortality *vs* abnormal CST, respectively), different number of explanatory variables (14 *vs* 10, respectively), troponin values (all values *vs* only normal values, respectively), and the use of different MLMs.

Zhang *et al*[14] reported a robust sensitivity, specificity, and PPV of 92.90%, 88.50%, and 90.80%, respectively, for the 30-d risk of AMI during internal validation[14]. They observed similar sensitivity, specificity, and PPV for 30-d risk of all-cause mortality (77.50%, 99.99%, and 90.80%, respectively)[14]. This represents one of the best models for risk stratification of patients who present to the ER with chest pain. In comparison, our study had a small sample size, used fewer explanatory variables, and included only normal troponins values, which likely led to lower predictive performance. Despite the robust performance of their MLM, Zhang *et al*[14] have not shared the MLM specifications in order to reproduce and externally validate their model. The heterogeneity of MLMs, lack of data sharing, and current lack of external validation are the major obstacles to widespread adoption of MLMs for risk stratification for patients presenting with chest pain.

Digitization of health records and exceptional computing power have enabled the use of artificial intelligence and MLMs in medicine. Taking advantage of these resources, our study created an MLM and is the first study to our knowledge that used an MLM for risk stratification of abnormal CST. Since abnormal CST can be used as a surrogate for the entire spectrum of CAD, this study promotes the idea that MLMs can be used to risk stratify for all CAD spectrums.

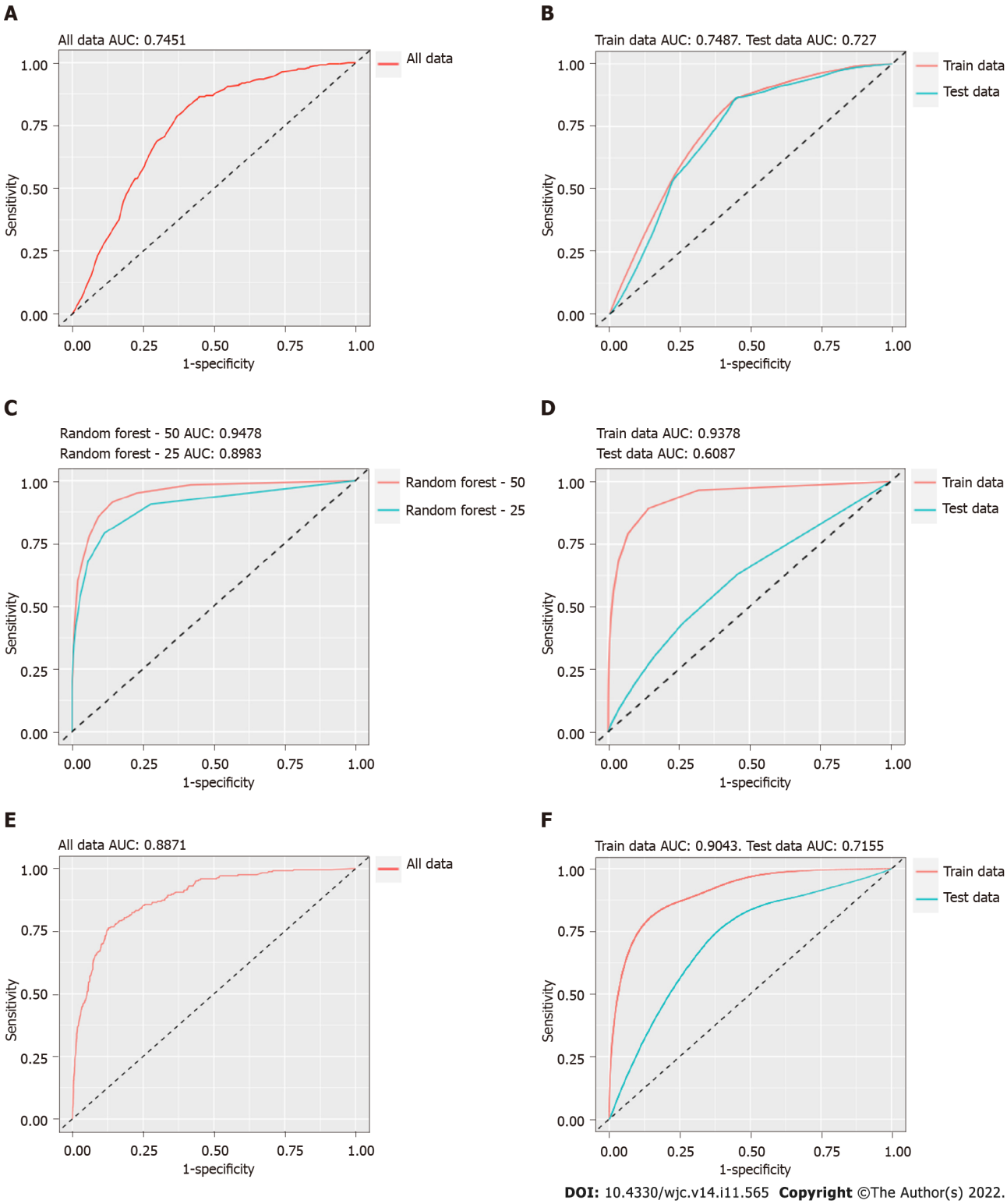

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Figure 2 Receiver operating characteristic curve. A: The binomial regression (BR) model; B: The interval validation of the BR model; C: The random forest models with 25 trees and 50 trees; D: The internal validation of the random forest model; E: The XGBoost model; F: The internal validation of the XGBoost model. AUC: Area under the receiver operating characteristic curve.

There are limitations to this study. First, ECG was not included in the study. ECG can improve both the PPV and NPV. Second, given the clear definitions of the computable phenotypes, the probability of missing a true risk factor or outcome is very low, but it is not zero. Third, we included only ten explanatory variables in this study, which is likely one of the reasons for lower NPV. Similar MLM studies with better predictive performance have incorporated 14 or more explanatory variables. Lastly, this study was a retrospective single-center study. Future studies replicating this study will strengthen the external validity of the current findings.

CONCLUSION

The current study achieved a better PPV for the entire spectrum of CAD (not just AMI) compared to the currently used risk stratification tools. These results highlight the potential of using MLMs in clinical decision-making. The results of this study also advanced the idea that a well-designed prospective study, which incorporates ECG and ensures proper follow-up, can achieve a much better PPV than currently used stratification tools (*i.e.*, the HEART pathway-ADP and the EDACS-ADP) while simultaneously maintaining an NPV of 99% for chest pain presentation to the ER. Data sharing and external validation of these prospective trials will be crucial to the recognition and adoption of MLMs.

ARTICLE HIGHLIGHTS

Research background

Risk stratification tools exist for patients presenting with chest pain to the emergency room and have achieved the recommended negative predictive value (NPV) of 99%. However, the current stratification tools result in unnecessary clinical interventions due to a low positive predictive value (PPV).

Research motivation

Healthcare costs are astronomical in the United States, including for patients who present with chest pain. These costs emphasize the need for a better stratification tool to safely identify patients who present with chest pain for early discharge without unnecessary testing.

Research objectives

This study aimed to create a machine learning model (MLM) for risk stratification of chest pain patients with a better PPV while maintaining an NPV of 99%.

Research methods

This retrospective cohort study used demographics, coronary artery disease history, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, obesity, and smoking as the covariates for the prediction of an abnormal cardiac stress test (CST). Binomial regression (BR), random forest, and XGBoost MLMs were used for prediction. Bootstrapping was used for the internal validation of the prediction models.

Research results

The XGBoost MLM had the best PPV of 24.33%, with an NPV of 91.34% for abnormal CST. The BR MLM had a PPV of 21.34% and an NPV of 92.55%. The random forest MLM had a PPV of 20.55% and an NPV of 90.24%.

Research conclusions

The XGBoost MLM provided a better PPV than currently used stratification tools (24.33% *vs* 13.00%-17.50%). Though the NPV from the XGBoost MLM remained lower than the recommended value of 99%, it highlights the potential use of MLMs in clinical decision-making.

Research perspectives

Data sharing and external validation of the MLMs will be crucial for their recognition and widespread adoption.

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FOOTNOTES

Author contributions: Shafiq M was involved in all aspects of this study, including but not limited to study design, data collection, data analyses, and writing of the abstract and manuscript; Mazzotti DR was involved in study design, data collection, and data analyses; Gibson CA assisted in writing the abstract and manuscript.

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ORIGINAL ARTICLE

Observational Study

Time trends in antithrombotic therapy prescription patterns: Real-world monocentric study in hospitalized patients with atrial fibrillation

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Abstract

BACKGROUND

Since 2010, the European Society of Cardiology has extended prescription criteria for oral antithrombotic therapy (OAT) in atrial fibrillation (AF). Direct oral anticoagulants (DOACs) were upgraded from an IIAa recommendation in 2012 to an IA in 2016. In real-world scenarios, however, OAC prescription is still suboptimal, mainly for DOACs.

AIM

To evaluate OAT temporal prescription patterns in a cohort of patients hospitalized with AF in a Cardiology Department.

METHODS

A retrospective observational study was conducted on a cohort of hospitalized patients in a secondary setting (Trapani, Italy) from 2010 to 2021 with AF as the

main or secondary diagnosis. For 4089 consecutive patients, the variables extracted from the Cardiology department database were: Sex, age, time of hospitalization, antithrombotic therapy (warfarin, acenocoumarol, apixaban, dabigatran, edoxaban, rivaroxaban, aspirin, clopidogrel, other antiplatelet agents, low molecular weight heparin, and fondaparinux), diagnosis at discharge and used resources. Basal features are presented as percentage values for categorized variables and as mean +/- SD for categorized once.

RESULTS

From January 1st, 2010 to October 6th, 2021, 25132 patients were hospitalized in our department; 4089 (16.27%, mean age 75.59+/-10.82) were discharged with AF diagnosis; of them, 2245 were males (54.81%, mean age 73.56+/-11.45) and 1851 females (45.19%, mean age 78.06+/-9.47). Average length of stay was 5.76+/-4.88 days; 154 patients died and 88 were moved to other Departments/Structures. AF was the main diagnosis in 899 patients (21.94%). The most frequent main diagnosis in patients with AF was acute myocardial infarction (1973 discharges, 48.19%). The most frequent secondary cardiac diagnosis was chronic coronary syndrome (1864 discharges, 45.51%), and the most frequent secondary associated condition was arterial hypertension (1010 discharges, 24.66%). For the analysis of antithrombotic treatments, the final sample included 3067 patients, after excluding in-hospital deaths, transferred out or self-discharged patients, as well as discharges lacking indications for prescribed treatments. OAC treatment increased significantly (35.63% in 2010-2012 *vs* 61.18% in 2019-2021, +25.55%, $P < 0.0001$), in spite of any antiplatelet agent use. This rise was due to increasing use of DOACs, with or without antiplatelet agents, from 3.04% in 2013-2015 to 50.06% in 2019-2021 (+47.02%, $P < 0.0001$) and was greater for factor Xa inhibitors, especially apixaban. In addition, treatment with a vitamin K antagonist, in spite of any antiplatelet agent use, decreased from 35.63% in 2010-2012 to 11.12% in 2019-2021 (-24.48%, $P < 0.0001$), as well as any antiplatelet therapy, alone or in double combination, (49.18% in 2010-2012 *vs* 34.18% in 2019-2021, -15.00%, $P < 0.0001$); and patients not receiving antithrombotic therapy declined with time (14.58% in 2010-2012 *vs* 1.97% in 2021, $P < 0.0001$).

CONCLUSION

Real-world patients with AF are elderly and affected by cardiovascular and non-cardiovascular diseases. The percentage of patients on OAT and DOACs increased. These data suggest a slow, gradual guidelines implementation process.

Key Words: Atrial fibrillation; Antithrombotic agents; Time series; Warfarin; Direct-acting oral anticoagulants; Aspirin

Core Tip: In this study, the proportion of patients on oral antithrombotic therapy, with or without an antiplatelet agent, increased significantly from 2010 to 2021. This rise was due to increasing use of direct oral anticoagulants, with or without antiplatelet agents. At the same time, there was a gradual decline in the use of vitamin K antagonists, with or without antiplatelet drugs, and of antiplatelet therapy, alone or in double combination, while the proportion of patients not receiving antithrombotic therapy decreased. These data suggest a slow and gradual guidelines implementation process.

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INTRODUCTION

Atrial fibrillation (AF) represents the most common type of sustained cardiac arrhythmia and an emerging epidemic throughout the world, affecting 1%–2% of the adult population[1]. Its prevalence rises steeply from 0.1% in patients < 60 years to approximately 20% in those ≥ 85 years[2,3]. With the progressive aging population and improved survival from other forms of cardiovascular disease[3], both AF prevalence and incidence have been progressively increasing[2,4-6], becoming a significant public health burden.

AF is often associated with increased rates of death, hospitalization, cardiovascular and non-cardiovascular complications, and degraded quality of life, and is a known independent cardiac risk factor (fourfold to fivefold) for ischemic stroke, due to high thromboembolic risk[7-9]. This risk is greater in the elderly (in patients 80-89 years old it reaches 23.5%)[7]. Up to 15%-20% of all strokes are due to AF. AF is often associated with other cardiovascular risk factors or conditions, such as diabetes mellitus, arterial hypertension, chronic coronary syndromes, or heart failure, linked to a further increase in thromboembolic risk[10].

Contemporary registry-based observational studies from various geographical regions have consistently shown that patients with thromboembolic complications, particularly ischemic stroke and systemic thromboembolism (acute mesenteric ischemia, and acute limb ischemia) and AF, have a worse prognosis, more disability, longer hospital stays, more medical and neurologic complications, and greater case fatality rates than those without AF[11]. This increases health-care related costs and reduces quality of life[12]. Stroke prevention is therefore central to the management of AF and is a major public health priority.

Fortunately, among patients with AF, stroke, thromboembolic events and death risk may be up to two-thirds mitigated *via* the usage of oral anticoagulants (OACs), that it is superior to no treatment or antiplatelet agents such as acetylsalicylic acid (ASA), until recently a treatment choice, in patients with different stroke risk profiles[13-17]. The net clinical benefit is almost universal, except for patients with a very low stroke risk.

The European Society of Cardiology (ESC)[18-21] as well as other societies[22-25], in their evidence-based guidelines dedicated to AF, have widened since 2010 the indications for antithrombotic therapy, and now claim OACs as the appropriate treatment for stroke prevention in most patients (namely with additional stroke risk factors, introducing use of the CHA_2DS_2-VASc and HAS-BLED scores for stroke and bleeding risk stratification, respectively. All patients with non-valvular AF (NVAF), except those who are at low risk or with contraindications, require antithrombotic prophylaxis in order to prevent thromboembolism[18-21].

OACs include vitamin K antagonists (VKAs) and, in recent years, direct oral anticoagulants (DOACs). VKAs (in particular warfarin, historically the first-line stroke prevention option and the only available OAC for decades) are effective for preventing stroke by up to two-thirds, regardless of renal function, and with minor costs[26]. The good anticoagulation control with VKAs is assessed by high time in the therapeutic range (TTR). However, previous randomized controlled trials and real-life settings have controversies regarding TTR values[27]. In low TTR values, VKAs were found to be associated with severe complications, and a minimum TTR of 58% should be achieved to expect a net benefit from being on OAC therapy[28]. VKAs have, however, important limitations such as a narrow therapeutic window, requirement for close monitoring and frequent follow-ups, drug–drug and drug–food interactions, unpredictable dose-response effects, and a slow onset and ebbing of action. As a result, in the past years many AF patients received ASA, other antiplatelet agents, or both, or no antithrombotic treatment[6].

Management of AF patients has dramatically improved following the introduction of DOACs, comprising factor Xa inhibitors, such as apixaban, edoxaban, and rivaroxaban, and direct thrombin inhibitors (dabigatran etexilate), first approved in 2010, that showed numerous advantages over warfarin. DOACs rapidly became preferred by both clinicians and patients due to their easier usage: easy dosing schedule, rapid onset of action, more predictable efficacy which allows a fixed-dose regimen, no need for frequent international normalized ratio (INR) controls and fewer interactions with co-medication or with food[29-31]. In terms of stroke and systemic thromboembolism prevention, all DOACs were demonstrated at least to be non-inferior and in some respects superior (*e.g.* fewer intracranial hemorrhages) compared with warfarin in randomized controlled trials[32-35], even in older populations[36]. Recently, there has been a significant price drop in DOACs and meta-analyses of randomized controlled trials[37-39], as well as observational data[40-42] confirm their efficacy and real-life effectiveness. However, DOACs have higher costs and need adjustment based on renal function.

Currently, all four DOACs are approved in Italy. The European Medicine Agency (EMA) authorized dabigatran and rivaroxaban use in 2008 (they became available for use in clinical practice on the Italian market in 2013). The EMA approved apixaban in 2011 (available in Italy since January 2014), and edoxaban (available since June 2015). Since 2013, the Agenzia Italiana del Farmaco authorized (AIFA) them for cardiovascular risk reduction in NVAF[43].

After the release of DOAC, several European and North American scientific societies updated their guidelines, now recommending DOACs as first choice treatment in most patients with NVAF[19-21,24,25]. The changes in guidelines, coupled with the emergence of DOACs, whose use has been steadily increasing over a decade[17], have the potential to transform clinical practice patterns.

It is important, however, that AF guidelines are adhered to, as non-adherence to OACs is associated with increased ischemic stroke and mortality in high-risk patients[44].

Notwithstanding the increasing percentage of patients treated with DOACs[45,46], observational studies and administrative databases widely reported the suboptimal use of OACs for stroke prevention [47-51].

In the past, patients with NVAF remained untreated for several reasons, including overestimation of patient bleeding risk and underestimation of stroke risk by physicians[52], and the presence of comorbidities, mainly in elderly patients[53]. Sociodemographic and economic factors can influence

prescription patterns[54-56]. On the other hand, DOAC prescription is subject to prior authorization in the Italian as well as in other National Health Systems[57,58]. Until recently, regulatory criteria placed DOAC as a second line therapy, limiting their use to patients in which VKA are contraindicated, or with objective difficulties in accessing INR control facilities, or with high intracranial hemorrhage risk[57].

Nevertheless, real-world studies in this population, are still scarce, in particular there is limited evidence on temporal trends of contemporary AF management since the introduction of DOACs[46,59-61], and treatment patterns at single country level are less known. In Italy, since their introduction, the rate of DOAC utilization is one of the lowest in Europe[43,58,61-63]. Thus, an updated analysis of DOAC treatment in Italy for NVAF patients could be useful.

Knowledge obtained from real-world scenarios may suggest strategies to improve the entire AF care process[63]. The questions are: do prescribers follow current guidelines for OACs prescription in AF patients, and has adherence to guidelines changed over time?

In this paper, the authors discuss the actual real-world status and the change, in its temporal trend, in the prescription of antithrombotic treatments in patient with AF consecutively discharged from a Cardiology Unit during an almost twelve-year period. We hypothesized that adherence to OACs prescription according to guidelines recommendations for patients with AF would improve over time.

MATERIALS AND METHODS

Study design and setting

This was a retrospective, single-center, observational study conducted in the Cardiology Unit of S. Antonio Abate Hospital of Trapani (Western Sicily, Italy). This unit takes care of all cardiovascular diseases and is also equipped with a cardiac catheterization and electrophysiology laboratory.

Study population

We reviewed the database of medical records of all patients aged ≥ 18 years who were consecutively discharged from a reference cardiology center from January 2010 to 2021. The following inclusion criteria were applied: any diagnosis of AF (both main and secondary) at discharge from hospital and hospitalization not resulting in death. Patients without indication of prescribed drugs were excluded.

Study variables and definitions

We collected data on demographic and clinical characteristics, including age and sex, main and secondary diagnosis at discharge, diagnostic and therapeutic procedures, and prescribed antithrombotic treatments from the discharge medication list.

The presence of AF was ascertained during the hospital stay by medical history taking, in-hospital diagnosis by 12-lead electrocardiography, or 24-h Holter monitoring.

The discharge diagnosis codes assessed for each patient and the diagnostic and therapeutic procedures were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

We considered: AF, ICD-9-CM code 42731; cardiovascular diseases (angina pectoris, ICD-9-CM codes 4111, 4131 and 4139; acute myocardial infarction, ICD-9-CM code 410; chronic coronary syndromes, ICD-9-CM codes 412, 414, 429, V4581, V4582; cardiomyopathies, ICD-9-CM codes 402 and 425; valvular diseases, ICD-9-CM codes: 394, 396, 397, 424, 394, V433; peripheral vascular disease, ICD-9-CM codes: 433.1, 440.2, 443.9; acute and chronic heart failure, ICD-9-CM codes: 428, 5184; cardiac arrhythmias, ICD-9-CM codes 426, 427, 727.89; endocarditis, ICD-9-CM codes 421, 424; pulmonary embolism, ICD-9-CM code 415; aortic aneurysm, ICD-9-CM code 493, chest pain, ICD-9-CM codes 786, V717), and other concomitant diseases, such as diabetes mellitus, ICD-9-CM code: 250; arterial hypertension, ICD-9-CM codes: 401–404; dyslipidemias, ICD-9-CM code 272; pulmonary diseases (chronic bronchitis, ICD-9-CM code: 491; asthma, ICD-9-CM code: 493; other, 518, 519, 492, 466, 491, 485, 486, 515, 518, V126; sleep apnea, ICD-9-CM codes: 780.51, 780.53, 780.57, 780.54); disorders of the thyroid gland, ICD-9-CM codes: 240–246; cerebrovascular diseases (stroke/transient ischemic attack (TIA)/hemorrhagic stroke, ICD-9-CM codes: 430–436, 438, 442, 4370); dementia, ICD-9-CM code: 290; other cerebral degenerations, ICD-9-CM code: 331; anemia, ICD-9-CM codes 280, 282, 283, 285; obesity, ICD-9-CM code 278; renal diseases, ICD-9-CM codes 584, 585, V560; neoplastic diseases, ICD-9-CM codes: 1419, 1420, 1479, 1512, 1519, 1534, 1537, 1539, 1540, 1541, 1561, 1590, 1599, 1619, 1629, 1749, 179,185, 1882, 1889, 1890, 1970, 1976, 1980, 1985.

In order to evaluate resource usage related to AF management we considered: length of hospital stay; diagnostic test prescription (such as echocardiogram, ICD-9-CM code: 8872; other ultrasound scan tests, ICD-9-CM code: 887; stress tests, ICD-9-CM code: 894; coronary angiography, ICD-9-CM codes: 885, 3721; peripheral angiography, ICD-9-CM code: 884; Holter ECG monitoring, ICD-9-CM code: 895; computed tomography, ICD-9-CM codes: 8703, 8704, 8741, 8742, 8801; and magnetic resonance imaging, ICD-9-CM code: 889); and interventional procedures (such as electrical cardioversion, ICD-9-CM code: 996; cardiac pacemaker implantation, ICD-9-CM codes: 377, 378; automatic cardiac defibrillator implantation, ICD-9-CM code: 379; percutaneous transluminal coronary angioplasty, ICD-9-CM codes: 885, 3721; peripheral percutaneous transluminal angioplasty, ICD-9-CM codes: 004, 0066, 3950; coronary

stenting, ICD-9-CM codes: 004, 360, 377; and peripheral stenting, ICD-9-CM code: 3990).

We searched antithrombotic drug prescription at discharge based on the Anatomical Therapeutic Chemical (ATC) Classification System codes.

The OACs in this study included VKA (warfarin and acenocoumarol) and DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban); antiplatelet drugs (aspirin, clopidogrel, ticlopidine, ticagrelor, and prasugrel), low molecular weight heparin (LMWH) and fondaparinux were also considered. We defined a subject as receiving a VKA prescription if he/she redeemed a discharge prescription with a drug having ATC code B01AA03 (warfarin) or B01AA07 (acenocoumarol). On the other hand, we defined DOAC users as those subjects redeeming prescriptions of dabigatran (ATC code: B01AE07), rivaroxaban (ATC code: B01AF01), apixaban (ATC code: B01AF02), and edoxaban (ATC code: B01AF03).

The patients were then further stratified into the following main categories: (1) Monotherapy with VKAs; (2) monotherapy with DOACs; (3) OAC therapy (VKAs or DOACs); (4) single antiplatelet therapy (SAPT); (5) double antiplatelet therapy (DAPT); (6) double antithrombotic therapy (DAT) (one OAC and one antiplatelet drug); (7) triple antithrombotic therapy (TAT) (DAPT plus OAC); and (8) without therapy.

Drug choice was based on the knowledge and expertise of each prescriber, thus ensuring the collection of real-life data.

Data source and analysis

We retrieved anonymized medical records stored in the Cardiology Unit databases, collected in electronic case report forms (Microsoft Office Access 2013, Redmond, Washington, United States). Data quality was monitored electronically as well as through periodic medical and data quality reviews, on-site monitoring, and audits.

Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. In compliance with privacy laws, the patients' identification codes were encrypted using a unique and anonymous personal identification code. According to the Italian law for confidentiality data, informed consent was not required for using anonymized retrospective information. Each patient, however, signed a written informed consent form at hospital admission, agreeing to the use of his/her data in anonymous form for any aim of medical research. No additional follow-up visits or testing was performed beyond those carried out as part of routine clinical care.

Statistical analysis

Data cleaning was performed by verifying minimum and maximum values and by analyzing missing data. Data from patients with missing values were not removed from the analyses of general AF patterns but removed from the analysis of treatment patterns.

The analysis provides descriptive statistics to summarize data patterns. Standard descriptive statistical methods were used to analyze the patient's demographics and clinical status, and to evaluate the proportion of treated patients in each drug category. The considered variables were year of discharge, age, sex, length of stay, discharge diagnosis, undertaken diagnostic and therapeutic procedures and prescribed drugs at discharge. Once the database was cleaned, a descriptive analysis was undertaken. Continuous variables were reported as mean and standard deviation (± SD), whereas categorical variables were expressed as absolute and relative frequencies with percentages, as appropriate. Continuous variables were compared using the Student's *t*. Categorical data were compared using the χ^2 test or Fisher's exact test, as appropriate. A two-tailed P value < 0.05 was considered statistically significant. The statistical analysis was performed using Microsoft Office Excel 2013 (Redmond, Washington, United States) and MedCalc (https://wwwmedcalc.org), and graphs were created using Microsoft Office Excel 2013 (Redmond, Washington, United States). The statistical methods of this study were reviewed by the authors themselves.

RESULTS

For the at-discharge analysis, we included data from 25132 discharges from January 1, 2010 to October 6, 2021.

A diagnosis of AF was present in 4089 discharges (16.27%). Figure 1 shows the behavior of hospital discharges in the considered period. Total discharges decreased from 2444 in 2010 to 1532 in 2020 (2021 data were not considered because they were partial) (-37.32%). Discharges without AF diagnosis decreased from 2022 in 2010 to 1362 in 2020 (-30.66%). Discharges with AF diagnosis decreased from 422 in 2010 to 216 in 2020 (-48.81%). The decrease in discharges with AF diagnosis was significantly superior to the decrease in discharges without AF diagnosis (-18.15, P < 0.0001). Discharges with AF as the main diagnosis decreased from 121 in 2010 to 17 in 2020 (-85.95%). Discharges with AF as a secondary diagnosis decreased from 301 in 2010 to 199 in 2020 (-33.88%). The decrease in discharges with AF as the

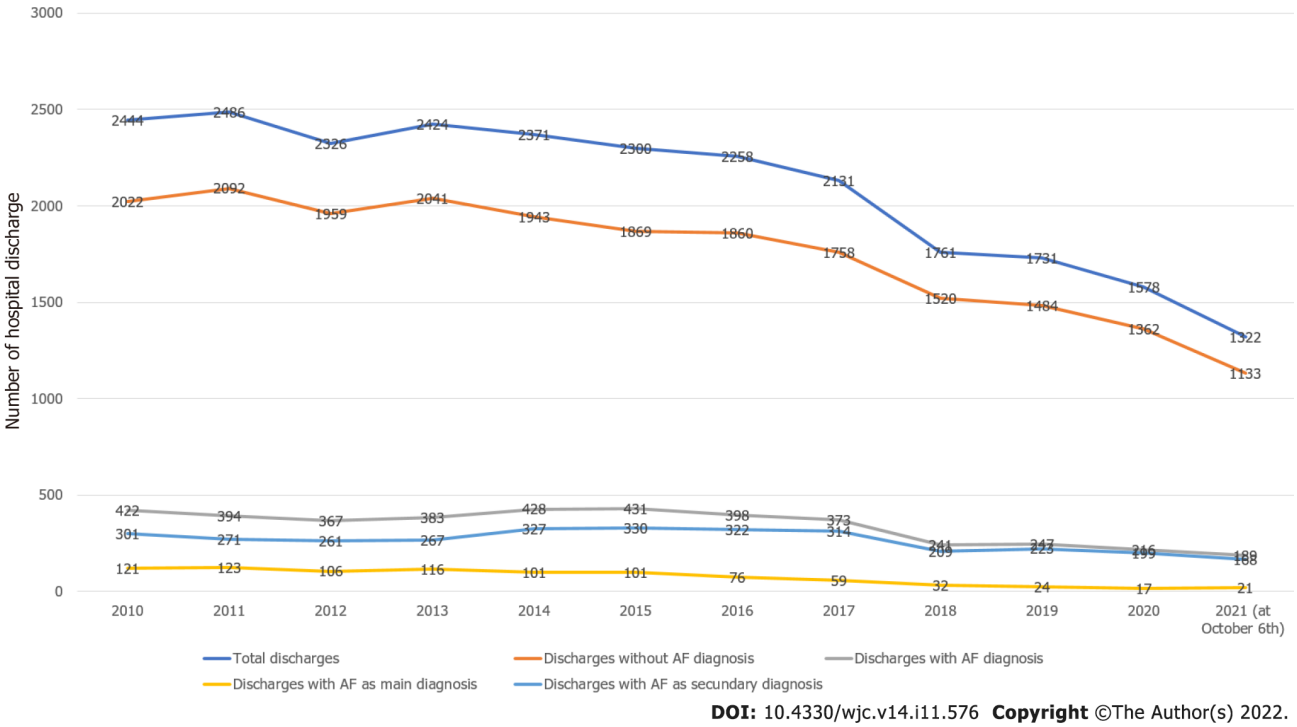

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Figure 1 Time trends in the number of hospital discharges (total, with and without atrial fibrillation diagnosis); discharges with atrial fibrillation were further divided into the main or secondary diagnosis. AF: Atrial fibrillation.

main diagnosis was superior to the decrease in discharges with AF as a secondary diagnosis (-52.07, $P <$ 0.0001).

Among AF patients, 1851 were females (45.19%) and 2245 males (54.81%), with a male/female ratio of 1.21. The mean age of AF patients was 75.59+/-10.82 years. Mean age was lower in males (73.56+/-11.45) than in females (78.06+/-9.47) ($P < 0.0001$).

AF was the main diagnosis in 899 discharges (21.94%) and the secondary diagnosis in 3190 discharges (88.06%). AF as the secondary diagnosis was observed more frequently than as the main diagnosis (+66.12%, $P < 0.0001$).

Other main diagnoses are shown in Table 1. The prevalence in this table is related to the total sample. The most frequent main diagnosis in patients with AF was acute myocardial infarction. Secondary diagnoses are shown in Table 2. The prevalence in this table is related to the total sample. Of course, the sum of these percentages exceeds 100%, as a patient could have more comorbidities at the same time. The most frequent secondary cardiac diagnosis was chronic coronary syndrome, and the most frequent secondary associated condition was arterial hypertension.

With regard to resource utilization, mean length of stay was 5.76+/-4.88 days in the total sample. Mean length of stay was 3.37+/-2.92 days in discharges with AF as the main diagnosis, and 6.48+/-5.11 days in discharges with AF as a secondary diagnosis. Length of stay was lower in discharges with AF as the main diagnosis ($P < 0.0001$).

Diagnostic and therapeutic procedures are shown in Table 3. The prevalence in this table is related to the total sample. Of course, the sum of these percentages exceeds 100%, as a patient could have received more diagnostic and therapeutic procedures at the same time. The most frequently used procedure was echocardiogram, whereas the most frequently performed intervention was percutaneous transluminal coronary angioplasty (PTCA)/stenting. Healthcare utilization was noticeable in this AF group.

For the analysis of antithrombotic treatments, we excluded in-hospital deaths, transferred out or self-discharged patients, as well as discharges lacking indications for prescribed treatments. The final sample was made of 3067 patients with AF diagnosis and known therapy. Figure 2 shows the flowchart of the study.

Antithrombotic drugs prescribed at discharge are shown in Figure 3. ASA was the most utilized drug (29% of prescribed drugs), followed by warfarin (27%) and clopidogrel (14%). VKAs were prescribed in 29% of total antithrombotic drugs. Among them, warfarin was undoubtedly the most prescribed drug (92.77% *vs* 7.23% of acenocoumarol). DOACs were prescribed in 20% of total drugs. Among them, apixaban was the most prescribed (39% of all DOACs). Antiplatelet agents were prescribed in 45% of drugs. Among them ASA was the most prescribed (63.65%), followed by clopidogrel (31.53%).

Changes over time in the prescribed antithrombotic drugs are shown in Table 4 (absolute numbers). After an initial increase, VKAs prescription progressively decreased. Antiplatelet drugs prescription decreased progressively over time. In contrast, DOAC prescription increased sharply from 0.5% in 2013

Table 1 Other main diagnosis excluding atrial fibrillation in the studied sample

Diagnosis	*n*	%
AMI	1973	48.19
Cardiac arrhythmias	210	5.37
Chest pain	201	4.91
Heart failure	143	3.49
Chronic coronary syndrome	80	1.95
Cardiomyopathies	77	1.88
Peripheral artery disease	74	1.81
Stable angina	55	1.34
Unstable angina	45	1.10
Pericarditis	29	0.71
Valvular heart diseases	27	0.66
Shock	21	0.51
Pulmonary embolism	22	0.49
Other	233	15.65

AMI: Acute myocardial infarction.

to 57% in 2021. The percentage of prescribed OACs increased from 27% in 2010 to 64% in 2021, whereas the percentage of patients without any antithrombotic therapy decreased from 13% in 2010 to 4% in 2021.

In order to avoid an accentuation of year-to-year variability, data on treatment were grouped in 3-year periods, as shown in Figure 4. VKAs prescription decreased from 35.63% in 2010-2012 to 11.12% in 2019-2021 (-24.48%, $P < 0.0001$). Antiplatelet drugs prescription decreased from 49.18% in 2010-2012 to 34.18% in 2019-2021 (-15.00%, $P < 0.0001$). On the contrary, DOACs prescription increased from 3.04% in 2013-2015 to 50.06% in 2019-2021 (+47.02%, $P < 0.0001$). OAC prescription increased from 35.63% in 2010-2012 to 61.18% in 2019-2021 (+25.55%, $P < 0.0001$), whereas the percentage of patients without any antithrombotic therapy decreased from 14.58% in 2010-2012 to 1.97% in 2021 ($P < 0.0001$).

It should be considered that antithrombotic treatments can be combined variously among patients, particularly as our population sample consisted of a large percentage of acute and chronic coronary heart disease patients. Thus, in Figure 5 we show the behavior over time of various antithrombotic combinations. SAPT, DAPT, VKAs, and no therapy decreased over time, whereas DOACs, DAT, TAT and global OACs increased over time.

Finally, these data have been corrected according to the total number of discharges, as their number is not stable over time, as shown in this study. Figure 6 shows the trend in prescribed antithrombotic therapy during the study period. The more relevant data are the sharp increase in patients treated with DOAC (from 0.78% in 2013 to 52.38% in 2021, $P < 0.0001$) and with OACs (from 34.31 in 2010 to 80.95 in 2021, $P < 0.0001$); conversely, the number of patients not receiving any antithrombotic therapy decreased from 16.67 in 2010 to 4.23 in 2021 ($P < 0.0003$).

DISCUSSION

In this retrospective, single center, contemporary real-world study we examined clinical characteristics, resource utilization, and temporal trends over a twelve-year interval in antithrombotic therapy prescription pattern in a cohort of patients discharged from a cardiology unit with a diagnosis of AF.

Discharges with AF diagnosis decreased over time, and the decrease in discharges with AF as the main diagnosis was significantly superior to the decrease in discharges with AF as the secondary diagnosis. We observed that AF patients were elderly, and predominantly male, with a high prevalence of concomitant cardiac and extra-cardiac diseases. Healthcare utilization in this group of patients was noticeable in terms of both diagnostic and therapeutic procedures.

In terms of antithrombotic treatments, from 2010 to 2021 patients on OAC therapy increased significantly, regardless of antiplatelet drugs use. The increasing use of DOACs, namely factor Xa (FXa) inhibitors (especially apixaban), can explain this phenomenon. Contextually, VKA use, regardless of antiplatelet treatments, declined, like antiplatelet therapy, alone or in double combination, while the

Table 2 Secondary cardiac and extra-cardiac diagnoses in the studied sample

Secondary diagnosis	*n*	%
Cardiac		
Chronic coronary syndromes	1864	45.51
Cardiomyopathies	1221	29.81
Valvular heart diseases	595	14.53
Heart failure	406	9.91
Arrhythmias	119	2.91
Angina pectoris	91	2.22
Extra-cardiac		
Arterial hypertension	1010	24.66
Renal diseases	985	24.05
Diabetes mellitus	932	22.75
Lung diseases	617	15.06
Dyslipidemias	345	8.42
Cerebrovascular & psychiatric diseases	313	7.64
Thyroid diseases	152	3.71
Anemia	166	4.05
Peripheral artery diseases	146	3.56
Obesity	137	3.12
Neoplastic diseases	83	2.03

proportion of patients not receiving antithrombotic therapy decreased.

In this study, a diagnosis of AF was present in 4089 on 25132 discharges from 2010 to 2021. Total discharges decreased (-37.32%) from 2010 to 2020. This phenomenon may be explained by the shift in medical treatments from hospital to territory. Also discharges with and without AF diagnosis decreased from 2010 to 2020 (respectively -48.81% and -30.66%), but the decrease in discharges with AF diagnosis was greater than the decrease in discharges without AF diagnosis (-18.15, $P < 0.0001$). Although the incidence and prevalence of AF are expected to increase due to progressive growth in the number of elderly people in the general population, our sample reflects only patients hospitalized in a cardiology unit. Thus, the decrease in discharges with AF diagnosis may be explained, in general, by the decrease in total hospital admissions and, in particular, by the reduction in admission of patients with a paroxysmal AF, that is now considered inappropriate; in fact, the decrease in discharges with AF as the main diagnosis was significantly superior to the decrease in discharges with AF as the secondary diagnosis (-52.07, $P < 0.0001$). However, AF as a secondary diagnosis was observed more often than as the main diagnosis (+66.12, $P < 0.0001$). This was due to the real-world nature of this observational study, focused on a global sample of patients admitted to a cardiology unit.

We observed that AF patients were elderly (mean age was 75.59+/-10.82 years), as shown in other studies[29,46,52,64,65]. Males accounted for the majority of patients in the whole study group: the male/female ratio was 1.21. This confirms the data from other studies[29,59,65,66]. An opposite trend, with a greater prevalence in women, was observed by Ermini[63]. The mean age was lower in males (73.56+/-11.45) than in females (78.06+/-9.47) ($P < 0.0001$).

The most frequent main diagnosis in patients with AF was acute myocardial infarction. The most frequent secondary cardiac diagnosis was chronic coronary syndrome, and the most frequent secondary associated condition was arterial hypertension. A high prevalence of concomitant cardiac and extra-cardiac diseases was shown, in particular arterial hypertension, diabetes mellitus, heart failure, and coronary artery disease. This profile of comorbidities at baseline was in agreement with previous analyses[46,53,63,67,68]. In the Akershus Cardiac Examination 1950 study, 87.6% of men with AF and 86.4% of women with AF had comorbidities, compared with 74.4% and 66.3%, respectively, without AF [3]. Thus, our subjects reflected real-world clinical practice, including a large proportion of patients with advanced age and many comorbidities.

With regard to resource utilization, mean length of stay was 5.76+/-4.88 days in the total sample. Mean length of stay was 3.37+/-2.92 days in discharges with AF as the main diagnosis, significantly lower than in discharges with AF as a secondary diagnosis (6.48+/-5.11, $P < 0.0001$). The procedure

Table 3 Main diagnostic and therapeutic procedures performed in the studied sample

Procedures	*n*	%
Diagnostic		
Echocardiogram	3588	87.60
Coronary angiography	804	19.63
Dynamic ECG monitoring	458	11.18
CT scan	299	7.30
Other echography	212	5.18
Stress test	139	3.39
Therapeutic		
Coronary PTCA/stenting	941	22.97
PM implantation	258	6.30
ICD implantation	90	2.20
Peripheral vessels angiography	90	2.20
Peripheral vessels PTCA/stenting	60	1.46
Electric cardioversion	56	3.71

PTCA: Percutaneous transluminal coronary angioplasty; ECG: Electrocardiogram; CT: Computerized tomography; PM: Pacemaker; ICD: Implantable cardiac defibrillator.

most frequently used was echocardiogram, whereas the most frequently performed intervention was PTCA/stenting. Thus, healthcare utilization in this group of patients is noticeable in terms of both diagnostic and therapeutic procedures.

Our study was able to show the trends in antithrombotic treatments in AF patients. During the study periods, several guidelines on antithrombotic AF management have been published. In practice, the ESC guidelines progressively extended the indication for OAC, excluded antiplatelet treatment, and gave greater importance to DOACs[18-21].

It is known, however, that real-world guideline implementation is not a simple process. The increasing prevalence of AF and AF-related comorbidities proves the need for comprehensive prevention and management strategies. The challenge is the optimization of therapy for each patient. However, there are still gaps in optimal stroke prevention[17].

Thus, the main purpose of this study was to investigate whether guideline recommendations in terms of antithrombotic treatment were actually applied in clinical practice, by evaluating antithrombotic treatment patterns in Italian patients with a discharge diagnosis of AF. In this setting, several disease-specific, prospective observational studies and registry programs were created to better understand AF populations, their demography, treatments, and clinical outcomes at world[45,46,69-72] and European level[9,10,44,73-76]. In addition, observational data are available from America[6,51,71,77,78], Europe [52,55,58,59,62,79-83], and Asia[53,84-93].

A progressive improvement in the guideline-recommended antithrombotic prophylaxis of stroke in AF patients, mainly in newly diagnosed cases, has been shown by these studies[59]; however, most of them belong to the pre-DOAC era, and there is still much to learn about how DOACs are being used in clinical practice. The present study adds to the few studies that have investigated the prescription pattern of antithrombotic agents in AF patients in recent years: Proietti[76] evaluated patients from Belgium, Denmark, Greece, Italy, Norway, Poland, Portugal, Romania, and the Netherlands; Huisman [45,46] evaluated patients from Asia, Africa/Middle East, Europe, Latin America and North America; and Apenteng[59] studied United Kingdom patients.

In our study, antiplatelet agents were prescribed in 45% of total drugs. Among them ASA was the most prescribed (63.65%), followed by clopidogrel (31.53%). ASA was also, in total, the most utilized drug, followed by warfarin and clopidogrel. SAPT, however, decreased significantly over time from 49.18% in 2010-2012 to 34.18% in 2019-2021 (-15.00%, $P < 0.0001$). Antiplatelet therapy was also commonly prescribed in other studies, regardless of whether there was coexistent myocardial infarction or coronary artery disease[74,75]. Other studies showed, for example, that antiplatelet agents were used in 30% of all patients with AF[63] and in 36% in the pre-DOAC era[58]. Antiplatelet agents are particularly used in the elderly; in 18.3%, 18.9%, 18.9%, and 18.7% of patients aged 75–< 80, 80–< 85, 85–< 90, and ≥ 90 years, respectively[87]. In other studies, treatment with ASA was also the most common (41.7% of patients in GARFIELD[45,46]), whereas in others was very low (3.3%)[68]. The proportion of patients

Table 4 Changes in prescribed antithrombotic drugs over time in the studied group (absolute numbers)

Yr	Warfarin	Acenocumarole	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Aspirin	Clopidogrel	Ticlopidine	Ticagrelor	Prasugrel	LMWH	Fondaparinux	No therapy
2010	32	3					41	35	1			2		17
2011	93	3					82	30				2		24
2012	100	11					99	47				1		58
2013	177	12		2			191	73	7	7	1	17	4	65
2014	114	7		10			108	28		12		7	4	41
2015	149	12		18	11		138	40	5	13	1	20	1	55
2016	127	6		29	25	3	138	48		13	5	26		34
2017	116	17	18	24	46	16	95	63		7		9	6	30
2018	56	4	20	45	54	21	52	43		4		3	1	7
2019	43	4	40	40	67	21	68	55		2		3	2	2
2020	31	1	19	30	55	27	49	46		5		7	5	7
2021	15	2	29	17	46	41	35	35				4	2	8

LMWH: Low molecular weight heparin.

treated with antiplatelet agents other than ASA was low (3.4%)[45,46], in contrast to the high clopidogrel use in our data. These differences may be explained by the fact that we studied unselected cardiology patients with high prevalence of acute and chronic coronary syndromes, and in whom antiplatelet therapy was still prescribed routinely with or without oral anticoagulation. Minor use of antiplatelet agents over time as sole therapy for stroke prevention in AF is a common finding and other studies showed a downward trend from 36% to 17% (in GARFIELD-AF)[70], from 18% to 8% (in the ORBIT-AF program)[71], from 6.1 to 2.5%[80], from 36,5% to 10,5%[59], and from 36% to 25%[58]. It is increasingly recognized that antiplatelet agents are of little benefit and have a not insignificant risk, although 2010 ESC guidelines still endorsed aspirin for patients at intermediate stroke risk according to $CHADS_2$ risk stratification[18]; however, in the 2012 update[19] antiplatelet drugs were to be considered only in patients refusing any OAC. In the 2014 AHA/ACC/HRS treatment guidelines[24] aspirin was still considered an option for AF patients with moderate stroke risk. Conversely, the 2019 AHA/ACC/HRS guidelines[25] suggested that NVAF patients, regardless of their stroke risk, should not be treated with antiplatelet drugs monotherapy, unless an OAC is contraindicated; thus, high risk patients would be considered undertreated whenever only ASA is used. However, antiplatelet therapy continues in part to be inappropriately prescribed instead of OAC[68]. A reason of the persistence of antiplatelet agents use may be that anticoagulant prophylactic therapy is especially difficult in patients in whom a high thromboembolic risk coexists with contraindications for OAC treatment, such as the

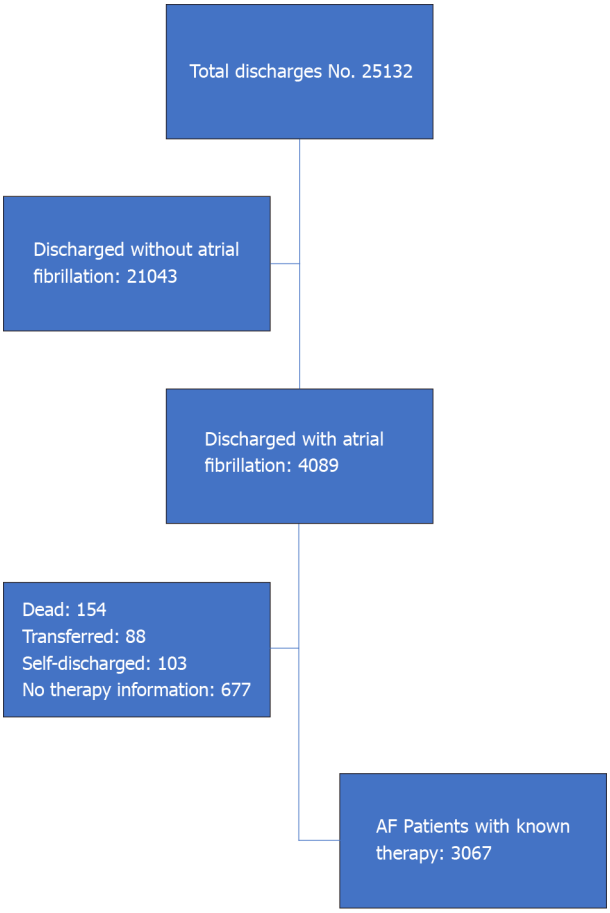

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Figure 2 Study flowchart.

elderly. OAC underuse, associated with antiplatelet therapy prescription, regardless of a known atheromatous disease, has been reported by Averlant *et al*[94] in elderly AF patients. In addition, in the post-DOAC era, patients who are receiving antiplatelet drugs have more comorbidities[58].

We observed that DAPT also decreased over time from 13.72% to 2.12%. In ACS patients treated with percutaneous coronary intervention (PCI), a DAPT is recommended to reduce stent thrombosis risk[67]. This reduced use of DAPT is likely due to a greater prescription of DAT or TAT in a population with noticeable prevalence of coronary syndromes.

In our study, VKAs were prescribed in 29% of total antithrombotic drugs. Among VKAs, warfarin was undoubtedly the most prescribed drug (92.77% *vs* 7.23% of acenocoumarol). VKAs prescription decreased significantly from 35.63% in 2010-2012 to 11.12% in 2019-2021 (-24.48%, $P < 0.0001$). In other studies, warfarin was also the most prescribed OAC (from 24.2% to 88.8%[29,64,75,79,90] according to the period and to the country. The PINNACLE study, conducted by the National Cardiovascular Data Registry, showed that only 55% of warfarin-eligible patients actually received that drug[77]. A gradual decrease in warfarin use was also observed in GARFIELD-AF[70,79,80], mainly after DOAC introduction. Geographical differences exist, however, in VKA therapy, with a notably greater use of VKAs in China, where it was the fastest growing OAC used[45,46,64], likely for economic reasons. Age and comorbidities (in particular decreased renal function) may guide the choice of warfarin instead of OACs[95]. In the post-DOAC era, patients receiving VKA have more comorbidities[58,87] in comparison to the pre-DOAC era, and are frequently treated with polypharmacy[96]. VKA use is also common in patients with acute and chronic coronary syndromes requiring both OAC and antiplatelet therapy[68,72].

We observed that DOACs represented 20% of the total prescriptions. Apixaban was the most frequently prescribed (39% of all DOACs). The more relevant data from this study are the sharp, statistically significant increase in patients treated with DOAC, from 0.78% in 2013 to 52.38% in 2021, $P < 0.0001$, and from 3.04% in 2013-2015 to 50.06% in 2019-2021, +47.02%, $P < 0.0001$. In 2018, DOAC use surpassed that of warfarin. Our study confirms apixaban as the most used DOAC[52,87,97]; however, other authors have observed the prevalent use of dabigatran[29,65,68] or rivaroxaban[43]. It is difficult to explain these differences, which are likely a consequence of local preferences.

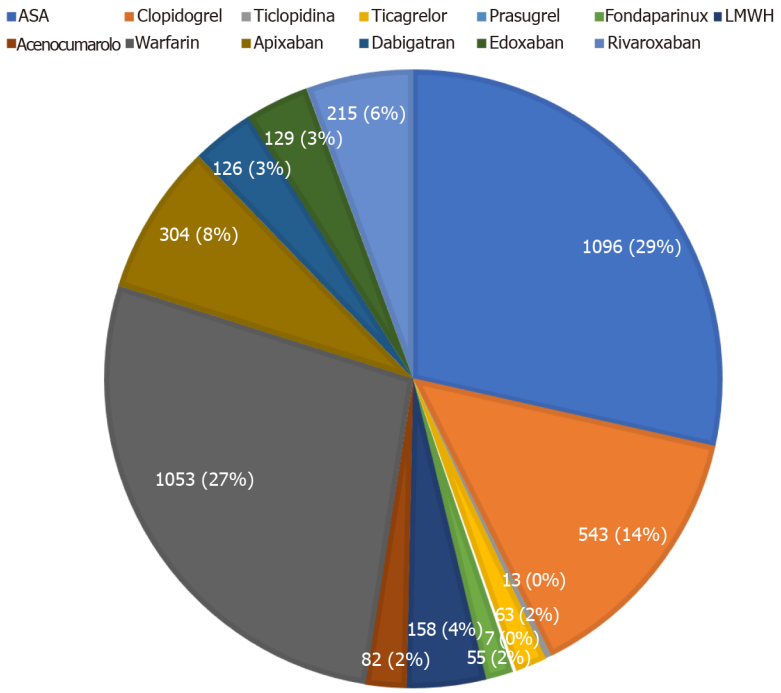

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Figure 3 Prevalence of different antithrombotic treatments as a percentage of total antithrombotic treatments. ASA: Acetylsalicylic acid; LMWH: Low molecular weight heparin.

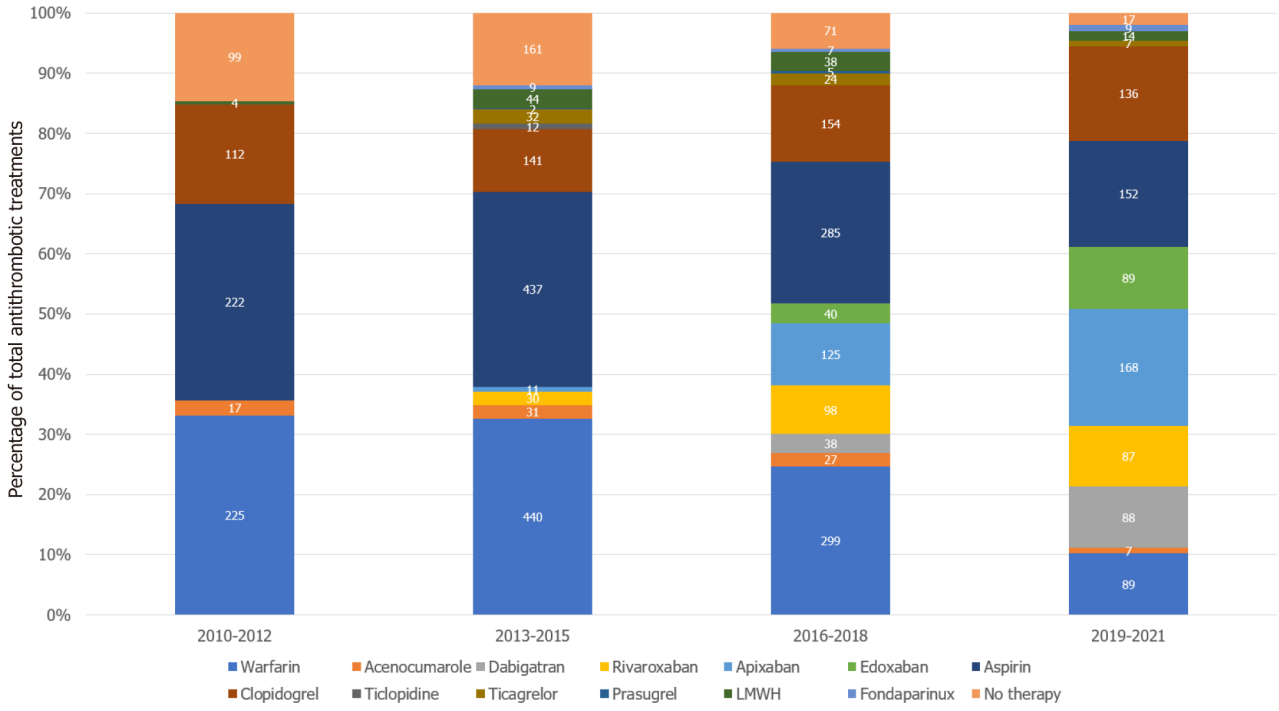

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Figure 4 Time trends over three-year periods (from 2010-2012 to 2019-2021) of the prevalence of different antithrombotic treatments as a percentage of total antithrombotic treatments. LMWH: Low molecular weight heparin.

The prescription rate of DOACs for NVAF, after their release in 2011, has increased significantly in recent years, as demonstrated by many other studies, which reported a substantial increase from 14.5% to 70.1%[68,71,80,98,99]. Some of these studies, however, used data from registries of cardiovascular care practices, which may favor enrolment of highly motivated patients under specialist care, and the applicability of these results to the general population may be limited[65]. Actually, DOAC adoption trends are quite variable, with slow integration into clinical practice reported in most countries[98]. A

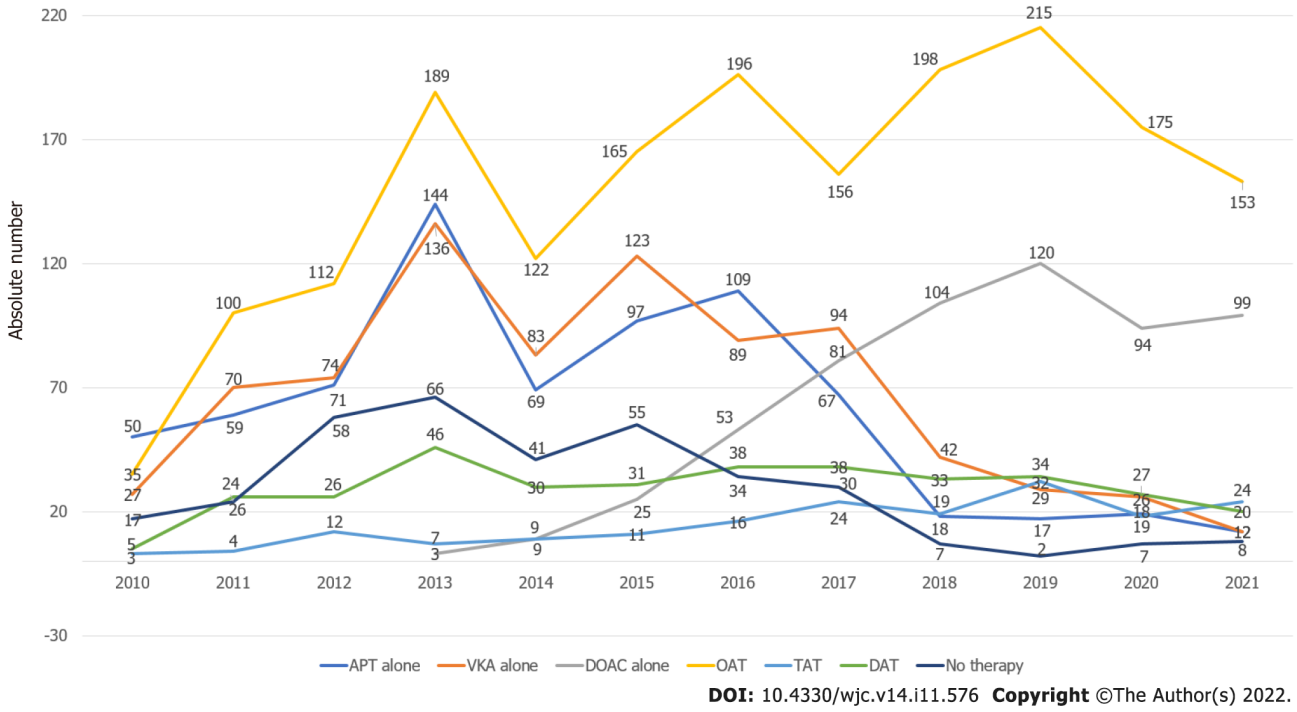

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Figure 5 Time trends by year (from 2010 to 2021) in prescription of different antithrombotic treatments (absolute number). APT: Antiplatelet treatment; VKA: vitamin K antagonist; DOAC: Direct oral anticoagulant; OAT: Oral antithrombotic therapy; TAT: Triple antithrombotic therapy; DAT: Double antithrombotic therapy.

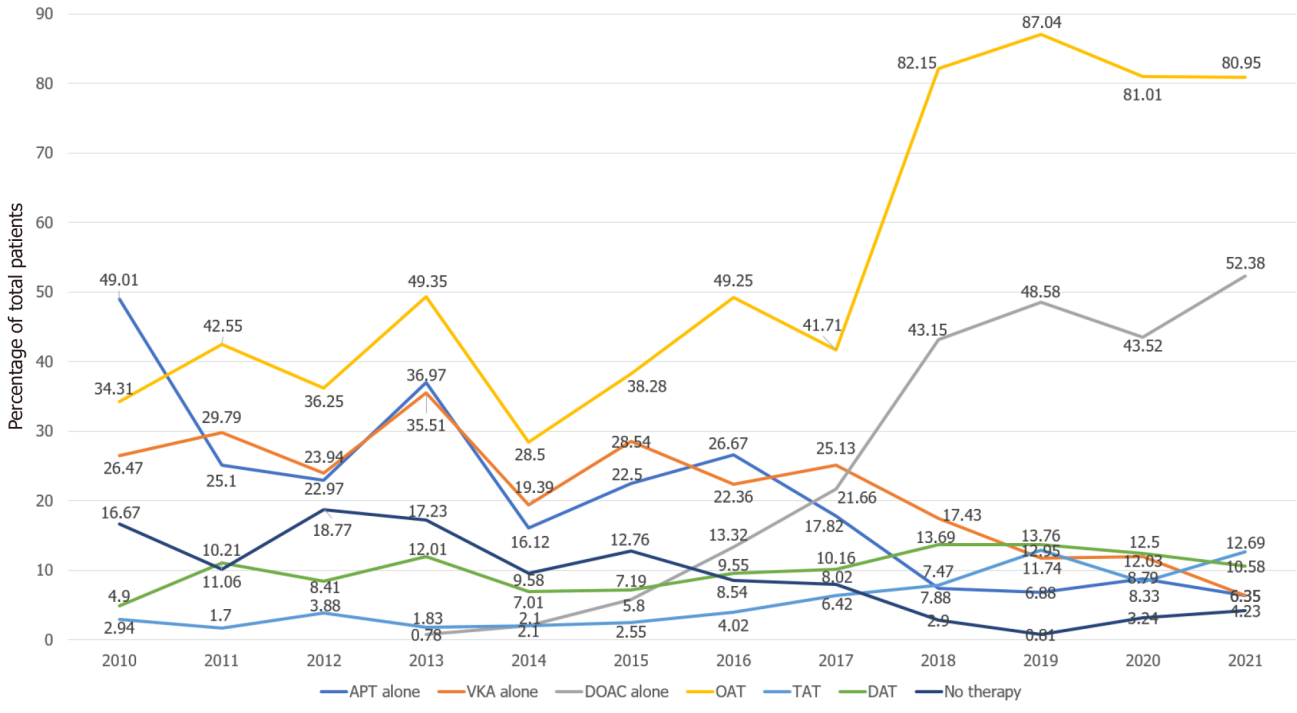

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Figure 6 Time trends by year (from 2010 to 2021) in prescription of different antithrombotic treatments (as a percentage of total patients). APT: Antiplatelet treatment; VKA: vitamin K antagonist; DOAC: Direct oral anticoagulant; OAT: Oral antithrombotic therapy; TAT: Triple antithrombotic therapy; DAT: Double antithrombotic therapy.

systematic literature review indicates that suboptimal OACs use is a persisting challenge, despite the availability of DOACs[100]. After the launch of the first DOAC in 2011, the proportion of DOACs as OAC increased from 3% in 2012 to 42% in 2016 (P < 0.0001 for the trend)[16]. A marked variability in NOAC use was observed between countries, ranging from 6.1% (in Thailand) to 87.5% (in Switzerland) of all OAC-treated patients[72]. Many countries have some limitations on DOAC usage due to its costs.

In Italy, in particular, reimbursement was possible only after mid-2013 for dabigatran, late 2013 for rivaroxaban, early 2014 for apixaban and late 2016 for edoxaban. In Italy, management with VKAs was better than in other European countries, allowing higher TTR[62]. Some studies aimed to determine the preference criteria in DOACs use. At patient level, prior stroke, transient ischemic attack, thromboembolism, thyroid disease, dyslipidemia, cancer, HAS-BLED ≥ 5, paroxysmal or non-permanent AF, and the presence of comorbidities were positive predictors of DOACs use over VKAs, whereas young age (≤ 64 years) and renal dysfunction (as they must be used with caution in this latter category of patients) were negative predictors of DOACs use over VKAs[57,68,99]. GARFIELD-AF showed that DOACs seemed to be favored for the management of patients with a low stroke risk (CHA_2DS_2-VASc 0 or 1)[72]. However, the extent of anticoagulant selection driven independently by ischemic stroke risk (predictions of treatment benefit) and bleeding risk (prediction of treatment harm) was marginal, as neither score explained much variation in the multivariable adjusted regression model[72,79]. Clinicians may be choosing warfarin in real-world clinical practice for patients with both high stroke risk and bleeding risk, indicating possible concerns about the lack of a reversal agent for the DOACs[29]. This contrasts with the reduced use of dabigatran in our study. DOAC use was more frequent than VKA in men and in the elderly[66,68,70,72], particularly apixaban[97], as they have fewer potential drug interactions in elderly patients. In the ANAFIE Registry, 72% of elderly AF patients receiving anticoagulant treatment were treated with DOACs[86]. However, in some studies DOACs were more frequently prescribed in female and young patients[55]. The rate of DOAC, rather than warfarin, was increased ($P < 0.0001$ for the trend) in patients with AF undergoing PCI[52]. OAC therapy at discharge was prescribed in approximately 30% of patients with AF and ACS requiring PCI (DOACs accounted for approximately half of them)[67].

In our study, both DAT (SAPT plus OAC) and TAT (the combination of OAC and DAPT to prevent both systemic embolism or stroke and coronary thrombosis, especially in the acute phase of the disease) increased over time (respectively from 4.90% in 2010 to 10.58% in 2021 and from 2.94% in 2010 to 12.69% in 2021). These data are in agreement with many other studies[52,59,63,68]. However, our data refer to a general population admitted to a cardiology unit with various diagnoses, while different results have been observed in selected samples such as patients with both AF and coronary artery disease (in particular those with ACS and/or undergoing PCI). Combined antithrombotic regimens present a great challenge in these real-world clinical scenarios. Previous studies have shown that warfarin alone was not sufficient to avoid stent thrombosis, and SAPT or DAPT alone was not adequate to prevent AF-related thromboembolic events; therefore, patients with AF undergoing PCI are typically prescribed multiple antithromboembolic drugs. Before the introduction of DOACs, from 2013 to 2014, only 1.7% of patients were treated using both warfarin and DAPT in the China acute myocardial infarction (CAMI) registry[92]. After DOAC introduction, in patients with ACS the rate of DAT prescription increased over the years (from 41% in 2010 to 59% in 2016, $P = 0.012$ for the trend) whereas TAT prescription decreased (from 14% in 2010 to 5% in 2016, $P = 0.010$ for the trend)[16] and the co-prescription of DOACs and antiplatelet drugs did not change much in recent years[59]. 'Triple therapy' is likely less prescribed by physicians due to concerns regarding bleeding risk. A greater risk-to-benefit ratio of DAT (DOAC plus a P_2Y_{12} inhibitor) in comparison to a VKA-based TAT has been shown in randomized controlled trials[101,102]. The Danish nationwide administrative registries showed that DOACs use exceeded that of warfarin, in any combination with antiplatelet drugs, by 2016[103]. These studies influenced current international guidelines, now favoring, in this setting, a DAT with a DOAC and a P_2Y_{12} inhibitor (especially clopidogrel).

From 2010 to 2021, globally, we observed that OAC was prescribed in 49% of all antithrombotic therapy, but even more we showed an increase in patients treated with OACs (from 34.31% in 2010 to 80.95% in 2021, $P < 0.0001$ and from 35.63% in 2010-2012 to 61.18% in 2019-2021, +25.55%, $P < 0.0001$). In a similar study, Mai[67] reviewed 3813 electronic medical records of patients aged ≥ 18 years, who were hospitalized from 2013 to 2018, which showed that prescription of OACs in patients with AF was low (29.7%). Another study, from 2014 to 2017, showed that 90.1% of patients received an OAC (either as a monotherapy or combined with antiplatelet drugs[68]. In other studies conducted in different temporal and geographical settings the rate of prescription of OACs, both in monotherapy and in association with antiplatelet drugs, varied from 41.2% to 92%[15,60,64,73,103]. These data, on the one hand, indicate how guidelines can be successfully applied in the real world, but, on the other hand, they suggest that OAC underuse persists, despite the growing awareness of anticoagulation benefits in AF[71,80]. OAC use seems especially low in Italy, as reported by the PREFER-AF registry[62]. Our results are in line with previous studies from different populations, demonstrating a recent increase in OAC use[44,46,60,70,104], particularly after the introduction of DOAC [15,59,72,89,91]. The proportion of patients treated with OAC monotherapy increased slowly, but gradually[52]. DOACs availability, together with comprehension of the reduced efficacy of antiplatelet drugs in comparison to OACs, have likely driven, at least in part, this paradigm shift in prescribing practice, notwithstanding an initial reluctance of healthcare payers due to the greater DOAC costs[70]. The prescription of OACs, as well as its temporal trend, is also related to various geographic and clinical patterns. In patients who underwent PCI, the OAC prescription rate increased from 56% in 2010 to 74% in 2016 ($P = 0.041$ for the trend) and OAC monotherapy gradually increased from 2% in 2010 to 9% in 2016 ($P = 0.041$ for the trend)[16]. Another study showed that OAC treatment was prescribed at discharge only in about 30% of patients with AF

and ACS requiring PCI[67]. Among the factors playing a role in OACS underuse, we should consider demographic patterns (*i.e.*, elderly and women), concomitant diseases such as hepatic or renal disease, lack of adherence, physicians' and patients' treatment fears, and lack of access to the healthcare system. With regard to age, for example, patients prescribed OACs at discharge were younger than those not prescribed OACs (mean age 71.7+/-10.6 *vs* 74.6+/-10.2 years)[64]. In the RAMSES prevention strategies trial[85], a national observational registry on Turkish adults with NVAF, OAC therapy was prescribed for 74.8% of participants younger than 80 years and 63% of those aged 80 and older ($P < 0.001$). Comorbidities and other individual-level characteristics may explain this difference in the elderly. Higher CHA_2DS_2-VASc score and lower HAS-BLED score were independent predictors of OAC prescription in participants aged 80 years and older[85]. OAC treatment was prescribed in only half of elderly patients in the Fushimi AF Registry[89]. A retrospective Chinese study showed that OACs were prescribed in only 41.1% of AF patients aged ≥ 65 years[15]. The overall OACs rate in older people, notwithstanding the higher risk of bleeding, was greater (87.3%) in another study[87], and 92% of patients ≥ 75 years old received OAC treatment in the All Nippon AF in the Elderly (ANAFIE) Registry [86], as well as 92% of patients ≥ 80 years old in the OCTOFA study[81]. Other factors, such as lower levels of education, lower income, prior antiplatelet use, having several cardiovascular comorbid conditions (including stroke or transient ischemic attack, hypertension, diabetes, dyslipidemia, valvular heart disease, heart failure, coronary syndromes, carotid stenosis, and peripheral vascular disease) were associated with not being prescribed an OAC[64,75]. OACs use was greater in low bleeding risk patients than in those with both high stroke and high bleeding risk (94.2% *vs* 91.3%, $P < 0.0001$)[88]. However, patients with contraindications to OACS are a minority. For example, in the elderly, only 4% of patients had such contraindications (primarily, active cancer and anemia)[68]. In 86,671 elderly AF patients, only 2% were ineligible for OAC therapy due to absolute contraindications (most often previous intracranial bleeding)[71]; also, OACs were contraindicated in less than 13% of 10130 patients in the ORBIT-AF trial [78].

In our study, LMWH and fondaparinux were used in approximately 6% of total antithrombotic drugs, but they were used in very low percentages as unique treatment throughout the 12-year period. Another study showed that LMWH, not endorsed just from the 2012 ESC guidelines[19], was used in 2.5% of patients[68].

Finally, we showed that the percentage of patients without any antithrombotic therapy, including antiplatelets and LMWH/fondaparinux, significantly decreased from 16.67% in 2010 to 4.23% in 2021 ($P < 0.0003$) and from 14.58% in 2010-2012 to about 1.5% in 2019-2021. These data are consistent with other studies, showing that a total varying from 21.9% to 30.2% did not receive any prophylactic antithrombotic therapy[46,60,70,75,90] with substantial variations across countries. A recent meta-analysis reviewed a total of 11,231 publications, demonstrating in patients with high stroke risk a rate of non-treatment of 23.3% (7.9%-51.1%)[100]. Undertreatment is frequent in female and older patients, notwithstanding their great stroke risk[36,87,93,105]. However, in the DOAC era, non-treatment rates in high-risk patients are lower than in the pre-DOAC era (11.1%, 95%CI 7.9%-40.2% *vs* 33.6%, 95%CI 13.4%-51.1%)[100]. Patients receiving no treatment are generally younger and healthier[70]. However, patients who received no treatment in the post-DOAC era had more comorbidities ($P < 0.01$, respectively)[58].

Strengths and limitations

Our study has several strengths, including the analysis of clinicians' preferences on antithrombotic treatment in a broad spectrum, consecutive, geographically defined population over a long period of time, providing a novel contribution by characterizing OAC prescriptions pattern among patients with AF.

However, our results should be interpreted in the context of the limitations of this study, whose purpose was restricted to the review of analyses of observational data collected through clinical databases, reflecting real-world clinical practice, which presented some limitations.

First, although efforts were made to standardize definitions and reduce missing data, this was a retrospective study with the limitations inherent to observational study design such as selection biases due to residual or not measured confounding factors (*i.e.* sociodemographic, patient preferences, biochemical parameters, and/or clinical confounding variables unavailable in the data, which would have likely impacted on the choice of treatment), all of which may restrict the interpretation of study results. In particular, data on CHA2DS2-VASc and HAS-BLED score were not available in the present analysis.

Second, data on detailed OAC types and the quality control of OAC use prior to hospitalization were not collected, likewise no follow-up was investigated, and therefore the effects of quality of warfarin control and of OAC adherence on outcome could not be evaluated.

Third, as all patients were discharged from a secondary center, the current registry is not free from referral bias. In addition, we studied patients managed only by cardiologists and discharged from a single center. The GARFIELD-AF registry found that patients who are managed in the outpatient setting are more likely to receive DOAC therapy than patients treated in emergency care or in the hospital setting[72].

Finally, we did not exclude valvular AF patients, in which VKA use is mandatory; however, only about 5% of all AF patients had mechanical heart valves or moderate-to-severe mitral stenosis[6] and an even lower proportion was observed in our study.

Thus, the results and conclusions of this study should be interpreted cautiously, as transferability to different contexts is limited.

CONCLUSION

AF has a negative impact on many cardiovascular diseases[106,107], but its most challenging is thromboprophylaxis. Although anticoagulation provides a net clinical benefit in patients with AF, a noticeable gap in antithrombotic prescription between real world and guideline recommendations was shown even in recent studies[108-111]. The long-awaited introduction of DOACs in the field of anticoagulation brought physicians a safer option, and in the last years, several real-world studies have confirmed their effectiveness and safety. The prescription trend of antithrombotic therapy in AF patients has noticeably changed over very recent years.

The main aim of our study was to describe patterns of OAC prescription for stroke prevention in a real-world population of Italian AF patients discharged by a cardiology ward. We demonstrated a significant increase from 2010 to 2021 in the proportion of OAC prescriptions, regardless of antiplatelet drugs use. This increase appears to be the consequence of greater DOACs use, mainly FXa inhibitors. Contextually, VKA use declined gradually regardless of antiplatelet drugs use, and the same phenomenon was shown for antiplatelet therapy alone or in double combination; finally we noted a decrease in the proportion of patients without any antithrombotic therapy.

These findings, in line with findings from other European and global datasets, appear consistent with recent changes in AF management guidelines; this suggests, in Italy, an improvement in adherence to guidelines clinical recommendations. Despite this significant improvement, we should highlight, however, that OAC prescription remains suboptimal over time; thus, a significant proportion of patients with AF still do not receive appropriate treatments for stroke prevention, suggesting that the increasing use of DOACs is not yet closing the gap between scientific evidence, recommendations from academic guidelines and clinical practice in the general population. Thus, an unmet medical need remains among patients with AF. Due to the nature of this study, we cannot, however, provide explanations as to the decision-making processes that underlie these apparent changes in prescriptions.

Improving adherence to AF guideline recommendations regarding OACs treatment requires still further efforts. Clinicians and policy makers should develop more specific educational intervention programs for physicians, to ensure that OACs, especially DOACs, are appropriately prescribed to eligible patients, in particular to vulnerable subgroups by age, socioeconomic status, and presence of comorbid conditions, in order to optimize health resources.

As the burden of disease continues to increase, it remains imperative to implement appropriate use of anticoagulation among AF patients with elevated stroke risk, targeted to local care delivery models, aiming to decrease both the risk of death and potentially preventable cardiovascular events, and associated medical costs for the healthcare systems. We need further studies investigating why OAC treatment in AF patients remains suboptimal, intervening on the relative barriers.

ARTICLE HIGHLIGHTS

Research background

International guidelines extended prescription criteria for oral antithrombotic therapy, in particular for direct oral anticoagulants (DOACs) in atrial fibrillation (AF). However, oral anticoagulant (OAC) prescription is still suboptimal, mainly for DOACs.

Research motivation

Considering the huge clinical impact and healthcare economic burden (in terms of both direct medical costs and indirect productivity losses), there are a number of reasons why it is important to complement experimental data with real-life or observational data, investigating OAC treatment in the real world, and the potential nonadherence to AF treatment guidelines. It is, in fact, important that AF guidelines are followed, as non-adherence to OACs is associated with increased ischemic stroke and mortality in high-risk patients.

Research objectives

We aimed to evaluate temporal prescription patterns of antithrombotic agents in a cohort of patients hospitalized with AF in a Cardiology Department. This should be useful in determining how AF guidelines are followed in the real-world.

Research methods

This was a retrospective, single-center, observational study conducted in the Cardiology Unit of S. Antonio Abate Hospital of Trapani (Western Sicily, Italy). We reviewed the database of medical records of all patients aged ≥ 18 years who were consecutively discharged from January 2010 to 2021. We collected data on demographic and clinical characteristics, including age and sex, main and secondary diagnosis at discharge, diagnostic and therapeutic procedures, and prescribed antithrombotic treatments from the discharge medication list.

Research results

From 2010 to 2021, we showed a significant increase in the proportion of AF patients on OAC therapy, regardless of antiplatelet agent use. The main reason for this increase was due to greater DOACs use, mainly FXa inhibitors. Contextually, VKA use, as well as antiplatelet therapy, alone or in double combination, declined; however, the proportion of patients not receiving any antithrombotic therapy globally decreased.

Research conclusions

These findings, in line with findings from other European and global datasets, appear consistent with recent changes in AF management guidelines; this suggests, in Italy, an improvement in adherence to guidelines clinical recommendations. Despite this, we should highlight, however, that OAC prescription remains suboptimal over time; thus, a significant proportion of patients with AF still do not receive appropriate treatments for stroke prevention, suggesting that the increasing use of DOACs is not yet closing the gap between scientific evidence, recommendations from academic guidelines and clinical practice in the general population.

Research perspectives

Improving the adherence to AF guideline recommendations for stroke prevention with OAC therapy requires further efforts. Clinicians and policy health makers need to develop more specific educational intervention programs for physicians to ensure that OACs, especially DOACs, are appropriately prescribed to eligible patients, in particular to vulnerable subgroups, in order to optimize health resources. We need further studies investigating why OAC treatment in AF patients remains suboptimal, intervening on the relative barriers.

FOOTNOTES

Author contributions: Abrignani MG was responsible for the conception and design of the study, and wrote the first draft of the manuscript; Lombardo A, Braschi A, Renda N, Abrignani V, and Lombardo RM contributed to the design of the study and made critical revisions of the manuscript related to its important intellectual content; and all authors gave final approval of the version of the article to be published.

Institutional review board statement: As this study was a retrospective review of a database with fully anonymized data and without risk of patients' identification, it does not require ethical approval in our Institution. Permission to use patient data from this facility has been obtained from the Head of Cardiology Unit, S. Antonio Abate Hospital of Trapani.

Informed consent statement: Patients were not required to give informed consent for the study as the analysis used anonymous clinical data that were obtained from a database.

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META-ANALYSIS

Potential for sodium-glucose cotransporter-2 inhibitors in the management of metabolic syndrome: A systematic review and meta-analysis

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Abstract

BACKGROUND

Landmark trials have established the benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) in cardiovascular disease including heart failure with reduced and preserved ejection fraction and renal diseases regardless of the presence of diabetes mellitus. However, studies evaluating the role of SGLT2-Is in metabolic syndrome (MetS) are limited.

AIM

This study primarily aimed to evaluate the impact of SGLT2-Is on the components of MetS.

METHODS

Two independent reviewers and an experienced librarian searched Medline, Scopus and the Cochrane central from inception to December 9, 2021 to identify placebo controlled randomized controlled trials that evaluated the impact of SGLT2-Is on the components of MetS as an endpoint. Pre- and post-treatment data of each component were obtained. A meta-analysis was performed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

RESULTS

Treatment with SGLT2-Is resulted in a decrease in fasting plasma glucose (–18.07

mg/dL; 95%CI: -25.32 to –10.82), systolic blood pressure (–1.37 mmHg; 95%CI: -2.08 to –0.65), and waist circumference (–1.28 cm; 95%CI: -1.39 to –1.18) compared to placebo. The impact on high-density lipoprotein cholesterol was similar to placebo (0.01 mg/dL; 95%CI: -0.05 to 0.07).

CONCLUSION
SGLT2-Is have a promising role in the management of MetS.

Key Words: Metabolic syndrome; Sodium-glucose cotransporter 2 inhibitors; Dapagliflozin; Empagliflozin; Cardiovascular disease

Core Tip: This meta-analysis of randomized, placebo-controlled trials aimed to evaluate the impact of dapagliglozin and empagliflozin on metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III. In doing so, it highlighted a statistically significant improvement in fasting plasma glucose, systolic blood pressure and waist circumference. The effect of dapagliflozin and empagliflozin on high-density lipoprotein cholesterol was similar to that of placebo. In addition to its primary aim, this study also highlighted an improvement in other cardiometabolic parameters including hemoglobin A1C, uric acid and body weight in patients that received dapagliflozin and empagliflozin.

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INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) are a relatively novel and revolutionary class of medications that reduce the reabsorption of glucose from the proximal tubules in the kidneys[1-4]. Their glycosuric effect led to their initial use in the management of patients with type 2 diabetes mellitus (DM)[1-4]. However, recent large, randomized control trials (RCTs) have highlighted the extension of their benefits to cardiovascular diseases (CVD) including heart failure with reduced and preserved ejection fraction and renal diseases regardless of the presence of DM[5-15]. However, to date, studies on the impact of SGLT2-Is in the management of metabolic syndrome (MetS) and its components remain inadequate. Metabolic syndrome is an emerging pandemic[16-19]. Its prevalence has risen from approximately 25% to 38% between the early 1990s to 2010s in the United States[16-19]. The prevalence has increased by 29.1% in people aged 40-60 years[16-19]. It has been defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III as the presence of 3 of 5 entities: (1) Waist circumference (WC) ≥ 102 cm in men and ≥ 88 cm in females; (2) Serum triglycerides (TGL) ≥ 150 mg/dL or on drug treatment for hypertriglyceridemia; (3) Serum high-density lipoprotein (HDL) cholesterol < 40 mg/dL in males and < 50 mg/dL; (4) Blood pressure (BP) ≥ 130/85 mmHg or on drug treatment for hypertension (HTN); and (5) Fasting plasma glucose (FPG) ≥ 100 mg/dL or on drug treatment for elevated blood glucose[20]. A growing body of evidence exists supporting the association of MetS with the development and progression of CVD[17-20]. In a meta-analysis by Mottillo *et al*[19] a 2-fold increase in the risk of CVD and CV mortality in patients with MetS was noted. DM is a component of the MetS and affords a 2-4-fold increase in CVD Risk[21]. Hence, there is an urgent need to improve the management of MetS, which currently ranges from lifestyle interventions such as physical activity and caloric restriction through dietary modification to pharmacological and surgical approaches that address components of the MetS[4]. The primary aim of this study is to evaluate the impact of the SGLT2-Is on the MetS parameters noted in NCEP ATP III criteria. The secondary aim is to highlight the effect of SGLT2-Is on other cardiometabolic parameters including hemoglobin A1C (HbA1c), body weight (BW) and uric acid (UA). This study is derived from placebo controlled RCTs that have evaluated the impact of these medications on CVD and its risk factors, as well as reported pre/post treatment values of MetS components.

Table 1 Jadad score of included studies

Ref.	Randomization	Blinding	Accountability	Jadad score
Bailey *et al*[24], 2015	2	1	1	4
Bailey *et al*[25], 2013	1	1	1	3
Rosenstock *et al*[26], 2012	1	1	1	3
Wilding *et al*[27], 2014	2	2	1	5
Matthaei *et al*[34], 2015	2	1	1	4
Jabbour *et al*[30], 2014	1	1	1	3
Anker *et al*[15], 2021	2	2	1	5
Sone *et al*[36], 2020	2	1	1	4
Bolinder *et al*[33], 2014	2	2	1	5
Rosenstock *et al*[37], 2015	2	1	1	4
Rosenstock *et al*[38], 2014	2	1	1	4
Kohan *et al*[28], 2016	1	1	1	3
Zinman *et al*[5], 2015	2	1	1	3
Brown *et al*[35], 2020	1	1	1	3
Qin *et al*[32], 2019	1	U	U	1
Gause-Nilsson 2014[1]	1	U	U	1
List *et al*[39], 2009	1	1	1	3
McMurray *et al*[31], 2019	2	2	1	5

[1]No baseline data reported for Gause-Nilsson 2014.
U: Unclear.

MATERIALS AND METHODS

Data sources and searches

Two authors independently searched the electronic library database in Medline, Scopus and the Cochrane central from inception to December 9, 2021, using the following keywords: SGLT2-I, metabolic, cardiometabolic, TGL, FPG, BP, HDL, waist, abdominal, circumference, lipids, waist-to-height ratio, hypertriglyceridemia, HTN, MetS, RCT, random allocation, randomly allocated, random, and allocated randomly. Additionally, different combinations of these keywords were applied in each database search. The search was extended to ClinicalTrials.gov. An independent search was also conducted by a qualified librarian using similar search terms.

Study selection

The eligible studies were RCTs, allocated patients to an SGLT2-I group (that received either Dapagliflozin or Empagliflozin) or a placebo group, reported baseline and post-treatment values ≥ 1 component of MetS, had a treatment duration 6 mo and were published in the English language. Studies not meeting these criteria were excluded. Disagreements on study selection were either resolved by consensus or by Farouk Mookadam. The study adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guideline[22] (PRISMA checklist).

Data extraction

Extracted data included duration of follow-up, sample size and dose of dapagliflozin and empagliflozin studied. Demographic and biomarker characteristics extracted at baseline and follow up included mean age, gender, race, DM, mean WC, FPG, TGL, HDL, systolic BP (SBP), diastolic BP (DBP), HbA1C, BW and UA.

Quality assessment

The methodologic quality of the RCTs was assessed using the Jadad score. Points were allocated for randomization, blinding and accountability of the study participants, with a total score range from 0 to 5 [23] (Table 1).

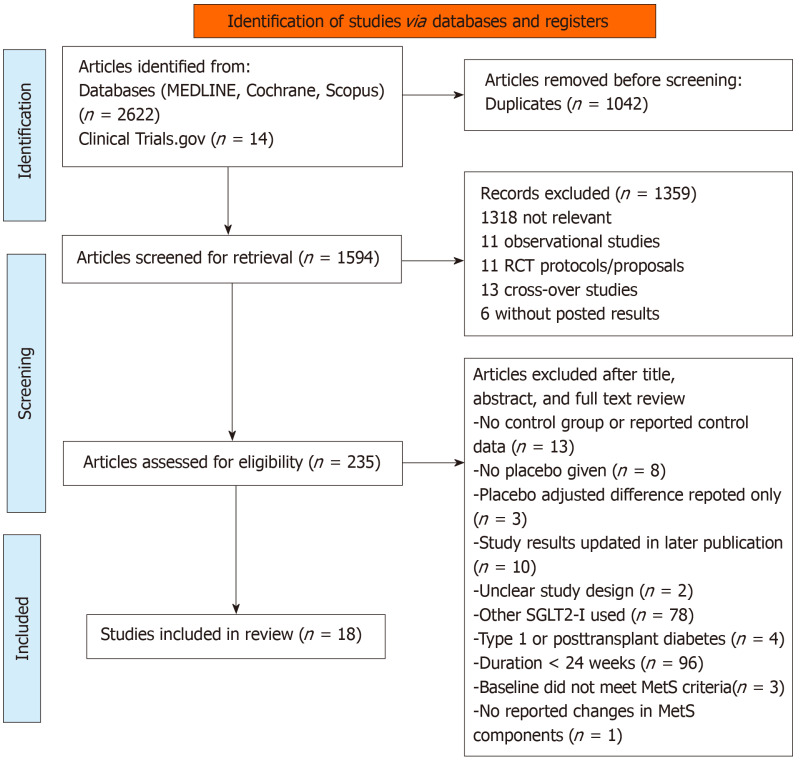

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Figure 1 PRISMA flow diagram showing outcomes of databases and registers search. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; Mets: Metabolic syndrome.

Outcomes

The primary outcomes of this study are post-treatment changes in WC, FPG, TGL, HDL, and BP. The secondary outcomes are post-treatment changes in BW, HbA1C and UA.

Statistical analysis

All outcome data were reported as mean with standard deviation and were converted to conventional units. Data analysis was performed using the RevMan (version 5.3; Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration). The forest plots of the above outcomes were visually represented after pooling the mean differences using the random-effects model. Heterogeneity was assessed with the I^2 test. Post-hoc subgroup analyses including doses and/or SGLT2-I type were performed if there was significant heterogeneity.

RESULTS

Search results and study inclusion

The initial literature search identified a total of 2636 potentially relevant studies, 14 of which were gathered from ClinicalTrials.gov. After excluding 1042 duplicates, a total of 1594 studies were screened. Of these, 235 studies were selected for abstract and/or full text review. An additional 217 studies were excluded either because they did not meet the above inclusion criteria, precursors of long-term studies, had a cross-over design or had no published results. A total of 18 studies[5,15,24-39] were eligible for meta-analysis (Figure 1). Of these, 3 studies reported WC[30,33,36], 9 reported FPG[24-27,29,30,34-36,39], 4 reported TGL[5,30,35,38], 3 reported HDL[34,37,38], 7 reported SBP[12,15,28,29,33,35,36] and 6 reported DBP[24,26,28,33,35,39] (Table 2 and 3).

Participant characteristics

A total of 26427 patients were included in the analysis. The SGLT2-I group comprised a total of 15914 patients. Of these, 7355 patients received dapagliflozin and 8559 received empagliflozin. The placebo group comprised a total of 10513 patients (Table 2 and 3). 59.4% were men. Among studies with reported data, 75% were White, 19.9% were Asian and 4.8% were Black. The mean treatment duration was 79 wk. The mean age in the SGLT2-I group was 53.4 years, and 54.8 years in the placebo group. The vast majority (78.6%) were DM patients. The baseline and post-treatment values of MetS components and the cardiometabolic variables are presented in Tables 3 and 4.

Table 2 Characteristics of included studies

				Treatment group		Placebo group	Participants (*n*)		Mean age (yr)		Race (*n*)		
Ref.	Duration (*wk*)	%male	%DM	SGLT2-I	Other therapy	Other therapy	SGLT2-I	Placebo	SGLT2-I	Placebo	White	Asian	Black
Bailey *et al*[25], 2013	102		100%	DAPA (2.5)	Metformin	Metformin	137	137	55.0 (9.3)	53.7 (10.3)			
				DAPA (5)	Metformin		137		54.3 (9.4)				
				DAPA (10)	Metformin		135		52.7 (9.9)				
Bailey *et al*[24], 2015	102		100%	DAPA (2.5)	Metformin	Metformin	65	75	53.0 (11.7)	52.7 (10.3)			
				DAPA (5)	Metformin		64		52.6 (10.9)				
				DAPA (10)	Metformin		70		50.6 (10.0)				
Bolinder *et al*[33], 2014	102	55.6%	100%	DAPA (10)		Placebo only	69	71	60.6 (8.2)	60.8 (6.9)	140	NR	NR
Brown *et al*[35], 2020	52	57.6%	100%	DAPA (10)		Placebo only	32	34	64.25 (7.01)	66.74 (6.62)			
Gause-Nilsson 2014[1]	104		100%	DAPA (10)	Insulin	Insulin	480	482					
Jabbour *et al*[30], 2014	48	54.8%	100%	DAPA (10)	Sitagliptin, metformin	Sitagliptin, metformin	223	224	54.8 (10.4)	55.0 (10.2)	332	4	17
Zinman *et al*[5], 2015	102			DAPA (2.5)		Placebo only	625	785	57.5 (9.9)	56.9 (10.2)			
				DAPA (5)			767		56.5 (10.1)				
				DAPA (10)			859		56.0 (9.9)				
List *et al*[39], 2009	12		100%	DAPA (2.5)		Placebo only	59	54	55 (11)	53 (11)			
				DAPA (5)		Metformin	58	56	55 (12)	54 (9)			
				DAPA (10)			47		54 (9)				
				DAPA (20)			59		55 (10)				
				DAPA (50)			56		53 (10)				
Matthaei *et al*[34], 2015	52	49.2%	100%	DAPA (10)		Placebo only	108	108	61.1 (9.7)	60.9 (9.2)	206	NR	NR
McMurray *et al*[31], 2019	72	77%	45%	DAPA (10)		Placebo only	2373	2371	66.2 (11.0)	66.5 (10.8)	3333	1116	226
Qin *et al*[32], 2019	16		100%	DAPA (10)		Placebo only	22	12					
				DAPA (10)	Saxagliptin		22						
Rosenstock *et al*[26], 2012	48		100%	DAPA (5)	Pioglitazone	Pioglitazone	141	139	53.2 (10.9)	53.5 (11.4)			
				DAPA (10)	Pioglitazone		140		53.8 (10.4)				

Wilding *et al*[27], 2014	104		100%	DAPA (2.5)	Insulin, existing OAD	Insulin, existing OAD	202	193	59.8 (7.6)	58.8 (8.6)			
				DAPA (5/10)[2]	Insulin, existing OAD		211		59.3 (7.9)				
				DAPA (10)	Insulin, existing OAD		194		59.3 (8.8)				
Anker *et al*[15], 2021	112	55%	49%	EMPA (10)		Placebo only	2997	2991	71.8 (9.3)	71.9 (9.6)	4542	824	258
Sone *et al*[36], 2020	52	72.6%	100%	EMPA (10)		Placebo only	86	90	58.3 (10.0)	59.1 (10.7)	NR	266	NR
				EMPA (25)			90		58.6 (9.5)				
Rosenstock *et al*[37], 2015	78	56%	100%	EMPA (10)		Placebo only	169	170	58.6 (9.8)	58.1 (9.4)	343	98	48
				EMPA (25)			155		59.9 (10.5)				
Rosenstock *et al*[38], 2014	52	45%	100%	EMPA (10)		Placebo only	186	188	56.7 (8.7)	55.3 (10.1)	531	NR	19
				EMPA (25)			189		58.0 (9.4)				
Zinman *et al*[5], 2015	220	71.5%	100%	EMPA (10)		Placebo only	2345	2333	63.0 (8.6)	63.2 (8.8)	5081	1517	357
				EMPA (25)			2342		63.2 (8.6)				

Data reported as mean (SD).

[1]No baseline data reported for Gause-Nilsson 2014.

[2]5 for 48 wk, 10 for 56 wk.

NR: Not reported; OAD: Oral antidiabetic drugs; SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; DM: Diabetes mellitus.

SGLT2-Is and FPG: Nine RCTs in which a total of 1474 patients received SGLT2-Is were analyzed. The random effect model demonstrated a mean reduction in FPG of –18.07 mg/dL (95%CI: -25.32 to –10.82; I^2 = 99%) (Figure 2A). The significant heterogeneity persisted after a subgroup analysis based on dose of SGLT2-Is (2.5 mg *vs* 10 mg). 463 participants received the 2.5 mg dose which had a similar impact as placebo on FPG: -1.45 mg/dL (95%CI: -8.73 to 5.82; I^2 = 71%) (Figure 2B). The 10 mg dose resulted in a higher reduction in mean FPG of –30.02 mg/dL (95%CI: -38.97 to –21.08; I^2 = 87%) (Figure 2B).

SGLT2-Is and BP: The analysis for SBP included a total of 6662 participants from seven RCTs. There was a modest mean reduction in SBP of –1.37 mmHg (95%CI: -2.08 to –0.65, I^2 = 85%) (Figure 3A). A subsequent post-hoc analysis based on SGLT2-I type demonstrated the empagliflozin RCTs were responsible for the high heterogeneity. The mean reduction noted with empagliflozin was not statistically significant: -0.70 mmHg (95%CI: 1.72 to 0.32; I^2 = 97%). Dapagliflozin use was associated with a higher mean SBP reduction of -2.03 mmHg (95%CI: -2.83 to –1.24; I^2 = 8%) (Figure 3B). The analysis of 6 RCTs that comprised 1018 total patients demonstrated no reduction in DBP with SGLT2-I use compared to placebo: -0.50 mmHg (-1.76 to 0.75; I^2 = 97%) (Figure 4).

SGLT2-Is and WC: A total of 378 patients from 3 RCTs received an SGLT2-I. The random effect model highlighted a mean reduction in WC of –1.28 cm (95%CI: -1.39 to –1.18; I^2 = 0%) (Figure 5).

Table 3 Baseline values for the MetS components

		Waist circumference (cm)		Triglyceride (mg/dL)		HDL (mg/dL)		SBP (mmHg)		DBP (mmHg)		Fasting plasma glucose	
Ref.	SGLT2-I (daily dose, mg)	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo	SGLT2-I	Placebo
Bailey *et al*[25], 2013	DAPA (2.5)							126.6 (14.5)	127.7 (14.6)	79.5 (8.7)	80.9 (9.0)	161.3 ± 43	165.42 (46.44)
	DAPA (5)							126.9 (14.3)		80.8 (8.5)		169.0 ± 49	
	DAPA (10)							126.0 (15.9)		79.0 (10.2)		155.9 ± 38.7	
Bailey *et al*[24], 2015	DAPA (2.5)	105.6 (14.9)	103.2 (13.8)					129.3 (16.1)	124.7 (16.3)	79.1 (7.9)	81.0 (9.5)	163.8 ± 48.6	160.2 (41.4)
	DAPA (5)	104.3 (11.7)						124.7 (15.3)		81.6 (8.9)		162 ± 45	
	DAPA (10)	108.1 (13.2)						125.1 (16.4)		80.2 (8.6)		167.4 ± 41.4	
Bolinder *et al*[33], 2014	DAPA (10)	105.6 ± 10.1	104.5 ± 12.3					136.1 ± 13.8	133.3 ± 13.7	80.6 ± 8.0	80.4 ± 8.3	147.6 ± 25.2	149.4 ± 25.2
Brown *et al*[35], 2020	DAPA (10)							137.25 ± 7.5	136.15 ± 9.11	79.16 ± 8.63	77.79 ± 8.25	140.4 ± 63	144.9 ± 54.0
Jabbour *et al*[30], 2014	DAPA (10)											162.2 (36.8)	163.0 (34.5)
Kohan *et al*[28], 2016	DAPA (2.5)							133.1 (17.2)	130.8 (15.8)	79.8 (9.3)	79.6 (9.0)		
	DAPA (5)							130.5 (16.2)		79.5 (8.9)			
	DAPA (10)							131.1 (16.3)		79.1 (9.3)			
List *et al*[39], 2009	DAPA (2.5)							127 ± 14	126 ± 16	78 ± 8	77 ± 8	145 ± 34	150 ± 46
	DAPA (5)							126 ± 13	126 ± 13	76 ± 8	78 ± 8	153 ± 48	143 ± 33
	DAPA (10)							127 ± 16		77 ± 8		148 ± 38	
	DAPA (20)							127 ± 15		77 ± 8		149 ± 41	
	DAPA (50)							126 ± 16		77 ± 9		153 ± 42	
Matthaei *et al*[34], 2015	DAPA (10)			185.9 ± 123.9	177.1 ± 79.7	46.44 ± 11.6	46.4 ± 11.6	134.5 ± 12.6	136.4 ± 14.2	80.4 ± 9.2	81.6 ± 7.9	167.4 ± 43.3	180.2 ± 43.1
McMurray *et al*[31], 2019	DAPA (10)									72.5 ± 13.2			
Rosenstock *et al*[26], 2012	DAPA (5)											168.6 +/-52.1	160.7 +/-47.0
	DAPA (10)											164.9 +/-46.3	
Wilding *et al*[27], 2014	DAPA (2.5)	109.7 (13.4)	110.2 (14.5)									180 ± 59.4	171 (57.6)
	DAPA (5/10)[1]	109.3 (13.4)										185.4 ± 59.4	
	DAPA (10)	109.6 (12.5)										172.8 ± 54	
Anker *et al*[15], 2021	EMPA (10)							131.8 ± 15.6	131.9 ± 15.7	78			

Rosenstock *et al*[37], 2015	EMPA (10)			175.23 ± 14.2	158.5 ± 7.97	46.1 ± 0.77	46 ± 0.77	132.4 ± 15.5	133.9 ± 16.3	78.4 ± 9.2	78.6 ± 10.9	138.6 ± 52.2	142.2 ± 46.8
	EMPA (25)			162.8 ± 0.8		46.1 ± 0.78		132.8 ± 15.1		77.9 ± 10.2		145.8 ± 25	
Rosenstock *et al*[38], 2014	EMPA (10)			171.7 ± 8.85	178.9 ± 12.4	46.1 ± 0.79	45.2 ± 0.77	134.2 ± 16.4	132.6 ± 15.8	79.5 ± 8.5	78.2 ± 8.8	158.9 ± 46.8	151.38 ± 45.72
	EMPA (25)			169.9 ± 7.08		46.4 ± 0.77		132.9 ± 14.2		78.7 ± 8.5		149.2 ± 48.6	
Sone *et al*[36], 2020	EMPA (10)	93.3 ± 8.8	93.8 ± 9.6					134.2 ± 14.6	135.7 ± 14.0	80.1 ± 10.2	79.6 ± 8.7	168.8 ± 43.1	159.1 ± 38.5
	EMPA (25)	93.1 ± 8.3						136.3 ± 14.3		80.0 ± 10.6		156.1 ± 37.7	
Zinman *et al*[5], 2015	EMPA (10)	104.9	105.1	168.4 ± 2.67	170.7 ± 2.53	44.7 ± 0.25	44.0 ± 0.24	134.9 ± 16.8	135.8 ± 17.2	76.6 ± 9.8	76.8 ± 10.1		
	EMPA (25)	104.9		172.6 ± 2.27		44.5 ± 0.25		135.6 ± 17.0		76.6 ± 9.7			

[1]5 mg for 48 wk, 10 for 56 wk.

HDL: High-density lipoprotein; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; SGLT2-I: Sodium-glucose cotransporter 2 inhibitor.

SGLT2-Is and HDL: A total of 1080 patients from 3 RCTs were analyzed for the impact of SGLT2-Is on HDL. There was no significant difference in post-treatment HDL between the SGLT2-I and placebo groups: 0.01 mg/dL (95%CI: -0.05 to 0.07; I^2 = 100%) (Figure 6).

SGLT2-Is and TGL: TGL levels pre or post treatment were not reported in all the trials. Hence this component of the MetS could not be analyzed in this meta-analysis.

SGLT2-Is and other cardiometabolic parameters: HbA1C, BW and UA.

SGLT2-Is resulted in a modest mean reduction in HbA1C: -0.68% (95%CI: -0.88 to –0.48; I^2 = 89%) (Figure 7A). A subgroup analysis based on doses (2.5 mg and 10 mg) demonstrated no change in heterogeneity and statistical significance. Both the 2.5 mg and 10 mg doses of SGLT2-I resulted in a statistically significant improvement in A1C (Figure 7B). There was a reduction in mean BW of –1.79 kg (95%CI: -2.07 to -1.51; I^2 = 97%) with SGLT2-I use (Figure 8A). This improvement in BW was noted regardless of SGLT2-I dose. The subgroup analysis based on dose and SGLT2-I type could not highlight the potential cause of the significant heterogeneity (Figures 8B and C). UA decreased with the use of SGLT2-I: -1.03 mg/dL (95%CI: -1.14 to –0.93; I^2 = 98%) (Figure 9A). This reduction was greater within the dapagliflozin subgroup: -4.52 mg/dL (95%CI: -8.96 to –0.08; I^2 = 100%) *vs* –0.20 mg/dL (95%CI: -0.51 to 0.12; I^2 = 88%) the empagliflozin subgroup. The impact on UA also appears to be dose-dependent: -1.05 mg/dL (95%CI: -1.98 to –0.12; I^2 = 99%) with 10 mg and –0.18 mg/dL (95%CI: -1.4 to 1.05; I^2 = 0%) (Figures 9B and C). Table 4 provides a summary of the placebo adjusted treatment effect of SGLT2-Is on metabolic parameters: HbA1C, BW and UA.

Table 4 Baseline data for HbA1C, BW, and UA

		Body weight (kg)		Hemoglobin A1c (%)		Uric acid (mg/dL)	
Ref.	**SGLT2-I (daily dose, mg)**	**SGLT2-I**	**Placebo**	**SGLT2-I**	**Placebo**	**SGLT2-I**	**Placebo**
Bailey *et al*[25], 2013	DAPA (2.5)	84.90 (17.77)	87.74 (19.24)	7.99 (0.90)	8.12 (0.96)		
	DAPA (5)	84.73 (16.26)		8.17 (0.96)			
	DAPA (10)	86.28 (17.53)		7.92 (0.82)			
Bailey *et al*[24], 2015	DAPA (2.5)	90.8 (22.8)	88.8 (19.0)	7.92 (0.90)	7.84 (0.87)	5.92 (1.42)	5.09 (1.32)
	DAPA (5)	87.6 (17.1)		7.86 (0.94)		5.55 (1.44)	
	DAPA (10)	94.2 (18.7)		8.01 (0.96)		5.67 (1.44)	
Bolinder *et al*[33], 2014	DAPA (10)	92.1 (14.1)	90.9 (13.7)	7.19 (0.44)	7.16 (0.53)		
Brown *et al*[35], 2020	DAPA (10)	91.58 (14.62)	91.48 (14.13)	7.8 (3.17)	7.66 (3.08)		
Jabbour *et al*[30], 2014	DAPA (10)	91.0 (21.6)	89.2 (20.9)	7.9 (0.8)	8.0 (0.8)		
Kohan *et al*[28], 2016	DAPA (2.5)			8.17 (0.86)	8.12 (0.92)		
	DAPA (5)			8.27 (0.95)			
	DAPA (10)			8.11 (0.93)			
List *et al*[39], 2009	DAPA (2.5)	90 (20)	89 (18)	7.6 (0.7)	7.9 (0.9)	5.5 (1.2)	5.5 (1.4)
	DAPA (5)	89 (17)		8.0 (0.9)		5.2 (1.3)	
	DAPA (10)	86 (17)		8.0 (0.8)		5.5 (1.2)	
	DAPA (20)	88 (18)		7.7 (0.9)		5.3 (1.3)	
	DAPA (50)	92 (19)		7.8 (1.0)		5.6 (1.4)	
Matthaei *et al*[34], 2015	DAPA (10)	88.6 (17.6)	90.1 (16.2)	8.08 (0.91)	8.24 (0.87)		
Rosenstock *et al*[26], 2012	DAPA (5)	87.8 (20.7)	86.4 (21.3)	8.40 (1.03)	8.34 (1.00)		
	DAPA (10)	84.8 (22.2)		8.37 (0.96)			
Wilding *et al*[27], 2014	DAPA (2.5)	93.0 (16.7)	94.5 (19.8)	8.46 (0.78)	8.47 (0.77)		
	DAPA (5/10)[1]	93.3 (17.4)		8.62 (0.89)			
	DAPA (10)	94.5 (16.8)		8.57 (0.82)			
Anker *et al*[15], 2021	EMPA (10)						
Sone *et al*[36], 2020	EMPA (10)	73.3 (11.5)	74.0 (11.3)	8.8 (0.7)	8.7 (0.7)		
	EMPA (25)	72.2 (11.4)		8.7 (0.7)			
Rosenstock *et al*[37], 2015	EMPA (10)	91.6 (20.1)	90.5 (22.5)	8.3 (0.8)	8.2 (0.8)	5.26 (1.71)	5.5 (2.1)
	EMPA (25)	94.7 (20.7)		8.3 (0.8)		5.63 (2)	
Rosenstock *et al*[38], 2014	EMPA (10)	96.7 (17.9)	95.5 (17.5)	8.39 (0.74)	8.33 (0.72)	5.48 (2.13)	5.5 (2.0)
	EMPA (25)	95.9 (17.3)		8.29 (0.72)		5.56 (2.07)	
Zinman *et al*[5], 2015	EMPA (10)	85.9 (18.8)	86.6 (19.1)	8.07 (0.86)	8.08 (0.84)	5.9	6
	EMPA (25)	86.5 (19.0)		8.06 (0.84)		5.98	

[1]5 for 48 wk, 10 for 56 wk.

SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; BW: Body weight; UA: Uric acid.

DISCUSSION

This meta-analysis of 18 placebo controlled RCTs was designed to primarily evaluate the impact of SGLT2-Is on the components of the MetS as defined by the NCEP ATP III criteria. In addition, it evaluated their impact on other cardiometabolic parameters including HbA1c, BW and UA. The major findings include: (1) An improvement in MetS components (FPG, WC and BP) in the SGLT2-I group compared to the placebo group, and (2) an improvement in HbA1c, BW and UA in the SGLT2-I group compared to the placebo group.

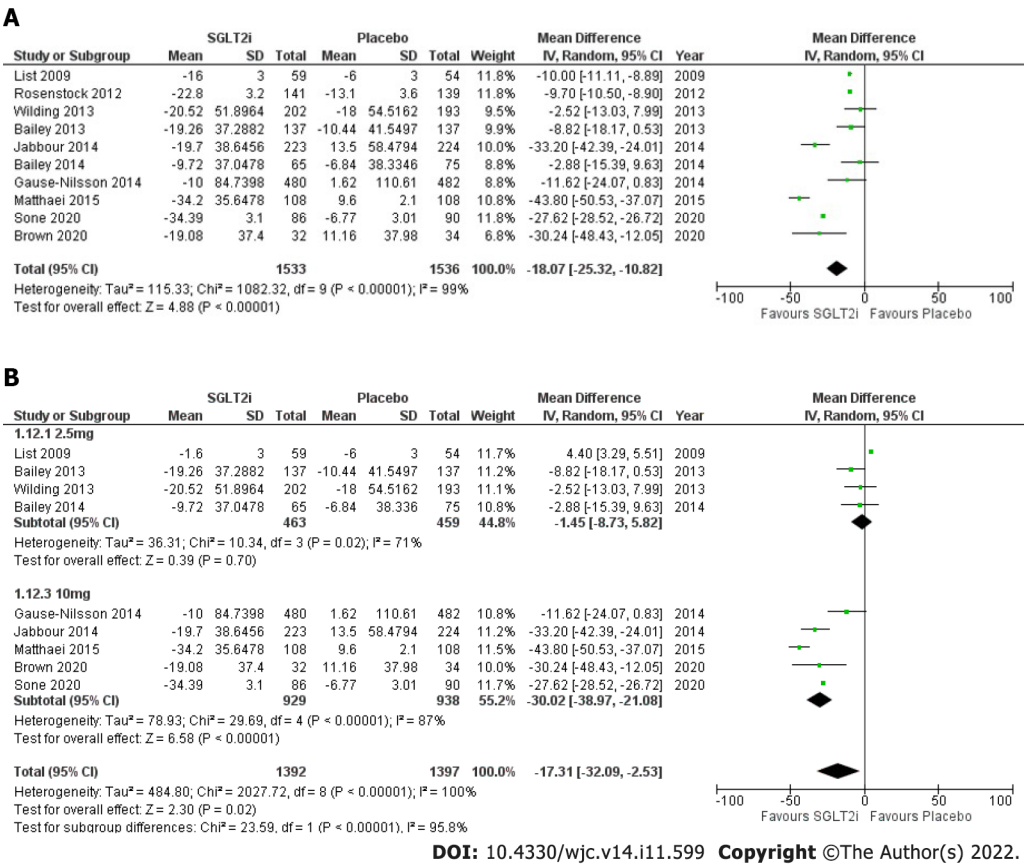

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Figure 2 Forest plot. A: Highlighting impact of SGLT2-I on FPG compared to placebo; B: SGLT2-I dose subgroup analysis performed for FPG. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; FPG: Fasting plasma glucose.

Previous meta-analyses[40-50] that evaluated the cardiometabolic effects of SGLT2-Is have only included at most four of the five components of MetS. Teo *et al*[40] evaluated WC, BP, FPG; Cho *et al*[49] analyzed WC, BP, HDL and Zaccardi *et al*[47] evaluated FPG, BP, HDL and TGL. In addition, the results of these studies have been inconsistent. While our study aimed to evaluate all components, we only had enough data for four components (FPG, BP, WC and HDL) owing to our inclusion criteria. In contrast to these studies[42,43,50], our study did not highlight a significant improvement in HDL with the use of SGLT2-Is. The reason behind this might be an inadequate statistical power; this study analyzed only 3 RCTs owing to the inclusion criteria compared to 47, 5 & 15 RCTs by Sánchez-García *et al*[41], Chen *et al*[42], and Shi *et al*[50] respectively. This study also evaluated the effect of low-dose SGLT2-Is on HDL, however it is unlikely this played a role in the outcome as the analysis by Chen *et al*[45] demonstrated a dose-independent impact. While this study has a higher mean treatment duration of 79 wk compared to prior meta-analyses which have a mean duration of 29 wk[40-50], the magnitude of the improvement in FPG, WC and BP appear similar between this study and its counterparts. This might suggest that SGLT2-Is have a ceiling effect on the components of MetS.

A high heterogeneity is noticed across all outcomes except for WC. This could be related to the differences in baseline diabetic medications taken by the patients, different doses, inclusion of more than one type of SGLT2-I and differences in the severity of hyperglycemia among the patients. However, the subgroup analysis for FPG based on dose revealed a significantly elevated heterogeneity with all doses evaluated. This study could not adjust for the differences in baseline diabetic medications and severity of hyperglycemia because these were universally different across the included RCTs, and a patient level meta-analysis would be needed for this. The heterogeneity associated with the SBP outcome in the empagliflozin subgroup may be due to the significant difference in sample size between the analyzed RCTs. A further sub-analysis based on the sample size was not completed because there were only 2 studies in the empagliflozin subgroup for SBP. The difference in efficacy between both SGLT2-Is on SBP appears to be largely due to the significant difference in the number of RCTs that constitute both SGLT2-I subgroup (2 RCTs in the empagliflozin subgroup *vs* 5 RCTs in the dapagliflozin subgroup). The small number of RCTs in the empagliflozin subgroup is due to this study's inclusion criteria. The differences between the patients' baseline antihypertensives could also be contributory to the high heterogeneity in the empagliflozin subgroup for SBP. The significant difference in treatment duration between the studies that evaluated DBP might explain the significant heterogeneity associated with the 10 mg dose of dapagliflozin. Inadequate power might explain the lack of statistical significance

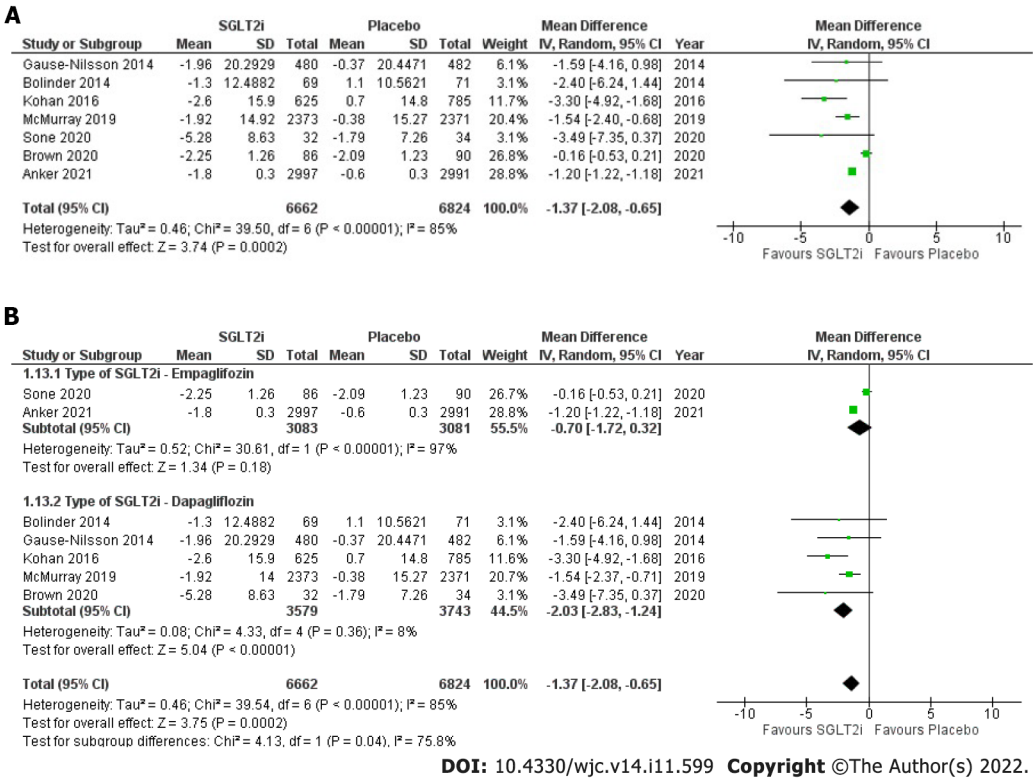

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Figure 3 Forest plot. A: Highlighting impact of SGLT2-I on SBP compared to placebo; B: SGLT2-I Type subgroup analysis performed for SBP. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; SBP: Systolic blood pressure.

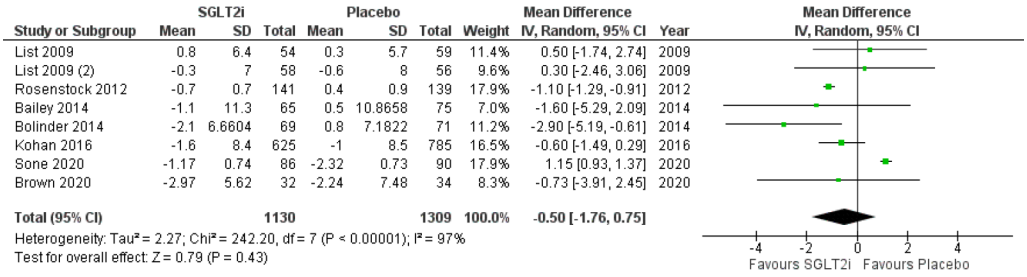

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Figure 4 Forest plot highlighting impact of SGLT2-I on DBP compared to placebo. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; DBP: Diastolic blood pressure.

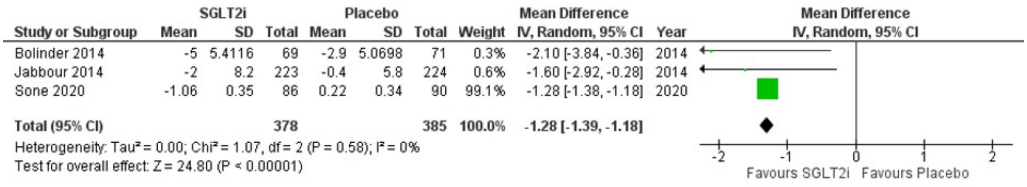

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Figure 5 Forest plot highlighting impact of SGLT2-I on WC compared to placebo. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; WC: Waist circumference.

in the reduction of DBP.

The mechanism by which SGLT2-Is lead to improvement in the components of MetS and other cardiometabolic parameters have been partially elucidated[1,51-55]. The glucosuria, osmotic diuresis and natriuresis induced by the inhibition of SGLT-2 and the sodium hydrogen exchanger appears to play an important role in the improvement of FPG, HTN and HbA1c[51,52]. Their impact on HTN also

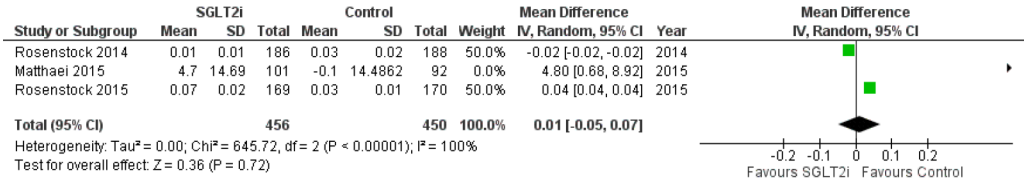

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Figure 6 Forest plot highlighting the absence of significant impact of SGLT2-I on HDL compared to placebo. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; HDL: High-density lipoprotein.

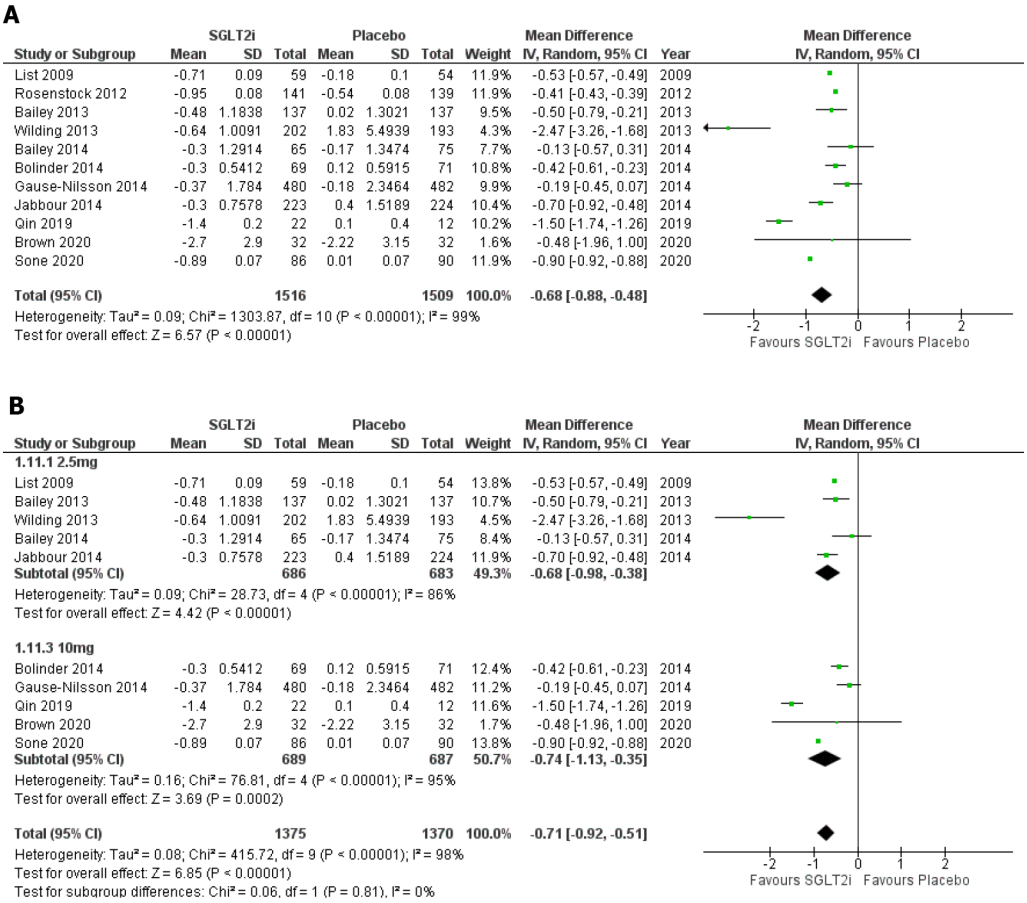

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Figure 7 Forest plot. A: Highlighting impact of SGLT2-I on HgbA1C compared to placebo; B: SGLT2-I Dose subgroup analysis performed for HgbA1C. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor.

stems from their ability to reduce arterial stiffness and endothelial dysfunction[51-53]. Furthermore, the improvement in UA noted with SGLT2-Is has been associated with the upregulation of the glucose transporter 9, a major urate transporter that secretes UA in the proximal kidney[1,53]. Interestingly, SGLT2-Is' cardiometabolic benefits have been linked to modification of certain genes involved in homeostasis[51,55]. These include a potential upregulation of Angiotensin 1-7 which leads to improvement in HTN and arterial stiffness[51]. The upregulation of genes involved in lipid metabolism including peroxisome proliferator-activated receptor alpha, acetyl-CoA carboxylase, fibroblast growth factor 21 and adenosine monophosphate-activated protein kinase have been associated with the improvement in TGL, HDL and BW[50]. SGLT2-Is have also been associated with increased levels of glucagon-like peptide 1, which is known to slow gastric emptying and reduce weight gain[54].

Perhaps through the improvement in MetS components, the combination of the above mechanisms might explain the improvement in CV mortality and heart failure hospitalization associated with SGLT2-Is in landmark trials[1-4,6,7,9-13]. In addition to its role in CVD, MetS is an independent risk factor in the development of DM[55,56]. Patients with MetS are approximately three to five times more likely to develop type 2 DM[55,56]. This highlights the complex yet incompletely understood connection between MetS, type 2 DM and CVD. Although the improvement in MetS components in this study

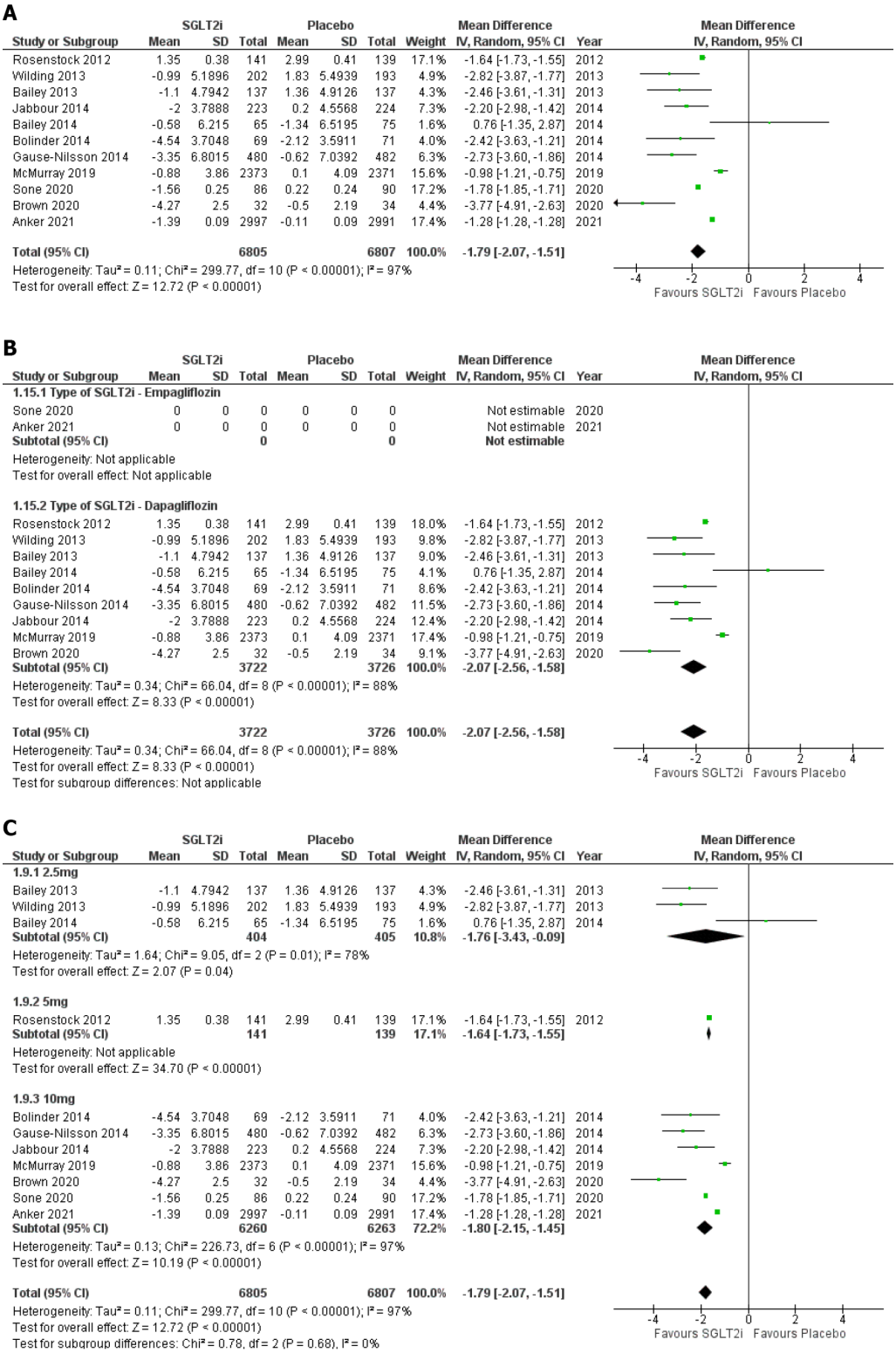

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Figure 8 Forest plot. A: Highlighting impact of SGLT2-I on BW compared to placebo; B: SGLT2-I Type subgroup analysis performed for BW; C: SGLT2-I Dose subgroup analysis performed for BW. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; BW: Body weight.

appears to be modest, our findings anticipate a possible role for SGLT2-Is in the management of MetS. Hence, it highlights the need for RCTs to evaluate the impact of SGLT2-Is on MetS compared with current management modalities including lifestyle modification.

Limitations

The findings of this study should be interpreted cautiously bearing several limitations. First, the mean baseline HDL and DBP of included RCTs did not meet threshold values for MetS. This is likely because

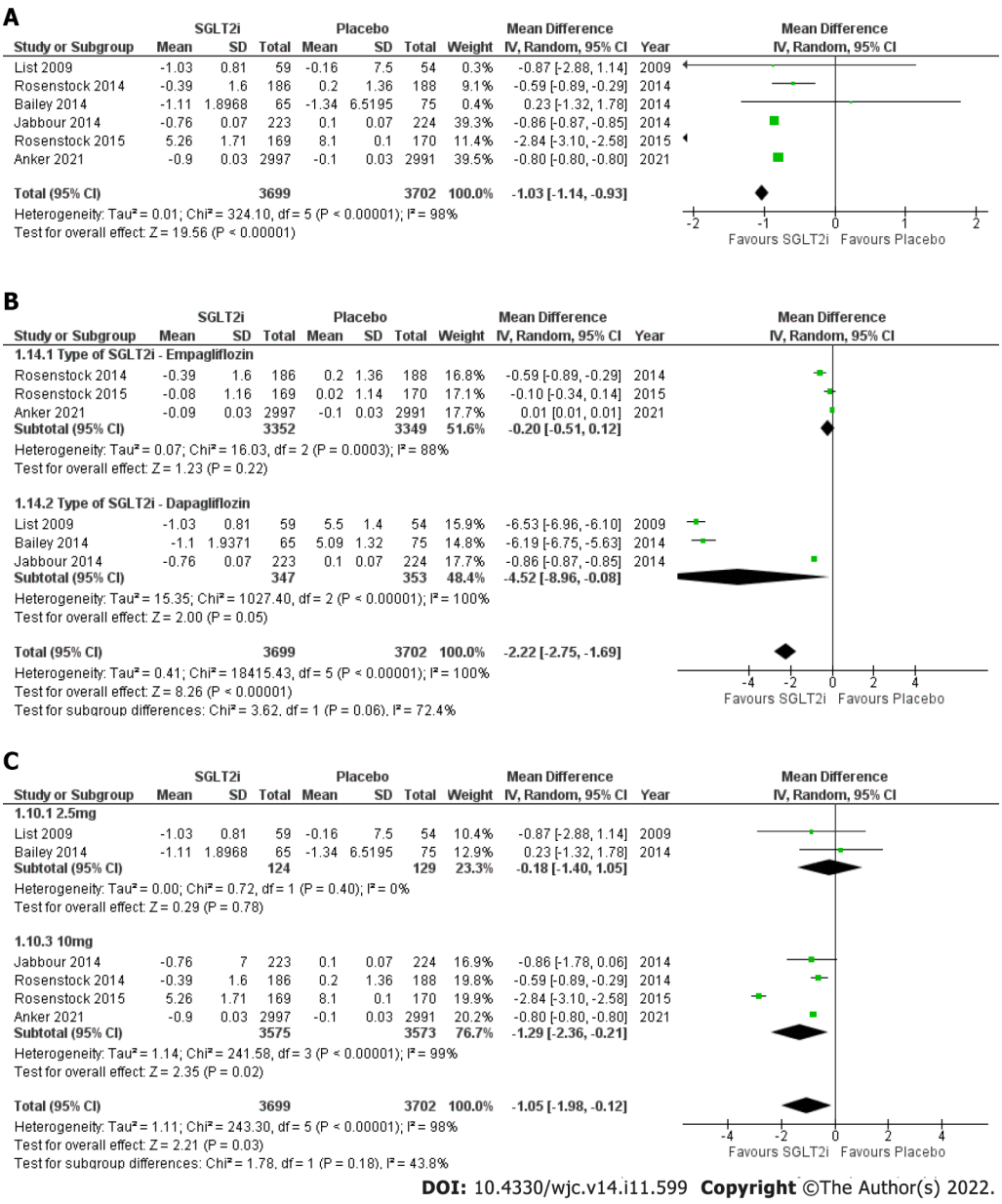

Figure 9 Forest plot. A: Highlighting impact of SGLT2-I on UA compared to placebo; B: SGLT2-I Type subgroup analysis performed for UA; C: SGLT2-I Dose subgroup analysis performed for UA. SGLT2-I: Sodium-glucose cotransporter 2 inhibitor; UA: Uric acid.

our primary objective was mostly a derivative of the secondary outcomes of the included RCTs. Second, owing to our inclusion criteria, only two of the included RCTs recruited patients without DM which limits the external validity of our study. Furthermore, we did not conduct a patient level analysis in those without DM. Third, this study limited its analysis to only dapagliflozin or empagliflozin and did not thoroughly compare the efficacy of both. Fourth, the improvement in MetS components noted by our analysis might be confounded by other medications taken by the RCTs' participants. Therefore, our analysis could not quantify the absolute effect of SGLT2-Is. This might imply the need for the evaluation of SGLT2-Is as a first line pharmacotherapy in treatment of MetS components. Additionally, MetS has multiple causes besides sedentary lifestyle, and unhealthy eating; it is usually heterogenous in its presentation due to the different possible combinations of its components; this study did not address these in its analysis. Lastly, not all included RCTs are open labelled and hence the risk of bias could not be reliably assessed by the Cochrane risk of bias tool.

CONCLUSION

SGLT2-Is were associated with an improvement in all components of MetS. There appears to be a role for their use in the management of patients with MetS regardless of the presence of DM and HF.

Prospective studies are needed to further evaluate the role of SGLT2-Is in patients with MetS either as first-line agents and/or add-on pharmacotherapy. This study, to the best of our knowledge, is the first to fully explore a possible role for SGLT2-Is in the management of MetS.

ARTICLE HIGHLIGHTS

Research background

According to the National Cholesterol Education Program Adult Treatment Panel III, metabolic syndrome is defined by the presence of three of five of the following: (1) Waist circumference (WC) ≥ 102 cm in men and ≥ 88 cm in females; (2) Serum triglycerides ≥ 150 mg/dL or on drug treatment for hypertriglyceridemia; (3) Serum high-density lipoprotein cholesterol < 40 mg/dL in males and < 50 mg/dL; (4) Blood pressure (BP) ≥ 130/85 mmHg or on drug treatment for hypertension; and (5) Fasting plasma glucose (FPG) ≥ 100 mg/dL or on drug treatment for elevated blood glucose.

Research motivation

The growing prevalence of metabolic syndrome (MetS), its association with the development of cardiovascular diseases (CVD) and the need to complement the therapeutic effect of lifestyle modification were the reasons behind conducting this study.

Research objectives

To evaluate the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2-Is) on metabolic syndrome (MetS) using data derived from randomized, placebo-controlled trials.

Research methods

A search of Medline, Scopus and the Cochrane central from inception to December 9, 2021 to identify randomized controlled trials (RCTs) that have evaluated the impact of SGLT2-Is on CVD and its risk factors, as well as reported pre/post treatment values of MetS components.

Research results

SGLT2-Is resulted in a decrease in FPG, systolic BP and WC.

Research conclusions

Further studies are needed to evaluate the use of SGLT2-Is as the first-line phamacotherapy in the management of MetS.

Research perspectives

This meta-analysis has highlighted the impact of SGLT2-Is on MetS using data from RCTs that have evaluated the impact of SGLT2-Is on CVD and its risk factors, as well as reported pre/post treatment values of MetS components. In an attempt to improve the management of MetS, we hope this study will be a precursor for future prospective studies that will establish the use of SGLT2-Is in the treatment of MetS.

FOOTNOTES

Author contributions: Olagunju A, Mookadam M and Mookadam F designed the research; Olagunju A, Kenny D, Yamani N performed the research; Olagunju A, Kenny D, Yamani N, Mookadam M, Mookadam F and Unzek S analysed the data; Olagunju A, Kenny D, Yamani N and Mookadam F wrote the paper.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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