Původní sdělení | Original research article

Cardiac Device Therapy in Heart Failure: Between Guidelines and Current Practice. Where Are We?

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ARTICLE INFO

Article history:
Submitted: 21. 8. 2020
Revised: 28. 11. 2020
Accepted: 1. 12. 2020
Available online: 1. 2. 2021

Klíčová slova:
Dodržování doporučených postupů (guidelines)
Klinický audit
Nákladová účinnost
Zvyšování kvality

SOUHRN

Kontext: V posledních několika desetiletích prodělala léčba srdečního selhání skok dopředu, zvláště v oblasti přístrojové léčby; výsledkem bylo snížení zátěže srdečním selháním a úmrtnosti na toto onemocnění. Nicméně u srdečního selhání se sníženou ejekční frakcí lze o zahájení přístrojové léčby uvažovat až po selhání maximální farmakoterapie podle doporučených postupů (guidelines). Z rozvíjejících se zemí je k dispozici omezené množství údajů o adherenci k doporučeným postupům pro diagnostiku a léčbu srdečního selhání. Cílem této studie bylo proto zjistit adherenci kardiologů k optimalizaci farmakoterapie podle doporučených postupů ještě před implantací přístrojů pacientům se srdečním selháním a sníženou ejekční frakcí.
Pacienti a metody: Do studie byli zařazeni pacienti se srdečním selháním a sníženou ejekční frakcí, přijatí pro implantaci příslušného přístroje (implantabilní kardioverter-defibrilátor) nebo zahájení srdeční resynchronizační léčby; byly shromažďovány údaje pacientů včetně demografických charakteristik, léků a jejich dávek užívaných při vstupu do studie stejně jako typ implantovaného přístroje a indikace k implantaci.
Výsledky: Z 31 pacientů zařazených do studie bylo 25,8 % žen. Průměrný věk byl 57,1 ± 11,6 roku. Beta-blokátory užívalo 83,9 % pacientů, inhibitory angiotenzin konvertujícího enzymu / blokátory receptoru AT_1 pro angiotenzin II 38,7 % a antagonisty mineralokortikoidních receptorů 67,74 % pacientů. Léčba byla zahájena nebo dávky titrovány směrem vzhůru méně než dva měsíce před implantací příslušného přístroje v 73,68 % primárně indikovaných případů. Třem pacientům (9,67 %) byl přes splnění indikací pro srdeční resynchronizační terapii (blokáda levého Tawarova raménka nebo kompletní blokáda) implantován kardioverter-defibrilátor. U pacientů s primárními indikacemi se rozhodnutí o implantaci opíralo o doporučení guidelines v 9,67 % případů, kdy byla podávána medikamentózní léčba podle doporučených postupů s titrací dávek směrem vzhůru až do dosažení maximálních, na důkazech založených dávek ještě před implantací příslušného přístroje.
Závěry: Naše studie prokázala špatnou adherenci k farmakoterapii podle doporučených postupů u pacientů se srdečním selháním a sníženou ejekční frakcí před implantací přístroje. Je třeba vyvinout maximální úsilí pro překonání tohoto nedostatku v praxi a dosáhnout u pacientů lepších výsledků nemluvě o nákladové účinnosti jako dosud přehlíženém ekonomickém faktoru zdravotní politiky.

ABSTRACT

Background: Over last few decades, treatment of heart failure witnessed a leap especially regarding device therapy which decreases heart failure burden and mortality, however; in heart failure with reduced ejection fraction introduction of device therapy should be considered after maximizing guideline directed medical therapy. There is limited data from emerging countries regarding adherence to guidelines in heart failure management. Accordingly, this study sought to investigate adherence of cardiologists to optimization of guideline directed medical therapy prior to device implantation in patients with heart failure and reduced ejection fraction.
Patients and methods: This study enrolled patients with heart failure and reduced ejection fraction who were admitted for cardiac device implantation (implantable cardioverter defibrillator or cardiac resynchronization therapy), patients' data were collected; including demographic characteristics, baseline medications and doses were recorded as well as type of implanted device and its indication.

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DOI: 10.33678/cor.2020.113

Please cite this article as: Dakhil ZA, Farhan HA, Mishlish SM. Cardiac Device Therapy in Heart Failure: Between Guidelines and Current Practice. Where Are We? Cor Vasa 2021;63:66–71.

Results: Thirty-one patients recruited in study, 25.8% were females. Mean age was 57.1±11.6 years, beta blockers were used in 83.9%, angiotensin converting enzyme inhibitor / angiotensin receptor blockers were used in 38.7%. Mineralocorticoid receptor antagonists were used in 67.74%. Treatment was initiated or up--titrated in less than two months prior to device implantation in 73.68% of primary indication cases. Three patients (9.67%) had implantable cardioverter defibrillator despite fulfilling the indications for cardiac resynchronization therapy (left bundle branch block or complete heart block). Among patients with primary indications; the decision of implantation was compatible with guidelines in 9.67% in form of following guideline directed medical therapy with up-titration until achieving maximum tolerated evidence-based doses prior to device implantation.

Conclusions: Current study cast a light on poor adherence to guideline directed medical therapy in patients with heart failure and reduced ejection prior to device implantation, every effort should be made to bridge this practice gap and achieve better patients' outcomes, not mentioning reconciling with cost-effectiveness; the overlooked economic standpoint of healthcare policy.

Keywords:
Clinical audit
Cost effectiveness
Guideline adherence
Quality improvement

Introduction

Heart failure (HF) has been defined as global pandemic as it affects around 26 million people worldwide, it is considered as major healthcare problem with remarkable impact on healthcare economics.[1,2] Over the last few decades, treatment of HF witnessed a leap which decreases HF burden and mortality.[3] Device therapy is one of these therapies which evolves over time and there is a temporal increase in its use in HF with reduced ejection fraction (HFrEF), with expected increasing economic burden in future.[4,5] According to international guidelines; device therapy in HF should be considered after maximizing guideline directed medical therapy (GDMT) particularly when device is recommended for primary prevention of sudden cardiac death (SCD).[6,7] There is limited data from emerging countries regarding optimization of pharmacotherapy prior to device therapy in patients with HF. In response, this study sought to investigate adherence of cardiologists to optimization of guideline directed medical therapy prior to device implantation in patients with HFrEF.

Patients and methods

Subjects and design

This study is a single centre, cross sectional study that enrolled patients with HFrEF (defined as an ejection fraction less than or equal to 40%),[7] who were admitted to a cardiac centre for cardiac device implantation (implantable cardioverter defibrillator [ICD] or cardiac resynchronization therapy [CRT]), patients' data were collected; including demographic characteristics, electrocardiogram (ECG) and echocardiography findings. Detailed baseline drug profile and doses were recorded. Timing of any treatment modification done by a treating physician (i.e. up-titration of doses or addition of new HF treatment) prior to admission was also confirmed. A type of device implanted and its indication were also recorded. The indications were classified into: primary; for CRT or ICD (improving NYHA class in CRT or primary prevention of SCD in ICD and CRT) and secondary; secondary prevention of SCD. Each case was assessed then according to ESC and ACC guidelines[6,7] to investigate whether decision of device implantation was compatible or not with any of guidelines recommendations regarding optimization of GDMT doses up to evidence-based doses.[6,7]

Ethical approval

The study was performed in accordance with the Declaration of Helsinki and approved by ethical and scientific committee in Iraqi Council of Cardiology / Iraqi Board for Medical Specializations. An acceptance consent to be enrolled in the study was obtained from all the patients.

Statistical analysis

Collected data were coded and input into computer using Excel 2016, then analysed statistically. Numerical variables were expressed as mean ± standard deviation, categorical variables were expressed as percentages. Reported frequencies of using drug therapies were compared between groups using Chi square test. Multiple regression analysis was structured to study the variables predicting prescription of GDMT. *P*-value <0.05 was considered statistically significant.

Results

Thirty-one patients were recruited in the study, baseline characteristics of study population were summarized in Table 1, 25.8% of patients were females, mean age was (57.1±11.6) years, coronary heart disease (CHD) and atrial fibrillation (AF) were evident in 61% and 12.9% respectively. Heart failure was caused by CHD in 61.3% and dilated cardiomyopathy (DCM) in 38.7%. Mean heart rate was 78.39±20.25 bpm and mean systolic blood pressure (SBP) was 118.33±16.82 mmHg. Mean EF was 30±6. Baseline drugs profile in patients with HFrEF are summarized in Table 2, B-blockers used in 80.6%; among whom only 8% had up-titration of doses up to guideline maximum tolerated doses. ACEI/ARBs (angiotensin-converting enzyme inhibitors / angiotensin-converting enzyme blockers) were used in 38.7%, of whom 16.7% had up-titration of doses up to guideline tolerated dose. Sacubitril-valsartan was used in 10.5% of those who had the device for primary prevention. A mineralocorticoid receptor antagonist (MRA) which was prescribed for our patients was spironolactone which was used in 67.74% of patients; 14.28% of them reached target dose (50 mg). Treatment was initiated or up-titrated in less than two months prior to device implantation in 73.68% of primary indication cases. Three patients (9.67%) had ICD implantation despite fulfilling the electrocardiographic indications for CRT implantation (left bundle branch block [LBBB] or complete

Table 1 – Baseline characteristics of patients with heart failure referred for cardiac device therapy

Baseline characteristics	Total number of patients = 31
Variable	**Mean±SD**
Age (years)	57.1±11.6
Heart rate (bpm)	78.4±20.2
SBP (mmHg)	118.3±16.82
DBP (mmHg)	73.2±8.7
Blood glucose (mmol/L)	12.13±7.67
Blood urea (mmol/L)	8.61±3.36
Serum creatinine (µmol/L)	102.57±23.87
Ejection fraction (%)	30±6
Clinical characteristics	**n (%)**
Female gender	8 (25.8%)
Hypertension	9 (29%)
Diabetes	14 (45.16%)
Smoking	4 (12.9%)
Coronary heart disease	19 (61.3%)
Dilated cardiomyopathy	12 (38.7%)
Atrial fibrillation	4 (12.9%)
Prior catheterization	10 (32.25%)
Prior PCI	6 (19.35%)
Prior CABG	2 (6.45%)
Prior hospital admission for HF	10 (32.25%)
Recurrent ischemic chest pain*	4 (12.9%)
LBBB or CHB in ECG	18 (58%)
Starting or modifying drugs in last two months	**23/31 (73.68%)**
Primary indication	15/19 (78.9%)
Secondary indication	8/12 (66.7%)
Implantable cardioverter defibrillator	**16**
Primary indication	8/16 (50%)
Secondary indication	8/16 (50%)
Cardiac resynchronization therapy	**15**
Primary indication	11/15 (73.3%)
Secondary indication	4/15 (26.7%)
Compatibility of device decision with guidelines**	**2/19 (9.67%)**

CABG – coronary artery bypass graft; CHB – complete heart block; DBP – diastolic blood pressure; HF – heart failure; LBBB – left bundle branch block; PCI – percutaneous coronary intervention; SBP – systolic blood pressure.
* Three patients did not undergo coronary angiography. ** For primary prevention.

heart block [CHB]). Among 19 patients with a primary indication for device therapy, the decision of implantation was compatible with guidelines in two patients (9.67%) in form of following GDMT with up-titration until achieving maximum tolerated doses prior to device implantation. β-blockers, ACEI/ARBs, MRA and diuretics were significantly prescribed more in those who had a primary prevention as an indication for device implantation while digoxin, statins, and antiplatelet therapy were more prescribed for those who had the device implantation for secondary prevention. β-blockers, statins, and antiplatelet therapy were significantly prescribed more in patients with ICD implantation while ACEI/ARBs, MRA, diuretics and digoxin were prescribed more in patients who received CRT implantation, as seen in Table 3. Multiple regression analysis revealed that higher pulse rate predicted more prescription of β-blockers 95% CI (0.0003–0.01), p = 00.04, age, gender, blood pressure and comorbidities did not predict prescription of GDMT, see Table 4.

Discussion

The current study reflects the real-world practice in treating patients with heart failure in a cardiac centre in Iraq. The fact that the issue is topical all over the world had been proven by similar registries from France, Spain and Germany with somewhat different results.[8] However, in Iraq, it is only recently when locally conducted audits started to focus on medical therapy in heart failure in general,[9,10] yet, current audit highlights the remarkable non-adherence to guidelines in applying GDMT (in terms of prescription and dose up-titration) in particular group of HF patients; those with HFrEF prior to implantation of cardiac device therapy.

In heart failure, ventricular arrhythmias are common and can range from asymptomatic premature ventricular contractions to sustained arrhythmias such as ventricular tachycardia (VT), ventricular fibrillation (VF), or SCD. The most common arrhythmia that causes SCD in this population is VT degenerating into VF, yet, pump failure or mechanical complications of myocardial infarction (MI) rather than arrhythmic event cause SCD in some patients with HF,[11] which explains how crucial device therapy in heart failure is to decrease mortality. However, international guidelines[6,7] recommended device ICD/CRT in HFrEF in primary prevention if there is no improvement in EF and/or symptoms of patients after three months or more of maximum tolerated GDMT providing that the patient is with good functional status and with expected life span longer than one year. Our study revealed significant underuse of ACEI/ARBs, β-blockers, and MRA in study population, earlier European registries of HF showed more adherence rate to GDMT in HF[8] regarding β-blockers, ACEI/ARBS in real world practice in Germany, Spain and France, however, use of MRA in these registries is more variable, with less use than what is reported in our study.[8] But these registries assessed the use of GDMT in HF patients according to NYHA class. Other studies[12,13] which assessed use of GDMT in patients with HF prior to device implantation give more validated results to compare our results with, as it had been reported that patients who had device implantation for HF (ICD or CRT) had been treated with ACEI/ARBs more than our patients,[12] GDMT was applied in HF patients prior to device implantation in 51–71%,[13] i.e. our study showed more patients to be treated with β-blockers and MRA but much less with ACEI/ARBs. The current study also revealed significant non-adherence to up-titration of GDMT up to maximum tolerated evi-

Table 2 – Baseline drug profile in patients with heart failure according to the indication of cardiac device therapy

Drug	Drug doses, mean±SD (mg/day)		*p*-value
	Primary prevention 19 (61.3%)*	Secondary prevention 12 (38.7%)*	
β-blockers	17/19 (89.5%)*	8/12 (66.7%)*	<0.0001
Up-titration to guideline maximum tolerated dose* 2/25 (8%)			
Carvedilol	19.7±12.2	9.4±5.3	
Metoprolol	50	50	
Bisoprolol	1.8±0.8	4.4±3.34	
ACEIs/ARBs	8/19 (42.1%)*	4/12 (33.3%)*	0.0002
Up-titration to guideline maximum tolerated dose* 2/12 (16.7%)			
Lisinopril	2.5	3.125±2.65	
Enalapril	2.5	–	
Ramipril	4.4±1.3	–	
Candesartan	16	–	
Losartan	50	–	
Telmisartan	–	80	
Valsartan	–	80	
Sacubitril/Valsartan	2/19 (10.5%)*	–	N/A
Dose	49/51	–	
Spironolactone	14/19 (73.7%)*	7/12 (58.3%)*	0.001
Up-titration to guideline maximum tolerated dose* 3/21 (14.28%)			
Dose	28.5±8.9	28.5±8.9	
Diuretics	16/19 (84.2%)*	9/12 (75%)*	0.0007
Furosemide	62.2±56	72±33.4	
Bumetanide	0.9±0.8	1	
Torsemide	10	–	
Hydrochlorothiazide	–	12.5	
Digoxin	4/19 (21.1%)*	3/12 (25%)*	<0.0001
Dose	0.25	0.25	
Statins	7/19 (36.9%)*	7/12 (58.3%)*	0.0007
Rosuvastatin	16.7±5.8	20	
Atorvastatin	30±11.5	52±26.8	
Antiplatelet	7/19 (36.9%)*	5/12 (41.7%)*	0.0002
Amiodarone	1/19 (5.3%)*	5/12 (41.7%)*	<0.0001

ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; N/A – not applicable. * Data are presented as number (%).

Table 3 – Baseline drug profile in patients with heart failure according to the type of cardiac device

Drug	Drug doses, mean±SD (mg/day)		*p*-value
	Implantable cardioverter defibrillator 16 (51.6%)*	Cardiac resynchronization therapy 15 (48.4%)*	
β-blockers	13/16 (81.3%)*	12/15 (80%)*	0.007
Carvedilol	14.1±7.3	15±4.4	
Metoprolol	66.7±28.9	50	
Bisoprolol	4.3±3.5	2.5	
ACEIs/ARBs	3/16 (18.8%)*	9/15 (60%)*	0.0001
Lisinopril	1.9±0.9	5	
Enalapril	–	2.5	
Ramipril	–	4.4±1.3	
Candesartan	–	16	
Losartan	–	50	
Telmisartan	–	80	
Valsartan	80	–	
Sacubitril/Valsartan	2/16 (12.5%)*	–	N/A

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Table 3 – Baseline drug profile in patients with heart failure according to the type of cardiac device *(Continued)*

Drug	Drug doses, mean±SD (mg/day)		*p*-value
	Implantable cardioverter defibrillator 16 (51.6%)*	Cardiac resynchronization therapy 15 (48.4%)*	
Dose	49/51	–	
Spironolactone	9/16 (56.3%)*	12/15 (80%)*	0.004
Dose	25	31.3±11.3	
Diuretics	12/16 (75%)*	13/15 (86.7%)*	0.004
Furosemide	67.5±57.5	63.3±36.7	
Bumetanide	1	0.9±0.2	
Torsemide	10	–	
Hydrochlorothiazide	12.5	–	
Digoxin	3/16 (18.8%)*	4/15 (26.7%)*	<0.0001
Dose	0.25	0.25	
Statins	9/16 (56.3%)*	5/15 (33.3%)*	0.0002
Rosuvastatin	20	15±7.1	
Atorvastatin	46.7±27.3	33.3±11.5	
Antiplatelet	7/16 (43.8%)*	5/15 (33.3%)*	0.0001
Amiodarone	3/16 (18.8%)*	3/15 (20%)*	<0.0001

ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; N/A – not applicable. * Data are presented as number (%).

Table 4 – Multivariate predictors of use of guideline directed medical therapy in patients with heart failure referred for cardiac device therapy

Predictor	Coefficient	Standard error	Lower 95% CI	Upper 95% CI	*p*-value
β-blockers					
Age	–0.004	0.007	–0.02	0.01	0.57
Gender	0.01	0.19	–0.38	0.42	0.9
IHD	0.01	0.17	–0.35	0.38	0.9
Prior revascularization	–0.3	0.2	–0.57	0.38	0.52
Pulse rate	0.009	0.004	0.0003	0.01	0.04
SBP	–0.01	0.007	–0.02	0.002	0.1
DBP	0.02	0.014	–0.004	0.05	0.09
Ejection fraction	–0.01	0.01	–0.04	0.007	0.1
ACEIs/ARBs/Sacubitril-valsartan					
Age	–0.001	0.01	–0.02	0.02	0.8
Gender	0.2	0.2	–0.36	0.79	0.4
Hypertension	0.3	0.2	–0.3	0.9	0.3
CHD	0.3	0.2	–0.16	0.79	0.19
Diabetes	–0.3	0.2	–0.9	0.19	0.18
SBP	0.003	0.01	–0.01	0.02	0.7
DBP	–0.02	0.02	–0.07	0.02	0.2
Serum creatinine	–0.5	0.4	–1.4	0.3	0.2
Ejection fraction	0.001	0.019	0.03	0.04	0.9

Prior revascularization: either prior percutaneous coronary intervention or coronary artery bypass graft. ACEIs – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; CHD – coronary heart disease; DBP – diastolic blood pressure; SBP – systolic blood pressure.

dence-based doses, which was consistent with other studies.[14,15] The current study assessed different predictors for prescription of GDMT; neither age, gender, cardiovascular risk factors nor blood pressure can predict prescription of GDMT in HF, apart from higher pulse rate that increases prescription of β-blockers. The main predictors reported in other studies for GDMT prescription were absence of chronic kidney diseases and presence of non-sustained VT,[13] while the main reported predictors for underutilization of GDMT in HF were older age group, frail patients with multiple comorbidities fearing from side effects of drugs, higher renal indices, hyperkalaemia, lower body weight and patient non-compliance; all contributed to under-prescription of GDMT.[12,13,15,16] Asthma and chronic

pulmonary diseases were reported to predict lower use of β-blockers in HF patients fearing from worsening of respiratory symptoms.[15] Poor education, low socioeconomic status and absence of proper communication with the patients about their symptoms, prognosis and importance of drugs that we prescribe; all can contribute further to non-adherence to GDMT as patients' non-adherence is a common reported problem in HF[17] that also needed to be addressed constantly in order to overcome it and improve outcomes.

The current study revealed that most of our patients (73.68%) had device therapy while their treatment was started or up-titrated within the last two months which contradicts guideline recommendation and it can be justified in secondary prevention cases but not in primary prevention cases that had their treatment started or modified recently in 78.9% in the current study. There is a critical waiting period of three months at least that should be considered for patients with newly diagnosed HFrEF after which reassessment of left ventricular function should be done prior to decision of device implantation.[18] Moreover, patients with chronic HFrEF should be kept on maximum tolerated GDMT for at least three months prior to implantation of cardiac device[6,7] to promote LV reverse remodelling. It had been suggested recently that in the context of underutilization of GDMT it is justified to wait up to one year after diagnosis of HFrEF prior to device implantation in order to allow for proper optimization of medical treatment, allowing the patient to have time to understand HF syndrome and its complications and allow the patient to understand the risks and benefits of device therapy.[19] Accordingly, serious consideration should be taken before proceeding with device implantation for primary prevention in patients with HFrEF without optimizing GDMT.

Main limitation of this study is the small sample size, we recommend larger sample size in the future to further validate the results.

Conclusions

Current study disclosed the remarkable poor adherence to international guidelines in prescribing pharmacotherapy in patients with HFrEF prior to device implantation despite evidence-based recommendations, future plans are needed to bridge this practice gap and increase adherence of physicians to guidelines in treating this population, with emphasizing on proper patients' education in order to achieve better patients' outcomes, not mentioning reconciling with cost-effectiveness; the overlooked economic standpoint of healthcare policy.

Acknowledgements
The authors thank all the medical staff and lab workers at Ibn Al-Bitar Cardiac Center for their help during data collection process.

Conflict of interest
None.

Funding
None.

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