

Medicines Management Programme

Preferred Drugs

Beta-adrenoreceptor blocking drugs for the treatment of heart-failure, angina and hypertension.



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List of abbreviations

ACE	Angiotensin converting enzyme
AHA/ACCF	American Heart Association/American College of Cardiology Foundation
ARB	Angiotensin-II receptor blocker
AV	Atrioventricular
BD	Twice daily
BHS	British Hypertension Society
CCB	Calcium channel blocker
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DDD	Defined daily dose
DPS	Drug Payment Scheme
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GI	Gastrointestinal
GMS	General Medical Services
HF	Heart failure
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
HT	Hypertension
ISH	International Society of Hypertension
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MMP	Medicines Management Programme
N	Number
NICE	National Institute for Health and Care Excellence
NMIC	National Medicines Information Centre
NNT	Number needed to treat
NYHA	New York Heart Association
OD	Once daily
OR	Odds ratio
PCRS	Primary Care Reimbursement Service
RCT	Randomised Controlled Trial
RRR	Relative risk reduction
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary of Product Characteristics
SR	Sustained release
WHO	World Health Organisation

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1. Purpose

There are nine licensed oral beta-adrenoreceptor blocking drugs (β -blockers) reimbursed in Ireland.¹ Annual expenditure on reimbursed β -blockers under the General Medical Services (GMS) scheme was almost €18.5 million for 2014.²

The selection of a preferred β -blocker under the Medicines Management Programme (MMP) is designed to support prescribers, in choosing a medicine of proven safety and efficacy in the management of patients with heart failure (HF), angina and hypertension. Prescribers are encouraged to consider the preferred drug when initiating a β -blocker and when there is a need to change from one β -blocker to another in the treatment of HF, angina and hypertension.

This guide may not be applicable in all situations and caution is required when prescribing to patients with certain medical conditions, for example renal and hepatic impairment, diabetes, uncontrolled heart failure, asthma and chronic obstructive pulmonary disease (COPD). β -blockers block the beta-adrenoreceptors in the heart resulting in slowing of the heart beat and depression of the myocardium.³ As a result they are contraindicated in patients with second or third degree heart block and should be avoided in patients with worsening unstable heart failure. β -blockers also block the beta-adrenoreceptors in the bronchi which may exacerbate bronchospasm in asthmatic and chronic obstructive pulmonary disease (COPD) patients. Furthermore, caution is recommended in patients with diabetes as β -blockers also alter the β -adrenoreceptors in the pancreas and as a result may alter metabolic and autonomic responses to hypoglycaemia and may lead to a deterioration in glucose tolerance.³

Prescribing of β -blockers in pregnancy should be under specialist supervision and is therefore outside the scope of this evaluation.

2. Definitions

For the purpose of this report, the associated cost refers to the reimbursed cost of the named β -blocker as listed in the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS) website. Only reimbursed β -blockers licensed for the treatment of HF, angina or HT are included in this review. Sotalol is not licensed for any of the above indications and therefore it is outside the scope of this review.

While some of these β -blockers are also licensed for the treatment of arrhythmias, migraine prophylaxis and hypertension of pregnancy (see Table 3), these indications are not considered in this review.

When two or more preparations of the same drug are listed (e.g. where there are different manufacturers/suppliers), the least expensive preparation with all the relevant indications has been selected for the evaluation. Costs are correct as of March 2016.

3. β -blocker classification

β -blockers bind selectively to the β -adrenoreceptors producing a competitive and reversible antagonism of the effects of β -adrenergic stimulation on various organs as seen in Table 1 below.⁴

Table 1: Effects mediated by β_1 - and β_2 - adrenoreceptors

Tissue	Receptor	Effect
Sinoatrial (SA) node	β_1, β_2	Increase in heart rate
Atrioventricular (AV) node	β_1, β_2	Increase in conduction velocity
Atria	β_1, β_2	Increase in contractility
Ventricles	β_1, β_2	Increase in contractility and conduction velocity
Arteries	β_2	Vasodilation
Veins	β_2	Vasodilation
Skeletal muscle	β_2	Vasodilation
Liver	β_2	Glycogenolysis and gluconeogenesis
Pancreas (β -cells)	β_2	Insulin and glucagon secretion
Bronchi	β_2	Bronchodilation
Kidney	β_1	Renin release
Urinary bladder detrusor	β_2	Relaxation
Uterus	β_2	Relaxation
Gastrointestinal	β_2	Relaxation
Thyroid gland	β_2	T4 – T3 conversion

β -blockers can be classified into ‘selective’ and ‘non-selective’ depending on their level of affinity for the β_1 rather than for the β_2 receptors. ‘Selective’ β -blockers (atenolol, bisoprolol, celiprolol, metoprolol and nebivolol) have a much higher affinity for β_1 than for the β_2 receptors and ‘non-selective’ β -blockers (carvedilol, labetalol, propranolol and sotalol) produce a competitive blockade of both β_1 - and β_2 -adrenergic receptors.^{4,5}

In addition, β -blockers also differ in their lipid constituents and are classed as either ‘lipophilic’ or ‘hydrophilic’.⁴ Table 2 highlights the properties of individual β -blockers. These properties are

significant with regard to adverse-effects as the extent of the adverse effects will vary depending on the characteristics of the individual β -blockers.⁵

Table 2: Properties and dosing of various β -blockers⁵

Drug	Lipid solubility	Route of Elimination	Selectivity	Typical Dose
Atenolol	-	Renal	Selective	Once daily
Bisoprolol	++	Hepatic/Renal	Selective	Once daily
Carvedilol	++	Hepatic	Non-selective	Twice daily
Celiprolol	-	Renal	Selective	Once daily
Labetalol	++	Hepatic	Non-selective	Twice daily
Metoprolol	++	Hepatic	Selective	Twice daily
Nebivolol	++	Hepatic	Selective	Once daily
Propranolol	+++	Hepatic	Non-selective	Up to four times daily
Sotalol	-	Renal	Non-selective	Twice daily

- *Hydrophilic*
 ++ *Moderately lipophilic*
 +++ *Highly Lipophilic*

3.1 Lipophilic β -blockers

Lipophilic β -blockers are rapidly and completely absorbed from the gastrointestinal tract and are extensively metabolised in the gut wall and in the liver via first-pass metabolism and therefore their bioavailability is low (10-30%).⁵ They generally have short half-lives and readily pass into the central nervous system (CNS) accounting for greater incidence of CNS adverse-effects.⁵

3.2 Hydrophilic β -blockers

Hydrophilic β -blockers are incompletely absorbed from the gastrointestinal tract and are excreted unchanged or as active metabolites by the kidney. As a result they have longer half-lives and do not interact with other liver metabolised drugs.⁵

Each β -blocker portrays different characteristics depending on their classification and these factors may be important when selecting a particular β -blocker to prescribe. A full description of the

individual β -blockers and their pharmacodynamic and pharmacokinetic properties are discussed in detail in Appendix A of this report.

4. Preferred β -blocker

BISOPROLOL is the preferred β -blocker for the treatment of heart failure, angina and hypertension under MMP guidance.

5. Consultation for β -blockers in the management and treatment of heart failure, angina and hypertension in adults

A period of consultation was undertaken in which submissions from relevant stakeholders, including the pharmaceutical industry and professional bodies representing clinicians and healthcare professionals, were invited. This consultation period closed on 18th March 2016.

6. Selection Criteria

A number of key criteria were considered in the MMP β -blocker selection process:

- **Licensed indications**
 - Clinical efficacy
 - Clinical outcome data
 - Clinical guidelines
- **Adverse drug reactions**
- **Cautions and contraindications**
- **Drug interactions**
- **Patient factors**
 - Dosing
 - Administration
- **Cost**
- **National prescribing trends**

6.1 Licensed therapeutic indications

The licensed indications for β -blockers are detailed in Table 3 below.³ The three principal indications for β -blockers, heart failure, angina and hypertension are reviewed in this document.

Table 3: Licensed indications for β -blockers in Ireland

Drug	HT	HF	Angina	Arrhythmia	HT of Pregnancy	Migraine prophylaxis
Atenolol* ⁶	✓		✓	✓		
Bisoprolol* ⁷	✓	✓	✓			
Carvedilol ⁸	✓	✓	✓			
Celiprolol* ⁹	✓		✓			
Labetalol ¹⁰	✓		✓		✓	
Metoprolol* ¹¹	✓		✓	✓		✓
Nebivolol* ¹²	✓	✓				
Propranolol ¹³	✓		✓	✓		✓
Sotalol ¹⁴				✓		

HT: hypertension; HF: heart failure

*Cardioselective β -blockers

Sotalol is licensed for symptomatic non-sustained ventricular tachyarrhythmias, prophylaxis of paroxysmal atrial tachycardia or fibrillation, AV re-entrant tachycardias, paroxysmal supraventricular tachycardia after cardiac surgery and maintenance of sinus rhythm following cardioversion of atrial fibrillation or flutter. Therefore sotalol is outside the scope of this review.³

6.1.1 Heart failure

Heart failure (HF) is defined as an abnormality of cardiac structure or function which leads to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolising tissues.¹⁵ The signs of heart failure include breathlessness, ankle swelling and fatigue and symptoms usually include elevated jugular venous pressure, pulmonary crackles and displaced apex

beat.¹⁵ β -blockers are recommended in addition to angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor blocker [ARB] if an ACE inhibitor is contraindicated) as first-line treatment in all patients with an ejection fraction <40% to reduce the risk of heart failure hospitalisation and premature death.¹⁵ Clinical guidelines for HF will be discussed in section 6.1.1.3. As shown in Table 3, currently the β -blockers licensed for the treatment of HF in Ireland are bisoprolol⁷, carvedilol⁸ and nebivolol.¹²

6.1.1.1 Clinical efficacy in heart failure

The efficacy and safety of the preferred β -blocker should be demonstrated by high-quality randomised controlled trials (RCTs). Table 4 below lists some of the main RCTs that compare β -blockers with placebo (with the exception of COMET) in the treatment of HF with mortality as a primary end point.

Table 4: Heart failure clinical trials

Trial	Agent	N	Follow-up	Primary Endpoint	Result
MDC (1993) ¹⁶	Metoprolol vs. Placebo	383	18 months	Death or progression to heart transplant	34% ↓ combined
MERIT-HF (2000) ¹⁷	Metoprolol SR vs. Placebo	3991	12 months	Death	34% ↓
COMET (2003) ¹⁸	Carvedilol vs. Metoprolol	3029	58 months	Death	17% ↓
CIBIS I (1994) ¹⁹	Bisoprolol vs. Placebo	641	23 months	Death	20% ↓
CIBIS II (1999) ²⁰	Bisoprolol vs. Placebo	2647	16 months	Death	34% ↓
US Carvedilol HF Trial Programme (1996) ²¹	Carvedilol vs. Placebo	1094	6 months	Death	65% ↓
COPERNICUS (2004) ²²	Carvedilol vs. Placebo	2289	10 months	Death	35% ↓
CAPRICORN (2001) ²³	Carvedilol vs. Placebo	1959	1.3 years	Death	23% ↓
SENIORS ²⁴	Nebivolol vs. Placebo	2128	21 months	Death or hospitalisation	14% ↓ combined

Metoprolol

Metoprolol was the first drug to be studied in HF in the MDC trial in 1993, where it was shown to reduce mortality and the need of transplantation by 34% compared to placebo as seen in Table 4 above.¹⁶ A subsequent trial MERIT-HF, investigated the efficacy of metoprolol in moderate HF patients with New York Heart Association (NYHA) functional class II-IV using a long-acting metoprolol formulation. This trial was stopped early due to a significant decrease in all-cause mortality of 34%. In addition to these findings, this trial showed a 39% decrease in cardiovascular mortality, 49% decrease in death caused by progressive heart failure and 35% reduction in hospitalisations.¹⁷ However, as shown in Table 3, metoprolol is not licensed for the treatment of HF in Ireland.

Bisoprolol

CIBIS I was also one of the early trials to demonstrate the importance of β -blocker therapy in HF. Patients with moderate HF treated with bisoprolol demonstrated a reduction in mortality and hospitalisation of 20%.¹⁹ CIBIS II followed in 1999 with greater statistical power and the trial was stopped early due the significant mortality benefits demonstrated.²⁵ The primary end-point showed a reduction of 34% in mortality and there were significantly fewer sudden deaths and all-cause hospital admissions in the bisoprolol group.²⁰

Carvedilol

The US Carvedilol Heart Failure Programme compared carvedilol to placebo in patients with chronic HF and a left ventricular ejection fraction (LVEF) <35%. Carvedilol was shown to reduce mortality risk by 65% compared with placebo as shown in Table 4 and also showed a 38% reduction in the combined end-point of hospitalisation or death.²¹ The COPERNICUS trial compared carvedilol to placebo in severe HF patients with NYHA III – IV. Carvedilol therapy demonstrated a significant 35% decrease in all-cause mortality and was well tolerated with fewer treatment discontinuations than the placebo group.²² The third study involving carvedilol, the CAPRICORN study, evaluated if the addition of carvedilol to standard management of myocardial infarction in patients with left ventricular dysfunction would reduce morbidity and mortality compared to placebo. The results confirmed that carvedilol decreased the risk of mortality by 23%.²³ COMET was the only study to compare two β -blockers, carvedilol and metoprolol, in terms of mortality in patients with chronic HF with reduced LVEF.¹⁸ The overall results demonstrated that carvedilol reduced mortality by 17%

compared with metoprolol (Table 4). However, it is important to note that in this trial the formulation of metoprolol was different to that used in MERIT-HF (metoprolol tartrate versus slow release metoprolol succinate) and the target dose used was lower (50mg/12h versus 100mg/12h). As a consequence, these results could not be considered for the purpose of this report but they demonstrate that the selection and dose of a β -blocker may have a significant impact in the treatment of patients with HF.⁵

Nebivolol

The SENIORS study was performed to assess the effects of the nebivolol in patients with HF ≥ 70 years irrespective of the ejection fraction. All-cause mortality and hospital admissions was significantly reduced by 14% with both clinical end points contributing equally to the primary outcome.²⁴

In summary, the use of β -blockers in clinical studies have been shown to reduce mortality and hospital admissions by approximately 34% when included as part of standard HF therapy.

6.1.1.2 Meta-analyses in the treatment of heart failure

Meta-analyses and systematic reviews were also considered as part of the review process.

Table 5: Summary table of meta-analyses in the treatment of heart failure

Meta-analysis	Authors	Year	N	Drugs reviewed	Conclusion
Benefits of β -blockers in patients with heart failure and reduced ejection fraction: network meta-analysis ²⁶	Chatterjee et al.	2013	23,122	Atenolol Bisoprolol Bucindolol Carvedilol Metoprolol Nebivolol	All β -blockers showed significant mortality benefits compared with placebo ($P < 0.001$). No obvious difference in the risk of death, death due to pump failure, drug discontinuation or ejection fraction.
Systematic review of the impact of β -blockers on mortality and hospital admissions in heart failure ²⁷	Shibata et al.	2001	10,480	Bisoprolol Bucindolol Carvedilol Metoprolol Nebivolol	Relative risk reduction in mortality was approximately 35%. $\frac{1}{3}$ of this result was attributable to MERIT-HF and CIBIS II trials involving the β -blockers metoprolol and bisoprolol respectively.
Clinical effects of β -adrenergic blockade in chronic heart failure: A meta-analysis of double-blind, placebo-controlled, randomised trials ²⁸	Lechat et al.	1998	19,209	Atenolol Bisoprolol Bucindolol Carvedilol Metoprolol Nebivolol	β -blockade reduced all-cause mortality by 32% ($P = 0.003$) and was greater for non-selective β -blockers (49% vs. 18%, $P = 0.049$).
Effects of β -blocker therapy on mortality in patients with heart failure ²⁹	Doughty et al.	1997	3,141	Acebutolol Bisoprolol Bucindolol Carvedilol Metoprolol Labetolol Nebivolol	31% \downarrow in odds of death. No statistical difference between individual β -blockers in this review.
Effect of β -blockade on mortality in patients with heart failure: A meta-analysis of randomised controlled trials ³⁰	Heidenreich et al.	1997	3,039	Bisoprolol Bucindolol Carvedilol Metoprolol Nebivolol	31% \downarrow in odds of death.

Key findings in the meta-analyses from Table 5 were as follows:

- A network meta-analysis on the benefits of β -blockers in patients with HF and reduced ejection fraction by Chatterjee *et al.* 2013 investigated 21 trials with 23,122 patients and focused on the β -blockers atenolol, bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol. All of the above showed significant mortality benefits compared with placebo ($p < 0.001$). However, there was no obvious differences when comparing the different β -

blockers head-to-head for the risk of death, death due to pump failure, drug discontinuation or ejection fraction. The analysis showed that among the different β -blockers in current use, bisoprolol, carvedilol, and metoprolol have been more extensively researched and had significant mortality benefits compared to placebo for HF treatment. This would support the selection of one of these drugs as the empiric drug of choice in the treatment of chronic HF with reduced ejection fraction.²⁶ The results of the meta-analysis are in line with the American Heart Association guidelines.³¹

- A systematic review of β -blockers in heart failure by Shibata *et al.* (2001) involved 22 randomised-controlled trials with 10,480 patients and included the β -blockers bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol. Death rates from patients randomised to receive a β -blocker compared to placebo was 8.0% vs. 12.8% respectively. Similar reductions were demonstrated for hospital admissions for worsening HF (11.3% vs. 17.1% respectively). This analysis demonstrated a relative risk reduction (RRR) in mortality and the need for heart failure hospital admission amongst patients randomised to a β -blocker compared to control of approximately 35%. One third of this result was attributable to MERIT-HF and CIBIS II trial involving the β -blockers metoprolol and bisoprolol respectively.²⁷
- A meta-analysis by Lechat *et al.* (1998) involving 23 trials and 19,209 patients assessed five measures of efficacy and demonstrated a significant outcome ($P < 0.05$) for all end-points in favour of treatment with the β -blockers atenolol, bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol. There was 32% reduction in death, 41% reduction in the risk of being hospitalised for HF and a 37% reduction in the combined risk of morbidity and mortality. In addition, there was also a 29% increase in LVEF and a 32% increase in the likelihood of functional improvement. Although β -blockers reduced all-cause mortality by 32% this varied according to the type of β -blocker tested i.e. the reduction in mortality was greater for non-selective β -blockers (bucindolol and carvedilol) than for β_1 -selective agents (bisoprolol, metoprolol and nebivolol) [49% vs. 18%, $p = 0.04$]. However, selective and non-selective β -blockers did not differ in their effects on the other measures discussed above.²⁸

- A systematic overview of the effects of β -blocker therapy on mortality in patients with HF by Doughty *et al.* (1997), assessed 24 randomised controlled trials involving 3,141 patients. Results showed a 31% reduction in the odds of death amongst patients assigned a β -blocker ($p=0.0035$). No statistically significant heterogeneity was observed between the results of the individual trials. This benefit was achieved against a background of standard care with an ACE inhibitor for most patients. The numbers of deaths observed in subgroups of trials defined by the type of β -blocker was individually small and therefore not possible to detect true differences between the individual β -blockers.²⁹
- A meta-analysis by Heidenreich *et al.* 1997 included 17 randomised controlled trials and 3,039 patients on the effects of β -blockade with bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol on mortality in HF. Results demonstrated the overall decrease in the odds of death was 31%. The benefit was consistent over the studies examined. A trend towards greater treatment effect with β -blockers was demonstrated for non-sudden cardiac death compared with sudden cardiac death (OR 0.58 vs. 0.84).³⁰

6.1.1.3 Clinical guidelines for the treatment of heart failure

Table 6: Clinical guidelines for the treatment of heart failure

Group	Guideline	Year	Initial treatment options	Preferred B-blocker
European Society of Cardiology (ESC) ³²	Heart Failure	2012	ACE inhibitor + β -blocker in all patients with an EF $\leq 40\%$	Not specified
National Institute for Health and Care Excellence (NICE) CG 108 ³³	Heart Failure	2010	ACE inhibitor + β -blocker	β -blocker licensed in treatment of HF
Scottish Intercollegiate Guidelines Network (SIGN) 95 ³⁴	Heart Failure	2007	ACE Inhibitor + β -blocker	-Bisoprolol -Carvedilol -Nebivolol
American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) ³¹	Heart Failure	2013	ACE inhibitor + β -blocker	-Bisoprolol -Carvedilol -Metoprolol SR

In line with NICE and SIGN guidelines, a β -blocker licensed for the treatment of HF should be used. The ACCF/AHA recommend three β -blockers bisoprolol, carvedilol and metoprolol SR (not licensed

in Ireland for HF).³¹ As mentioned previously, there are currently three β -blockers authorised for HF in Ireland: bisoprolol, carvedilol and nebivolol.

In summary, clinical studies have shown that all β -blockers are statistically effective in the treatment of HF and meta-analyses to date has not been effective in differentiating between them. Clinical guidelines recommend that β -blockers for the treatment of HF be used according to the licensed indication.³³ Bisoprolol is licensed in stable moderate to severe HF with reduced systolic left ventricular function in addition to ACE Inhibitors, diuretics and optionally cardiac glycosides.⁷ Carvedilol is licensed for adjunctive therapy for the treatment of congestive HF.⁸ Nebivolol is licensed for the treatment of stable mild and moderate chronic HF in addition to standard therapies in elderly patients ≥ 70 years.¹²

6.1.2 Angina

Stable angina is a clinical syndrome characterised by discomfort in the chest, jaw, shoulder, back or arms.³⁵ The duration of this discomfort is brief, no longer than 10 minutes in most cases. An important characteristic is in relation to exercise, specific activities or emotional stress.³⁵ Symptoms classically deteriorate with increased levels of exertion such as walking up an incline or against a breeze and rapidly disappear within a few minutes when causal factors abate.³⁵ Anti-anginal treatment should be initiated as soon as diagnosis is suspected.³ The goal of therapy is to reduce angina symptoms and exercise-induced ischemia.³⁵ Particular attention should be given to the resting heart rate and blood pressure. β -blockers work primarily by decreasing myocardial oxygen consumption through reductions in heart rate, blood pressure and myocardial contractility.³⁶ Patients with mild to moderate stable angina should receive a β -blocker first-line to prevent further attacks and reduce the risk of cardiovascular events.³ The β -blockers licensed for the treatment of angina in Ireland are atenolol, bisoprolol, carvedilol, celiprolol, labetalol, metoprolol and propranolol as previously outlined in Table 3.^{6-11,13}

6.1.2.1 Clinical efficacy in angina

The clinical trials for stable angina are listed in Table 7. Head-to-head comparative trials have not demonstrated that any single class of drugs has greater anti-anginal efficacy than the others.³⁷

Table 7: Angina clinical trials

Trial	Agent	N	Follow-up	Primary Endpoint	Result
TIBBS 1995 ³⁸	Bisoprolol vs. Nifedipine	330	8 weeks	Number and duration of ischemic episodes	Bisoprolol statistically superior ($p < 0.0001$)
TIBET 1996 ³⁹	Atenolol vs. Nifedipine & in combination	608	24 months	Exercise duration and ischemic burden	No significant difference
ASIST 1994 ⁴⁰	Atenolol vs. Placebo	306	12 months	Event-free survival at 1 year	Atenolol significantly ↓ ischemic episodes ($p = 0.0066$)
APSYS 1996 ⁴¹	Metoprolol vs. Verapamil	809	39 months	Death	No significant difference ($p = 0.63$)
IMAGE 1996 ⁴²	Metoprolol vs. Nifedipine	280	10 weeks	Control exercise induced ischemia	Metoprolol superior ($p < 0.05$)

Bisoprolol

The TIBBS study consisted of 330 patients from 30 centres and compared the effects of bisoprolol and nifedipine on transient myocardial ischemia in patients with chronic stable angina. The reduction of ischemic episodes as well as total ischemic burden was marked and statistically significant for both drugs. All reductions were statistically greater in the bisoprolol group ($p < 0.0001$) as seen in Table 7. The effects of bisoprolol were approximately twice that of nifedipine. Bisoprolol also showed a marked circadian effect by reducing the morning peak of ischemic activity by 68%. This was unchanged in the nifedipine group.³⁸ It is also important to note that the frequency of administration in this trial was once daily in the bisoprolol group and twice daily in the nifedipine group.³⁸

Atenolol

The TIBET study consisted of 608 patients from 69 centres and compared atenolol and nifedipine alone and in combination on exercise parameters and ischemic activity. Both drugs alone and in combination showed significant improvements in exercise parameters and in ischemic activity compared with placebo. There were however, no significant differences between the groups for any of the measured ischemic parameters although combination of atenolol and nifedipine resulted in a greater fall in resting systolic and diastolic blood pressure compared to either treatment alone ($p < 0.05$).³⁹

The ASIST trial was a randomised, double-blinded, placebo controlled study analysing 306 patients assigned to either atenolol or placebo. The primary outcome was event-free survival at one year.

During follow-up, event-free survival was significantly increased ($p=0.0066$) in the atenolol group as seen in Table 7. The number and average duration of ischemic episodes per 48 hours of ambulatory testing decreased in the atenolol compared to the placebo group ($p<0.001$). There was a non-significant trend for fewer serious adverse-events in the atenolol-treated group ($p=0.175$). Side-effects were similar in both groups although bradycardia was more frequent in the atenolol treated group.⁴⁰

Metoprolol

In the APSIS trial, 809 patients with stable angina <70 years were randomised to receive either metoprolol or verapamil and the primary end-point was death and non-fatal cardiovascular events. In the 39 month follow-up, total mortality occurred in 5.4% in the metoprolol group and 6.2% in the verapamil group ($p=0.63$) as shown in Table 7. Non-fatal cardiovascular events occurred in 106 patients in the metoprolol group and 98 patients in the verapamil group ($p=0.56$). The types of cardiovascular events were similar in both groups. This long term study indicated that both metoprolol and verapamil were well tolerated and no difference shown on the effect of mortality and cardiovascular end-points.⁴¹

The IMAGE trial assessed 280 patients with stable angina to determine whether combination therapy with metoprolol and nifedipine provides a greater ischemic effect than monotherapy in individual patients. At the six week follow-up, both metoprolol and nifedipine increased mean exercise time compared to week 0 (both $p<0.01$). Metoprolol was more effective than nifedipine ($p<0.05$).⁴²

6.1.2.2 Meta-analyses in the treatment of angina

Meta-analyses, systematic reviews and expert consensus were also considered as part of the review process.

Table 8: Summary table of meta-analysis in the treatment of stable angina

Meta-analysis	Author	Year	N	Drugs reviewed	Conclusion
Long-term β -blockers for stable angina: systematic review and meta-analysis ⁴³	De Fin et al.	2012	6,108	β -blockers CCB	Treatment with β -blockers significantly \downarrow all-cause mortality compared to control but not CCBs.
Meta-analysis of trials comparing β -blockers, calcium antagonists, and nitrates for stable angina ⁴⁴	Heidenreich et al.	1999	143 studies included	β -blockers CCB Long-acting nitrates	No significant difference between β -blockers and CCBs in rates of death & MI ($p=0.79$) but β -blockers were associated with fewer side-effects ($p<0.079$).
The impact of β -blockers on mortality in stable angina: a meta-analysis ⁴⁵	Huang et al.	2012	-	β -blockers CCB Nitrates	No statistical difference in mortality comparing β -blockers to CCBs and nitrates. Cardioselective β -blockers showed better mortality results in the β -blockers investigated.
Expert consensus document on β -adrenergic receptor blockers ⁴	Sendon et al.	2004	-	Atenolol Bisoprolol Metoprolol	No clinically relevant differences were found when comparing β -blockers with CCBs in the control of ischemia.

CCB=Calcium Channel Blocker; MI=Myocardial Infarction

Key findings from Table 8 are as follows:

- De Fin *et al.* (2012) undertook a systematic review and meta-analysis to assess the effects of long term β -blockers in patients with stable angina. Twenty-six trials including 6,108 patients were evaluated. This showed that β -blockers significantly decreased all-cause mortality (OR 0.92) compared to placebo but had no statistical differences compared to calcium channel blockers. There was a significant reduction in nitrate consumption when β -blockers were compared to calcium channel blockers (OR -1.18, 95% CI -1.54 to -0.82).⁴³
- A meta-analysis by Heidenreich *et al.* (1999) compared β -blockers, calcium channel antagonists and nitrates for stable angina. Results showed that the rates of cardiac death and myocardial infarction were not significantly different for treatment with β -blockers vs. calcium channel blockers ($p=0.79$). However, β -blockers were associated with fewer adverse

effects ($p < 0.01$) and fewer episodes of angina per week ($p = 0.05$) compared with calcium channel blockers.⁴⁴

- A meta-analysis of randomised trials of β -blockers for stable angina by Huang *et al.* (2012) suggested that β -blockers do not have a statistically significant impact on mortality versus placebo (OR 0.42) or versus other active comparators (OR 0.97). A subgroup analysis showed that there was a greater reduction in mortality with cardioselective β -blockers.⁴⁵
- These results reflect an expert consensus document on β -blockers in 2004 where analysis showed no clear difference had been demonstrated between different β -blockers in the treatment of angina and no clinically relevant differences were found when comparing β -blockers with calcium channel blockers in the control of ischaemia.⁴

6.1.2.3 Clinical guidelines for the treatment of angina

Current guidelines recommend a β -blocker or a calcium channel blocker alone or in combination and a nitrate for the long-term treatment of chest pain resulting from coronary heart disease as shown in Table 9 below.³⁵ This differs from the US guidelines which recommend treatment with a β -blocker and/or an ACE inhibitor or an ARB.⁴⁶

Table 9: Clinical guidelines for the treatment of angina

Group	Guideline	Year	Initial drug treatment options	Preferred B-blocker
European Society of Cardiology (ESC) ³⁵	Stable Angina	2006	-Short acting nitrate - β -blocker or CCB	β_1 blocker
National Institute for Health and Care Excellence (NICE) CG126 ⁴⁷	Stable Angina	2011	- β -blocker or CCB -Long acting nitrate	Not specified
Scottish Intercollegiate Guidelines Network (SIGN) 96 ⁴⁸	Stable Angina	2007	- β -blocker or CCB -Long acting nitrate	β -blocker with lowest cost & accommodates best compliance
-American College of Cardiology (ACC) -American Heart Association (AHA) ⁴⁶	Chronic Stable Angina	2007	- β -blocker -ACE or ARB	Not specified

In summary, clinical studies have shown that all β -blockers are effective in the treatment of angina. There are no head-to-head clinical trials comparing individual β -blockers and therefore it is difficult

to draw firm conclusions. However, meta-analyses did provide additional information in that Huang et al. demonstrated that cardioselective β -blockers showed better mortality results.⁴⁵ Clinical guidelines do not recommend a specific β -blocker to be used but ESC guidelines make reference to the fact that β -1 selective β -blockers may be favourable.³⁵ SIGN guideline 96 state a β -blocker with lowest acquisition cost and also accommodates compliance be used.⁴⁸

Bisoprolol proves most favourable with regard the above criteria for the following reasons.

- It is highly selective β -1 adrenoceptor blocker.
- It has good clinical efficacy as demonstrated in the TIBBS study.
- It has once daily dosing.
- It has a low acquisition cost.

6.1.3 Hypertension

β -blockers currently licensed for the treatment of hypertension as outlined in Table 3 are: atenolol, bisoprolol, carvedilol, celiprolol, labetalol, metoprolol, nebivolol and propranolol.⁶⁻¹³ Current guidelines as shown in Table 11 below indicates that diuretics, calcium channel blockers, ACE inhibitors and ARBs are all appropriate for the initiation and maintenance of antihypertensive treatment either as monotherapy or in combination. β -blockers are not recommended as first line for hypertension as outcomes demonstrate that they are inferior to other classes of antihypertensives.⁴⁹ This is highlighted in Table 10 below. Studies have demonstrated the ability of β -blockers to effectively reduce blood pressure however, compared to other therapies they show only a modest reduction in stroke and no significant reduction in mortality or coronary heart disease.⁵⁰

6.1.3.1 Reviews for the treatment of hypertension

Table 10: Systematic review and meta-analysis of β -blockers in the treatment of hypertension

Review	Author	Year	N	Drugs reviewed	Conclusion
β -blockers for hypertension ⁴⁹	Wiyonge <i>et al.</i>	2009	91,561	β -blockers vs. Diuretics, CCB, ACE, ARB & placebo	β -blockers are not recommended as 1 st line treatment for hypertension. This is due to the weak effect of β -blockers to reduce stroke and the absence of an effect on coronary heart disease compared with placebo.
Should β -blockers remain first choice in the treatment of primary hypertension? A meta-analysis ⁵⁰	Lindholm <i>et al.</i>	2005	105,951	β -blockers vs. Diuretics, ACE, ARB & CCB	The relative risk of stroke was 16% higher for β -blockers than any other antihypertensive. There was no difference for MI or mortality.

- A cochrane review by Wiyonge *et al.* (2009) involving 13 RCTs and 91,561 patients compared β -blockers to diuretics, CCB, ACE inhibitors, ARBs and placebo. The β -blockers involved in this review included atenolol, metoprolol, oxprenolol (unlicensed in Ireland), and propranolol. Results showed that β -blockers were inferior to CCBs for all-cause mortality, stroke and total cardiovascular events and to ACE inhibitors and ARBs for stroke. In addition, patients on β -blockers were more likely to discontinue treatment due to side-effects compared to diuretics, ACE inhibitors and ARBs but there was no significant difference with CCBs. Therefore the available evidence does not support the use of β -blockers as first-line agents in the treatment of hypertension. Although β -blockers are a heterogeneous group of pharmacological agents varying in their individual properties there are no head-to-head comparisons in the treatment of hypertension. Therefore no conclusions can be made in comparing these agents in the treatment of hypertension.⁴⁹
- A meta-analysis by Lindholm *et al.* in 2005 involving 105,951 patients and 13 RCTs analysed β -blockers with other antihypertensive medicines for patients with primary hypertension. The β -blockers in the analysis included atenolol, metoprolol, oxyprenolol (unlicensed in Ireland), pindolol (unlicensed in Ireland) and propranolol. Results showed that the relative risk of stroke was 16% higher with β -blockers than with any other antihypertensive (p=0.009). Treatment

with β -blockers did not reduce the risk of myocardial infarction or mortality. Although β -blockers do have an effect in primary hypertension their effect is suboptimum.⁵⁰

6.1.3.2 Clinical guidelines for the treatment of hypertension

Table 11: Clinical guidelines for the treatment of hypertension

Group	Guideline	Year	Initial drug treatment options	Preferred B-blocker
European Society of Hypertension (ESH) ⁵¹ European Society of Cardiology (ESC) ⁵²	Arterial Hypertension	2013	<55years and non-Black: -ACE inhibitor and/or ARB >55years and Black: -Diuretic and/or CCB - β -blockers	Not specified
National Institute for Health and Care Excellence (NICE) [CG127] ⁵³	Hypertension	2011	<55years and non-Black: -ACE inhibitor and/or ARB >55years and Black: -Diuretic and/or CCB * β -Blocker only if ACE or ARB are contraindicated, women with child-bearing potential & patients with increased sympathetic drive.	- β -blockers with once daily dosing. - Non-propriety drugs at minimum cost.
British Hypertension Society (BHS) ^{54,55}	Hypertension	2013	Same as NICE above	Not Specified
International Society of Hypertension (ISH) with American Society of Hypertension (ASH) ⁵⁶	Hypertension	2014	All ages and non-Black: -Thiazide-type diuretic, ACE, ARB, CCB alone or in combination. All ages and Black: -Thiazide-type diuretic or CCB alone or in combination	β -blockers only recommended if there is a compelling indication

ACE=Angiotensin converting enzyme; ARB=Angiotensin receptor blocker; CCB=Calcium channel blocker

In conclusion, β -blockers are not recommended as first line therapy in the treatment of hypertension but they do play a role as add-on therapy or when other antihypertensive agents are contraindicated. They may also have a role in reducing blood pressure in patients with pre-existing HF and angina where β -blockers are recommended as first line agents. Clinical guidelines do not recommend a particular β -blocker to use and there are no head-to-head trials showing superiority of any β -blocker in the treatment of hypertension.⁴⁹

6.2 Adverse Drug Reactions

β -blockers are generally well tolerated and most adverse-effects are mild and transient. The most frequent adverse-effects are related to their β -adrenergic blocking activity. These include gastrointestinal disturbances, bradycardia, hypotension, peripheral vasoconstriction,

bronchospasm, headache, fatigue, sleep disturbances, sexual dysfunction, exacerbation of psoriasis, alopecia and dyspnoea.³

Table 12 illustrates the very common (≥ 1 in 10) and common (≥ 1 in 100 to < 1 in 10) adverse-effects of individual β -blockers as a result of their individual properties.

Table 12: Adverse-effects of β -blockers (very common (1/10) and common ($\geq 1/100$ to $< 1/10$))

Adverse-effect	Atenolol**6	Bisoprolol*7	Carvedilol*8	Celiprolol**9	Labetolol*10	Metoprolol*11	Nebivolol*12	Propranolol*13
Bradycardia	✓	✓	✓			✓		✓
Coldness in extremities	✓	✓	✓	✓		✓		✓
GI disturbance	✓	✓	✓	✓	✓	✓	✓	
Fatigue	✓	✓	✓		✓	✓	✓	✓
Dizziness		✓	✓	✓	✓	✓	✓	
Headache		✓	✓	✓	✓	✓	✓	
Hypervolemia Oedema Fluid Overload			✓		✓		✓	
Worsening of HF		✓	✓					
Orthostatic hypotension			✓			✓		
Depression				✓	✓			
Visual impairment Dry eye Eye irritation			✓		✓			
Weight gain			✓					
Impaired glucose control			✓					
Sleep disturbance/ nightmares								✓
Anaemia			✓					
Skin rash Pruritus					✓			
Erectile dysfunction				✓				

*Lipophilic; **Hydrophilic

As seen in Table 12, bradycardia, coldness in the extremities, GI disturbances, fatigue, dizziness and headache are the most common adverse-effects associated with all β -blockers. There is no β -blocker that exhibits a more favourable adverse-effect profile. On the contrary, carvedilol clearly portrays the widest ‘common and very common’ adverse-effects. This is due to its non-selective α - and β - properties and also its high lipid solubility compared to other β -blockers as outlined in pharmacodynamic and pharmacokinetic properties of carvedilol in Appendix A.⁸

6.3 Cautions and contraindications

Table 13 below highlights the cautions and contraindications when prescribing all β -blockers. Prescribers are required to regularly monitor all patients when prescribing a β -blocker where caution is advised and to avoid prescribing β -blockers where they are deemed contraindicated.³ It is advisable to consult the SmPC of the individual β -blockers for cautions and contraindications at www.hpra.ie or www.medicines.ie.

Table 13: Cautions and contraindications for β -blockers

Cautions	Contraindications
Mild to moderate airway disease- monitor peak flow prior to and following initiation	Severe bronchial asthma or bronchospasm
Renal and hepatic disease	Uncontrolled heart failure
β -blockers may mask early signs of hypoglycaemia	Prinzmetal's angina
Worsening control of blood glucose may occur	Sinus bradycardia <50bpm
First degree AV block	Sick sinus syndrome including sino-atrial block, second or third degree AV block
Use of concomitant medication that may increase risk of bradycardia	Hypotension- Systolic BP <90mmHg
Symptoms of thyrotoxicosis may be masked	Cardiogenic shock
Psoriasis	Metabolic acidosis
General anaesthesia	Severe peripheral arterial disease
	Phaeochromocytoma- apart from specific use with α-blockers
	Patients treated with verapamil

6.4 Drug interactions

Below is an overview of potential drug-drug interactions that may occur with β -blockers. This list is not exhaustive and it is advisable to consult the SmPC of the individual β -blockers for a comprehensive list of drug interactions at www.hpra.ie or www.medicines.ie

- **Class I antiarrhythmic drugs** (e.g. Quinidine, flecainide, disopyramide and lidocaine): The use of class I antiarrhythmic drugs and β -blockers may have additive cardiac depressive effects and cause marked bradycardia. The effect on atrio-ventricular conduction time may be potentiated and the negative inotropic effect increased. This interaction may also occur with β -blocker eye-drops (e.g. timolol).⁵⁷

- **Class III antiarrhythmic drugs** (e.g. amiodarone): The concurrent use of amiodarone and a β -blocker may lead to hypotension, bradycardia, ventricular fibrillation and asystole in a few patients. Amiodarone may also inhibit the metabolism of β -blockers metabolised by CYP2D6 (e.g. metoprolol) and this may also be a factor in the interaction.⁵⁷
- **Calcium channel antagonists of verapamil/diltiazem type**: The cardiac depressant effects of verapamil and diltiazem with β -blockers are additive and a number of patients have developed serious and potentially life-threatening bradycardia. However, concomitant use may be beneficial in certain circumstances. Diltiazem increases serum levels of propranolol and metoprolol but not atenolol.⁵⁷
- **Calcium channel antagonists of dihydropyridine type** (e.g. amlodipine and felodipine): β -blockers and calcium channel blockers may be used in combination for certain indications. Severe hypotension and heart failure have occurred rarely when a β -blocker was given with nifedipine.⁵⁷
- **Centrally-acting antihypertensives** (e.g. clonidine and methyldopa): Concomitant use of β -blockers with centrally-acting antihypertensive drugs can be therapeutically valuable but a sharp and serious rise in blood pressure (rebound hypertension) can occur with sudden withdrawal of clonidine.⁵⁷
- **Insulin and oral anti-diabetic agents**: In patients with diabetes using insulin, if hypoglycaemia occurs the normal recovery time may be impaired to some extent by β -blockers (e.g. propranolol). Cardioselective β -blockers seem less likely to interact. The blood glucose lowering effect of the sulfonylureas may be reduced by β -blockers. Hypoglycaemia in patients taking β -blockers has been noted to result in increases in blood pressure and possibly bradycardia in some studies.⁵⁷
- **Selective serotonin reuptake inhibitors** (e.g. fluoxetine, paroxetine, citalopram, escitalopram): Fluoxetine increases celiprolol levels and to a lesser extent metoprolol and propranolol. Paroxetine appears to increase carvedilol levels and may also increase

metoprolol levels leading to pronounced β -blocking effects. Citalopram and escitalopram may also increase metoprolol levels.⁵⁷

6.5 Patient factors

6.5.1 Dosing

As highlighted previously (sections 6.1.2.3 and 6.1.3) SIGN and NICE guidelines recommend use of β -blockers that accommodate patient compliance.^{48,53} Studies have shown that once daily dosing supports greater compliance compared to twice daily regimens.^{58,59} A meta-analysis of 29 centres assessing the effects of dosage frequency on chronic cardiovascular disease medication adherence showed that compliance to twice and thrice daily dosing had a lower weighted mean adherence compared to once daily regimens and this in turn had an impact on health outcomes and mortality.⁶⁰ Therefore, prescribers are advised to consider the effect of dosing frequency on medication adherence.⁶¹ Bisoprolol⁷ and nebivolol¹² are available as once daily dosing for all indications while carvedilol⁸ requires twice daily dosing for HF and angina. Standard dose propranolol may need to be administered three times daily for the treatment of angina.¹³

β -blockers should always be initiated in a 'start low, go slow' manner in the treatment of HF.⁶²

The recommended dosing regimen and titration requirements of β -blockers for the treatment of HF are outlined in Table 14 below.³

Table 14: Initiation and dose titration of β -blockers in heart failure

Drug	Week 1	Week 2	Week 3	Weeks 4 - 7	Weeks 8 - 11	Week 12
Bisoprolol ⁵	1.25mg od	2.5mg od	3.75mg od	5mg od	7.5mg od	10mg od
Drug	Weeks 1 - 2		Weeks 3 - 4		Weeks 5 - 6	Weeks 7 - 8
Carvedilol ⁶	3.125mg bd		6.25mg bd		12.5mg bd	25mg bd
Nebivolol ¹⁰	1.25mg od		2.5md od		5mg od	10mg od

od: once daily; bd: twice daily

This differs for the treatment of angina and hypertension, as is outlined in Table 15 and Table 16 below.³

Table 15: Initiation and dose titration of β -blockers in angina pectoris

B-blocker	Initial Dose	Maintenance Dose
Atenolol ⁶	100mg daily or 50mg twice daily	It is unlikely that additional benefit will be gained by \uparrow the initial dose
Bisoprolol ⁷	5mg once daily	10mg once daily. Max 20mg daily
Carvedilol ⁸	12.5mg twice daily	After 2 days \uparrow to 25mg twice daily. Max 50mg twice daily
Celiprolol ⁹	200mg once daily	\uparrow to 400mg once daily if necessary
Labetalol ¹⁰	100mg twice daily	\uparrow at 14 day intervals to 200mg twice daily
Metoprolol ¹¹	50mg-100mg 2-3 times daily	50mg-100mg 2-3 times daily
Propranolol ¹³	40mg 2-3 times daily	\uparrow at 7 day intervals to a maintenance dose 80mg-320mg daily

Table 16: Initiation and dose titration of β -blockers in hypertension

B-blocker	Initial Dose	Maintenance Dose
Atenolol ⁶	25mg-50mg once daily	Higher doses rarely necessary
Bisoprolol ⁷	5mg once daily	10mg once daily. Max 20mg daily
Carvedilol ⁸	12.5mg once daily	After 2 days \uparrow to 25mg once daily. If necessary can be \uparrow at intervals of 2 weeks to max. 50mg daily
Celiprolol ⁹	200mg once daily	\uparrow to 400mg once daily if necessary
Labetalol ¹⁰	100mg twice daily	\uparrow at 14 day intervals to 200mg twice daily
Metoprolol ¹¹	100mg once daily	\uparrow if necessary to 200mg daily in 1-2 divided doses. Max 400mg daily
Nebivolol ¹²	5mg once daily	5mg daily
Propranolol ¹³	80mg twice daily	\uparrow at 7 day intervals to a maintenance dose 160mg-320mg daily.

Bisoprolol is the β -blocker of choice with regards dosing for the following reasons:

- Once daily dosing for all indications.
- Dosing and up-titration in the treatment of heart failure is straightforward.
- All dosage strengths are available.
- Dosing and up-titration is the same for the treatment of angina and hypertension and is more straightforward.

BISOPROLOL is the β -blocker of choice with regards dosing for the treatment of heart failure, angina and hypertension under MMP guidance.

6.6 Cost

Value for money is also an important consideration when choosing a preferred β -blocker. A drug of lower acquisition cost is preferred unless the more expensive has a proven advantage in terms of either safety or efficacy.⁶³ Cost is also an important consideration for patients who pay for their medicines. Figure 1 below clearly illustrates the price comparison between all the β -blockers currently available on the Irish market.⁶⁴ This price is based on the typical reimbursement cost per month based on the defined daily dose (DDD). The DDD is listed by the World Health Organisation (WHO) collaborating centre for drug statistics methodology and it is by this method that the price of each individual β -blocker is compared.⁶⁵ In the case where the DDD is not available as a single dose preparation the combination of tablets that make up the dose is used e.g. the DDD for atenolol is 75 mg, therefore a 25mg and a 50mg tablet is used to calculate the cost per DDD per month. The DDD for bisoprolol is 10mg.⁶⁵

Figure 1 shows the typical reimbursement cost per month (28 days) exclusive of pharmacist fees and mark-up of available β -blockers based on the defined daily dose (DDD).⁶⁴

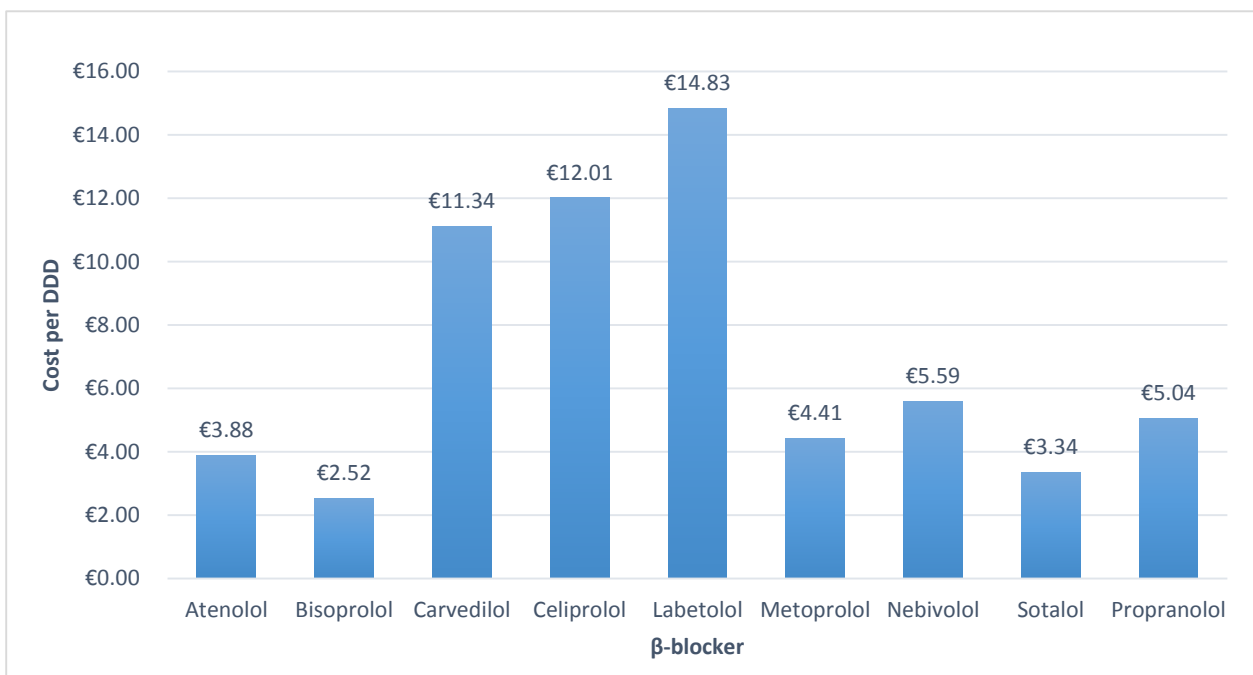


Figure 1: Reimbursement cost per month based on DDD

Carvedilol, celiprolol and labetalol are the most expensive β -blockers while bisoprolol is the least expensive based on DDD. Therefore bisoprolol is the β -blocker of choice based on cost.

BISOPROLOL is the β -blocker of choice with regards cost under MMP guidance.

6.7 National prescribing trends in Ireland

The MMP recognises that clinical experience is an important factor for prescribers when choosing a medication. In order to determine prescribing trends for the β -blockers under review, analyses of the PCRS pharmacy claims were performed by the MMP. Figure 2 illustrates the Irish market share for each of the β -blockers based on the number of claims received by the PCRS for October 2015 for the GMS scheme.⁶⁶

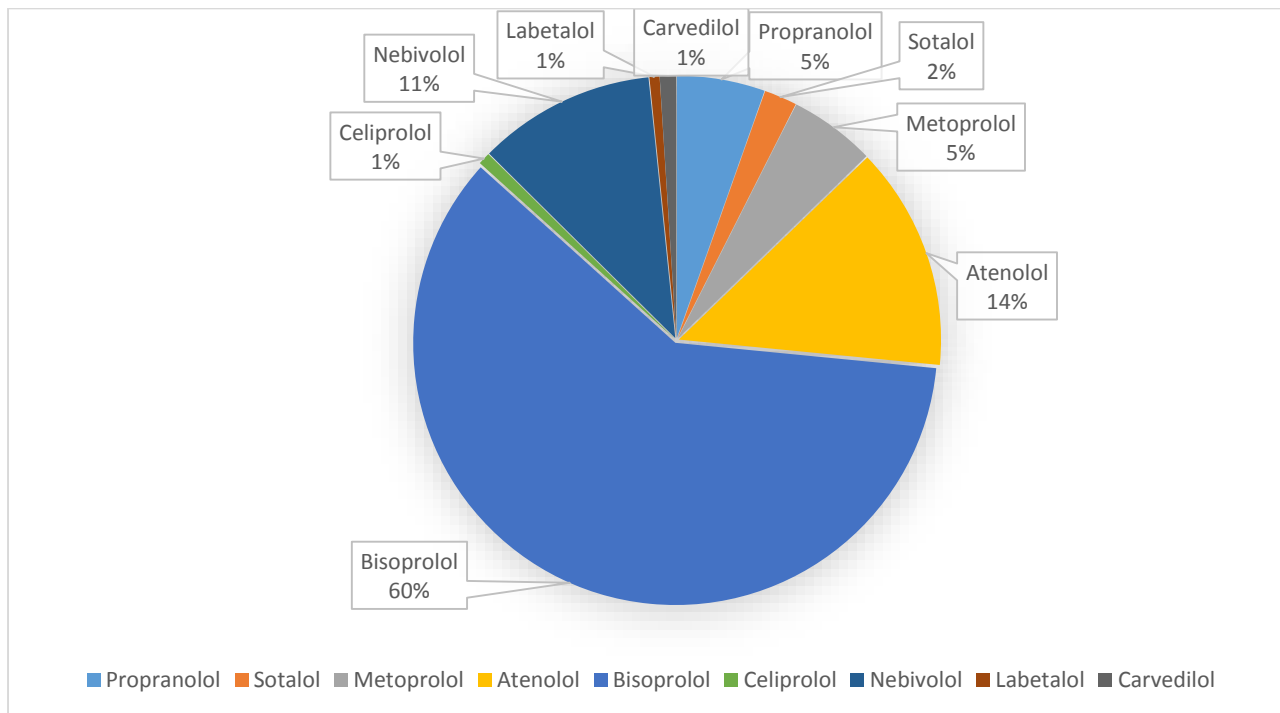


Figure 2: Market share for β -blockers as per number of dispensing claims (GMS) October 2015

Bisoprolol represents 60% of the market share and is by far the most frequently prescribed β -blocker on the Irish market. It is also the 5th most commonly prescribed item on the GMS with over 1.2 million prescriptions in 2014.⁶⁶

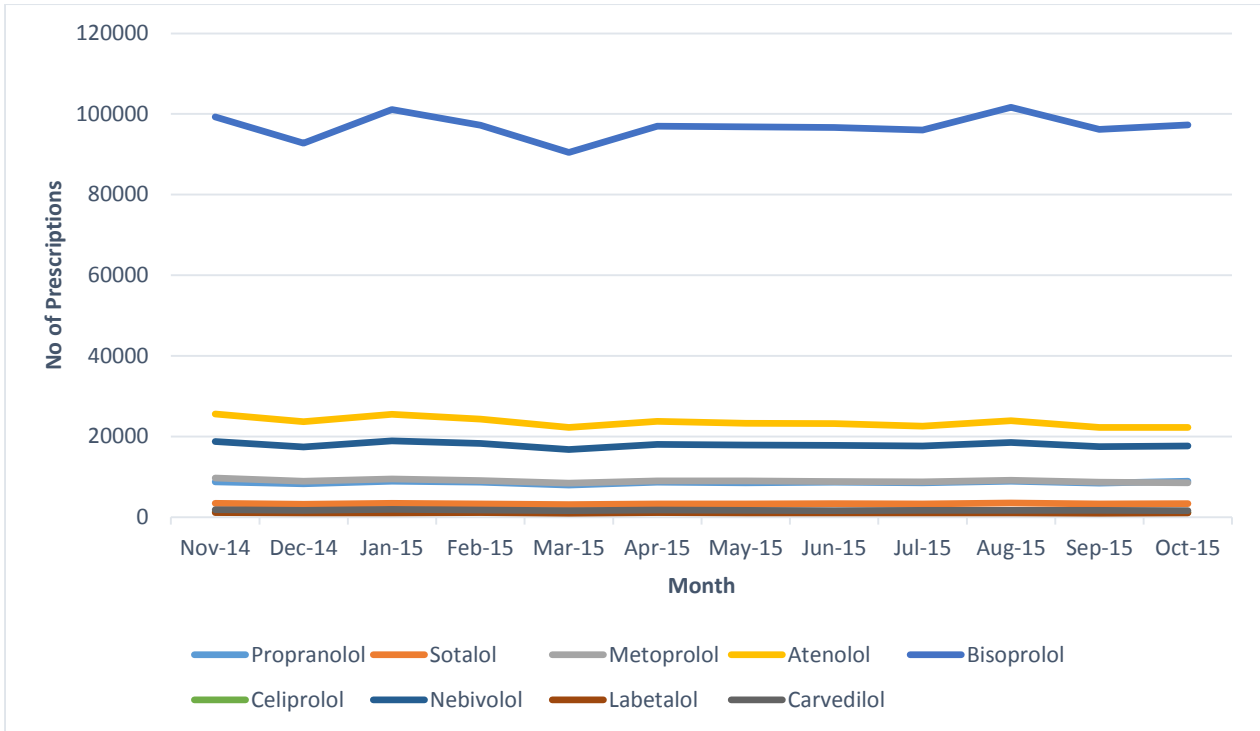


Figure 3: Number of Prescriptions for β -blockers (GMS) October 2014-October 2015

Figure 3 clearly highlights that in the 12 months from October 2014 to October 2015 bisoprolol remained the most commonly prescribed β -blocker with limited fluctuation in the number of prescriptions for other available β -blocker preparations.

BISOPROLOL is the β -blocker of choice in terms of national prescribing trends and market-share under MMP guidance.

7. Conclusion

Following a review of the available evidence and taking into account the following criteria: licensed therapeutic indications, clinical efficacy, clinical outcome, current clinical guidelines, patient factors, cost and national prescribing trends, bisoprolol is recommended by the MMP as the preferred β -blocker for the treatment of heart failure, angina and hypertension.

Bisoprolol is the preferred β -blocker for the treatment of heart failure, angina and hypertension under MMP guidance.

- ✓ Bisoprolol is licensed for hypertension, heart failure and angina
- ✓ Bisoprolol has once daily dosing for all indications
- ✓ Many strengths are available
- ✓ Dosing and titration of bisoprolol is the same for angina and hypertension
- ✓ Bisoprolol has a favourable clinical outcome data
- ✓ Bisoprolol has a favourable side-effect profile
- ✓ Bisoprolol has the lowest acquisition cost
- ✓ Bisoprolol currently holds 60% of market share in Ireland

A clear and concise summary to facilitate the prescribing and monitoring of bisoprolol is included in 'Prescribing Tips and Tools for bisoprolol' in Appendix B. This summary will enable prescribers to prescribe and monitor bisoprolol safely and appropriately.

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Appendix A: Individual β -blocker properties

All β -blockers vary according to their unique properties. Pharmacodynamic and pharmacokinetic properties for each β -blocker is summarised below.

Atenolol

Atenolol is a selective β_1 -adrenoreceptor blocker. It has a preferential effect on the β_1 -receptors located primarily in the heart. This selectivity decreases with increasing dose.

Atenolol is hydrophilic although human studies indicate it does cross the blood brain barrier but only to a negligible extent indicating that atenolol also has mild lipophilic properties.¹

Atenolol is well absorbed after oral dosing with peak plasma levels occurring 2 to 4 hours after dosing. There is no significant first-pass metabolism and more than 90% of the absorbed drug reaches the systemic circulation unaltered. Plasma protein binding is low at approximately 3%. The plasma half-life is about 6 hours but this may rise in severe renal impairment as the kidneys are the major route of elimination. Atenolol is effective for 24 hours after a single oral daily dose.¹

Bisoprolol

Bisoprolol is a highly selective β_1 -adenoreceptor blocker. It shows a much lower affinity for the β_2 -adrenoceptors of the smooth muscle of the bronchi and vessels, as well as the β_2 receptors concerned with metabolic regulation.² Bisoprolol is moderately lipophilic and has a bioavailability of 90% after oral administration. The plasma protein binding is approximately 30%. Bisoprolol has a half-life in plasma of 10-12 hours giving a 24 hour effect after dosing once daily.³ Bisoprolol is excreted by the body via two routes, 50% is metabolised by the liver to inactive metabolites and then excreted by the kidneys. The remaining 50% is excreted by the kidneys in an unmetabolised form. Since the elimination takes place in the kidneys and the liver to the same extent a dose adjustment is not required for patients with impaired liver function or renal insufficiency.³

Carvedilol

Carvedilol is a vasodilating, non-selective, β -blocker and acts on the α_1 , β_1 and β_2 receptors in the heart and the peripheral vasculature.⁴ Vasodilation is predominantly mediated through the α_1 -receptor antagonism. Carvedilol is well absorbed after oral dosing and peak plasma levels reached after 1.5 hours. It is extensively metabolised by the liver that results in an oral bioavailability of approximately 25%. Carvedilol is moderately lipophilic showing plasma protein binding of

approximately 95%. As a result of the extensive first-pass metabolism and poor bioavailability carvedilol requires twice daily dosing.⁴

Celiprolol

Celiprolol is a vasodilating, selective β_1 -adrenoceptor blocker with partial β_2 -agonist activity. The β_2 -agonist activity is thought to account for the mild vasodilating and positive inotropic properties.⁵ The absorption of celiprolol is reduced by food and therefore should be taken one hour before or two hours after eating.⁵ Celiprolol is hydrophilic and has an oral bioavailability of 30%-70%. It is excreted via the kidneys with only a very low percentage being excreted as metabolites. The elimination half-life is about 5 hours.⁶

Labetalol

Labetalol is a non-selective β -adrenoreceptor blocker that acts on α - and β - receptors in the heart and the peripheral vasculature.⁷ The plasma half-life of labetalol is about 4 hours and about 50% of labetalol is protein bound. Labetalol is metabolised mainly the liver via conjugation. Only negligible amounts of the drug cross the blood brain barrier.⁸ It has a low oral bioavailability (30%-65%) depending on age and requires twice daily dosing.^{4,9}

Metoprolol

Metoprolol is a cardioselective β_1 -adrenoceptor blocker with a strong affinity for the β_1 -receptors in the heart and a lower affinity for the β_2 -adrenoreceptors mainly located in the bronchi and peripheral vasculature.¹⁰ Metoprolol is moderately lipophilic and is almost completely absorbed after an oral dose and peak plasma concentrations occurring after 1.5 to 2 hours. Due to a pronounced first-pass metabolism the bioavailability of a single oral dose is approximately 50%.¹¹ Metoprolol is widely distributed. It crosses the blood brain barrier, the placenta and is excreted in breast milk. Metoprolol is metabolised by the liver and more than 95% of the oral dose is excreted in the urine. The elimination half-life is 3.5 hours and requires twice daily dosing.¹⁰

Nebivolol

Nebivolol is a competitive and selective β_1 -receptor antagonist and also possesses mild vasodilating properties due to its interaction with the L-arginine/nitric oxide pathway.¹¹ Nebivolol is moderately

lipophilic in nature and is rapidly absorbed after oral administration and undergoes extensive first-pass metabolism through the cytochrome P450 2D6 enzyme system.¹² The oral bioavailability of nebivolol averages 12% in fast metabolisers and is virtually complete in slow metabolisers. Due to the variation in rates of metabolism the dose of nebivolol should always be adjusted to the individual requirements of the patient. Poor metabolisers may therefore require lower doses.¹¹

Propranolol

Propranolol is a competitive antagonist at both the β_1 - and β_2 - adrenoceptors. It is highly lipophilic and almost completely absorbed after oral administration and peak plasma levels occur 1-2 hours after oral administration. Due to the non-selectivity and lipophilic nature of propranolol, it crosses the blood-brain-barrier. It also undergoes first-pass metabolism and 90% of the oral dose is removed by the liver and has an elimination half-life of 3-6 hours.¹² As a consequence, standard release propranolol may need to be taken two to three times daily for the treatment of hypertension and angina.¹³ However, prolonged-release capsules release propranolol hydrochloride at a controlled and predictable rate. Peak blood levels following dosing with prolonged release propranolol occur at approximately 6 hours.¹²

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Appendix B: Prescribing Tips and Tools for Bisoprolol

Prescribing Tips and Tools for Bisoprolol

There are many preparations of bisoprolol available. An up-to-date listing is available on the Health Products Regulatory Authority website at www.hpra.ie.

Therapeutic Indications

- Treatment of chronic stable heart failure with reduced systolic left ventricular function in addition to ACE inhibitors and diuretics and optionally cardiac glycosides.
- Treatment of chronic stable angina pectoris.
- Treatment of hypertension.

Dosing and Administration

Full prescribing information is available in Summary of Product Characteristics (SmPC) which may be accessed freely online at www.medicines.ie or www.hpra.ie. Please consult the SmPC for guidance on prescribing in special patient populations e.g. asthma, COPD, diabetes, renal and hepatic failure.

Dose

Adjunct in heart failure: initiate at 1.25mg once daily and titrate as directed in Table 1 below to a maximum of 10mg once daily.

Hypertension & Angina: 10mg once daily (5mg may be adequate in some patients); max 20mg daily.

Dose titration in heart failure

- ✓ Patients should be **stable** when bisoprolol is initiated.
- ✓ Start at a low dose and increase slowly titrating the dose as per Table 1 below.
- ✓ Aim for optimal target dose of 10mg or, if not tolerated, the highest tolerated dose.

Table 1: Dose titration for bisoprolol in heart failure (HF)

Heart Failure Titration	Week 1	Week 2	Week 3	Weeks 4-7	Weeks 8-11	Week 12
Bisoprolol	1.25mg once daily	2.5mg once daily	3.75mg once daily	5mg once daily	7.5mg once daily	10mg once daily



Cautions

- Mild/moderate airway disease
- Prinzmetal's angina
- Diabetes mellitus
- First degree AV block
- Psoriasis
- General anaesthesia
- Thyrotoxicosis
- Severe renal impairment
- Severe liver impairment

Contraindications

- Severe bronchial asthma & COPD
- Uncontrolled heart failure
- Sick sinus syndrome
- Second or third degree AV block
- Sinus bradycardia <50bpm
- Severe peripheral arterial disease
- Untreated phaeochromocytoma
- Severe hypotension BP<90mmHg
- SA block

Bisoprolol interactions for all indications

- ❑ Calcium channel blockers- (e.g.diltiazem)- ↑ risk AV block, bradycardia & hypotension.
- ❑ Calcium channel blockers-dihydropyridines (e.g. amlodipine)- ↑ risk of hypotension.
- ❑ Cardiac glycosides (e.g. digoxin)- ↓ in heart rate. ↑ AV conduction time.
- ❑ Class I and class III antiarrhythmics (e.g. flecainide, amiodarone)- Effect on AV conduction time may be potentiated and negative inotropic effect ↑.
- ❑ Insulin and oral antidiabetic drugs- Blood sugar lowering effect ↑. Symptoms of hypoglycaemia may be masked.

Monitoring for all indications

- ✓ Heart Rate
- ✓ Blood Pressure

Additional monitoring in heart failure

- ✓ Symptoms of Heart Failure
- ✓ Signs of Congestion

Counselling Points

- Take in the **MORNING** with or without food. Swallow **whole** with liquid.
- Treatment should not be withdrawn abruptly; The dosage should be reduced slowly by a weekly halving of the dose.
- Transient worsening of heart failure, hypotension or bradycardia may occur during initiation phase and can be resolved by titrating the dose.

AV=Atrioventricular; COPD= Chronic obstructive pulmonary disease; SA= Sinusatrial; HF= Heart failure.

Version 1.0 September 2016. References: SmPC & PIL Bisop 5mg*, BNF March 2016.