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### Efficacy and Safety of Addition of Teneligliptin to Type 2 Diabetes Patients Inadequately Controlled with Triple Drug Treatment with Glimepride + Metformin + Voglibose

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#### Abstract

Type 2 diabetes is a significant health problem and its prevalence is increasing globally. There are several challenges to the management of type 2 diabetes in the Indian population. A single-center study evaluated the efficacy and safety of addition of teneligliptin 20 mg/day to type 2 diabetes patients inadequately controlled with triple drug treatment with glimepride + metformin + voglibose. Overall, 81 were prescribed teneligliptin in addition to triple drug treatment. At study end, 62.12% patients achieved HbA1c levels  $\leq$ 7%. Patients reported only mild/transient adverse effects during the study period. It was concluded that addition of teneligliptin to triple drug therapy with glimepride + metformin + voglibose is efficacious to attain HbA1c below 7% in diabetes patients inadequately controlled with the triple therapy. It is also a safe drug since the adverse effects reported following the addition of teneligliptin were mild/transient. **Keywords:** Teneligliptin, type 2 diabetes, triple drug therapy.

#### Introduction

Type 2 diabetes is a significant health problem with an increasing worldwide prevalence.<sup>1</sup> There were more than 72 million cases of diabetes in India in 2017.<sup>2</sup> The prevalence of diabetes has been rising in India, not only in urban areas but in rural areas too.<sup>3</sup>

The management of type 2 diabetes is relatively challenging. Most international guidelines recommend an individualized management approach and an optimal HbA1c target tailored to every patient.<sup>1</sup> To strike a balance, it is mandatory to attain optimal control of blood sugar levels and prevent microvascular events, and severe hypoglycemia. Cost, efficacy, potential side effects of the drugs, impact on body weight, comorbidities, and patient preferences also have significant roles to play in diabetes management.<sup>1</sup> In a country like India, medical professionals face some major challenges in the prevention and management f type 2 diabetes. Some of these include increasing prevalence in both urban and rural areas; high prevalence of pre diabetes; genetic and environmental risk factors; delay in diagnosis; low levels of awareness among people; limited resources and health care facilities; high cost; suboptimal control of diabetes; and increased complications.<sup>3</sup>

All major guidelines recommend metformin as the first-line treatment in patients with diabetes unless contraindicated and tolerated well.<sup>1</sup> The American Diabetes Association recommends that dual therapy should be considered in patients with newly diagnosed type 2 diabetes who have A1C  $\geq$ 9%. Among patients without atherosclerotic cardiovascular disease (ASCVD), if monotherapy or dual therapy fails to achieve or maintain the goal over 3 months, an additional A1C antihyperglycemic agent can be added based on drug-specific and patient factors. In those with established ASCVD, management should begin with lifestyle management and metformin and then a drug known to reduce major adverse cardiovascular events and cardiovascular mortality can be added after giving due consideration to drug-specific and patient factors.4 It is important to reevaluate the medication regimen and adjust it as needed.4 When dual therapy fails to control blood glucose, a third agent can be added to the treatment regimen.<sup>1</sup>

If A1C target is not achieved after about 3 months on triple therapy, The ADA recommends combination injectable therapy.4 However, there may be situations where insulin and other injectables are not an option.

This study thus sought to evaluate the effect of adding an oral hypoglycemic agent, teneligliptin, to a triple drug therapy regimen in patients not adequately controlled with the triple therapy.

#### Objective

The study was conducted to evaluate the efficacy and safety of addition of teneligliptin to type 2 diabetes patients inadequately controlled with triple drug treatment with glimepride + metformin + voglibose.

#### **Patients and Methods**

This was a single-center study that included 81 patients with type 2 diabetes whose blood sugar levels were not adequately controlled on triple drug therapy with glimepride + metformin + voglibose. All the subjects were prescribed teneligliptin 20 mg OD in addition to triple drug treatment. The patients were studied for a period of 3 months.

Patients with a significant complication were not included in the study. Fifteen patients dropped out from the study. Of these, 4 developed significant osmotic symptoms, 2 had acute myocardial infarction, 2 patients had a cerebrovascular accident, 1 developed urinary tract infection (UTI), 2 had pneumonia and 4 patients were lost to follow-up. Therefore, data was available for 66 patients.

All patients underwent blood sugar evaluation before, 1 month, 2 months and 3 months after the addition of teneligliptin. HbA1c levels were evaluated before and 3 months after teneligliptin addition.

The demographic characteristics of the patients enrolled in the study are summarized in table 1. The study population was in the age range of 38-70 years with 40 males and 26 females.

Sex	Age	Height	Weight	Duration	UR	CR	ТС	TG	LD	HD	VD
		(cm)	(kg)	of DM							
М	46	166	64	3 YRS	36	0.8	208	244	124	36	48
М	63	164	72	2 YRS	24	1.0	267	174	195	40	32
М	52	170	80	2 YRS	30	1.3	204	160	120	52	32
М	61	144	59	1YRS	24	0.8	168	84	116	36	16
F	70	158	62	3 YRS	31	1.2	184	120	124	40	24
F	62	154	48	2 YRS	26	1.0	190	140	120	35	35
М	47	165	46	2 YRS	16	0.6	154	174	79	40	35
F	50	162	50	4 YRS	20	1.0	162	150	90	42	30
Μ	60	163	54	3 YRS	18	0.8	140	110	77	41	22
F	64	170	64	4 YRS	34	12	220	160	138	50	32

Table 1. Demographic characteristics of study population

F	47	154	50	2 YRS	28	08	176	144	94	54	28
М	47	166	60	1 YRS	30	1.1	217	190	119	60	38
М	50	144	57	2 YRS	18	0.7	142	112	79	41	22
М	54	169	72	1 YR	30	1.2	224	210	120	62	42
М	52	`174	70	1 YR	26	1.0	250	208	151	58	41
M	60	172	74	2 YRS	31	11	301	400	27	50	80
F	48	160	56	3 YRS	26	1.0	170	142	98	44	28
F	54	154	50	3 YRS	20	1.0	184	136	107	50	20
F	54	160	54	2 VPS	18	0.8	210	174	118	58	3/
M	18	164	54 60		24	0.0	240	200	146	54	40
F	40	104	58	1 VP	18	0.8	161	140	02	J4 //1	28
Г	42 59	1.54	50		10	0.8	220	140	92 125	41 62	20
Г	38	161	60		20	1.1	220	100	123	03 54	32
M E	44	104	02		20	1.1	202	1/0	114	34	34
Г	38	157	44		10	0.8	1/4	140	104	41	29
M	65	1/4	68	2 YRS	20	1.2	217	154	125	62	30
M	70	169	70	1 YR	21	1.1	273	180	163	74	36
M	64	166	65	1 YR	14	1.0	172	144	83	61	28
M	48	160	68	2 YRS	22	1.0	188	151	107	51	30
М	50	168	70	1 YR	30	1.0	264	500		81	
F	48	170	71	6 YRS	36	1.4	300	190	182	70	38
F	60	161	56	2 YRS	24	0.8	202	200	110	52	40
F	56	158	53	1 YR	20	1.1	246	200	140	60	40
М	42	156	64	1 YR	30	1.2	300	200	203	57	40
М	52	162	66	5 YRS	31	1.4	267	304	142	64	61
М	64	170	70	3 YRS	28	1.3	220	170	125	61	34
М	54	168	68	1 YR	22	1.2	194	94	112	64	18
Sov	Age	Height	Weight	Duration	UP	CP	тс	TC	ID	HD	VD
DLA	Age	(cm)	(kg)	of DM	UN	CK	10	10	LD	ш	<b>VD</b>
F	60	154	52	4 YRS	28	11	220	161	122	66	32
F M	60 63	154	52 64	4 YRS	28 24	1.1	220	161 400	122	66 60	32
F M F	60 63 45	154 164 160	52 64 54	4 YRS 6 YRS 3 YRS	28 24 20	1.1 1.0	220 360 216	161 400 188	122 122 121	66 60 58	32 8 37
F M F	60 63 45 52	154 164 160	52 64 54 56	4 YRS 6 YRS 3 YRS 5 YRS	28 24 20	1.1 1.0 1.1	220 360 216	161 400 188 200	122 122 121	66 60 58 60	32 8 37 50
F M F F	60 63 45 52 61	154 164 160 156	52 64 54 56 58	4 YRS 6 YRS 3 YRS 5 YRS 4 YPS	28 24 20 18 24	1.1 1.0 1.1 0.8	220 360 216 176 241	161 400 188 200 216	122 122 121 66	66 60 58 60	32 8 37 50 43
F M F F M	60 63 45 52 61 56	154     164     160     156     164     158	52 64 54 56 58 62	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YPS	28 24 20 18 24 20	1.1 1.0 1.1 0.8 1.2	220 360 216 176 241	161 400 188 200 216 201	122 122 121 66 132	66 60 58 60 66 56	32 8 37 50 43 41
F M F M F	60 63 45 52 61 56	$     \begin{array}{r}       154 \\       164 \\       160 \\       156 \\       164 \\       158 \\       161 \\       161     \end{array} $	52 64 54 56 58 62 63	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS	28 24 20 18 24 29 20	1.1 1.0 1.1 0.8 1.2 1.4	220 360 216 176 241 196	161 400 188 200 216 201 214	122 122 121 66 132 99	66 60 58 60 66 56 58	32 8 37 50 43 41 42
F M F F M F F	$ \begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ \end{array} $	$     \begin{array}{r}       154 \\       164 \\       160 \\       156 \\       164 \\       158 \\       161 \\       164 \\       164     \end{array} $	52 64 54 56 58 62 63 50	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS 4 YRS	28 24 20 18 24 29 30 26	$ \begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ \end{array} $	220 360 216 176 241 196 184 222	161 400 188 200 216 201 214	122 122 121 66 132 99 84 128	66 60 58 60 66 56 58 61	32 8 37 50 43 41 42 23
F M F F F F F F	$ \begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ \end{array} $	$     \begin{array}{r}       154 \\       164 \\       160 \\       156 \\       164 \\       158 \\       161 \\       164 \\       164 \\       164 \\       164     \end{array} $	52 64 54 56 58 62 63 59 60	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS 4 YRS 4 YRS	28 24 20 18 24 29 30 26	$ \begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ \end{array} $	220 360 216 176 241 196 184 222 264	161 400 188 200 216 201 214 166 206	122 122 121 66 132 99 84 128	66           60           58           60           66           56           58           61	32 8 37 50 43 41 42 33 41
F           M           F           M           F           F           M           F           M           M           M           M	$ \begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 62\\ 62\\ 62\\ 62\\ 62\\ 62\\ 62\\ 62\\ 62$	$     \begin{array}{r}       154 \\       164 \\       160 \\       156 \\       164 \\       158 \\       161 \\       164 \\       163 \\       163 \\       162     \end{array} $	52 64 54 56 58 62 63 59 60 60	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS 4 YRS 4 YRS 5 YRS 2 YRS	28 24 20 18 24 29 30 26 17 27	$ \begin{array}{c} 1.1\\ 1.0\\ 1.1\\ 0.8\\ 1.2\\ 1.4\\ 0.9\\ 1.1\\ 0.8\\ 1.1 \end{array} $	220 360 216 176 241 196 184 222 264	161 400 188 200 216 201 214 166 206 256	122 122 121 66 132 99 84 128 164	66 60 58 60 66 56 58 61 59 90	32 8 37 50 43 41 42 33 41 51
F           M           F           M           F           F           M           M           M           M	$ \begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 50\\ \end{array} $	$     \begin{array}{r}       154 \\       164 \\       160 \\       156 \\       164 \\       158 \\       161 \\       164 \\       163 \\       163 \\       163 \\       163     \end{array} $	$ \begin{array}{c} 52\\ 64\\ 54\\ 56\\ 58\\ 62\\ 63\\ 59\\ 60\\ 69\\ 69\\ 60\\ 69\\ 60\\ 69\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 3 YRS	28 24 20 18 24 29 30 26 17 27	$ \begin{array}{c} 1.1\\ 1.0\\ 1.1\\ 0.8\\ 1.2\\ 1.4\\ 0.9\\ 1.1\\ 0.8\\ 1.1\\ 1.2\\ 0.8\\ 1.1\\ 0.8\\ 0.8\\ 0.8\\ 0.8\\ 0.8\\ 0.8\\ 0.8\\ 0.8$	220 360 216 176 241 196 184 222 264 361	161 400 188 200 216 201 214 166 206 256	122 122 121 66 132 99 84 128 164 230	66 60 58 60 66 56 58 61 59 80	32 8 37 50 43 41 42 33 41 51 27
F           M           F           M           F           M           M           M           M           M           M	$ \begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 50\\ \end{array} $	$\begin{array}{r} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 150\\ \end{array}$	52 64 54 56 58 62 63 59 60 69 68 68	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS	28 24 20 18 24 29 30 26 17 27 33	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.2 \end{array}$	220 360 216 176 241 196 184 222 264 361 294	161 400 188 200 216 201 214 166 206 256 186	122 122 121 66 132 99 84 128 164 230 191	66           60           58           60           66           56           58           61           59           80           66	32 8 37 50 43 41 42 33 41 51 37 26
F           M           F           M           F           M           M           M           M           M           F	$ \begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 59\\ 61\\ \end{array} $	$\begin{array}{r} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 166\\ 158\\ 162\\ \end{array}$	$ \begin{array}{c} 52\\ 64\\ 54\\ 56\\ 58\\ 62\\ 63\\ 59\\ 60\\ 69\\ 68\\ 60\\ 62\\ 68\\ 60\\ 68\\ 60\\ 60\\ 62\\ 68\\ 60\\ 68\\ 60\\ 62\\ 68\\ 60\\ 60\\ 68\\ 68\\ 60\\ 68\\ 60\\ 68\\ 60\\ 68\\ 60\\ 68\\ 68\\ 60\\ 68\\ 60\\ 68\\ 68\\ 60\\ 68\\ 68\\ 60\\ 68\\ 68\\ 68\\ 68\\ 68\\ 68\\ 68\\ 68\\ 68\\ 68$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 4 YRS 5 YRS 5 YRS 5 YRS 5 YRS	28 24 20 18 24 29 30 26 17 27 33 26 24	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192	161           400           188           200           216           201           214           166           206           256           186           180           200	122 122 121 66 132 99 84 128 164 230 191 96	66           60           58           60           66           56           58           61           59           80           66           60           66	32 8 37 50 43 41 42 33 41 51 37 36 42
F           M           F           M           F           M           M           M           F           F	$\begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 59\\ 61\\ 57\end{array}$	$\begin{array}{r} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 162\\ 156\end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 52 \\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 5 YRS 5 YRS 5 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\$	220 360 216 176 241 196 184 222 264 361 294 192 204	161 400 188 200 216 201 214 166 206 256 186 180 200	122 121 66 132 99 84 128 164 230 191 96 100	66           60           58           60           66           56           58           61           59           80           66           60           64           60	32 8 37 50 43 41 42 33 41 51 37 36 40
F           M           F           M           F           M           M           M           F           F	$\begin{array}{r} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 7\end{array}$	$\begin{array}{r} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 162\\ 162\\ 162\\ 162\\ 162\\ 162\\ 162$	52 64 54 56 58 62 63 59 60 69 60 69 68 60 62 58	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 5 YRS 6 YRS 6 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34 28	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210	161           400           188           200           216           201           214           166           206           256           186           180           200           254	122 121 66 132 99 84 128 164 230 191 96 100 100	66           60           58           60           66           56           58           61           59           80           66           60           64           60	32 8 37 50 43 41 42 33 41 51 37 36 40 50 50
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F           M           F           M           F           M           M           M           F           F           M           M           M           M           M           M           M           M           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ \end{array}$	$\begin{array}{c} (154) \\ 154 \\ 164 \\ 160 \\ 156 \\ 164 \\ 158 \\ 161 \\ 164 \\ 163 \\ 163 \\ 163 \\ 163 \\ 163 \\ 166 \\ 158 \\ 162 \\ 158 \\ 160 \\ 157 \\ 166 \\ 157 \\ 166 \\ \end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ \hline \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 6 YRS 6 YRS 4 YRS 5 YRS 6 YRS 5 YRS	28 24 20 18 29 30 26 17 27 33 26 34 28 24 20 30	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.0 \\ 0.8 \\ 1.1 \\ 1.1 \\ \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150	66           60           58           60           56           58           61           59           80           66           60           64           60           64           60           64           60           64           60           63           74	$\begin{array}{r} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 40\\ 42\\ 60\\ \end{array}$
F           M           F           M           F           M           M           M           F           F           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ \end{array}$	$\begin{array}{r} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 162\\ 158\\ 160\\ 157\\ 166\\ 170\\ \end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ 68 \\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 5 YRS 6 YRS 6 YRS 4 YRS 5 YRS 5 YRS 3 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.0 \\ 0.8 \\ 1.1 \\ 1.2 \\ \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150 142	66           60           58           60           56           58           61           59           80           66           60           64           60           48           63           74           80	$\begin{array}{r} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 42\\ 60\\ 41\\ \end{array}$
F           M           F           M           F           M           M           M           F           F           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ \end{array}$	$\begin{array}{c} (154) \\ 154 \\ 164 \\ 160 \\ 156 \\ 164 \\ 158 \\ 161 \\ 164 \\ 163 \\ 163 \\ 163 \\ 163 \\ 166 \\ 158 \\ 162 \\ 158 \\ 160 \\ 157 \\ 166 \\ 170 \\ 186 \end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ 68 \\ 70 \\ 68 \\ 70 \\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 6 YRS 6 YRS 4 YRS 5 YRS 6 YRS 3 YRS 2 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.0 \\ 0.8 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194	161           400           188           200           216           201           214           166           206           256           180           200           254           201           214           302           201           214	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150 142 89	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 56\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 48\\ 63\\ 74\\ 80\\ 63\\ 63\\ \end{array}$	32           8           37           50           43           41           42           33           41           51           37           36           40           50           40           50           40           50           40           42           60           41           42
F           M           F           F           F           F           M           M           M           F           F           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 56\\ \end{array}$	$\begin{array}{c} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 160\\ 157\\ 166\\ 170\\ 186\\ 168\\ 168\\ \end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ 68 \\ 70 \\ 68 \\ 70 \\ 68 \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 6 YRS 6 YRS 6 YRS 4 YRS 5 YRS 3 YRS 2 YRS 3 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.0 \\ 0.8 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.3 \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           194	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150 142 89 127	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 48\\ 63\\ 74\\ 80\\ 63\\ 51\\ \end{array}$	32         8           37         50           43         41           42         33           41         51           37         36           40         50           40         60           41         42           38         38
F           M           F           F           F           F           F           M           M           F           F           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M           F	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ \end{array}$	$\begin{array}{c} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 160\\ 157\\ 166\\ 170\\ 186\\ 168\\ 168\\ 163\\ \end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ 68 \\ 70 \\ 68 \\ 60 \\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 5 YRS 6 YRS 4 YRS 4 YRS 5 YRS 6 YRS 4 YRS 2 YRS 3 YRS 2 YRS 2 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 26	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.0 \\ 0.8 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.2 \\$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           302           201           214           302           316	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150 142 89 127 97	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 80\\ 63\\ 51\\ 51\\ 44\\ \end{array}$	$\begin{array}{r} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 40\\ 42\\ 60\\ 41\\ 42\\ 38\\ 63\\ \end{array}$
F           M           F           F           F           F           M           M           M           F           F           M           M           M           M           M           M           M           M           M           M           M           M           M           F           F           F           F           F           F           F           F           F           F	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ \end{array}$	$\begin{array}{r} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 160\\ 157\\ 166\\ 170\\ 186\\ 168\\ 163\\ 164\\ 164\\ \end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ 68 \\ 70 \\ 68 \\ 60 \\ 60 \\ 60 \\ 60 \\ 60 \\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 5 YRS 6 YRS 6 YRS 4 YRS 5 YRS 6 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 26 20	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.0 \\ 0.8 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           302           201           214           194           316           160	122 121 66 132 99 84 128 164 230 191 96 100 100 100 98 207 150 142 89 127 97 107	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 80\\ 63\\ 74\\ 80\\ 63\\ 51\\ 44\\ 451\\ \end{array}$	$\begin{array}{r} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 42\\ 60\\ 41\\ 42\\ 60\\ 41\\ 42\\ 38\\ 63\\ 32\\ \end{array}$
F           M           F           F           F           F           M           M           M           F           F           M           M           M           M           F           F           F           F           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ 68\\ \end{array}$	$\begin{array}{c} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 162\\ 158\\ 160\\ 157\\ 166\\ 170\\ 186\\ 168\\ 168\\ 163\\ 164\\ 166\\ \end{array}$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ 68 \\ 70 \\ 68 \\ 60 \\ 60 \\ 60 \\ 61 \\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 6 YRS 6 YRS 4 YRS 5 YRS 6 YRS 3 YRS 2 YRS 3 YRS 3 YRS 2 YRS 3	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 26 20 18	$\begin{array}{c} 1.1\\ 1.0\\ 1.1\\ 0.8\\ 1.2\\ 1.4\\ 0.9\\ 1.1\\ 0.8\\ 1.1\\ 1.3\\ 1.3\\ 1.2\\ 1.3\\ 1.2\\ 1.3\\ 1.2\\ 1.3\\ 1.2\\ 1.1\\ 1.2\\ 1.1\\ 1.3\\ 1.2\\ 1.1\\ 1.1\\ 1.1\\ 1.1\\ 1.1\\ 1.1\\ 1.1$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190 261	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           302           201           214           302           201           214           302           201           214           194           316           160           240	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150 142 89 127 97 107 142	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 80\\ 63\\ 74\\ 80\\ 63\\ 51\\ 44\\ 40\\ 51\\ 61\\ \end{array}$	$\begin{array}{r} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 42\\ 60\\ 41\\ 42\\ 60\\ 41\\ 42\\ 38\\ 63\\ 32\\ 58\\ 58\\ \end{array}$
F           M           F           M           F           F           M           M           M           F           F           F           F           F           F           F           F           F           F           F           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ 68\\ 70\\ \end{array}$	$\begin{array}{c} 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 162\\ 158\\ 162\\ 158\\ 166\\ 157\\ 166\\ 170\\ 186\\ 168\\ 163\\ 164\\ 166\\ 168\\ 168\\ 168\\ 168\\ 168\\ 168\\ 168$	$\begin{array}{c} 52 \\ 54 \\ 54 \\ 56 \\ 58 \\ 62 \\ 63 \\ 59 \\ 60 \\ 69 \\ 68 \\ 60 \\ 62 \\ 58 \\ 64 \\ 60 \\ 70 \\ 68 \\ 70 \\ 68 \\ 60 \\ 60 \\ 61 \\ 62 \\ \hline \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 5 YRS 6 YRS 6 YRS 4 YRS 5 YRS 5 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 26 31 24 26 20 18 22	$\begin{array}{c} 1.1\\ 1.0\\ 1.1\\ 0.8\\ 1.2\\ 1.4\\ 0.9\\ 1.1\\ 0.8\\ 1.1\\ 1.3\\ 1.3\\ 1.2\\ 1.3\\ 1.2\\ 1.3\\ 1.0\\ 0.8\\ 1.1\\ 1.2\\ 1.1\\ 1.2\\ 1.1\\ 1.2\\ 1.1\\ 1.2\\ 1.1\\ 0.9\\ \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190 261 201	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           302           201           214           302           201           214           302           201           214           194           316           160           240           196	122 121 66 132 99 84 128 164 230 191 96 100 100 100 100 98 207 150 142 89 127 97 107 142 108	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 80\\ 63\\ 74\\ 80\\ 63\\ 51\\ 44\\ 51\\ 51\\ 44\\ 51\\ 54\\ \end{array}$	32         8           37         50           43         41           42         33           41         51           37         36           40         50           40         42           60         41           42         38           63         32           58         39
F           M           F           M           F           F           M           M           M           M           M           M           M           F           F           F           F           F           F           F           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ 68\\ 70\\ 56\\ \end{array}$	$\begin{array}{c} (154) \\ 154 \\ 164 \\ 160 \\ 156 \\ 164 \\ 158 \\ 161 \\ 164 \\ 163 \\ 163 \\ 163 \\ 163 \\ 166 \\ 158 \\ 162 \\ 158 \\ 160 \\ 157 \\ 166 \\ 170 \\ 186 \\ 168 \\ 163 \\ 164 \\ 166 \\ 168 \\ 162 \\ 162 \\ \end{array}$	$\begin{array}{c} 52\\ 52\\ 64\\ 54\\ 56\\ 58\\ 62\\ 63\\ 59\\ 60\\ 69\\ 68\\ 60\\ 62\\ 58\\ 64\\ 60\\ 62\\ 58\\ 64\\ 60\\ 70\\ 68\\ 70\\ 68\\ 70\\ 68\\ 60\\ 60\\ 61\\ 62\\ 59\\ 59\\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 4 YRS 3 YRS 4 YRS 4 YRS 4 YRS 6 YRS 6 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 26 31 24 26 20 18 22 20	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190 261 201 309	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           302           201           214           302           201           214           302           201           214           194           316           160           240           196           257	122 121 66 132 99 84 128 164 230 191 96 100 100 100 98 207 150 142 89 127 97 107 142 108 208	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 63\\ 51\\ 44\\ 51\\ 51\\ 61\\ 54\\ 50\\ 50\\ \end{array}$	$\begin{array}{r} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 42\\ 60\\ 41\\ 42\\ 60\\ 41\\ 42\\ 38\\ 63\\ 32\\ 58\\ 39\\ 51\\ \end{array}$
F           M           F           M           F           F           M           M           M           F           F           M           M           M           M           F           F           F           F           F           F           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ 68\\ 70\\ 56\\ 63\\ \end{array}$	$\begin{array}{c} (154) \\ 154 \\ 164 \\ 160 \\ 156 \\ 164 \\ 158 \\ 161 \\ 164 \\ 163 \\ 163 \\ 163 \\ 166 \\ 158 \\ 162 \\ 158 \\ 160 \\ 157 \\ 166 \\ 170 \\ 186 \\ 168 \\ 163 \\ 164 \\ 166 \\ 168 \\ 162 \\ 166 \\ 168 \\ 162 \\ 166 \\ 166 \end{array}$	$\begin{array}{c} 52\\ 52\\ 64\\ 54\\ 56\\ 58\\ 62\\ 63\\ 59\\ 60\\ 69\\ 68\\ 60\\ 62\\ 58\\ 64\\ 60\\ 62\\ 58\\ 64\\ 60\\ 70\\ 68\\ 70\\ 68\\ 70\\ 68\\ 60\\ 60\\ 61\\ 62\\ 59\\ 63\\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 4 YRS 4 YRS 4 YRS 4 YRS 4 YRS 6 YRS 6 YRS 3 YRS 2 YRS 3 YRS 3 YRS 2 YRS 3	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 20 30 26 31 24 20 20 18 22 20 24	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.1 \\ 0.9 \\ 1.3 \\ 1.2 \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190 261 201 309 244	161           400           188           200           216           201           214           166           206           256           188           200           254           201           214           302           201           214           302           201           214           302           201           214           302           201           214           302           201           214           194           316           160           240           196           257           210	122 121 66 132 99 84 128 164 230 191 96 100 100 100 98 207 150 142 89 127 97 107 142 108 208 139	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 80\\ 63\\ 51\\ 44\\ 51\\ 61\\ 54\\ 50\\ 63\\ 80\\ 63\\ 51\\ 61\\ 54\\ 50\\ 63\\ 80\\ 63\\ 51\\ 61\\ 54\\ 50\\ 63\\ 80\\ 63\\ 51\\ 50\\ 63\\ 80\\ 51\\ 50\\ 63\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60$	$\begin{array}{r} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 42\\ 60\\ 41\\ 42\\ 60\\ 41\\ 42\\ 38\\ 63\\ 32\\ 58\\ 39\\ 51\\ 42\\ \end{array}$
F           M           F           M           F           F           M           M           M           M           M           M           M           F           F           F           F           F           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ 68\\ 70\\ 56\\ 63\\ 49\\ \end{array}$	$\begin{array}{c} (154)\\ 154\\ 164\\ 160\\ 156\\ 164\\ 158\\ 161\\ 164\\ 163\\ 163\\ 163\\ 166\\ 158\\ 162\\ 158\\ 160\\ 157\\ 166\\ 170\\ 186\\ 168\\ 163\\ 164\\ 168\\ 162\\ 168\\ 162\\ 166\\ 168\\ 168\\ 162\\ 166\\ 168\\ 168\\ 168\\ 168\\ 162\\ 166\\ 168\\ 168\\ 168\\ 168\\ 168\\ 168\\ 168$	$\begin{array}{c} 52\\ 52\\ 64\\ 54\\ 56\\ 58\\ 62\\ 63\\ 59\\ 60\\ 69\\ 68\\ 60\\ 62\\ 58\\ 64\\ 60\\ 60\\ 62\\ 58\\ 64\\ 60\\ 70\\ 68\\ 70\\ 68\\ 60\\ 60\\ 61\\ 62\\ 59\\ 63\\ 70\\ 63\\ 70\\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 3 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 5 YRS 6 YRS 4 YRS 6 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 10 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 20 30 26 31 24 20 20 18 22 20 24 17	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 0.9 \\ 1.3 \\ 1.2 \\ 0.9 \\ 0.9 \end{array}$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190 261 201 309 244 314	161           400           188           200           216           201           214           166           206           256           188           200           254           201           214           302           201           214           302           201           214           302           201           214           302           201           214           302           201           214           194           316           160           240           196           257           210           307	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150 142 89 127 97 107 142 108 208 139 193	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 63\\ 51\\ 61\\ 51\\ 61\\ 54\\ 50\\ 63\\ 60\\ 60\\ 63\\ 60\\ \end{array}$	32         8           37         50           43         41           42         33           41         51           37         36           40         50           40         60           41         42           50         40           50         40           42         60           41         42           58         39           51         42           61         61
F           M           F           M           F           F           M           M           M           M           M           M           M           F           F           F           F           M           F	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ 68\\ 70\\ 56\\ 63\\ 49\\ 58\\ \end{array}$	$\begin{array}{c} (154) \\ 154 \\ 164 \\ 160 \\ 156 \\ 164 \\ 158 \\ 161 \\ 164 \\ 163 \\ 163 \\ 163 \\ 166 \\ 158 \\ 162 \\ 158 \\ 160 \\ 157 \\ 166 \\ 157 \\ 166 \\ 170 \\ 186 \\ 168 \\ 163 \\ 164 \\ 166 \\ 168 \\ 162 \\ 166 \\ 168 \\ 163 \\ 164 \\ 163 \\ 163 \\ 163 \\ 163 \\ 163 \\ 164 \\ 163 \\ 163 \\ 163 \\ 164 \\ 163 \\ 163 \\ 164 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 163 \\ 164 \\ 165 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105 \\ 105$	$\begin{array}{c} 52\\ 52\\ 64\\ 54\\ 56\\ 58\\ 62\\ 63\\ 59\\ 60\\ 69\\ 68\\ 60\\ 62\\ 58\\ 64\\ 60\\ 60\\ 62\\ 58\\ 64\\ 60\\ 70\\ 68\\ 60\\ 60\\ 61\\ 62\\ 59\\ 63\\ 70\\ 60\\ 60\\ 61\\ 62\\ 59\\ 63\\ 70\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 60\\ 6$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 4 YRS 5 YRS 6 YRS 4 YRS 4 YRS 5 YRS 6 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3 YRS 10 YRS 12 YRS	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 20 30 26 31 24 20 20 24 17 34	$\begin{array}{c} 1.1 \\ 1.0 \\ 1.1 \\ 0.8 \\ 1.2 \\ 1.4 \\ 0.9 \\ 1.1 \\ 0.8 \\ 1.1 \\ 1.3 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.3 \\ 1.2 \\ 1.1 \\ 1.2 \\ 1.1 \\ 1.1 \\ 0.9 \\ 1.3 \\ 1.2 \\ 0.9 \\ 1.1 \\ 1.1 \\ 0.9 \\ 1.1 \\ 1.1 \\ 0.9 \\ 1.1 \\ 1.1 \\ 0.9 \\ 0.9 \\ 1.1 \\ 0.9 \\$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190 261 201 309 244 314 304	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           302           201           214           302           201           214           194           316           160           240           196           257           210           307           264	122 121 66 132 99 84 128 164 230 191 96 100 100 98 207 150 142 89 127 97 107 142 108 208 139 193 171	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 51\\ 61\\ 51\\ 61\\ 54\\ 50\\ 63\\ 60\\ 71\\ \end{array}$	32         8         37         50         43         41         42         33         41         51         37         36         40         50         40         50         40         50         40         42         60         41         42         60         41         42         58         39         51         42         61         52
F           M           F           F           F           F           F           M	$\begin{array}{c} 60\\ 63\\ 45\\ 52\\ 61\\ 56\\ 60\\ 61\\ 62\\ 63\\ 59\\ 59\\ 61\\ 57\\ 56\\ 60\\ 70\\ 66\\ 60\\ 70\\ 66\\ 60\\ 56\\ 46\\ 42\\ 68\\ 70\\ 56\\ 63\\ 49\\ 58\\ 60\\ \end{array}$	$\begin{array}{c} (154) \\ 154 \\ 164 \\ 160 \\ 156 \\ 164 \\ 158 \\ 161 \\ 164 \\ 163 \\ 163 \\ 163 \\ 166 \\ 158 \\ 162 \\ 158 \\ 160 \\ 157 \\ 166 \\ 157 \\ 166 \\ 170 \\ 186 \\ 168 \\ 163 \\ 164 \\ 166 \\ 168 \\ 162 \\ 166 \\ 168 \\ 163 \\ 161 \\ 161 \\ 161 \\ 161 \\ 161 \\ 161 \\ 161 \\ 164 \\ 161 \\ 161 \\ 161 \\ 161 \\ 161 \\ 164 \\ 161 \\ 161 \\ 161 \\ 161 \\ 164 \\ 161$	$\begin{array}{c} 52\\ 52\\ 64\\ 54\\ 56\\ 58\\ 62\\ 63\\ 59\\ 60\\ 69\\ 68\\ 60\\ 62\\ 58\\ 64\\ 60\\ 62\\ 58\\ 64\\ 60\\ 70\\ 68\\ 60\\ 60\\ 61\\ 62\\ 59\\ 63\\ 70\\ 63\\ 70\\ 60\\ 64\\ \end{array}$	4 YRS 6 YRS 3 YRS 5 YRS 4 YRS 4 YRS 4 YRS 4 YRS 5 YRS 3 YRS 4 YRS 5 YRS 6 YRS 4 YRS 6 YRS 4 YRS 5 YRS 3 YRS 2 YRS 3 YRS 3 YRS 2 YRS 3 YRS 2 YRS 3	28 24 20 18 24 29 30 26 17 27 33 26 34 28 24 20 30 26 31 24 20 30 26 31 24 26 20 18 22 20 24 17 34 22	$\begin{array}{c} 1.1\\ 1.0\\ 1.1\\ 0.8\\ 1.2\\ 1.4\\ 0.9\\ 1.1\\ 0.8\\ 1.1\\ 1.3\\ 1.3\\ 1.2\\ 1.3\\ 1.2\\ 1.3\\ 1.2\\ 1.3\\ 1.2\\ 1.1\\ 1.2\\ 1.1\\ 1.2\\ 1.1\\ 1.2\\ 1.1\\ 1.1$	220 360 216 176 241 196 184 222 264 361 294 192 204 210 186 312 284 263 194 216 204 190 261 201 309 244 314 304 210	161           400           188           200           216           201           214           166           206           256           186           180           200           254           201           214           302           201           214           302           201           214           302           201           214           302           201           214           302           201           214           194           316           160           240           196           257           210           307           264           125	122 121 66 132 99 84 128 164 230 191 96 100 100 100 98 207 150 142 89 127 97 107 142 108 208 139 193 171 115	$\begin{array}{c} 66\\ 60\\ 58\\ 60\\ 58\\ 60\\ 56\\ 58\\ 61\\ 59\\ 80\\ 66\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 60\\ 64\\ 51\\ 61\\ 51\\ 61\\ 51\\ 61\\ 55\\ 60\\ 63\\ 60\\ 71\\ 60\\ \end{array}$	$\begin{array}{c} 32\\ 8\\ 37\\ 50\\ 43\\ 41\\ 42\\ 33\\ 41\\ 51\\ 37\\ 36\\ 40\\ 50\\ 40\\ 40\\ 42\\ 60\\ 40\\ 42\\ 60\\ 41\\ 42\\ 60\\ 41\\ 42\\ 58\\ 38\\ 63\\ 32\\ 58\\ 39\\ 51\\ 42\\ 61\\ 52\\ 35\\ \end{array}$

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#### Results

It was observed that at the end of the study period, 62.12% (n=41) patients attained HbA1c levels  $\leq$ 7%. There were only mild/transient adverse effects in the patients, with no drop outs due to an adverse reaction. About 4% patients developed a UTI and 6% developed an upper respiratory tract infection (URTI) during the course of the study. No death was reported during the study.

Table 2 summarizes the blood sugar levels before teneligliptin and 1-, 2-, and 3-months after teneligliptin treatment. It also depicts the HbA1c levels at the start and end of study period.

Sl. No.	Sl. No. Blood sugar before teneligliptin		Blood sugar 1 month		Blood sugar 2 months after		Blood	l sugar 3	HbA1c		
			after ten	mont			ths after				
			addi	teneligl	iptin	tene	ligliptin				
	addition				addit	ion	ad	dition			
	F	PP	F	PP	F	PP	F	PP	Before study	After study	
1	216	317	160	195	130	190	114	170	7.6	6.8	
2	250	380	150	210	140	194	130	176	10.2	7.1	
3	175	287	160	202	142	180	124	166	9.1	7.0	
4	163	306	130	260	126	200	110	180	8.7	6.8	
5	140	284	110	204	114	180	120	161	7.6	6.6	
6	201	314	170	301	120	204	114	180	9.4	6.8	
7	190	293	140	209	134	170	140	160	9.6	7.0	
8	154	275	134	175	126	170	110	180	7.7	6.7	
9	170	297	120	214	124	180	114	174	7.4	6.6	
10	204	317	190	287	184	304	214	314	9.4	9.0	
11	190	320	160	260	144	170	130	174	8.3	6.7	
12	184	290	161	210	130	180	126	160	8.1	6.9	
13	198	303	154	190	120	174	124	180	8.4	7.0	
14	204	354	160	210	144	190	120	164	9.1	6.9	
15	176	307	164	268	137	204	124	180	9.4	7.3	
16	184	403	190	368	170	344	154	302	10.3	9.7	
17	160	290	130	240	120	170	110	168	8.4	6.7	
18	110	260	90	140	94	162	101	170	7.7	6.6	
19	216	376	170	340	160	310	166	300	11.4	9.4	
20	170	266	140	204	130	170	124	174	7.6	6.8	
21	204	344	190	284	176	270	160	284	10.1	9.3	
22	191	250	130	164	110	170	124	180	8.0	7.4	
23	170	274	160	217	140	240	144	230	7.6	7.4	
24	210	294	154	198	130	170	114	180	8.3	7.1	
25	140	281	130	204	126	177	120	164	7.4	6.6	
26	201	377	154	317	124	170	117	168	10.1	7.4	
27	214	356	190	284	194	270	201	264	11.1	9.8	
28	194	314	120	219	116	170	110	174	9.3	7.3	
29	174	287	124	194	114	180	112	163	8.0	7.0	
30	168	301	151	237	130	201	114	190	8.1	7.2	
31	191	317	174	284	160	231	140	212	8.3	7.9	
32	201	311	140	174	114	164	94	170	8.1	6.8	
32	166	302	130	214	114	170	92	160	83	6.9	
33	160	264	110	170	99	160	84	141	7.8	6.4	
34	190	287	104	180	101	154	93	144	8.1	6.3	
35	210	367	121	190	117	170	101	163	9.1	7.0	
36	180	271	140	230	116	191	117	174	9.4	6.9	
37	174	301	160	276	154	290	160	280	9.0	8.6	
38	190	341	130	241	134	206	130	184	9.2	7.2	
39	163	257	124	191	107	184	94	163	8.7	7.0	
40	154	240	114	184	90	170	86	154	7.4	6.6	
41	184	257	130	203	110	174	101	167	7.6	6.9	

#### **Table 2** Blood sugar and HbA1c levels before and after teneligliptin treatment

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42	184	314	140	190	104	174	84	170	9.1	7.3
43	190	344	174	274	160	284	154	270	11.1	9.3
44	163	271	120	164	114	170	94	154	8.4	6.9
45	172	244	124	190	110	164	97	154	7.4	6.6
46	191	287	144	214	104	170	90	157	8.1	6.7
47	170	301	130	190	101	164	84	161	8.2	6.6
48	201	377	194	354	200	334	170	300	11.7	10.4
49	206	204	134	180	120	176	110	170	9.4	7.3
50	170	301	160	214	154	197	184	211	8.7	8.5
51	160	271	130	197	124	161	110	154	7.8	6.9
52	154	244	110	184	90	170	93	168	7.7	6.5
53	150	270	108	191	97	175	101	171	7.7	6.8
54	190	317	114	214	104	190	106	201	8.1	7.4
55	201	314	140	200	136	180	126	174	8.4	7.3
56	164	281	121	174	114	161	90	154	7.6	6.7
57	166	301	101	201	96	174	97	163	8.1	7.1
58	141	222	90	174	92	190	84	174	7.4	6.9
59	161	284	99	163	92	166	87	154	7.5	6.7
60	184	314	114	184	110	178	90	174	8.3	6.8
61	140	281	104	170	90	166	88	160	7.6	6.4
62	210	344	170	302	166	312	154	301	9.7	9.3
63	160	270	106	184	94	172	90	166	7.7	6.6
64	174	284	121	193	91	174	84	170	7.9	6.4
65	145	230	130	190	126	184	127	190	7.3	6.9
66	150	274	94	204	96	190	94	199	7.4	7.1

#### Discussion

Quadruple therapy regimen is a possible approach in the management of type 2 diabetes,<sup>5</sup> and warrants research. In this study, a fourth oral drug was added to triple oral therapy in patients with inadequately controlled diabetes mellitus. Teneligliptin 20 mg OD was added to the triple drug therapy regimen in the patients and the patients were analyzed for 3 months. At the end of the third month, nearly 62% of the patients attained an HbA1c of  $\leq$ 7%, which is quite encouraging. The adverse effects were only mild and the drug was well tolerated overall.

Teneligliptin is a relatively new oral dipeptidyl peptidase 4 (DPP-4) inhibitor employed for the management of type 2 diabetes mellitus. Published literature highlights the efficacy of teneligliptin as monotherapy and in combination with other oral agents, and insulin in short-term and long-term studies. Teneligliptin has been shown to yield a reduction in HbA1c of 0.8%–0.9% within 12 weeks of treatment. This is a safe and well-tolerated drug. It is also safe to be used in patients with mild, moderate, or severe renal impairment or end-stage renal disease without the

need for any dose adjustment. Patients with mildto-moderate hepatic impairment can also be prescribed teneligliptin.<sup>6</sup>

Eto et al<sup>7</sup> assessed blood glucose control over 24 h and the safety of teneligliptin 10 and 20 mg in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. Patients given teneligliptin had significantly lower 2-h postprandial glucose (2-h PPG), 24-h mean glucose and fasting plasma glucose levels as compared to placebo group. No hypoglycemic symptoms or serious adverse events were seen in the patients. In a study by Kadowaki and Kondo,<sup>8</sup> treatment with teneligliptin for 12 weeks was to yield significant and clinically found meaningful reductions in HbA1c and FPG. Teneligliptin has been found to be effective in combination therapy as well. Kim et al<sup>9</sup> determined the efficacy and safety of teneligliptin in combination with metformin in type 2 diabetes patients inadequately controlled with metformin monotherapy. The differences between the teneligliptin and placebo groups for changes in HbA1c and fasting plasma glucose levels were -0.78 % -1.24 mmol/l (22.42 mg/dl), and

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respectively, at week 16. The addition of teneligliptin once daily to metformin was effective and well tolerated.

Considering the efficacy of teneligliptin in the management of diabetes, I decided to include this drug as the fourth add-on oral hypoglycemic agent in my diabetes patients not controlled well on triple therapy and found the drug to yield positive outcomes. The drug was effective in attaining target HbA1c level in a large number of the study patients and was well-tolerated.

Therefore, teneligliptin could well be the choice of fourth drug added to a triple therapy regimen in patients who cannot be given insulin treatment, in order to achieve the desired HbA1c target.

#### Conclusion

Addition of teneligliptin to type 2 diabetes patients inadequately controlled with triple drug treatment with glimepride + metformin + voglibose is safe and effective. This regimen led to the achievement of HbA1c  $\leq$ 7% in about 62.12% patients.

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